First Latin American Guidelines for the Treatment of Systemic Lupus Erythematosus: Latin American Group for the Study of Lupus (GLADEL, *Grupo Latinoamericano De Estudio del Lupus*) – Pan-American League of Associations of Rheumatology (PANLAR).

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1.1.1.1

| **ABT plus CYC plus AZA compared to CYC plus AZA plus placebo for lupus related nephropathy** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| Outcome № of participants (studies) | Relative effect (95% CI) | **Anticipated absolute effects (95% CI)** | | | Quality | What happens |
| **Without ABT** | **With ABT** | **Difference** |
| Partial remission follow up: 24 weeks № of participants: 134 (1 RCT) | **RR 0.92** (0.50 to 1.70) | 27.9% | **25.7%** (14.0 to 47.5) | **2.2% fewer** (14 fewer to 19.6 more) | ⨁⨁◯◯ LOW 1,2 | ABT may make little or no difference to partial remission |
| Complete remission - Induction follow up: 24 weeks № of participants: 134 (1 RCT) | **RR 1.08** (0.63 to 1.85) | 30.9% | **33.4%** (19.5 to 57.1) | **2.5% more** (11.4 fewer to 26.3 more) | ⨁⨁◯◯ LOW 1,2 | ABT may make little or no difference to complete remission -induction |
| Complete remission - Maintenance follow up: 52 weeks № of participants: 199 (1 RCT) | **RR 1.49** (0.83 to 2.72) | 17.0% | **25.3%** (14.1 to 46.2) | **8.3% more** (2.9 fewer to 29.2 more) | ⨁⨁◯◯ LOW 1,2 | ABT may improve complete response - maintenance |
| Serious adverse events follow up: 24 weeks № of participants: 134 (1 RCT) | **RR 0.68** (0.40 to 1.17) | 35.3% | **24.0%** (14.1 to 41.3) | **11.3% fewer** (21.2 fewer to 6 more) | ⨁⨁◯◯ LOW 1,2 | ABT may not significantly increase the risk of serious adverse events |
| Specific adverse events - SERIOUS INFECTIONS follow up: 24 weeks № of participants: 134 (1 RCT) | **RR 1.65** (0.51 to 5.62) | 7.4% | **12.1%** (3.8 to 41.3) | **4.8% more** (3.6 fewer to 34 more) | ⨁⨁◯◯ LOW 1,2 | ABT may increase serious infections |

1. Wide confidence intervals include significant benefit and harm
2. Risk of bias

* Askanase A, Byron M, Keyes-Elstein L, Cagnoli P, McCune WJ, Chatham WW, et al. Treatment of lupus nephritis with abatacept: the abatacept and cyclophosphamide combination efficacy and safety study. Arthritis & rheumatology 2014; 66: 3096-104.

1.1.1.2

| **AZA plus GCs compared to GCs for lupus related nephropathy** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| Outcome № of participants (studies) | Relative effect (95% CI) | **Anticipated absolute effects (95% CI)** | | | Quality | What happens |
| **Without AZA vs placebo** | **With AZA vs placebo** | **Difference** |
| Death follow up: 6 months № of participants: 131 (4 RCTs) | **RR 0.58** (0.35 to 0.95) | 41.3% | **23.9%** (14.4 to 39.2) | **17.3% fewer** (26.8 fewer to 2.1 fewer) | ⨁⨁◯◯ LOW 2,3 | AZA may reduce death |
| Dialysis requirement follow up: 6 months № of participants: 70 (3 RCTs) | **RR 0.66** (0.17 to 2.55) | 31.0% | **20.5%** (5.3 to 79.1) | **10.6% fewer** (25.8 fewer to 48.1 more) | ⨁⨁◯◯ LOW 2,3 | AZA may reduce dialysis requirement |
| Hospitalization for relapse follow up: 4 years № of participants: 35 (1 RCT) | **RR 2.53** (0.82 to 7.78) | 18.8% | **47.4%** (15.4 to 100.0) | **28.7% more** (3.4 fewer to 127.1 more) | ⨁◯◯◯ VERY LOW 1,2 | It is uncertain if AZA affects this outcome |
| Doubling Creatinine values follow up: 6 months № of participants: 105 (4 RCTs) | **RR 0.87** (0.36 to 2.07) | 12.5% | **10.9%** (4.5 to 25.9) | **1.6% fewer** (8 fewer to 13.4 more) | ⨁⨁◯◯ LOW 2,3 | AZA may have little or no impact on creatinine values |
| Change in creatinine greater than 10% follow up: 4 years № of participants: 35 (1 RCT) | **RR 2.53** (0.82 to 7.78) | 18.8% | **47.4%** (15.4 to 100.0) | **28.7% more** (3.4 fewer to 127.1 more) | ⨁◯◯◯ VERY LOW 1,2 | It is uncertain if AZA affects this outcome |
| Proteinuria fewer a 0.8 gr follow up: 6 months № of participants: 80 (3 RCTs) | **RR 0.85** (0.56 to 1.29) | 47.6% | **40.5%** (26.7 to 61.4) | **7.1% fewer** (21 fewer to 13.8 more) | ⨁⨁◯◯ LOW 2,3 | AZA may reduce proteinuria |
| Specific Adverse effects follow up: 4 years № of participants: 32 (1 RCT) | 2 patients of 16 in the AZA group presented agranulocytosis. Adverse events in placebo group not reported. | | | | ⨁◯◯◯ VERY LOW 1,2 | It is uncertain if AZA affects this outcome |
| Specific Adverse effects follow up: 6 months № of participants: 101 (4 RCTs) | **RR 1.11** (0.57 to 2.16) | 16.7% | **18.5%** (9.5 to 36.0) | **1.8% more** (7.2 fewer to 19.3 more) | ⨁⨁◯◯ LOW 2,3 | AZA may have little or no impact on specific adverse effects |
| Adverse effects follow up: 6 months № of participants: 44 (2 RCTs) | **RR 0.53** (0.19 to 1.53) | 68.2% | **36.1%** (13.0 to 100.0) | **32.0% fewer** (55.2 fewer to 36.1 more) | ⨁⨁◯◯ LOW 2,3 | AZA may reduce adverse effects |
| \***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).   **CI:** Confidence interval; **RR:** Risk ratio | | | | | | |

1. Open-label study
2. Low number of patients and events, possible benefits or harm
3. Unclear randomization and concealed allocation. Important lost of follow up.
4. Low number of patients not reaching optimal information data

* Cade R, Spooner G, Schlein E, Pickering M, DeQuesada A, Holcomb A, et al. Comparison of azathioprine, prednisone, and heparin alone or combined in treating lupus nephritis. Nephron. 1973;10:37–56.
* Donadio JV, Holley KE, Wagoner RD, Ferguson RH, McDuffie FC. Treatment of lupus nephritis with prednisone and combined prednisone and azathioprine. Ann Intern Med. 1972 ;77:829–35.
* Hahn BH, Kantor OS, Osterland CK. Azathioprine plus prednisone compared with prednisone alone in the treatment of systemic lupus erythematosus. Report of a prospective controlled trial in 24 patients. Ann Intern Med. 1975 ;83:597–605.
* Austin HA, Klippel JH, Balow JE, le Riche NG, Steinberg AD, Plotz PH, et al. Therapy of lupus nephritis. Controlled trial of prednisone and cytotoxic drugs. N Engl J Med. 1986 6;314:614–9.

1.1.1.3

| **Belimumab plus usual treatment compared to placebo plus usual treatment for lupus related nephropathy** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| Outcome № of participants (studies) | Relative effect (95% CI) | **Anticipated absolute effects (95% CI)** | | | Quality | What happens |
| **Without belimumab** | **With belimumab** | **Difference** |
| Death (any dose) follow up: 1 years № of participants: 2133 (3 RCTs) | **RR 1.30** (0.41 to 4.14) | 0.4% | **0.6%** (0.2 to 1.8) | **0.1% more** (0.3 fewer to 1.4 more) | ⨁⨁⨁◯ MODERATE 1 | Belimumab probably makes no difference to death |
| Remission (any dose) follow up: 6 months № of participants: 220 (1 RCT) | **RR 1.16** (0.93 to 1.45) | 58.7% | **68.1%** (54.6 to 85.1) | **9.4% more** (4.1 fewer to 26.4 more) | ⨁⨁◯◯ LOW 1 | Belimumab may increase remission |
| BILAG improvement (any dose) follow up: 6 months № of participants: 179 (1 RCT) | **RR 1.07** (0.73 to 1.57) | 39.0% | **41.7%** (28.5 to 61.2) | **2.7% more** (10.5 fewer to 22.2 more) | ⨁⨁◯◯ LOW 1 | Belimiumab may improve BILAG score |
| BILAG improvement in 2 or more levels (any dose) follow up: 6 months № of participants: 179 (1 RCT) | **RR 0.86** (0.38 to 1.94) | 13.6% | **11.7%** (5.2 to 26.3) | **1.9% fewer** (8.4 fewer to 12.7 more) | ⨁⨁◯◯ LOW 1 | Belimumab may not affect BILAG score in 2 or more levels |
| Creatinine triplication (any dose) follow up: 1 years № of participants: 1677 (1 RCT) | **RR 0.36** (0.11 to 1.13) | 1.2% | **0.4%** (0.1 to 1.4) | **0.8% fewer** (1.1 fewer to 0.2 more) | ⨁⨁⨁◯ MODERATE 1 | Belimumab probably reduces creatinine triplication |
| Proteinuria <2 gr (any dose) follow up: 1 years № of participants: 1666 (1 RCT) | **RR 1.07** (0.66 to 1.72) | 4.3% | **4.6%** (2.8 to 7.4) | **0.3% more** (1.5 fewer to 3.1 more) | ⨁⨁◯◯ LOW 1 | Belimumab may have little or no effect on proteinuria |
| Relapses (any dose) follow up: 1 years № of participants: 1684 (1 RCT) | **RR 0.65** (0.35 to 1.21) | 3.0% | **2.0%** (1.1 to 3.7) | **1.1% fewer** (2 fewer to 0.6 more) | ⨁⨁⨁◯ MODERATE 1 | Belimumab probably slightly reduces relapses |
| Major Adverse effects (any dose) follow up: 1 years № of participants: 2133 (3 RCTs) | **RR 0.97** (0.79 to 1.20) | 16.0% | **15.5%** (12.6 to 19.2) | **0.5% fewer** (3.4 fewer to 3.2 more) | ⨁⨁⨁◯ MODERATE 1 | Belimumab probably makes little or no difference to major adverse effects at 1 year |
| Infections (any dose) follow up: 1 years № of participants: 2143 (3 RCTs) | **RR 1.08** (1.01 to 1.14) | 66.4% | **71.7%** (67.1 to 75.7) | **5.3% more** (0.7 more to 9.3 more) | ⨁⨁⨁⨁ HIGH | Belimumab increases the risk of infections |

1. 95% CI makes possible benefits and harms or absence of benefits

* Navarra SV, Guzmán RM, Gallacher AE, Hall S, Levy RA, Jimenez RE, et al. Efficacy and safety of belimumab in patients with active systemic lupus erythematosus: a randomised, placebo-controlled, phase 3 trial. Lancet. 2011 26;377:721–31.
* Furie R, Petri M, Zamani O, Cervera R, Wallace DJ, Tegzová D, et al. A phase III, randomized, placebo-controlled study of belimumab, a monoclonal antibody that inhibits B lymphocyte stimulator, in patients with systemic lupus erythematosus. Arthritis Rheum. 2011;63:3918–30
* Wallace DJ, Stohl W, Furie RA, Lisse JR, McKay JD, Merrill JT, et al. A phase II, randomized, double-blind, placebo-controlled, dose-ranging study of belimumab in patients with active systemic lupus erythematosus. Arthritis Rheum. 2009 15;61(9):1168–78.
* Dooley MA, Houssiau F, Aranow C, D’Cruz DP, Askanase A, Roth DA, et al. Effect of belimumab treatment on renal outcomes: results from the phase 3 belimumab clinical trials in patients with SLE. Lupus. 2013;22:63–72.
* Manzi S, Sánchez-Guerrero J, Merrill JT, Furie R, Gladman D, Navarra SV, et al. Effects of belimumab, a B lymphocyte stimulator-specific inhibitor, on disease activity across multiple organ domains in patients with systemic lupus erythematosus: combined results from two phase III trials. Ann Rheum Dis. 2012;71:1833–8.

1.1.1.4

| **Misoprostol plus GCs compared to placebo plus GCs for induction therapy in lupus nephritis** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| Outcome № of participants (studies) | Relative effect (95% CI) | **Anticipated absolute effects (95% CI)** | | | Quality | What happens |
| **Without Misoprostol** | **With Misoprostol** | **Difference** |
| Doubling serum creatinine follow up: 12 weeks № of participants: 14 (1 RCT) | not estimable | 14.3% | **0.0%** (0.0 to 0.0) | **14.3% fewer** | ⨁⨁◯◯ VERY LOW 1,2 | It is uncertain if misoprostol affects this outcome |

1. Unclear randomization
2. Small number of events

* Belmont HM, Kitsis E, Skovron ML, Buyon J, McCullagh E, Abramson S. Misoprostol and Prednisone Treatment of Lupus Nephritis. Am J Ther. 1995;2:928–32.

| 1.1.1.5 | | | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| **Ocrelizumab plus MMF or CYC plus GCs compared to placebo plus MMF or CYC plus GCs for lupus related nephropathy** | | | | | | |
| Outcome № of participants (studies) | Relative effect (95% CI) | **Anticipated absolute effects (95% CI)** | | | Quality | What happens |
| **Without Ocrelizumab** | **With Ocrelizumab** | **Difference** |
| Death follow up: 48 weeks № of participants: 251 (1 RCT) | **RR 0.50** (0.10 to 2.18) | 4.8% | **2.4%** (0.5 to 10.5) | **2.4% fewer** (4.3 fewer to 5.7 more) | ⨁⨁◯◯ LOW 1,2 | Ocrelizumab may reduce death |
| Complete remission follow up: 48 weeks № of participants: 150 (1 RCT) | **RR 1.23** (0.80 to 1.92) | 34.7% | **42.6%** (27.7 to 66.6) | **8.0% more** (6.9 fewer to 31.9 more) | ⨁⨁◯◯ LOW 1,2 | Ocrelizumab may slightly improve complete remission |
| Partial remission follow up: 48 weeks № of participants: 150 (1 RCT) | **RR 1.20** (0.62 to 2.34) | 20.0% | **24.0%** (12.4 to 46.8) | **4.0% more** (7.6 fewer to 26.8 more) | ⨁⨁◯◯ LOW 1,2 | Ocrelizumab may slightly improve partial remission |
| Serious adverse events follow up: 48 № of participants: 251 (1 RCT) | **RR 1.31** (0.89 to 1.96) | 27.2% | **35.6%** (24.2 to 53.3) | **8.4% more** (3 fewer to 26.1 more) | ⨁⨁⨁◯ MODERATE 1 | Ocrelizumab probably increases serious adverse events |
| Specific adverse events INFECTION follow up: 48 weeks № of participants: 251 (1 RCT) | **RR 1.49** (0.84 to 2.70) | 14.4% | **21.5%** (12.1 to 38.9) | **7.1% more** (2.3 fewer to 24.5 more) | ⨁⨁⨁◯ MODERATE 1 | Ocrelizumab probably increases specific adverse events |

1. Wide confidence intervals include significant benefit and harm
2. Risk of bias

* Mysler EF, Spindler AJ, Guzman R, Bijl M, Jayne D, Furie RA, et al. Efficacy and Safety of Ocrelizumab in Active Proliferative Lupus Nephritis: Results From a Randomized, Double-Blind, Phase III Study: Ocrelizumab in Lupus Nephritis. Arthritis & Rheumatism. 2013;65:2368–79.

1.1.1.6

| **TPE compared to GCs / placebo for lupus related nephropathy** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| Outcome № of participants (studies) | Relative effect (95% CI) | **Anticipated absolute effects (95% CI)** | | | Quality | What happens |
| **Without TPE** | **With TPE** | **Difference** |
| Death  Follow up: 3 months to 5 years № of participants: 125 (2 RCTs) | **RR 1.62** (0.64 to 4.09) | 9.2% | **15.0%** (5.9 to 37.8) | **5.7% more** (3.3 fewer to 28.5 more) | ⨁⨁◯◯ LOW 1,2 | TPE may increase death |
| Renal replacement therapy  Follow up: 3 months to 5 years № of participants: 143 (3 RCTs) | **RR 1.24** (0.60 to 2.57) | 14.9% | **18.4%** (8.9 to 38.2) | **3.6% more** (5.9 fewer to 23.3 more) | ⨁⨁◯◯ LOW 1,2 | TPE may slightly increase the need for renal replacement therapy |
| Doubling of serum creatinine  Follow up: 3 months to 5 years № of participants: 51 (2 RCTs) | **RR 0.20** (0.01 to 3.46) | 20.0% | **4.0%** (0.2 to 69.2) | **16.0% fewer** (19.8 fewer to 49.2 more) | ⨁◯◯◯ VERY LOW 1,2,3 | We are uncertain whether TPE improves/reduces doubling of serum creatinine |
| Serious adverse events INFECTION  Follow up: 3 months to 5 years № of participants: 125 (1 RCT) | **RR 0.69** (0.35 to 1.37) | 24.6% | **17.0%** (8.6 to 33.7) | **7.6% fewer** (16 fewer to 9.1 more) | ⨁⨁◯◯ LOW 1,2 | TPE may make little or no difference to serious adverse events |

1. Risk of bias
2. Wide confidence intervals include significant benefit and harm
3. Few patients and events

* Clark WF, Balfe JW, Cattran DC, Williams W, Lindsay RM, Linton AL. Long-term plasma exchange in patients with systemic lupus erythematosus and diffuse proliferative glomerulonephritis. Plasma Ther Transfusion Technol. 1984;5:353-360.
* Lewis EJ, Hunsicker LG, Lan SP, Rohde RD, Lachin JM. A controlled trial of plasmapheresis therapy in severe lupus nephritis. The Lupus Nephritis Collaborative Study Group. N Engl J Med. 1992 21;326:1373–9.
* Wallace DJ, Goldfinger D, Pepkowitz SH, Fichman M, Metzger AL, Schroeder JO, et al. Randomized controlled trial of pulse/synchronization cyclophosphamide/apheresis for proliferative lupus nephritis. J Clin Apher. 1998;13:163–6.

1.1.1.7

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| --- | --- | --- | --- | --- | --- | --- |
| **RTX plus MMF plus GCs compared to placebo plus MMF plus GCs for lupus related nephropathy** | | | | | | |
| Outcome № of participants (studies) | Relative effect (95% CI) | **Anticipated absolute effects (95% CI)** | | | Quality | What happens |
| **Without RTX** | **With RTX** | **Difference** |
| Death  follow up: 52 weeks № de participants : 144  (1 RCT) | **OR 5.14** (0.24 a 109.01) | 0.1% | 0.7% (0.0 a 13.2) | 0.6% more (0.1 fewer a 13 more ) | ⨁⨁◯◯ LOW 1 | RTX may make little or no difference in death |
| Urine protein: creatinine ratio (UPC) <1 (Basal UPC >3)  follow up: 52 weeks № de participants : 79  (1 RCT) | **OR 0.78** (0.32 a 1.88) | 53.7% | **47.5%**  (27.0 a 68.5) | **6.2% fewer**  (26.6 fewer a 14.9 more ) | ⨁⨁◯◯ LOW 1 | RTX may decrease proteinuria |
| Partial remission follow up: 52 weeks № de participants: 144  (1 RCT) | **OR 2.44** (1.08 a 5.51) | 15.3% | **30.6%** (16.3 a 49.8) | **15.3% more** (1 more a 34.6 more ) | ⨁⨁⨁◯ MODERATE 1 | RTX probably increases partial remission at 52 weeks |
| Partial remission follow up: 78 weeks № de participants: 144  (1 RCT) | **OR 1.84** (0.75 a 4.53) | 12.5% | **20.8%** (9.7 a 39.3) | **8.3% more** (2.8 fewer a 26.8 more ) | ⨁⨁◯◯ LOW 1 | RTX may increase partial remission at 78 weeks |
| Complete Remission follow up: 52 weeks № de participants: 144  (1 RCT) | **OR 0.81**  (0.39 a 1.68) | 30.6% | **26.3%**  (14.6 a 42.5) | **4.3% fewer**  (15.9 fewer a 11.9 more ) | ⨁⨁◯◯  LOW 1 | RTX may have little or no effect on complete remission at 52 weeks |
| Complete Remission follow up: 78 weeks № de participants: 144  (1 RCT) | **OR 1.13** (0.57 a 2.27) | 31.9% | **34.7%** (21.1 a 51.6) | **2.7% more** (10.8 fewer a 19.6 more ) | ⨁⨁◯◯ LOW 1 | RTX may have little or no effect on complete remission at 78 weeks |
| Major adverse effects follow up: 52 weeks № de participants: 144  (1 RCT) | **OR 0.71** (0.36 a 1.40) | 40.8% | **32.9%** (19.9 a 49.2) | **7.9% fewer** (20.9 fewer a 8.3 more ) | ⨁⨁◯◯  LOW 1 | RTX may have little or no effect on major adverse effects |
| Infusion reactions follow up: 52 weeks № de participants: 144  (1 RCT) | **RR 1.9**4 (0.71 a 5.6) | 8.4% | **16.2%** (5.9 a 47) | **7.8% more** (2.5 fewer a 38.6 more ) | ⨁⨁⨁◯  MODERATE 1 | RTX probably increases infusion reactions |

1. 95% CI includes the possibility of benefits and harms or abcense of benefits

* Rovin BH, Furie R, Latinis K, Looney RJ, Fervenza FC, Sanchez-Guerrero J, et al. Efficacy and safety of rituximab in patients with active proliferative lupus nephritis: the Lupus Nephritis Assessment with Rituximab study. Arthritis Rheum. 2012;64:1215–26.

1.1.1.8

| **TAC plus GCs compared to placebo plus GCs for lupus nephritis** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| Outcome № of participants (studies) | Relative effect (95% CI) | **Anticipated absolute effects (95% CI)** | | | Quality | What happens |
| **Without TAC** | **With TAC** | **Difference** |
| Stable renal function follow up: 28 weeks № of participants: 35 (1 RCT) | **RR 1.06** (0.80 to 1.39) | 74.3% | **78.7%** (59.4 to 100.0) | **4.5% more** (14.9 fewer to 29 more) | ⨁⨁◯◯ LOW 1 | TAC may slightly increase stable renal function |
| Proteinuria less to 0.8 gr follow up: 28 weeks № of participants: 35 (1 RCT) | **RR 5.00** (0.59 to 42.25) | 2.9% | **14.3%** (1.7 to 100.0) | **11.4% more** (1.2 fewer to 117.9 more) | ⨁⨁◯◯ LOW 1 | TAC may reduce proteinuria |
| Major adverse events follow up: 28 № of participants: 35 (1 RCT) | **RR 0.63** (0.21 to 1.86) | 22.9% | **14.4%** (4.8 to 42.5) | **8.5% fewer** (18.1 fewer to 19.7 more) | ⨁⨁◯◯ LOW 1 | TAC probably makes little or no difference in major adverse events in patients with lupus nephritis |
| Infections follow up: 28 weeks № of participants: 35 (1 RCT) | **RR 1.04** (0.68 to 1.59) | 57.1% | **59.4%** (38.9 to 90.9) | **2.3% more** (18.3 fewer to 33.7 more) | ⨁⨁◯◯ LOW 1 | TAC may increase the risk of infections |

1. Wide confidence interval includes the possibility of benefits and harms

* Miyasaka N, Kawai S, Hashimoto H. Efficacy and safety of tacrolimus for lupus nephritis: a placebo-controlled double-blind multicenter study. Mod Rheumatol. 2009;19:606–15.

1.1.1.9

| **AMs compared to placebo for lupus related nephropathy** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| Outcome № of participants (studies) | Relative effect (95% CI) | **Anticipated absolute effects (95% CI)** | | | Quality | What happens |
| **Without AMs** | **With AMs** | **Difference** |
| Death № of participants: 2785 (4 observational studies) | In two cohort studies, HCQ was found to be an independent protective factor for death (HR between 0.20 and 0.23). In a case control study, using a propensity score, HCQ reduced the risk of death (OR = 0.32 95%CI 0.12 - 0.86).  A Latin American cohort found a HR = 0.64 (95%CI 0.39 – 0.99)  In some cases, possible lack of adjustment for potential design bias may rise concerns | | | | - |  |
| Development of renal damage (SLICC Damage Index) follow up: 10 years № of participants: 203 (1 observational study) | **OR 0.51** (0.29 to 0.91) | **White** | | | ⨁⨁◯◯ LOW 3 | HCQ may reduce the risk of renal damage development |
| 22.6% 1 | **13.0%** (7.8 to 21.0) | **9.6% fewer** (14.8 fewer to 1.6 fewer) |
| **Hispanic - Low** | | |
| 31.0% 1 | **18.6%** (11.5 to 29.0) | **12.4% fewer** (19.5 fewer to 2 fewer) |
| **Hispanic - High** | | |
| 65.4% 2 | **49.1%** (35.4 to 63.2) | **16.3% fewer** (30 fewer to 2.2 fewer) |
| First serious hospitalized infection follow up: mean 2.1 years № of participants: 7113 (1 observational study) | **HR 0.78** (0.71 to 0.87) | 25.7% | **20.6%** (19.0 to 22.7) | **5.0% fewer** (6.7 fewer to 2.9 fewer) | ⨁⨁◯◯ LOW | HCQ may reduce the risk of (time to) first hospitalized infection |

1. Feldman CH, Hiraki LT, Liu J, Fischer MA, Solomon DH, Alarcón GS, et al. Epidemiology and sociodemographics of systemic lupus erythematosus and lupus nephritis among US adults with Medicaid coverage, 2000-2004. Arthritis Rheum 2013 ;65 :753-63.
2. Pons-Estel GJ, Alarcón GS, Burgos PI, Hachuel L, Boggio G, Wojdyla D, et al; Grupo Latino Americano de Estudio de Lupus (GLADEL). Mestizos with systemic lupus erythematosus develop renal disease early while antimalarials retard its appearance: data from a Latin American cohort. Lupus 2013;22:899-907.
3. Analysis adjusted for potential design bias

* Zheng ZH, Zhang LJ, Liu WX, Lei YS, Xing GL, Zhang JJ, et al. Predictors of survival in chinese patients with lupus nephritis. Lupus 2012;21:1049-56.
* Alarcón GS, McGwin G, Bertoli AM, Fessler BJ, Calvo-Alén J, Bastian HM, et al. Effect of hydroxychloroquine on the survival of patients with systemic lupus erythematosus: data from LUMINA, a multiethnic US cohort. Ann Rheum Dis 2007;66:1168-72.
* Sisó A, Ramos-Casals M, Bové A, Brito-Zerón P, Soria N, Muñoz S, et al.. Previous antimalarial therapy in patients diagnosed with lupus nephritis: influence on outcomes and survival. Lupus 2008;17:281-8.
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* Pons-Estel GJ, Alarcón GS, McGwin G Jr, Danila MI, Zhang J, Bastian HM, et al; Protective effect of hydroxychloroquine on renal damage in patients with lupus nephritis: LXV, data from a multiethnic US cohort. Arthritis Rheum 2009;61:830-9.
* Pons-Estel GJ, Alarcón GS, Hachuel L, Boggio G, Wojdyla D, Pascual-Ramos V, et al. Anti-malarials exert a protective effect while mestizo patients are at increased risk of developing SLE renal disease: data from a latin-american cohort. Rheumatology (Oxford) 2012;51:1293-8.
* Vinet E, Bernatsky S, Suissa S. Have some beneficial effects of hydroxychloroquine been overestimated? Potential biases in observational studies of drug effects: comment on the article by Pons-Estel et al. Arthritis Rheum 2009;61:1614-5.
* Vlad SC. Protective effect of hydroxychloroquine on renal damage may be biased: comment on the article by Pons-Estel et al. Arthritis Rheum 2009;61:1614.
* Feldman CH, Hiraki LT, Winkelmayer WC, Marty FM, Franklin JM, Kim SC, et al. Serious infections among adult medicaid beneficiaries with systemic lupus erythematosus and lupus nephritis. Arthritis Rheumatol 2015 ;67:1577-85.

1.1.1.10

| **CYC compared to GCs for lupus nephritis (induction)** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| Outcome № of participants (studies) | Relative effect (95% CI) | **Anticipated absolute effects (95% CI)** | | | Quality | What happens |
| **Without CYC** | **With CYC** | **Difference** |
| Death № of participants: 226 (5 RCTs) | **RR 0.98** (0.53 to 1.82) | **High** | | | ⨁⨁◯◯ LOW 1 | CYC may reduce death |
| 43.0% | **42.1%** (22.8 to 78.3) | **0.9% fewer** (20.2 fewer to 35.3 more) |
| ESKD № of participants: 278 (5 RCTs) | **RR 0.63** (0.39 to 1.03) | **High** | | | ⨁⨁⨁◯ MODERATE 1 | CYC probably reduces ESKD |
| 31.0% 2 | **19.5%** (12.1 to 31.9) | **11.5% fewer** (18.9 fewer to 0.9 more) |
| Doubling of Cr follow up: 4 № of participants: 228  (5 RCTs) | **RR 0.59** (0.40 to 0.88) | **High** | | | ⨁⨁⨁◯ MODERATE 3 | CYC probably reduces doubling of Cr |
| 12.5% 2 | **7.4%** (5.0 to 11.0) | **5.1% fewer** (7.5 fewer to 1.5 fewer) |
| Renal relapse № of participants: 42 (1 RCT) | **RR 0.30** (0.10 to 0.94) | **Low** | | | ⨁⨁⨁◯ MODERATE 3 | CYC probably reduces renal relapse |
| 15.0% 4 | **4.5%** (1.5 to 14.1) | **10.5% fewer** (13.5 fewer to 0.9 fewer) |
| **High** | | |
| 30.0% d | **9.0%** (3.0 to 28.2) | **21.0% fewer** (27 fewer to 1.8 fewer) |

1. 95% CI includes benefits and harms
2. Basal risk extracted from table 1.1.1.2 (AZA vs GCs)
3. Optimal information size not met
4. Risk assumed based on other comparisons

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1.1.2.1

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **AZA plus GCs compared to CYC plus GCs for lupus related nephropathy** | | | | | | |
| Outcome № of participants (studies) | Relative effect (95% CI) | **Anticipated absolute effects (95% CI)** | | | Quality | What happens |
| **Without AZA** | **With AZA** | **Difference** |
| Death follow up: 5 a 10 years № of participants: 128 (2 RCTs) | **RR 1.46** (0.73 to 2.95) | 16.0% | **23.4%**  (11.7 to 47.2) | **7.4% more**  (4.3 fewer to 31.2 more) | ⨁⨁◯◯  LOW 1,2 | AZA treatment may increase death |
| ESRD  follow up: 10 years № of participants: 87 (1 RCT) | **RR 1.35** (0.20 to 9.16) | 4.0% | **5.4%** (0.8 to 36.6) | **1.4% more** (3.2 fewer to 32.6 more) | ⨁⨁◯◯  LOW 1,2 | AZA treatment may increase the probability of ESRD |
| Complete remission follow up: 5 a 10 years  № of participants: 128 (2 RCTs) | **RR 0.91** (0.41 to 2.01) | 48.0% | **43.7%** (19.7 to 96.5) | **4.3% fewer** (28.3 fewer to 48.5 more) | ⨁⨁◯◯  LOW 1,2 | AZA treatment may decrease complete remission |
| Partial remission follow up: 5 a 10 years  № of participants: 128 (2 RCTs) | **RR 0.93** (0.62 to 1.41) | 70.7% | **65.7%** (43.8 to 99.6) | **4.9% fewer** (26.9 fewer to 29 more) | ⨁⨁◯◯  LOW 1,2 | AZA treatment may decrease partial remission |
| Creatinine doubling follow up: 10 years № of participants: 87 (1 RCT) | **RR 2.16** (0.77 to 6.08) | 10.0% | **21.6%** (7.7 to 60.8) | **11.6% more** (2.3 fewer to 50.8 more) | ⨁⨁◯◯  LOW 1,2 | AZA treatment may increase the probability of doubling of creatinine |

1. No blinding

2. 95%CI includes benefits and harms

* Dyadyk A, Vasilenko I, Bagriy A, Dyadyk O, Yarovaya N, Roschin Y, et al. Azathioprine and cyclophosphamide in treatment of patients with diffuse proliferative lupus nephritis - a randomized controlled study [abstract]. Nephrology Dialysis Transplantation 2001;16:A57.
* Grootscholten C, Ligtenberg G, Hagen EC, van den Wall Bake AW, de Glas-Vos JW, Bijl M, et al. Azathioprine/methylprednisolone versus cyclophosphamide in proliferative lupus nephritis. A randomized controlled trial. Kidney Int 2006;70:732-42.
* Arends S, Grootscholten C, Derksen RH, Berger SP, de Sévaux RG, Voskuyl AE, et al. Long-term follow-up of a randomised controlled trial of azathioprine/methylprednisolone versus cyclophosphamide in patients with proliferative lupus nephritis. Ann Rheum Dis 2012;71:966-73.
* Oglesby A, Shaul AJ, Pokora T, Paramore C, Cragin L, Dennis G, et al. Adverse event burden, resource use, and costs associated with immunosuppressant medications for the treatment of systemic lupus erythematosus: a systematic literature review. Int J Rheumatol 2013;2013:1-9.

1.1.2.2

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **CsA compared con CYC for lupus related nephropathy** | | | | | | |
| Outcome № of participants (studies) | Relative effect (95% CI) | **Anticipated absolute effects (95% CI)** | | | Quality | What happens |
| **Without CsA** | **With CsA** | **Difference** |
| Complete remission  follow up: 9 months № de participants: 40 (1 RCT) | **OR 1.14** (0.27 a 4.79) | 23.8% | **26.3%** (7.8 a 59.9) | **2.5% more** (16 fewer a 36.1 more) | ⨁◯◯◯  VERY LOW 1,2 | It is uncertain if CsA affects this outcome |
| Remission partial follow up: 9 months № de participants : 40 (1 RCT) | **OR 0.47** (0.10 a 2.22) | 28.6% | **15.8%** (3.8 a 47.0) | **12.7% fewer** (24.7 fewer a 18.5 more ) | ⨁◯◯◯  VERY LOW 1,2 | It is uncertain if CsA affects this outcome |
| Remission follow up: 18 months № de participants: 40 (1 RCT) | **OR 3.50** (0.75 a 16.28) | 14.3% | **36.8%** (11.1 a 73.1) | **22.6% more** (3.2 fewer a 58.8 more ) | ⨁◯◯◯  VERY LOW 1,2 | It is uncertain if CsA affects this outcome |
| Major adverse effects follow up: 18 months № de participants: 40 (1 RCT) | **OR 1.11** (0.06 a 19.09) | 4.8% | **5.3%** (0.3 a 48.8) | **0.5% more** (4.5 fewer a 44.1 more ) | ⨁◯◯◯  VERY LOW 1,2 | It is uncertain if CsA affects this outcome |

1. No blinding

2. 95%CI includes benefits and harms

* Zavada, J., Ss Pesickova, R. Rysava, M. Olejarova, P. Horák, Z. Hrncír, I. Rychlík, et al. Cyclosporine A or intravenous cyclophosphamide for lupus nephritis: the Cyclofa-Lune study. Lupus 2010;19:1281-9.

1.1.2.3

| **LFN compared to CYC for lupus related nephropathy** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| Outcome № of participants (studies) | Relative effect (95% CI) | **Anticipated absolute effects (95% CI)** | | | Quality | What happens |
| **Without LEF** | **With LEF** | **Difference** |
| Partial remission - Induction № of participants: 442 (8 RCTs) | **RR 1.03** (0.83 to 1.26) | 42.3% | **43.5%** (35.1 to 53.3) | **1.3% more** (7.2 fewer to 11 more) | ⨁⨁◯◯ LOW 1,2 | LEF may make little or no difference to partial remission |
| Complete remission - Induction № of participants: 442 (8 RCTs) | **RR 1.41** (1.10 to 1.82) | 29.1% | **41.0%** (32.0 to 52.9) | **11.9% more** (2.9 more to 23.9 more) | ⨁⨁◯◯ LOW 1,3 | LEF probably improves complete remission |
| Complete remission - Maintenance № of participants: 18 (1 RCT) | In one trial, eighteen patients entered maintenance therapy (7 LEF and 11 CYC). No patient relapsed in LEF arm and 3 patients relapsed in CYC arm. | | | | ⨁◯◯◯ VERY LOW 1,2 |  |
| Minor adverse events - Induction № of participants: 369 (7 RCTs) | **RR 0.45** (0.31 to 0.64) | 37.9% | **17.1%** (11.8 to 24.3) | **20.9% fewer** (26.2 fewer to 13.6 fewer) | ⨁⨁⨁◯ MODERATE 1 | LEF probably reduces minor adverse events |

1. Risk of bias
2. Wide confidence intervals include significant benefit and harm
3. Optimal information size not met

* Cao LO, Ni ZH, Qian JL, Lin AW, Zhang WM, Fang W. Induction and maintenance treatment for IV and V with leflunomide: a prospective study. Chinese Journal of Nephrology. 2007; 23: 3–7.
* Chen KY. The efficacy of leflunomide in thirty-seven lupus nephritis patients.” Jilin Medical Journal. 2010: 31: 2615–2616.
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* Zhu Y. A randomized controlled trials of leflunomide in lupus nephritis. Hebei Medical Journal. 2013:35: 1815–1816.

1.1.2.4

| **Mizorbine compared to CYC for lupus related renal disease** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| Outcome № of participants (studies) | Relative effect (95% CI) | **Anticipated absolute effects (95% CI)** | | | Quality | What happens |
| **Without Mizorbine** | **With Mizorbine** | **Difference** |
| Complete remission follow up: 24 weeks № of participants: 50 (1 RCT) | **RR 0.18** (0.01 to 1.30) | 25.0% | **4.5%** (0.3 to 32.5) | **20.5% fewer** (24.8 fewer to 7.5 more) | ⨁◯◯◯ VERY LOW 1,2 | We are uncertain whether Mizorbine reduces complete remission |
| Minor adverse events follow up: 24 weeks № of participants: 63 (1 RCT) | **RR 0.14** (0.01 to 0.97) | 3.0% | **0.4%** (0.0 to 2.9) | **2.6% fewer** (3 fewer to 0.1 fewer) | ⨁◯◯◯ VERY LOW 1,2 | We are uncertain whether Mizorbine improves/reduces minor adverse events |

1. Risk of bias
2. 95%CI includes benefits and harms

* Xuebing F, Fei G, Weiwei C, Yan L, Hua W, Lin L, et al. Mizoribine versus mycophenolate mofetil or intravenous cyclophosphamide for induction treatment of active lupus nephritis. Chinese Medical Journal. 2014;127: 3718–23.

1.1.2.5

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **MMF compared with CYC for lupus related renal disease** | | | | | | |
| Outcome № of participants (studies) | Relative effect (95% CI) | **Anticipated absolute effects (95% CI)** | | | Quality | What happens |
| **Without MMF** | **With MMF** | **Difference** |
| Death № de participants: 332 (4 RCT) | **RR 0.68** (0.25 to 1.84) | 9.4% | **6.4%** (2.4 to 17.3) | **3.0% fewer** (7.1 fewer to 7.9 more) | ⨁◯◯◯  VERY LOW 1,2 | It is uncertain whether MMF reduces death |
| Complete remission № de participants: 826 (8 RCT) | **RR 1.13** (0.81 to 1.56) | 23.0% | **26.0%** (18.6 to 35.9) | **3.0% more** (4.4 fewer to 12.9 more) | ⨁⨁◯◯  LOW 1,2 | MMF may make little or no difference to complete remission |
| Partial Remission № de participants: 813 (8 RCT) | **RR 0.99** (0.77 to 1.26) | 42.3% | **41.8%** (32.5 to 53.2) | **0.4% fewer** (9.7 fewer to 11 more) | ⨁⨁◯◯  LOW 1,2 | MMF may make little or no difference to partial remission |
| Renal Failure № de participants: 140 (1 RCT) | **RR 0.56**  (0.17 a 1.81) | 10.1% | **5.7%**  (1.7 a 18.4) | **4.5% fewer**  (8.4 fewer a 8.2 more) | ⨁◯◯◯  VERY LOW 1,2 | It is uncertain whether MMF reduces renal failure |
| Major adverse effects № de participants: 650 (5 RCT) | **RR 0.99** (0.66 a 1.47) | 19.4% | **19.3%** (12.8 a 28.6) | **0.2% fewer** (6.6 fewer a 9.1 more ) | ⨁⨁◯◯  LOW 1,2 | MMF may make little or no difference to Major adverse effects |

1. No blinding

2. 95%CI includes benefits and harms

* Ong LM, Hooi LS, Lim TO, Goh BL, Ahmad G, Ghazalli R, et al. Randomized controlled trial of pulse intravenous cyclophosphamide versus mycophenolate mofetil in the induction therapy of proliferative lupus nephritis. Nephrology (Carlton). 2005;10:504–10.
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* Appel GB, Contreras G, Dooley MA, Ginzler EM, Isenberg D, Jayne D, et al. Mycophenolate mofetil versus cyclophosphamide for induction treatment of lupus nephritis. J Am Soc Nephrol. 2009;20:1103–12.
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1.1.2.6

| **TPE compared to CYC for lupus related nephritis** | | | | | |
| --- | --- | --- | --- | --- | --- |
| Outcome № of participants (studies) | Relative effect (95% CI) | **Anticipated absolute effects (95% CI)** | | | Quality |
| **Without TPE** | **With TPE** | **Difference** |
| Renal replacement therapy № of participants: 20 (1 RCT) | Two patients in CYC arm and none in TPEarm had the event | | | | ⨁◯◯◯ VERY LOW 1,2 |
| Specific adverse events – serious infection  № of participants: 20 (1 RCT) | One patient in CYC arm and none in TPE arm had the event | | | | ⨁◯◯◯ VERY LOW 1,2 |

1. High risk of bias
2. Few patients and events

* Derksen RH, Hené RJ, Kallenberg CG, Valentijn RM, Kater L. Prospective multicentre trial on the short-term effects of plasma exchange versus cytotoxic drugs in steroid-resistant lupus nephritis. Neth J Med. 1988;33: 168–77.

1.1.2.7

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| --- | --- | --- | --- | --- | --- | --- |
| **TAC compared to CYC for lupus nephritis** | | | | | | |
| Outcome № of participants (studies) | Relative effect (95% CI) | **Anticipated absolute effects (95% CI)** | | | Quality | What happens |
| **Without TAC** | **With TAC** | **Difference** |
| Death № of participants: 131 (2 RCTs) | **RR 0.42** (0.07 to 2.75) | 4.3% | **1.8%** (0.3 to 12.0) | **2.5% fewer** (4 fewer to 7.6 more) | ⨁◯◯◯ VERY LOW 1,2 | It is uncertain if TAC affects death |
| Creatinine duplication № of participants: 40 (1 RCT) | **RR 3.00** (0.13 to 69.50) | No estimable | | | ⨁◯◯◯ VERY LOW 1,2 | It is uncertain if TAC reduces creatinine duplication |
| Proteinuria  assessed with: Less than 0.8gr № of participants: 149 (3 RCTs) | **RR 1.30** (0.93 to 1.83) | 38.7% | **50.3%** (36.0 to 70.8) | **11.6% more** (2.7 fewer to 32.1 more) | ⨁⨁◯◯ LOW 1,2 | TAC may reduce proteinuria |
| Complete remission № of participants: 272 (7 RCTs) | **RR 1.64** (1.22 to 2.22) | 29.4% | **48.2%** (35.9 to 65.3) | **18.8% more** (6.5 more to 35.9 more) | ⨁⨁⨁◯ MODERATE 1 | TAC probably significantly increases complete remission |
| Partial remission № of participants: 219 (5 RCTs) | **RR 1.08** (0.82 to 1.43) | 44.4% | **48.0%** (36.4 to 63.6) | **3.6% more** (8 fewer to 19.1 more) | ⨁⨁◯◯ LOW 1,2 | TAC may increase partial remission |
| Infections № of participants: 121 (2 RCTs) | **RR 0.65** (0.21 to 1.96) | 20.3% | **13.2%** (4.3 to 39.9) | **7.1% fewer** (16.1 fewer to 19.5 more) | ⨁⨁◯◯ LOW 1,2 | TAC may reduce infections |
| Irregular menstruation or amenorrhea № of participants: 183 (4 RCTs) | **RR 0.14** (0.04 to 0.50) | 18.0% | **2.5%** (0.7 to 9.0) | **15.5% fewer** (17.3 fewer to 9 fewer) | ⨁⨁⨁⨁ HIGH 1 | TAC decreases irregular menstruation or amenorrhea |
| Abnormal liver function № of participants: 223 (5 RCTs) | **RR 0.51** (0.24 to 1.09) | 15.6% | **8.0%** (3.7 to 17.0) | **7.6% fewer** (11.9 fewer to 1.4 more) | ⨁⨁◯◯ LOW 1,2 | TAC may decrease abnormal liver function |

1. Unclear randomization, allocation and blinding in most of the trials included

2. 95%CI includes benefits and harms

* Zhang H, Hu W, Xie H, Zeng C, Chen H, Liu Z. Tacrolimus versus intravenous cyclophosphamide in the induction therapy of diffuse proliferative lupus nephritis. J. Nephrol. Dialy transplant 2006;15: 501–507.
* Zhang H, Hu W, Xie H, Zeng C, Chen H, Liu Z. Randomized controlled trial of tacrolimus versus intravenous cyclophosphamide in the induction therapy of class plus lupus nephritis . J. Nephrol. Dialy transplant2006;15: 508–514
* Xu A, Lu J, Liang Y, Wang Z, Li J, Wan X. Prospective study of induction therapy with tacrolimus. Zhongshan Yi Ke Da Xue Xue Bao 2007;28: 683-717.
* Ren H, Yu H, Wang X, Hao G, Chen N. A preliminary study of tacrolimus versus cyclophosphamide in patients with diffuse proliferative lupus nephritis [CCTR abstract]. Nephrol Dial Transplant 2007;22: vi276.
* Li X, Ren H, Zhang Q, Zhang W, Wu X, Xu Y, et al. Mycophenolate mofetil or tacrolimus compared with intravenous cyclophosphamide in the induction treatment for active lupus nephritis. Nephrology Dialysis Transplantation. 2012;27:1467–72.
* Hong R, Haijin Y, Xianglin W, Cuilan H, Nan C. A preliminary study of tacrolimus versus cyclophosphamide in patients with diffuse proliferative lupus nephritis [abstract SAP131]. Nephrol Dial Transplantation. 2007;22(Suppl 6):vi276.
* Chen W, Tang X, Liu Q, Chen W, Fu P, Liu F, et al. Short-term Outcomes of Induction Therapy With Tacrolimus Versus Cyclophosphamide for Active Lupus Nephritis: A Multicenter Randomized Clinical Trial. American Journal of Kidney Diseases. 2011;57:235–44.

1.1.2.8

| **TAC plus MMF vs CYC for lupus related nephritis** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| Outcome № of participants (studies) | Relative effect (95% CI) | **Anticipated absolute effects (95% CI)** | | | Quality | What happens |
| **Without TAC plus MMF** | **With TAC plus MMF** | **Difference** |
| Creatinine duplication № of participants: 402 (2 RCTs) | **RR 0.98** (0.10 to 9.23) | 0.5% | **0.5%** (0.0 to 4.6) | **0.0% fewer** (0.4 fewer to 4.1 more) | ⨁◯◯◯ LOW 1,3 | TAC plus MMF may have no effect on creatinine duplication |
| Partial remission № of participants: 40 (1 RCT) | **RR 1.75** (0.95 to 3.22) | 40.0% | **70.0%** (38.0 to 100.0) | **30.0% more** (2 fewer to 88.8 more) | ⨁◯◯◯ LOW 1,3 | TAC plus MMF may increase partial remission |
| Complete remission № of participants: 402 (2 RCTs) | **RR 2.38** (1.07 to 5.30) | 24.4% | **58.0%** (26.1 to 100.0) | **33.6% more** (1.7 more to 104.8 more) | ⨁◯◯◯ LOW 2,3 | TAC plus MMF may increase complete remission |
| Major adverse effects № of participants: 362 (1 RCT) | **RR 2.60** (0.95 to 7.14) | 2.8% | **7.2%** (2.6 to 19.7) | **4.4% more** (0.1 fewer to 17 more) | ⨁◯◯◯ LOW 1,3 | TAC plus MMF may increase major adverse effects |
| Specific adverse effects № of participants: 362 (1 RCT) | **RR 1.11** (0.79 to 1.56) | 25.4% | **28.2%** (20.1 to 39.6) | **2.8% more** (5.3 fewer to 14.2 more) | ⨁◯◯◯ LOW 1,3 | TAC plus MMF may increase specific adverse effects |

1. 95%CI include significant benefits and harms

2. Low number of events not reaching minimal information size.

3. No blinding

* Bao H, Liu Z-H, Xie H-L, Hu W-X, Zhang H-T, Li L-S. Successful Treatment of Class V+IV Lupus Nephritis with Multitarget Therapy. Journal of the American Society of Nephrology. 2008;19:2001–10.
* Liu Z, Zhang H, Liu Z, Xing C, Fu P, Ni Z, et al. Multitarget therapy for induction treatment of lupus nephritis: a randomized trial. Ann Intern Med. 2015;162:18–26.

1.1.3.1

| **MMF compared to CsA for lupus related renal disease** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| Outcome № of participants (studies) | Relative effect (95% CI) | **Anticipated absolute effects (95% CI)** | | | Quality | What happens |
| **Without MMF** | **With MMF** | **Difference** |
| Partial remission № of participants: 40 (1 RCT) | **RR 1.00** (0.33 to 3.05) | 30.0% | **30.0%** (9.9 to 91.5) | **0.0%**  (20.1 fewer to 61.5 more) | ⨁◯◯◯ VERY LOW 1,2 | Uncertain effect on partial remission |
| Complete remission № of participants: 40 (1 RCT) | **RR 1.50** (0.60 to 4.04) | 30.0% | **45.0%** (18.0 to 100.0) | **15.0% more** (12 fewer to 91.2 more) | ⨁◯◯◯ VERY LOW 1,2 | Uncertain effect on complete remission |
| Serious adverse events - Major Infection № of participants: 40 (1 RCT) | **RR 0.86** (0.30 to 2.42) | 35.0% | **30.1%** (10.5 to 84.7) | **4.9% fewer** (24.5 fewer to 49.7 more) | ⨁◯◯◯ VERY LOW 1,2 | Uncertain of effect on major infections |

1. Risk of bias
2. Wide confidence intervals include significant benefit and harm, and few participants and events

* Li X, Ren H, Zhang W, Xu Y, Shen P, Zhang Q, etal. Induction therapies for proliferative lupus nephritis: mycophenolate mofetil, tacrolimus and intravenous cyclophosphamide [abstract]. Journal of the American Society of Nephrology 2009;20:391A.

1.1.3.2

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| **MMF compared to TAC for lupus related renal disease** | | | | | | |
| Outcome  № of participants  (studies) | Relative effect  (95% CI) | **Anticipated absolute effects (95% CI)** | | | Quality | What happens |
| **Without MMF** | **With MMF** | **Difference** |
| Death  № of participants: 190 (2 RCTs) | **RR 1.57**  (0.2 to 12.2) | 1.0% | **1.5%**  (0.2 to 12.2) | **0.5% More**  (0.8 fewer to 11.2 more) | ⨁⨁◯◯  LOW 1,2 | There may be little or no differences between the interventions |
| Complete remission № of participants: 208 (3 RCTs) | **RR 1.06** (0.69 to 1.62) | 53.3% | **56.5%** (36.8 to 86.4) | **3.2% more** (16.5 fewer to 33.1 more) | ⨁⨁◯◯  LOW 1,2 | There may be little or no differences between the interventions |
| Partial remission № of participants: 208 (3 RCTs) | **RR 0.80** (0.50 to 1.29) | 28.6% | **22.9%** (14.3 to 36.9) | **5.7% fewer** (14.3 fewer to 8.3 more) | ⨁⨁◯◯  LOW 1,2 | There may be little or no differences between the interventions |
| Severe adverse effects № of participants: 208 (3 RCTs) | **RR 2.06** (0.93 to 4.56) | 7.6% | **15.7%** (7.1 to 34.7) | **8.1% more** (0.5 fewer to 27.1 more) | ⨁⨁◯◯  LOW 1,2 | MMF may slightly increase the risk of severe adverse effects |

1. No blinding

2. CI95% includes benefits and harms

* Li X, Ren H, Zhang Q, Zhang W, Wu X, Xu Y, et al. Mycophenolate mofetil or tacrolimus compared with intravenous cyclophosphamide in the induction treatment for active lupus nephritis. Nephrology Dialysis Transplantation. 2012 ;27:1467–72.
* Mok CC, Ying SK, Tong KH, Siu YP, To CH, Yim CW, et al. Mycophenolate mofetil versus tacrolimus for active lupus nephritis: an extended observation of a randomized controlled trial [abstract]. Annals of the Rheumatic Diseases 2009;68(Suppl 3):246.
* Yap DYH, Yu X, Chen X-M, Lu F, Chen N, Li X-W, et al. Pilot 24 month study to compare mycophenolate mofetil and tacrolimus in the treatment of membranous lupus nephritis with nephrotic syndrome. Nephrology (Carlton). 2012;17:352–7.

1.1.4.1

| **High dose CYC3 compared to low dose CYC for lupus related nephropathy (induction)** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| Outcome № of participants (studies) | Relative effect (95% CI) | **Anticipated absolute effects (95% CI)** | | | Quality | What happens |
| **Without High dose CYC** | **With High dose CYC** | **Difference** |
| Doubling of serum creatinine № of participants: 135 (2 RCTs) | **RR 0.46** (0.08 to 2.57) | 6.3% | **2.9%** (0.5 to 16.1) | **3.4% fewer** (5.8 fewer to 9.8 more) | ⨁⨁◯◯ LOW 1,2 | High dose CYC may make little or no difference to the risk of doubling serum creatinine |
| Doubling of serum creatinine follow up: 10 years № of participants: 90 (1 RCT) | **RR 0.80** (0.26 to 2.42) | 13.6% | **10.9%** (3.5 to 33.0) | **2.7% fewer** (10.1 fewer to 19.4 more) | ⨁⨁◯◯ LOW 1,2 | High dose CYC may make little or no difference to the risk of doubling serum creatinine |
| ESRD follow up: 10 years № of participants: 90 (1 RCT) | **RR 1.91** (0.37 to 9.92) | 4.5% | **8.7%** (1.7 to 45.1) | **4.1% more** (2.9 fewer to 40.5 more) | ⨁⨁◯◯ LOW 1,2 | High dose CYC may increase the risk of ESRD |
| Severe infection follow up: median 41 months № of participants: 89 (1 RCT) | **RR 1.96** (0.73 to 5.26) | 11.4% | **22.3%** (8.3 to 59.8) | **10.9% more** (3.1 fewer to 48.4 more) | ⨁⨁◯◯ LOW 1,2 | High dose CYC may increase the risk of severe infection |
| Cancer follow up: 10 years № of participants: 90 (1 RCT) | **RR 0.16** (0.02 to 1.27) | 13.6% | **2.2%** (0.3 to 17.3) | **11.5% fewer** (13.4 fewer to 3.7 more) | ⨁⨁◯◯ LOW 1,2 | High dose CYC may reduce the risk of cancer |
| \* High dose: initial CYC dose was 0.5 gm/m2 of body surface area; subsequent doses were increased by 250 mg according to the white blood cell count nadir measured on day 14 (16), with a maximum of 1,500 mg per pulse. Low dose: 6 fortnightly IV CYC pulses at a fixed dose of 500 mg. | | | | | | |

1. Risk of bias
2. Wide confidence intervals include benefits and harms

* Houssiau FA, Vasconcelos C, D’Cruz D, Sebastiani GD, de Ramon Garrido E, Danieli MG, et al. The 10-year follow-up data of the Euro-Lupus Nephritis Trial comparing low-dose and high-dose intravenous cyclophosphamide. Ann Rheum Dis. 2010;69:61–4.
* Houssiau FA, Vasconcelos C, D’Cruz D, Sebastiani GD, Garrido Ed E de R, Danieli MG, et al. Immunosuppressive therapy in lupus nephritis: the Euro-Lupus Nephritis Trial, a randomized trial of low-dose versus high-dose intravenous cyclophosphamide. Arthritis Rheum. 2002;46:2121–31.
* Sabry A, Abo-Zenah H, Medhat T, Sheashaa H, Mahmoud K, El-Huseini A. A comparative study of two intensified pulse cyclophosphamide remission-inducing regimens for diffuse proliferative lupus nephritis: an Egyptian experience. International Urology and Nephrology. 2009;41:153–61.

1.2.1

| **CYC compared to GCs for lupus related renal disease (maintenance)** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| Outcome № of participants (studies) | Relative effect (95% CI) | **Anticipated absolute effects (95% CI)** | | | Quality | What happens |
| **Without CYC** | **With CYC** | **Difference** |
| Death follow up: 18 months № of participants: 226 (5 RCTs) | **RR 0.98** (0.53 to 1.82) | 17.0% | **16.7%** (9.0 to 31.0) | **0.3% fewer** (8 fewer to 14 more) | ⨁⨁◯◯ LOW 1,2 | CYC may have little or no effect on death |
| Need for renal replacement therapy follow up: 18 months № of participants: 278 (5 RCTs) | **RR 0.63** (0.39 to 1.03) | 24.3% | **15.3%** (9.5 to 25.0) | **9.0% fewer** (14.8 fewer to 0.7 more) | ⨁⨁◯◯ LOW 1,2 | CYC may reduce the need for renal replacement therapy |
| Creatinine doubling follow up: 18 months № of participants: 224 (4 RCTs) | **RR 1.13** (0.43 to 2.97) | 29.5% | **33.3%** (12.7 to 87.5) | **3.8% more** (16.8 fewer to 58.1 more) | ⨁◯◯◯ VERY LOW 1,2,3 | It is uncertain if CYC modifies this outcome |
| Stable renal function follow up: 18 months № of participants: 278 (5 RCTs) | **RR 1.20** (1.00 to 1.45) | 58.9% | **70.7%** (58.9 to 85.4) | **11.8% more** (0 fewer to 26.5 more) | ⨁⨁⨁◯ MODERATE 1,4 | CYC probably increases stable renal function |
| Proteinuria fewer than 0.3 gr follow up: 18 months № of participants: 40 (2 RCTs) | **RR 2.80** (1.18 to 6.63) | 19.0% | **53.3%** (22.5 to 100.0) | **34.3% more** (3.4 more to 107.2 more) | ⨁⨁⨁◯ MODERATE 5 | CYC probably reduces proteinuria |
| Severe infections follow up: 18 months № of participants: 226 (4 RCTs) | **RR 0.93** (0.50 to 1.72) | 16.1% | **15.0%** (8.1 to 27.7) | **1.1% fewer** (8.1 fewer to 11.6 more) | ⨁⨁◯◯ LOW 1,2 | CYC may have little or no effect on severe infections |

1. 3 trials with high risk of bias.
2. 95% CI comprehends possible benefits and harms
3. I2 80%, 95% CI of Austin 1986 does not overlap with the rest of the trials
4. 95% CI comprehends the possibility of no effect
5. Both trials have moderate risk of bias

* Austin HA, Klippel JH, Balow JE, le Riche NG, Steinberg AD, Plotz PH, et al. Therapy of lupus nephritis. Controlled trial of prednisone and cytotoxic drugs. N Engl J Med. 1986;314:614–9.
* Boumpas DT, Austin HA, Vaughn EM, Klippel JH, Steinberg AD, Yarboro CH, et al. Controlled trial of pulse methylprednisolone versus two regimens of pulse cyclophosphamide in severe lupus nephritis. Lancet. 1992;340:741–5.
* Donadio JV, Holley KE, Ferguson RH, Ilstrup DM. Treatment of diffuse proliferative lupus nephritis with prednisone and combined prednisone and cyclophosphamide. N Engl J Med. 1978;299:1151–5.
* Gourley MF, Austin HA, Scott D, Yarboro CH, Vaughan EM, Muir J, et al. Methylprednisolone and cyclophosphamide, alone or in combination, in patients with lupus nephritis. A randomized, controlled trial. Ann Intern Med. 1996;125:549–57.
* Sesso R, Monteiro M, Sato E, Kirsztajn G, Silva L, Ajzen H. A controlled trial of pulse cyclophosphamide versus pulse methylprednisolone in severe lupus nephritis. Lupus. 1994;3:107–12.

1.2.2

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| --- | --- | --- | --- | --- | --- | --- |
| **IVIG compared to CYC for lupus related renal disease (maintenance)** | | | | | | |
| Outcome № of participants (studies) | Relative effect (95% CI) | **Anticipated absolute effects (95% CI)** | | | Quality | What happens |
| **Without IVIG** | **With IVIG** | **Difference** |
| Stable creatinine values follow up: 18 months № of participants: 14 (1 RCT) | **RR 1.08** (0.76 to 1.54) | 88.9% | **96.0%** (67.6 to 100.0) | **7.1% more** (21.3 fewer to 48 more) | ⨁⨁◯◯ LOW 1,2 | IVIG may slightly increase stable creatinine values |
| Proteinuria fewer than 0.8 gr follow up: 18 months № of participants: 14 (1 RCT) | **RR 0.90** (0.38 to 2.11) | 66.7% | **60.0%** (25.3 to 100.0) | **6.7% fewer** (41.3 fewer to 74 more) | ⨁⨁◯◯ LOW 1,2 | IVIG may slightly reduce proteinuria |
| Stable proteinuria follow up: 18 months № of participants: 14 (1 RCT) | **RR 1.08** (0.43 to 2.72) | 55.6% | **60.0%** (23.9 to 100.0) | **4.4% more** (31.7 fewer to 95.6 more) | ⨁⨁◯◯ LOW 1,2 | IVIG may slightly reduce proteinuria |

1. Not clear randomization or concealed allocation
2. 95% CI comprehends possible benefits and harms

* Boletis JN, Ioannidis JP, Boki KA, Moutsopoulos HM. Intravenous immunoglobulin compared with cyclophosphamide for proliferative lupus nephritis. Lancet. 1999;354:569–70.

1.2.3

| **MMF compared to AZA for lupus related renal disease (maintenance)** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| Outcome № of participants (studies) | Relative effect (95% CI) | **Anticipated absolute effects (95% CI)** | | | Quality | What happens |
| **AZA** | **MMF** | **Difference** |
| Death  follow up: 1 year № of participants: 144 (2 RCTs) | **RR 0.92** (0.26 to 3.20) | 2.3% | **2.2%** (0.6 to 7.5) | **0.2% fewer** (1.7 fewer to 5.2 more) | ⨁⨁◯◯ LOW 1,2 | MMF may slightly decrease death |
| Renal replacement therapy follow up: 1 year № of participants: 144 (2 RCTs) | **RR 0.79** (0.15 to 4.25) | 2.8% | **2.2%** (0.4 to 12.0) | **0.6% fewer** (2.4 fewer to 9.2 more) | ⨁⨁◯◯ LOW 1,2 | MMF may slightly decrease renal replacement therapy requirement |
| Creatinine duplication follow up: 1 year № of participants: 144 (2 RCTs) | **RR 0.67** (0.20 to 2.29) | 8.3% | **5.6%** (1.7 to 19.1) | **2.7% fewer** (6.7 fewer to 10.8 more) | ⨁⨁◯◯ LOW 1 | MMF may slightly decrease creatinine duplication |
| Relapse  follow up: 1 year № of participants: 144 (2 RCTs) | **RR 0.80** (0.51 to 1.25) | 38.9% | **31.1%** (19.8 to 48.6) | **7.8% fewer** (19.1 fewer to 9.7 more) | ⨁⨁◯◯ LOW 1 | MMF may decrease relapse |
| Adverse effects leading to treatment suspension follow up: 1 year № of participants: 446 (4 RCTs) | **RR 0.75** (0.42 to 1.36) | 25.5% | **19.1%** (10.7 to 34.6) | **6.4% fewer** (14.8 fewer to 9.2 more) | ⨁⨁◯◯ LOW 1,2 | MMF may slightly reduce adverse effects leading to treatment suspension |
| Severe infections follow up: 1 year № of participants: 101 (2 RCTs) | **RR 0.64** (0.15 to 2.64) | 10.0% | **6.4%** (1.5 to 26.4) | **3.6% fewer** (8.5 fewer to 16.4 more) | ⨁⨁◯◯ LOW 1 | MMF may slightly reduce severe infections |
| Amenorrhea follow up: 3 years № of participants: 39 (1 RCTs) | The risk of amenorrhea was 6% in the MMF group and 8% en the AZA group. The risk of amenorrhea may be similar with AZA and MMF treatment. | | | | ⨁⨁◯◯ LOW 1 | - |

1. 95%CI includes benefits and harms
2. Unclear concealed allocation and blinding

* Chan T-M, Tse K-C, Tang CS-O, Mok M-Y, Li F-K, Hong Kong Nephrology Study Group. Long-term study of mycophenolate mofetil as continuous induction and maintenance treatment for diffuse proliferative lupus nephritis. J Am Soc Nephrol. 2005;16:1076–84.
* Contreras G, Pardo V, Leclercq B, Lenz O, Tozman E, O’Nan P, et al. Sequential therapies for proliferative lupus nephritis. N Engl J Med. 2004;350:971–80.
* Dooley MA, Jayne D, Ginzler EM, Isenberg D, Olsen NJ, Wofsy D, et al. Mycophenolate versus azathioprine as maintenance therapy for lupus nephritis. N Engl J Med. 2011;365:1886–95.
* Houssiau FA, D’Cruz D, Sangle S, Remy P, Vasconcelos C, Petrovic R, et al. Azathioprine versus mycophenolate mofetil for long-term immunosuppression in lupus nephritis: results from the MAINTAIN Nephritis Trial. Ann Rheum Dis. 2010;69:2083–9.
* Tamirou F, D’Cruz D, Sangle S, Remy P, Vasconcelos C, Fiehn C, et al. Long-term follow-up of the MAINTAIN Nephritis Trial, comparing azathioprine and mycophenolate mofetil as maintenance therapy of lupus nephritis. Ann Rheum Dis. 2016;75:526–31.

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| 1.2.4 | | | | | | |
| **AZA compared to TAC for lupus related renal disease (maintenance)** | | | | | | |
| Outcome № of participants (studies) | Relative effect (95% CI) | **Anticipated absolute effects (95% CI)** | | | Quality | What happens |
| **Without AZA** | **With AZA** | **Difference** |
| Renal relapse  follow up: 6 months № of participants: 70 (1 RCT) | **RR 4.73**  (0.24 to 95.09) | 0.0% | **0.1%**  (0.0 to 2.8) | **0.1% more**  (0 fewer to 2.8 more) | ⨁◯◯◯  VERY LOW 1,2 | We are uncertain whether AZA improves/reduces the risk of renal relapse |
| Partial remission follow up: 6 months № of participants: 70 (1 RCT) | **RR 0.69** (0.37 to 1.29) | 44.1% | **30.4%** (16.3 to 56.9) | **13.7% fewer** (27.8 fewer to 12.8 more) | ⨁◯◯◯  VERY LOW 1,2 | We are uncertain whether AZA improves/reduces the risk of partial remission |
| Complete remission follow up: 6 months № of participants: 70 (1 RCT) | **RR 1.14** (0.78 to 1.68) | 55.9% | **63.7%** (43.6 to 93.9) | **7.8% more** (12.3 fewer to 38 more) | ⨁◯◯◯  VERY LOW 1,2 | We are uncertain whether AZA improves/reduces the risk of partial remission |
| Infections follow up: 6 months № of participants: 70 (1 RCT) | **RR 0.94** (0.20 to 4.36) | 8.8% | **8.3%** (1.8 to 38.5) | **0.5% fewer** (7.1 fewer to 29.6 more) | ⨁◯◯◯  VERY LOW 1,2 | We are uncertain whether AZA improves/reduces the risk of infections |
| Leucopenia follow up: 6 months № of participants: 70 (1 RCT) | **RR 5.35** (1.72 to 16.64) | 8.8% | **47.2%** (15.2 to 100.0) | **38.4% more** (6.4 more to 138 more) | ⨁⨁◯◯  LOW 1,3 | AZA may increase the risk of leucopenia |

1. No blinding

2. CI95% including significant benefits and risks

3. Optimal information size not met

* Chen W, Liu Q, Chen W, Tang X, Fu P, Liu F, et al. Outcomes of maintenance therapy with tacrolimus versus azathioprine for active lupus nephritis: a multicenter randomized clinical trial. Lupus. 2012;21:944–52.

1.2.5

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **CsA compared to AZA for lupus related renal disease (maintenance)** | | | | | | |
| Outcome № of participants (studies) | Relative effect (95% CI) | **Anticipated absolute effects (95% CI)** | | | Quality | What happens |
| **Without CsA** | **With CsA** | **Difference** |
| Death  № of participants: 69 (1 RCT) | No events | | | | - |  |
| Dialysis requirement № of participants: 69 (1 RCT) | No events | | | | - |  |
| Undetectable proteinuria  follow up: 2 years  № of participants: 69 (1 RCT) | **RR 2.75** (1.12 to 6.73) | 15.2% | **41.7%** (17.0 to 100.0) | **26.5% more** (1.8 more to 86.8 more) | ⨁⨁◯◯  LOW 1,2 | CsA may increase the probability of undetectable proteinuria |
| Nephritic or proteinuric flares follow up: 2 years № of participants: 69  (1 RCT) | **RR 0.65** (0.23 to 1.86) | 21.2% | **13.8%** (4.9 to 39.5) | **7.4% fewer** (16.3 fewer to 18.2 more) | ⨁◯◯◯  VERY LOW 1,3 | We are uncertain whether CsA reduces the probability of nephritic or proteinuric flares |
| Severe adverse effects  follow up: 1 - 2 years № of participants: 159 (2 RCTs) | **RR 1.05** (0.54 to 2.06) | 17.1% | **18.0%** (9.2 to 35.2) | **0.9% more** (7.9 fewer to 18.1 more) | ⨁⨁◯◯  LOW 1,3 | CsA and AZA may have a similar rate of severe adverse events |

1. Open study

2. Optimal information size not met

3. 95%CI including significant benefits and harms

* Griffiths B, Emery P, Ryan V, Isenberg D, Akil M, Thompson R, et al. The BILAG multi-centre open randomized controlled trial comparing ciclosporin vs azathioprine in patients with severe SLE. Rheumatology. 2010;49:723–32.
* Moroni G, Doria A, Mosca M, Alberighi ODC, Ferraccioli G, Todesco S, et al. A randomized pilot trial comparing cyclosporine and azathioprine for maintenance therapy in diffuse lupus nephritis over four years. Clin J Am Soc Nephrol. 2006;1:925–32.

1.2.6

| **MMF compared to CYC for SLE nephritis (maintenance)** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| Outcome № of participants (studies) | Relative effect (95% CI) | **Anticipated absolute effects (95% CI)** | | | Quality | What happens |
| **Without MMF** | **With MMF** | **Difference** |
| Death follow up: 36 months № of participants: 40 (1 RCT) | **RR 0.025** (0.00 to 1.40) | 20.0% | **0.5%** (0.0 to 28.0) | **19.5% fewer** (20 fewer to 8 more) | ⨁◯◯◯ VERY LOW 1,2 | It is uncertain if MMF modifies Death |
| Relapse rate follow up: 36 months № of participants: 40 (1 RCT) | **RR 0.37** (0.08 to 1.30) | 40.0% | **14.8%** (3.2 to 52.0) | **25.2% fewer** (36.8 fewer to 12 more) | ⨁◯◯◯ VERY LOW 1,2 | It is uncertain if MMF modifies relapse rate |
| Chronic renal failure follow up: 36 months № of participants: 40 (1 RCT) | **RR 0.33** (0.01 to 3.30) | 15.0% | **5.0%** (0.1 to 49.5) | **10.0% fewer** (14.8 fewer to 34.5 more) | ⨁◯◯◯ VERY LOW 1,2 | It is uncertain if MMF modifies Chronic renal failure |
| Severe infections № of participants: 610 (4 RCTs) | **RR 0.55** (0.22 to 1.42) | 12.0% | **6.6%** (2.6 to 17.0) | **5.4% fewer** (9.3 fewer to 5 more) | ⨁⨁◯◯ LOW 2 | MMF may decrease the risk of severe infections |
| Gonadal failure № of participants: 240 (3 RCTs) | **RR 0.16** (0.04 to 0.70) | 9.5% | **1.5%** (0.4 to 6.6) | **8.0% fewer** (9.1 fewer to 2.8 fewer) | ⨁⨁⨁◯ MODERATE 3 | MMF probably reduces gonadal failure |

1. No blinding
2. 95%CI includes benefits and harms
3. Optimal information size not met

* Ginzler EM, Dooley MA, Aranow C, Kim MY, Buyon J, Merrill JT, et al. Mycophenolate mofetil or intravenous cyclophosphamide for lupus nephritis. N Engl J Med. 2005;353: 2219–28.
* Contreras G, Pardo V, Leclercq B, Lenz O, Tozman E, O’Nan P, et al. Sequential therapies for proliferative lupus nephritis. N Engl J Med. 2004;350:971–80.
* Appel GB, Contreras G, Dooley MA, Ginzler EM, Isenberg D, Jayne D, et al. Mycophenolate mofetil versus cyclophosphamide for induction treatment of lupus nephritis. J Am Soc Nephrol. 2009;20:1103–12.
* Chan T-M, Tse K-C, Tang CS-O, Mok M-Y, Li F-K, Hong Kong Nephrology Study Group. Long-term study of mycophenolate mofetil as continuous induction and maintenance treatment for diffuse proliferative lupus nephritis. J Am Soc Nephrol. 2005;16:1076–84.

1.2.7

| **AZA compared to CYC for SLE nephritis (maintenance)** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| Outcome № of participants (studies) | Relative effect (95% CI) | **Anticipated absolute effects (95% CI)** | | | Quality | What happens |
| **Without AZA** | **With AZA** | **Difference** |
| Death № of participants: 39 (1 RCT) | **RR 0.02** (0.00 to 1.40) | 20.0% | **0.4%** (0.0 to 28.0) | **19.6% fewer** (20 fewer to 8 more) | ⨁◯◯◯ VERY LOW 1,2 | It is uncertain whether AZA reduces death |
| Relapse № of participants: 39 (1 RCT) | **RR 0.78** (0.28 to 2.00) | 40.0% | **31.2%** (11.2 to 80.0) | **8.8% fewer** (28.8 fewer to 40 more) | ⨁◯◯◯ VERY LOW 1,2 | It is uncertain whether AZA reduces Relapse |
| Chronic renal failure № of participants: 39 (1 RCT) | **RR 0.35** (0.01 to 3.50) | 15.0% | **5.3%** (0.1 to 52.5) | **9.8% fewer** (14.8 fewer to 37.5 more) | ⨁◯◯◯ VERY LOW 1,2 | It is uncertain whether AZA reduces Chronic renal failure |
| Severe infections № of participants: 76 (2 RCTs) | **RR 0.25** (0.06 to 1.13) | 21.1% | **5.3%** (1.3 to 23.8) | **15.8% fewer** (19.8 fewer to 2.7 more) | ⨁⨁◯◯ LOW 2 | AZA may reduce severe infections |
| Gonadal failure № of participants: 76 (2 RCTs) | **RR 0.26** (0.11 to 0.62) | 50.0% | **13.0%** (5.5 to 31.0) | **37.0% fewer** (44.5 fewer to 19 fewer) | ⨁⨁⨁◯ MODERATE 3 | AZA probably reduces ovarian failure |

1. No blinding
2. 95%CI includes benefits and harms
3. Optimal information size not met

* Austin HA, Klippel JH, Balow JE, le Riche NG, Steinberg AD, Plotz PH, et al. Therapy of lupus nephritis. Controlled trial of prednisone and cytotoxic drugs. N Engl J Med. 1986;314:614–9.
* Contreras G, Pardo V, Leclercq B, Lenz O, Tozman E, O’Nan P, et al. Sequential therapies for proliferative lupus nephritis. N Engl J Med. 2004;350:971–80.

2.1.1

| **ABT compared to placebo for active lupus** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| Outcome № of participants (studies) | Relative effect (95% CI) | **Anticipated absolute effects (95% CI)** | | | Quality | What happens |
| **Without ABT** | **With ABT** | **Difference** |
| Flares assessed with: BILAG A or B follow up: 12 months № of participants: 175 (1 RCT) | **RR 0.97** (0.84 to 1.16) | 82.5% | **80.0%** (69.3 to 95.6) | **2.5% fewer** (13.2 fewer to 13.2 more) | ⨁⨁◯◯ LOW 1,2 | ABT may make little or no difference to BILAG A o B flares |
| Flares assessed with: BILAG A follow up: 12 months № of participants: 175 (1 RCT) | **RR 0.75** (0.54 to 1.01) | 54.4% | **40.8%** (29.4 to 54.9) | **13.6% fewer** (25 fewer to 0.5 more) | ⨁⨁◯◯ LOW 1,2 | ABT may slightly reduce BILAG A flares |
| Serious adverse events follow up: 12 months № of participants: 180 (1 RCT) | **RR 2.93** (1.04 to 9.77) | 6.8% | **19.9%** (7.1 to 66.2) | **13.1% more** (0.3 more to 59.5 more) | ⨁⨁◯◯ LOW 1,3 | ABT may increase serious adverse events |

1. Risk of bias
2. Wide confidence intervals include significant benefit and harm
3. Few patients and events

* Merrill JT, Burgos-Vargas R, Westhovens R, Chalmers A, D’Cruz D, Wallace DJ, et al. The efficacy and safety of abatacept in patients with non-life-threatening manifestations of systemic lupus erythematosus: results of a twelve-month, multicenter, exploratory, phase IIb, randomized, double-blind, placebo-controlled trial. Arthritis Rheum. 2010;62:3077–87.

2.1.2

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Abetimus compared to placebo for active lupus** | | | | | | |
| Outcome  № of participants  (studies) | Relative effect  (95% CI) | **Anticipated absolute effects (95% CI)** | | | Quality | What happens |
| **Without Abetimus** | **With Abetimus** | **Difference** |
| Death  follow up: 2 years  № of participants: 317  (1 RCT) | **RR 3.02**  (0.32 to 28.71) | 0.6% | **1.9%**  (0.2 to 18.1) | **1.3% more**  (0.4 fewer to 17.4 more) | ⨁⨁◯◯  LOW 1 | Abetimus may make little  or no difference to the risk of death |
| Flares  follow up: 2 years  № of participants: 298  (1 RCT) | **RR 0.79**  (0.54 to 1.14) | 30.7% | **24.3%**  (16.6 to 35.0) | **6.5% fewer**  (14.1 fewer to 4.3 more) | ⨁⨁◯◯  LOW 1 | Abetimus treatment probably reduces the risk of SLE flares |
| Serious adverse events  follow up: 2 years  № of participants: 317  (1 RCT) | **RR 0.94**  (0.60 to 1.47) | 20.1% | **18.9%**  (12.1 to 29.6) | **1.2% fewer**  (8.1 fewer to 9.5 more) | ⨁⨁◯◯  LOW 1 | Abetimus may make little  or no difference to the risk of serious adverse events |

1. Wide confidence intervals include significant benefit and harm

* Cardiel MH, Tumlin JA, Furie RA, Wallace DJ, Joh T, Linnik MD, et al. Abetimus sodium for renal flare in systemic lupus erythematosus: results of a randomized, controlled phase III trial. Arthritis Rheum. 2008;58:2470–80.

2.1.3

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Atacicept 75 mg compared to placebo for lupus** | | | | | | |
| Outcome  № of participants  (studies) | Relative effect  (95% CI) | **Anticipated absolute effects (95% CI)** | | | Quality | What happens |
| **Without Atacicept 75mg** | **With Atacicept 75mg** | **Difference** |
| Flares  assessed with: BILAG A or B  follow up: 52 weeks  № of participants: 316  (1 RCT) | **OR 1.15**  (0.73 to 1.80) | 54.1% | **57.6%**  (46.3 to 68.0) | **3.4% more**  (7.9 fewer to 13.9 more) | ⨁⨁◯◯  LOW 2 | Atacicept may make little  or no difference to the risk of flare |
| Time to first flare  follow up: 52 weeks  № of participants: 316  (1 RCT) | **HR 0.98**  (0.69 to 1.40) | 54.1% | **53.4%**  (41.6 to 66.4) | **0.7% fewer**  (12.5 fewer to 12.3 more) | ⨁⨁◯◯  LOW 2 | Atacicept may make little  or no difference to the time to first flare |
| Serious adverse effects  follow up: 52 weeks  № of participants: 311  (1 RCT) | **OR 1.11**  (0.60 to 2.00) | 19.5% | **21.2%**  (12.7 to 32.6) | **1.7% more**  (6.8 fewer to 13.1 more) | ⨁⨁◯◯  LOW 2 | Atacicept may slightly  Increase the risk of serious adverse events |
| Severe infections  follow up: 52 weeks  № of participants: 311  (1 RCT) | **OR 1.15**  (0.46 to 2.80) | 7.1% | **8.1%**  (3.4 to 17.7) | **1.0% more**  (3.7 fewer to 10.6 more) | ⨁⨁◯◯  LOW 2 | Atacicept may slightly  Increase the risk of serious infections |

1. There were 2 severe infections in the 150mg arm which was stopped early.
2. Wide confidence intervals include significant benefit and harm

* Isenberg D, Gordon C, Licu D, Copt S, Rossi CP, Wofsy D. Efficacy and safety of atacicept for prevention of flares in patients with moderate-to-severe systemic lupus erythematosus (SLE): 52-week data (APRIL-SLE randomised trial). Ann Rheum Dis. 2015;74:2006–15.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Atacicept 150 mg compared to placebo for lupus** | | | | | | |
| Outcome  № of participants  (studies) | Relative effect  (95% CI) | **Anticipated absolute effects (95% CI)** | | | Quality | What happens |
| **Without Atacicept 150mg** | **With Atacicept 150mg** | **Difference** |
| Flares  assessed with: BILAG A or B  follow up: 52 weeks  № of participants: 302  (1 RCT) | **OR 0.48**  (0.30 to 0.77) | 54.1% | **36.2%**  (26.2 to 47.6) | **18.0% more**  (28 fewer to 6.5 fewer) | ⨁⨁⨁◯  MODERATE 1 | Atacicept probably decreases the risk of flares |
| Time to first flare  follow up: 52 weeks  № of participants: 302  (1 RCT) | **HR 0.56**  (0.36 to 0.87) | 54.1% | **35.4%**  (24.5 to 49.2) | **18.8% fewer**  (29.7 fewer to 4.9 fewer) | ⨁⨁⨁◯  MODERATE 1 | Atacicept probably decreases the risk of flares |
| Serious adverse effects  follow up: 52 weeks  № of participants: 298  (1 RCT) | **OR 0.89**  (0.47 to 1.72) | 17.5% | **15.9%**  (9.1 to 26.8) | **1.6% more**  (8.4 fewer to 9.2 more) | ⨁⨁⨁◯  MODERATE 1 | Atacicept probably makes little or no difference to the risk of serious adverse events |
| Severe infections  follow up: 52 weeks  № of participants: 298  (1 RCT) | **OR 1.08**  (0.42 to 2.77) | 7.1% | **7.7%**  (3.1 to 17.6) | **0.5% more**  (4 fewer to 10.4 more) | ⨁⨁⨁◯  MODERATE 1 | Atacicept probably makes little or no difference to the risk of serious infection |

1. Optimal information size not met

* Isenberg D, Gordon C, Licu D, Copt S, Rossi CP, Wofsy D. Efficacy and safety of atacicept for prevention of flares in patients with moderate-to-severe systemic lupus erythematosus (SLE): 52-week data (APRIL-SLE randomised trial). Ann Rheum Dis. 2015;74:2006–15.

2.1.4

| Belimumab **compared to placebo for active lupus** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| Outcome № of participants (studies) | Relative effect (95% CI) | **Anticipated absolute effects (95% CI)** | | | Quality | What happens |
| **Without** belimumab | **With** belimumab | **Difference** |
| Significant clinical improvement (any dose) № of participants: 721 (1 RCT) | **RR 1.93** (1.32 to 2.83) | 10.9% | **21.1%** (14.4 to 30.9) | **10.1% more** (3.5 more to 20 more) | ⨁⨁⨁⨁ HIGH | Belimumab increases the chance of significant clinical improvement |
| No worsening in BILAG (any dose) № of participants: 1586 (2 RCTs) | **RR 1.21** (0.99 to 1.48) | 69.4% | **84.0%** (68.7 to 100.0) | **14.6% more** (0.7 fewer to 33.3 more) | ⨁⨁⨁◯ MODERATE 1 | Belimumab probably decreases the chance of worsening |
| Mortality (any dose) № of participants: 1586 (2 RCTs) | **RR 1.29** (0.37 to 4.50) | 0.5% | **0.7%** (0.2 to 2.4) | **0.2% more** (0.3 fewer to 1.9 more) | ⨁⨁⨁◯ MODERATE 1 | Belimumab probably makes little or no difference to the risk of death |
| Flares (any dose) № of participants: 1586 (2 RCTs) | **RR 0.89** (0.82 to 0.95) | 53.4% | **47.5%** (43.8 to 50.7) | **5.9% fewer** (9.6 fewer to 2.7 fewer) | ⨁⨁⨁⨁ HIGH | Belimumab reduces the risk of flares |
| Any adverse events (any dose) № of participants: 2133 (3 RCTs) | **RR 0.89** (0.74 to 1.07) | 92.7% | **82.5%** (68.6 to 99.2) | **10.2% fewer** (24.1 fewer to 6.5 more) | ⨁⨁⨁◯ MODERATE 1 | Belimumab probably reduces the risk of serious adverse events |
| Severe adverse events (any dose) № of participants: 2133 (3 RCTs) | **RR 0.97** (0.79 to 1.20) | 16.0% | **15.5%** (12.6 to 19.2) | **0.5% fewer** (3.4 fewer to 3.2 more) | ⨁⨁⨁◯ MODERATE 1 | Belimumab probably makes little or no difference to the risk of severe adverse events |
| Infection (any dose) № of participants: 2133 (3 RCTs) | **RR 1.06** (1.00 to 1.13) | 67.4% | **71.5%** (67.4 to 76.2) | **4.0% more** (0 fewer to 8.8 more) | ⨁⨁⨁◯ MODERATE 1 | Belimumab probably increases the risk of infection |

1. Wide confidence intervals include significant benefit and harm

* Furie R, Petri M, Zamani O, Cervera R, Wallace DJ, Tegzová D, et al. A phase III, randomized, placebo-controlled study of belimumab, a monoclonal antibody that inhibits B lymphocyte stimulator, in patients with systemic lupus erythematosus. Arthritis Rheum. 2011;63:3918–30.
* Navarra SV, Guzmán RM, Gallacher AE, Hall S, Levy RA, Jimenez RE, et al. Efficacy and safety of belimumab in patients with active systemic lupus erythematosus: a randomised, placebo-controlled, phase 3 trial. Lancet. 2011;377:721–31.
* Wallace DJ, Stohl W, Furie RA, Lisse JR, McKay JD, Merrill JT, et al. A phase II, randomized, double-blind, placebo-controlled, dose-ranging study of belimumab in patients with active systemic lupus erythematosus. Arthritis Rheum. 2009;61:1168–78.

2.1.5

| **Blisibimod compared to placebo for lupus** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| Outcome № of participants (studies) | Relative effect (95% CI) | **Anticipated absolute effects (95% CI)** | | | Quality | What happens |
| **Without Blisibimod** | **With Blisibimod** | **Difference** |
| Significant clinical improvement SELENA SLEDAI follow up: 24 weeks № of participants : 546 (1 RCT) | **RR 1.11** (0.79 to 1.58) | 17.8% | **19.8%** (14.1 to 28.2) | **2.0% more**  (3.7 fewer to 10.3 more ) | ⨁⨁⨁◯ MODERATE 1 | Blisibimod probably slightly increases the risk of clinical improvement |
| Mortality follow up: 24 weeks № of participants : 546 (1 RCT) | **RR 1.29** (0.29 to 5.73) | 1.1% | **1.4%** (0.3 to 6.4) | **0.3% more**  (0.8 fewer to 5.3 more) | ⨁⨁⨁◯ MODERATE 1 | Blisibimod probably slightly increases the risk of clinical death |
| Flares (only 200 mg dosis) follow up: 24 weeks № of participants : 546 (1 RCT) | **RR 0.86** (0.55 to 1.33) | 25.3% | **21.7%** (13.9 to 33.6) | **3.5% less**  (11.4 fewer to 8.3 more) | ⨁⨁⨁◯ MODERATE 1 | Blisibimod probably makes little o no difference to the risk of flare |
| Any adverse events follow up: 24 weeks № of participants : 546 (1 RCT) | **RR 0.99** (0.92 to 1.07) | 84.0% | **83.2%** (77.3 to 89.9) | **0.8% less**  (6.7 fewer to 5.9 more) | ⨁⨁⨁◯ MODERATE 1 | Blisibimod probably makes little o no difference to serious adverse events |
| Severe adverse events follow up: 24 weeks № of participants : 546 (1 RCT) | **RR 0.72** (0.47 to 1.10) | 15.6% | **11.2%** (7.3 to 17.2) | **4.4% less**  (8.3 fewer to 1.6 more) | ⨁⨁⨁◯ MODERATE 1 | Blisibimod probably slightly reduces the risk of severe adverse events |
| Drug-related adverse events follow up: 24 weeks № of participants : 546 (1 RCT) | **RR 1.10** (0.89 to 1.36) | 36.8% | **40.5%** (32.8 to 50.1) | **3.7% more**  (4 fewer to 13.2 more) | ⨁⨁⨁◯ MODERATE 1 | Blisibimod probably increases the risk of severe adverse events |

1. Wide confidence intervals including significant benefit and harm

* Furie RA, Leon G, Thomas M, Petri MA, Chu AD, Hislop C, et al. A phase 2, randomised, placebo-controlled clinical trial of blisibimod, an inhibitor of B cell activating factor, in patients with moderate-to-severe systemic lupus erythematosus, the PEARL-SC study. Annals of the Rheumatic Diseases. 2015;74:1667–75.

2.1.6

|  |  |  |  |
| --- | --- | --- | --- |
| **CsA compared to placebo for active lupus** | | |  |
| Outcome  № of participants  (studies) | **Impact** | Quality |  |
|  |
| Symptoms improvement  follow up: 12 months  № of participants: 18  (1 RCT) | The study informed a significant reduction in the mean SLEDAI score. The proportion of patients achieving remission was 9/10 in the cyclosporine arm and 7/8 in placebo arm | ⨁⨁◯◯  LOW 1,2 |  |
| Adverse effects  follow up: 12 months  № of participants: 18  (1 RCT) | The study reported 6 patients with minor adverse effects in the cyclosporine arm and 5 patients with minor adverse effects in placebo arm | ⨁⨁◯◯  LOW 1,2 |  |

1. Risk of bias
2. Optimal information size not met

* Dammacco F, Della Casa Alberighi O, Ferraccioli G, Racanelli V, Casatta L, Bartoli E. Cyclosporine-A plus steroids versus steroids alone in the 12-month treatment of systemic lupus erythematosus. Int J Clin Lab Res. 2000;30:67–73.

2.1.7

| **CQ compared to placebo for lupus** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| Outcome № of participants (studies) | Relative effect (95% CI) | **Anticipated absolute effects (95% CI)** | | | Quality | What happens |
| **Without CQ** | **With CQ** | **Difference** |
| Flares follow up: 1 year  № of participants : 70 (2 RCTs) | **RR 0.40** (0.16 to 0.99) | 61.8% | **24.7%** (9.9 to 61.1) | **37.1% fewer** (51.9 fewer to 0.6 fewer) | ⨁⨁⨁◯ MODERATE 1 | CQ probably reduces the risk of flares |
| Flares - Begin follow up: 1 year  № of participants: 23 (1 RCT) | **RR 0.22** (0.06 to 0.78) | 83.3% | **18.3%** (5.0 to 65.0) | **65.0% fewer** (78.3 fewer to 18.3 fewer) | ⨁⨁⨁◯ MODERATE 1 | CQ probably reduces the risk of flares |
| Flares - Maintain follow up: 1 year  № of participants: 47 (1 RCT) | **RR 0.56** (0.26 to 1.19) | 50.0% | **28.0%** (13.0 to 59.5) | **22.0% fewer** (37 fewer to 9.5 more ) | ⨁⨁◯◯ LOW 1,2 | CQ may slightly reduce the risk of flares |
| Severe adverse events follow up: 1 year  № of participants: 23 (1 RCT) | **RR 0.36** (0.02 to 8.04) | 8.3% | **3.0%** (0.2 to 67.0) | **5.3% fewer**  (8.2 fewer to 58.7 more ) | ⨁⨁⨁◯ MODERATE 2 | CQ probably increases the risk of severe adverse events |

1. Risk of bias: unclear concealed allocation and selective outcome reporting
2. Wide confidence intervals include significant benefit and harm

* Tsakonas E, Joseph L, Esdaile JM, Choquette D, Senécal JL, Cividino A, et al. A long-term study of hydroxychloroquine withdrawal on exacerbations in systemic lupus erythematosus. Lupus. 1998;7:80–5.
* Meinão IM, Sato EI, Andrade LE, Ferraz MB, Atra E. Controlled trial with chloroquine diphosphate in systemic lupus erythematosus. Lupus. 1996;5:237–41.

2.1.8

| **CYC plus GCs compared to GCs for active lupus** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| Outcome № of participants (studies) | Relative effect (95% CI) | **Anticipated absolute effects (95% CI)** | | | Quality | What happens |
| **Without CYC plus GCs** | **With CYC plus GCs** | **Difference** |
| Improvement (20% change from basal conditions) follow up: 1 year  № of participants: 32 (1 RCT) | **RR 2.05** (1.13 to 3.73) | 46.2% | **94.6%** (52.2 to 100.0) | **48.5% more**  (6 more to 126 more) | ⨁⨁◯◯ LOW 1 | CYC plus GCs may increase the risk of improvement |
| Mortality follow up: 1 year  № of participants : 32 (1 RCT) | **RR 2.05** (0.24 to 17.63) | 7.7% | **15.8%** (1.8 to 100.0) | **8.1% more**  (5.8 fewer to 127.9 more ) | ⨁⨁◯◯ LOW 1 | CYC plus GCs may increases the risk of death |
| Early suspension due to adverse events follow up: 1 year  № of participants : 32 (1 RCT) | **RR 0.14** (0.01 to 2.70) | 15.4% | **2.2%** (0.2 to 41.5) | **13.2% fewer**  (15.2 fewer to 26.2 more) | ⨁⨁◯◯ LOW 1 | CYC plus GCs may make little or no difference to early suspension |

1. Wide confidence intervals include significant benefit and harm/absence of benefits

* Barile-Fabris L, Ariza-Andraca R, Olguin-Ortega L, Jara LJ, Fraga-Mouret A, Miranda-Limon JM, et al. Controlled clinical trial of IV cyclophosphamide versus IV methylprednisolone in severe neurological manifestations in systemic lupus erythematosus. Ann Rheum Dis 2005;64:620-5.

2.1.9

|  |  |  |  |
| --- | --- | --- | --- |
| **DHEA compared to placebo for active lupus** | | |  |
| Outcome  № of participants  (studies) | **Impact** | Quality |  |
|  |
| GCs use  follow up: 3 months  № of participants: 28  (1 RCT) | The trial reported a significant reduction in the prednisone dose at the end of the trial. | ⨁⨁OO  LOW 1,2 |  |
| Flares  follow up: 3 months  № of participants: 28  (1 RCT) | 8 patients presented a flare in the placebo arm and 3 in the DHEA | ⨁⨁OO  LOW 1,2 |  |
| Symptom improvement  follow up: 6-12 months  № of participants: 28  (1 RCT) | The study informed a significant reduction in the mean SLEDAI score (Mean difference 1.7). | ⨁⨁OO  LOW 1,2 |  |
| Adverse effects  follow up: 6-12 months  № of participants: 101  (2 RCTs) | The study reported 12 minor adverse effects in the DHEA arm and 10 minor adverse effects in placebo arm | ⨁⨁OO  LOW 1,2 |  |

1. Absence of blinding.
2. Wide confidence intervals include significant benefit and harm

* van Vollenhoven RF, Engleman EG, McGuire JL. Dehydroepiandrosterone in systemic lupus erythematosus. Results of a double-blind, placebo-controlled, randomized clinical trial. Arthritis Rheum 1995;38:1826–31.

2.1.10

| **Epratuzumab compared to placebo for active lupus** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| Outcome № of participants (studies) | Relative effect (95% CI) | **Anticipated absolute effects (95% CI)** | | | Quality | What happens |
| **Without Epratuzumab** | **With Epratuzumab** | **Difference** |
| BILAG improvement assessed with: BILAG-2004 improvement (all A scores at baseline improved to B/C/D, and all B scores improved to C or D) follow up: 12 weeks № of participants: 301 (3 RCTs) | **RR 1.27** (0.84 to 1.93) | 29.4% | **37.4%** (24.7 to 56.8) | **7.9% more** (4.7 fewer to 27.4 more) | ⨁⨁◯◯ LOW 1,2 | Epratuzumab may make little or no difference to BILAG improvement |
| PGA improvement (Increase of 20% or higher) follow up: 12 weeks № of participants: 74 (2 RCTs) | **RR 1.29** (0.91 to 1.84) | 60.0% | **77.4%** (54.6 to 100.0) | **17.4% more** (5.4 fewer to 50.4 more) | ⨁⨁◯◯ LOW 1,2 | Epratuzumab may make little or no difference to PGA improvement |
| HR-QOL assessed with: SF-36 follow up: 12 weeks № of participants: 301 (3 RCTs) | No statistical difference between intervention and control arms were observed during follow up | | | | - |  |
| GCs use follow up: range 12 weeks to 24 weeks № of participants: 287 (3 RCTs) | In EMBLEM trial, changes in GCs use at week 12 versus baseline were minimal in all arms, and no statistical difference between them was reported. In ALLEVIATE trial, at week 24, median GCs dose was lower in both epratuzumab groups than in placebo group | | | | - |  |
| Serious adverse events follow up: 12 weeks № of participants: 313 (2 RCTs) | **RR 0.88** (0.49 to 1.59) | 18.7% | **16.4%** (9.1 to 29.7) | **2.2% fewer** (9.5 fewer to 11 more) | ⨁⨁◯◯ LOW 1,2 | Epratuzumab may make little or no difference to serious adverse events |

1. Risk of bias
2. Wide confidence intervals include significant benefit and harm

* Wallace DJ, Gordon C, Strand V, Hobbs K, Petri M, Kalunian K, et al. Efficacy and safety of epratuzumab in patients with moderate/severe flaring systemic lupus erythematosus: results from two randomized, double-blind, placebo-controlled, multicentre studies (ALLEVIATE) and follow-up. Rheumatology (Oxford). 2013;52:1313–22.
* Wallace DJ, Kalunian K, Petri MA, Strand V, Houssiau FA, Pike M, et al. Efficacy and safety of epratuzumab in patients with moderate/severe active systemic lupus erythematosus: results from EMBLEM, a phase IIb, randomised, double-blind, placebo-controlled, multicentre study. Ann Rheum Dis. 2014;73:183–90.
* Wallace DJ, Hobbs K, Clowse MEB, Petri M, Strand V, Pike M, et al. Long-Term Safety and Efficacy of Epratuzumab in the Treatment of Moderate-to- Severe Systemic Lupus Erythematosus: Results From an Open-Label Extension Study. Arthritis Care Res (Hoboken). 2016;68:534–43.

2.1.11

| **GCs compared to placebo for lupus** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| Outcome № of participants (studies) | Relative effect (95% CI) | **Anticipated absolute effects (95% CI)** | | | Quality | What happens |
| **Without GCs** | **With GCs** | **Difference** |
| Clinical improvement follow up: 28 days № of participants: 25 (1 RCT) | **RR 0.90** (0.37 to 2.20) | 46.2% | **41.5%** (17.1 to 100.0) | **4.6% fewer** (29.1 fewer to 55.4 more) | ⨁⨁◯◯ LOW 1,2 | GCs may slightly increase the probability of clinical improvement |
| Clinical worsening follow up: 28 days № of participants: 25 (1 RCT) | **RR 0.36** (0.02 to 8.05) | 7.7% | **2.8%** (0.2 to 61.9) | **4.9% less**  (7.5 fewer to 54.2 more ) | ⨁◯◯◯ VERY LOW 1,2,3 | It is uncertain if GCs affect this outcome |
| Mortality follow up: 18 months № of participants: 25 (1 RCT) | **RR 3.23** (0.14 to 72.46) | 1 death reported in GCs arm | |  |  |  |
| Flares  follow up: 18 months  № of participants: 41 (1 RCT) | **RR 0.54** (0.19 to 1.58) | 35.0% | **18.9%** (6.6 to 55.3) | **16.1% fewer** (28.3 m fewer to 20.3 more) | ⨁⨁◯◯ LOW 1,2 | GCs may make little or no difference to flares |
| Severe Flares  follow up: 18 months № of participants: 41 (1 RCT) | **RR 0.07** (0.00 to 1.22) | 30.0% | **2.1%** (0.0 to 36.6) | **27.9% fewer**  (30 fewer to 6.6 more) | ⨁⨁◯◯ LOW 1,2 | GCs may reduce de risk of severe flares |
| Any adverse events follow up: 18 months № de participantes : № of participants: 66 (2 RCT) | **RR 0.96** (0.59 to 1.57) | 48.5% | **46.5%** (28.6 to 76.1) | **1.9% fewer** (19.9 fewer to 27.6 more) | ⨁⨁⨁◯ MODERATE 2 | GCs probably make little or no difference to adverse events |
| Severe adverse events follow up: 18 months № of participants: 66 (2 RCT) | **RR 1.00** (0.11 to 9.15) | 3.0% | **3.0%** (0.3 to 27.7) | **0.0% fewer**  (2.7 fewer to 24.7 more) | ⨁⨁⨁◯ MODERATE 2 | GCs probably increase the risk of severe adverse events |

1. Selective outcome reporting
2. Wide confidence intervals include significant benefit and harm
3. Optimal information size not met

* Mackworth-Young CG, David J, Morgan SH, Hughes GR. A double blind, placebo controlled trial of intravenous methylprednisolone in systemic lupus erythematosus. Ann Rheum Dis. 1988;47:496–502.
* Tseng C-E, Buyon JP, Kim M, Belmont HM, Mackay M, Diamond B, et al. The effect of moderate-dose corticosteroids in preventing severe flares in patients with serologically active, but clinically stable, systemic lupus erythematosus: findings of a prospective, randomized, double-blind, placebo-controlled trial. Arthritis Rheum. 2006;54:3623–32.

2.1.12

| **Placebo (HCQ withdrawal) compared to HCQ mantainance for lupus** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| Outcome № of participants (studies) | Relative effect (95% CI) | **Anticipated absolute effects (95% CI)** | | | Quality | What happens |
| **With HCQ** | **Withdrawing HCQ** | **Difference** |
| Flares assessed with: clinical evaluation follow up: 24 weeks № of participants: 47 (1 RCT) | **HR 2.50** (1.08 to 5.58) | 36.0% | **67.2%** (38.2 to 91.7) | **31.2% more** (2.2 more to 55,7 more) | ⨁⨁⨁◯ MODERATE 1 | HCQ withdrawal probably increases flares at 24 weeks |
| Flares assessed with: clinical evaluation follow up: 42 months № of participants: 47 (1 RCT) | **RR 1.96** (0.86 to 4.59) | 28.0% | **54.9%** (24.1 to 100.0) | **26.9% more** (3.9 fewer to 100.5 more) | ⨁⨁◯◯ LOW 2,3 | HCQ withdrawal may increase flares at 42 months |
| Any adverse event follow up: 24 weeks № of participants: 47 (1 RCT) | **RR 1.32** (0.19 to 11.00) | 9.1% | **12.0%** (1.7 to 100.0) | **2.9% more** (7.4 fewer to 90.9 more) | ⨁⨁◯◯ LOW 3,4 | HCQ withdrawal may not decrease the risk of adverse effects |
| Prednisone dose follow up: 24 weeks № of participants: 47 (1 RCT) | Changes in the dose of prednisone were not different in the two groups. | | | | - |  |

1. Optimal information size not met
2. Risk of bias
3. Wide confidence intervals include significant benefit and harm
4. Serious adverse events not reported in separate

* The Canadian Research Group. A Randomized Study of the Effect of Withdrawing Hydroxychloroquine Sulfate in Systemic Lupus Erythematosus. New England Journal of Medicine. 1991;324:150–4.
* Tsakonas E, Joseph L, Esdaile JM, Choquette D, Senécal JL, Cividino A, et al. A long-term study of hydroxychloroquine withdrawal on exacerbations in systemic lupus erythematosus. Lupus;7:80–5.

2.1.13

| **Infliximab compared to placebo for active lupus** | | |
| --- | --- | --- |
| Outcome № of participants (studies) | **Impact** | Quality |
| SLEDAI follow up: 6 months № of participants: 27 (1 RCT) | Mean change treatment and control group was -27.75 and -13.33 respectively (p=0.035) | ⨁⨁◯◯ LOW 1,2 |
| Quality of Life assessed with: SF-36 № of participants: 27 (1 RCT) | Mean change in total score in treatment and control group was 25.48 and 11.92 respectively (No statistical evaluation of the difference was provided) | ⨁⨁◯◯ LOW 1,2 |
| PGA follow up: 6 months № of participants: 27 (1 RCT) | Mean change in treatment and control group was -5.75 and -0.7 respectively (p=0.067) | ⨁⨁◯◯ LOW 1,2 |
| Corticoid use assessed with: Corticoid dose requirements follow up: 6 months № of participants: 27 (1 RCT) | Mean change in dose in treatment and control group was -38.75 and -4.0 respectively (p=0.052) | ⨁⨁◯◯ LOW 1,2 |

1. Risk of bias
2. Optimal information size not met

* Uppal SS, Hayat SJ, Raghupathy R. Efficacy and safety of infliximab in active SLE: a pilot study. Lupus. 2009;18:690–7.

2.1.14

| **LFN compared to placebo for active lupus** | | |
| --- | --- | --- |
| Outcome № of participants (studies) | **Impact** | Quality |
| Corticoid use follow up: 24 weeks № of participants: 12 (1 RCT) | Prednisolone dosage was similar between the two groups | ⨁◯◯◯ VERY LOW 1,2 |
| SLEDAI improvement follow up: 24 weeks № of participants: 12 (1 RCT) | Reduction in SLEDAI was significantly greater in the leflunomide group compared with the placebo group (11.0+6.1 vs 4.5+2.4 respectively, P = 0.026) | ⨁◯◯◯ VERY LOW 1,2 |

1. Risk of bias
2. Optimal information size not met

* Tam L-S, Li E, Wong C-K, Lam C, Szeto C-C. Double-blind, randomized, placebo-controlled pilot study of leflunomide in systemic lupus erythematosus. Lupus. 2004;13:601–4.

2.1.15

|  |  |  |
| --- | --- | --- |
| **MTX compared to placebo for active lupus** | | |
| Outcome  № of participants  (studies) | **Impact** | Quality |
|
| GCs use follow up: 6-12 months  № of participants: 101  (2 RCTs) | Both trials showed a significant reduction in the prednisone dose at the end of the trial. | ⨁⨁◯◯  LOW 1,2 |
| Symptom improvement  follow up: 6-12 months  № of participants: 101  (2 RCTs) | Both studies showed benefits with MTX. One study informed a significant reduction in the mean SLEDAI score (Mean difference 8). The other study informed a significant difference in the SLAM-R score. | ⨁⨁◯◯  LOW 1,2 |
| Adverse effects  follow up: 6-12 months  № of participants: 101  (2 RCTs) | Seven patients in the MTX arms and four patients in the placebo arm withdrew the medication because of severe adverse effects. | ⨁⨁◯◯  LOW 1,2 |

1. Risk of bias
2. Optimal information size not met

* Carneiro JR, Sato EI. Double blind, randomized, placebo controlled clinical trial of methotrexate in systemic lupus erythematosus. J Rheumatol. 1999;26:1275–9.
* Fortin PR, Abrahamowicz M, Ferland D, Lacaille D, Smith CD, Zummer M, et al. Steroid-sparing effects of methotrexate in systemic lupus erythematosus: a double-blind, randomized, placebo-controlled trial. Arthritis Rheum. 2008;59:1796–804.

2.1.16

| **OMACOR compared to placebo for lupus** | | |
| --- | --- | --- |
| Outcome № of participants (studies) | **Impact** | Quality |
| SLAM-R follow up: 24 weeks № of participants: 60 (1 RCT) | In treatment arm, there was a significant reduction in SLAM-R at 12 weeks and 24 weeks. There was no significant difference in SLAM-R with placebo (no statistical comparison between groups was provided) | ⨁⨁◯◯ LOW 1,2 |
| BILAG follow up: 24 weeks № of participants: 27 (1 RCT) | In treatment arm, there was a significant reduction in BILAG at 12 weeks and 24 weeks. There was no significant difference in BILAG with placebo (no statistical comparison between groups was provided) | ⨁⨁◯◯ LOW 1,2 |

1. Risk of bias
2. Optimal information size not met

* Wright SA, O’Prey FM, McHenry MT, Leahey WJ, Devine AB, Duffy EM, et al. A randomised interventional trial of omega-3-polyunsaturated fatty acids on endothelial function and disease activity in systemic lupus erythematosus. Ann Rheum Dis. 2008;67:841–8.

2.1.17

| **RTX compared to placebo for active lupus** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| Outcome № of participants (studies) | Relative effect (95% CI) | **Anticipated absolute effects (95% CI)** | | | Quality | What happens |
| **Without RTX** | **With RTX** | **Difference** |
| Major clinical response (BILAG A to C, no flares) follow up: 6 months  № of participants: 257 (1 RCT) | **RR 0.76** (0.40 to 1.42) | 15.9% | **12.1%** (6.4 a 22.6) | **3.8% fewer**  (9.5 fewer to 6.7 more) | ⨁⨁◯◯ LOW 1,2 | RTX may make little or no difference to major clinical response |
| Major clinical response (BILAG A to C, no flares) - African americans and Hispanics follow up: 6 months  № of participants: 64 (1 RCT) | **RR 1.50** (0.32 to 7.14) | 8.3% | **12.5%** (2.7 to 59.5) | **4.2% more**  (5.7 fewer to 51.2 more) | ⨁⨁◯◯ LOW 1,2 | RTX may improve major clinical response |
| Major clinical response (BILAG A to C, no flares) - No AA/H follow up: 6 months  № of participants: 193 (1 RCT) | **RR 0.66** (0.33 to 1.31) | 18.8% | **12.4%** (6.2 to 24.6) | **6.4% fewer**  (12.6 fewer to 5.8 more) | ⨁⨁◯◯ LOW 1,2 | RTX may make little or no difference to major clinical response |
| Quality of life SF 36 MID 3 follow up: 6 months  № of participants: 257 (1 RCT) | **RR 1.06** (0.85 to 1.33) | 55.7% | **59.0%** (47.3 to 74.1) | **3.3% more**  (8.4 fewer to 18.4 more) | ⨁⨁◯◯ LOW 1,2 | RTX may lead to slightly better QoL |
| Mortality follow up: 6 months  № of participants: 257 (1 RCT) | **RR 2.08** (0.24 to 18.35) | 1.1% | **2.4%** (0.3 to 20.9) | **1.2% more**  (0.9 fewer to 19.7 more) | ⨁⨁◯◯ LOW 1,2 | RTX may slightly increase the risk of death |
| Flares follow up: 6 months  № of participants: 257 (1 RCT) | **RR 0.83** (0.55 to 1.25) | 30.7% | **25.5%** (16.9 to 38.4) | **5.2% fewer**  (13.8 fewer to 7.7 more) | ⨁⨁◯◯ LOW 1,2 | RTX may slightly decrease the risk of flares |
| Any adverse events follow up: 6 months  № of participants: 257 (1 RCT) | **RR 1.04** (0.74 to 1.46) | 36.4% | **37.8%** (26.9 to 53.1) | **1.5% more**  (9.5 fewer to 16.7 more) | ⨁⨁◯◯ LOW 1,2 | RTX may slightly increase the risk of any adverse event |
| Drug-related adverse events follow up: 6 months  № of participants: 257 (1 RCT) | **RR 0.85** (0.36 to 1.96) | 9.1% | **7.7%** (3.3 to 17.8) | **1.4% fewer**  (5.8 fewer to 8.7 more) | ⨁⨁◯◯ LOW 1,2 | RTX may make little or no difference to drug-related adverse event |

1. Important lost to follow up
2. Wide confidence intervals include significant benefit and harm

* Merrill JT, Neuwelt CM, Wallace DJ, Shanahan JC, Latinis KM, Oates JC, et al. Efficacy and safety of rituximab in moderately-to-severely active systemic lupus erythematosus: the randomized, double-blind, phase II/III systemic lupus erythematosus evaluation of rituximab trial. Arthritis Rheum. 2010;62:222–33.

2.1.18

| **Rontalizumab (IV) compared to placebo for active lupus** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| Outcome № of participants (studies) | Relative effect (95% CI) | **Anticipated absolute effects (95% CI)** | | | Quality | What happens |
| **Without Rontalizumab IV** | **With Rontalizumab IV** | **Difference** |
| Improvement assessed with: BILAG Index Response follow up: 24 weeks № of participants: 120 (1 RCT) | **RR 1.96** (0.86 to 4.59) | 34.1% | **66.9%** (29.4 to 100.0) | **32.8% more** (4.8 fewer to 122.6 more) | ⨁⨁⨁◯ MODERATE 1 | Rontalizumab probably increases the risk of improvement assessed by BILAG |
| Improvement assessed with: SLEDAI response index -4 follow up: 24 weeks № of participants: 120 (1 RCT) | **RR 1.18** (0.76 to 1.93) | 41.5% | **48.9%** (31.5 to 80.0) | **7.5% more** (10 fewer to 38.6 more) | ⨁⨁⨁◯ MODERATE 1 | Rontalizumab probably slightly increases improvement assessed by SLEDAI |
| Flares assessed with: SELENA-SLEDAI follow up: 24 weeks № of participants: 120 (1 RCT) | **RR 0.86** (0.70 to 1.13) | 78.0% | **67.1%** (54.6 to 88.2) | **10.9% fewer** (23.4 fewer to 10.1 more) | ⨁⨁⨁◯ MODERATE 1 | Rontalizumab probably slightly reduces flares |
| Serious adverse events follow up: 24 weeks № of participants: 120 (1 RCT) | **RR 1.30** (0.40 to 4.78) | 9.8% | **12.7%** (3.9 to 46.6) | **2.9% more** (5.9 fewer to 36.9 more) | ⨁⨁⨁◯ MODERATE 1 | Rontalizumab probably increases de risk serious adverse events |

1. Wide confidence intervals include significant benefit and harm

* Kalunian KC, Merrill JT, Maciuca R, McBride JM, Townsend MJ, Wei X,et al. A phase II study of the efficacy and safety of rontalizumab (rhuMAb interferon-α) in patients with systemic lupus erythematosus (ROSE). Ann Rheum Dis. 2016;75:196-202.

2.1.19

| **Rontalizumab (SC) compared to placebo for active lupus** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| Outcome № of participants (studies) | Relative effect (95% CI) | **Anticipated absolute effects (95% CI)** | | | Quality | What happens |
| **Without Rontalizumab SC** | **With Rontalizumab SC** | **Difference** |
| Improvement assessed with: BILAG Index Response follow up: 24 weeks № of participants: 115 (1 RCT) | **RR 1.07** (0.73 to 1.67) | 50.0% | **53.5%** (36.5 to 83.5) | **3.5% more** (13.5 fewer to 33.5 more) | ⨁⨁⨁◯ MODERATE 1 | Rontalizumab probably slightly increases improvement assessed by BILAG |
| Improvement assessed with: SLEDAI response index -4 follow up: 24 weeks № of participants: 115 (1 RCT) | **RR 1.07** (0.73 to 1.67) | 50.0% | **53.5%** (36.5 to 83.5) | **3.5% more** (13.5 fewer to 33.5 more) | ⨁⨁⨁◯ MODERATE 1 | Rontalizumab probably slightly increases improvement assessed by SLEDAI |
| Flares assessed with: SELENA-SLEDAI follow up: 24 weeks № of participants: 115 (1 RCT) | **RR 0.86** (0.68 to 1.18) | 73.7% | **63.4%** (50.1 to 86.9) | **10.3% fewer** (23.6 fewer to 13.3 more) | ⨁⨁⨁◯ MODERATE 1 | Rontalizumab probably slightly reduce the risk of flare |
| Serious adverse events follow up: 24 weeks № of participants: 115 (1 RCT) | **RR 0.49** (0.05 to 4.83) | 10.5% | **5.2%** (0.5 to 50.8) | **5.4% fewer** (10 fewer to 40.3 more) | ⨁⨁◯◯ LOW 1,2 | Rontalizumab may not increase the risk of serious adverse events |

1. Wide confidence intervals include significant benefit and harm
2. Very few events

* Kalunian KC, Merrill JT, Maciuca R, McBride JM, Townsend MJ, Wei X,et al. A phase II study of the efficacy and safety of rontalizumab (rhuMAb interferon-α) in patients with systemic lupus erythematosus (ROSE). Ann Rheum Dis. 2016;75:196-202.

2.1.20

| **Sifalimumab compared to placebo for active lupus** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| Outcome № of participants (studies) | Relative effect (95% CI) | **Anticipated absolute effects (95% CI)** | | | Quality | What happens |
| **Without Sifalimumab** | **With Sifalimumab** | **Difference** |
| Flare assessed with: Worsening SELENA–SLEDAI of 3 points from baseline or as a new grade A or B BILAG follow up: 26 weeks № of participants: 161 (1 RCT) | **RR 1.07** (0.54 to 2.93) | 22.5% | **24.1%** (12.2 to 65.9) | **1.6% more** (10.3 fewer to 43.4 more) | ⨁⨁◯◯ LOW 1,2 | Sifalimumab may slightly increase the risk of flares |
| BILAG assessed with: MID -7 follow up: 26 weeks № of participants: 161 (1 RCT) | **RR 1.74** (0.61 to 4.92) | 10.0% | **17.4%** (6.1 to 49.2) | **7.4% more** (3.9 fewer to 39.2 more) | ⨁⨁◯◯ LOW 1,2 | Sifalimumab may slightly increase BILAG |
| Serious adverse events follow up: 26 weeks № of participants: 161 (1 RCT) | **RR 1.54** (1.02 to 2.45) | 47.5% | **73.1%** (48.4 to 100.0) | **25.7% more** (1 more to 68.9 more) | ⨁⨁◯◯ LOW 1,2 | Sifalimumab may increase serious adverse events |

1. Risk of bias
2. Wide confidence intervals include significant benefit and harm

* Petri M, Wallace DJ, Spindler A, Chindalore V, Kalunian K, Mysler E, et al. Sifalimumab, a human anti-interferon-α monoclonal antibody, in systemic lupus erythematosus: a phase I randomized, controlled, dose-escalation study. Arthritis Rheum. 2013;65:1011–21.

2.1.21

| **Tabalumab compared to placebo for active lupus** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| Outcome № of participants (studies) | Relative effect (95% CI) | **Anticipated absolute effects (95% CI)** | | | Quality | What happens |
| **Without Tabalumab** | **With Tabalumab** | **Difference** |
| Clinical improvement (SELENA SLEDAI MID 7) follow up: 1 year  № of participants: 2272 (2 RCTs) | **RR 0.99** (0.93 to 1.06) | 85.4% | **84.6%** (79.5 to 90.6) | **0.9% fewer**  (6 fewer to 5.1 more) | ⨁⨁⨁◯ MODERATE 1 | Tabalumab probably makes little or no difference to clinical iprovement |
| No worsening in BILAG follow up: 1 year  № of participants: 2272 (2 RCTs) | **RR 1.07** (1.00 a 1.15) | 60.0% | **64.2%** (60.0 to 69.0) | **4.2% more**  (0 fewer to 9 more) | ⨁⨁⨁◯ MODERATE 1 | Tabalumab probably increases the probability of no worsening BILAG |
| Mortality s follow up: 1 year  № of participants: 2272 (2 RCTs) | **RR 0.78** (0.25 to 2.44) | 0.7% | **0.5%** (0.2 a 1.6) | **0.1% fewer**  (0.5 fewer to 1 more) | ⨁⨁⨁◯ MODERATE 1 | Tabalumab probably makes little or no difference to the risk of death |
| Any adverse events follow up: 1 year  № of participants: 2272 (2 RCTs) | **RR 0.72** (0.36 to 1.43) | 81.7% | **58.8%** (29.4 to 100.0) | **22.9% fewer**  (52.3 fewer to 35.1 more) | ⨁⨁⨁◯ MODERATE 1,2 | Tabalumab probably makes little or no difference to the risk of any adverse event |
| Severe adverse events follow up: 1 year  № of participants: 2272 (2 RCTs) | **RR 0.85** (0.65 to 1.09) | 16.0% | **13.6%** (10.4 to 17.5) | **2.4% fewer**  (5.6 fewer to 1.4 more) | ⨁⨁⨁◯ MODERATE 1 | Tabalumab probably makes little or no difference to the risk of severe adverse event |
| Drug-related adverse events follow up: 1 year  № of participanst: 2272 (2 RCTs) | **RR 0.90** (0.58 to 1.40) | 39.3% | **35.4%** (22.8 to 55.1) | **3.9% fewer**  (16.5 fewer to 15.7 more) | ⨁⨁◯◯ LOW 1,2 | Tabalumab may make little or no difference to the risk of drug-related adverse event |

1. Wide confidence intervals include significant benefit and harm
2. Optimal information size not met

* Isenberg DA, Petri M, Kalunian K, Tanaka Y, Urowitz MB, Hoffman RW, et al. Efficacy and safety of subcutaneous tabalumab in patients with systemic lupus erythematosus: results from ILLUMINATE-1, a 52-week, phase III, multicentre, randomised, double-blind, placebo-controlled study. Annals of the Rheumatic Diseases. 2016;75:323–31.
* Merrill JT, van Vollenhoven RF, Buyon JP, Furie RA, Stohl W, Morgan-Cox M, et al. Efficacy and safety of subcutaneous tabalumab, a monoclonal antibody to B-cell activating factor, in patients with systemic lupus erythematosus: results from ILLUMINATE-2, a 52-week, phase III, multicentre, randomised, double-blind, placebo-controlled study. Ann Rheum Dis. 2016;75:332–40.

2.2.1

| **AZA withdrawal compared to AZA for Lupus** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| Outcome № of participants (studies) | Relative effect (95% CI) | **Anticipated absolute effects (95% CI)** | | | Quality | What happens |
| **Without AZA withdrawal** | **With AZA withdrawal** | **Difference** |
| Flares follow up: 12 months № of participants: 16 (1 RCT) | **RR 5.44** (1.03 to 112.00) | 14.3% | **77.7%** (14.7 to 100.0) | **63.4% more** (0.4 more to 1585.7 more) | ⨁⨁◯◯ LOW 1,2 | AZA withdrawal may increase the risk of flares |
| Corticoid use assessed with: Prednisone mg follow up: 12 months № of participants: 16 (1 RCT) | Mean GCs dose at the end of the study period was higher in the withdrawal group compared to the continuation group. | | | | - |  |

1. Risk of bias
2. Wide confidence intervals include significant benefit and harm

* Sharon E, Kaplan D, Diamond HS. Exacerbation of systemic lupus erythematosus after withdrawal of azathioprine therapy. N Engl J Med. 1973;288:122–4.

2.2.2

| **CsA compared to AZA for lupus** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| Outcome № of participants (studies) | Relative effect (95% CI) | **Anticipated absolute effects (95% CI)** | | | Quality | What happens |
| **Without CsA** | **With CsA** | **Difference** |
| Response (A or 2B to C, Active Lupus) follow up: 1 year  № of participants: 33 (1 RCT) | **RR 1.11** (0.50 to 2.49) | 40.0% | **44.4%** (20.0 to 99.6) | **4.4% more**  (20 fewer to 59.6 more ) | ⨁⨁◯◯ LOW 1,2 | CsA may slightly increase the risk of response |
| Quality of life follow up: 1 year  (1 RCT) | SD of mean difference not reported, 95% CI of difference betweeen means in both cohorts not statistically different (-2 95%, CI -8 to +4) favouring cyclosporine | | | | ⨁⨁⨁◯ MODERATE 2 |  |
| Mortality follow up: 1 year № of participants: 90 (1 RCT) | No events reported | | | | - |  |
| Flares follow up: 1 year № of participants: 90 (1 RCT) | **RR 1.05** (0.41 to 2.64) | 16.3% | **17.1%** (6.7 o 43.0) | **0.8% more**  (9.6 fewer to 26.7 more) | ⨁⨁◯◯ LOW 1,2 | Cyclosporine may slightly increase the risk of flares |
| Drug suspension due to adverse event follow up: 1 year № of participants: 90 (1 RCT) | **RR 1.05** (0.41 to 2.64) | 16.3% | **17.1%** (6.7 to 43.0) | **0.8% more**  (9.6 fewer to 26.7 more) | ⨁⨁⨁◯ MODERATE 2 | Cyclosporine probably slightly increases the risk of discontinuation due to adverse events |
| Severe adverse events follow up: 1 year № of participants: 90 (1 RCT) | **RR 1.02** (0.46 to 2.26) | 20.9% | **21.3%** (9.6 to 47.3) | **0.4% more**  (11.3 fewer to 26.4 more) | ⨁⨁⨁◯ MODERATE 2 | Cyclosporine probably slightly increases the risk of severe adverse events |

1. Selective outcome reporting
2. Wide confidence intervals include significant benefit and harm

* Griffiths B, Emery P, Ryan V, Isenberg D, Akil M, Thompson R, et al. The BILAG multi-centre open randomized controlled trial comparing ciclosporin vs azathioprine in patients with severe SLE. Rheumatology. 2010;49:723–32.

2.2.3

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **HCQ stable dose compared to HCQ incremental dose (target 1000 ng/ml) for lupus** | | | | | | |
| Outcome  № of participants  (studies) | Relative effect  (95% CI) | **Anticipated absolute effects (95% CI)** | | | Quality | What happens |
| **Without Hydroxychloroquine dosis estable** | **With Hydroxychloroquine dosis estable** | **Difference** |
| Flares  follow up: 7 months  № of participants: 171  (1 RCT) | **RR 1.14**  (0.54 to 2.30) | 25.0% | **28.5%**  (13.5 to 57.5) | **3.5% more**  (11.5 fewer to 32.5 more) | ⨁⨁◯◯  LOW 1 | Incremental dose of HCQ may slightly increase the risk of flares |
| Severe flares  assessed with: SELENA-SLEDAI  follow up: 7 months  № of participants: 171  (1 RCT) | **RR 0.72**  (0.13 to 3.70) | 4.8% | **3.4%**  (0.6 to 17.6) | **1.3% fewer**  (4.1 fewer to 12.9 more) | ⨁⨁◯◯  LOW 1 | Incremental dose of HCQ may slightly increase the risk of severe flares |
| Adverse effects  follow up: 7 months  № of participants: 171  (1 RCT) | **RR 0.71**  (0.38 to 1.20) | 27.4% | **19.4%**  (10.4 to 32.9) | **7.9% fewer**  (17 fewer to 5.5 more) | ⨁⨁◯◯  LOW 1 | Incremental dose of hydroxychloroquine may slightly reduce the risk of adverse events |

1. Wide confidence intervals include significant benefit and harm

* Costedoat-Chalumeau N, Galicier L, Aumaître O, Francès C, Le Guern V, Lioté F, et al. Hydroxychloroquine in systemic lupus erythematosus: results of a French multicentre controlled trial (PLUS Study). Ann Rheum Dis. 2013;72:1786–92.

2.2.4

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **MMF compared to CYC for active lupus** | | | | | | |
| Outcome  № of participants  (studies) | Relative effect  (95% CI) | **Anticipated absolute effects (95% CI)** | | | Quality | What happens |
| **Without MMF** | **With MMF** | **Difference** |
| Symptom improvement (In patients with BILAG baseline scores A or B)  assessed with: BILAG C or D  follow up: 24 weeks  № of participants: 109  (1 RCT) | **RR 1.08**  (0.94 to 1.12) | 89.9% | **97.0%**  (84.5 to 100.0) | **7.2% more**  (5.4 fewer to 10.8 more) | ⨁⨁◯◯  LOW 1 | MMF may increase the probability of symptom improvement |
| Remission  assessed with: SELENA- SLEDAI  follow up: 24 weeks  № of participants: 369  (1 RCT) | **RR 1.40**  (0.84 to 2.36) | 13.0% | **18.3%**  (11.0 to 30.8) | **5.2% more**  (2.1 fewer to 17.7 more) | ⨁⨁◯◯  LOW 1 | MMF may increase the probability of remission |
| Severe adverse effects  follow up: 24 weeks  № of participants: 364  (1 RCT) | **RR 1.20**  (0.83 to 1.77) | 22.8% | **27.3%**  (18.9 to 40.3) | **4.6% more**  (3.9 fewer to 17.5 more) | ⨁⨁◯◯  LOW 1 | MMF may increases the risk of severe adverse effects |

1. Wide confidence intervals include significant benefit and harm

* Ginzler EM, Wofsy D, Isenberg D, Gordon C, Lisk L, Dooley M-A, et al. Nonrenal disease activity following mycophenolate mofetil or intravenous cyclophosphamide as induction treatment for lupus nephritis: findings in a multicenter, prospective, randomized, open-label, parallel-group clinical trial. Arthritis Rheum. 2010;62:211–21.

2.2.5

| **MTX compared to CQ for Lupus** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| Outcome  № of participants  (studies) | Relative effect  (95% CI) | **Anticipated absolute effects (95% CI)** | | | Quality | What happens |
| **Without MTX** | **With MTX** | **Difference** |
| Proportion of patients with significant clinical improvement follow up: 24 weeks № of participants: 41 (1 RCT) | No statistical difference between MTX and Chloroquine group (mean difference not informed). Mean SLEDAI score in MTX group 2.8 +/- 2.4 and Chloroquine group 2.5 +/-2.4. | | | | ⨁⨁◯◯ LOW 1,2 |  |
| Quality of life follow up: 24 weeks follow up: 24 weeks № of participants: 41 (1 RCT) | No statistical difference between MTX and Chloroquine group (mean difference not informed). Mean PGAI score in MTX group 1.6 +/- 1.2 and Chloroquine group 1.9 +/-1.1. | | | | ⨁⨁◯◯ LOW 1,2 |  |
| Any adverse events follow up: 24 weeks № of participants: 41 (1 RCT) | **RR 3.90** (1.45 to 10.51) | 15.4% | **60.0%** (22.3 to 100.0) | **44.6% more**  (6.9 more to 146.3 more) | ⨁⨁◯◯ LOW 1,4 | MTX may increase the risk of any adverse event |

1. Open Label
2. Wide confidence intervals include significant benefit and harm
3. Selective outcome reporting (no events reported)
4. Very few events

* Islam MN, Hossain M, Haq SA, Alam MN, Ten Klooster PM, Rasker JJ. Efficacy and safety of methotrexate in articular and cutaneous manifestations of systemic lupus erythematosus. Int J Rheum Dis. 2012;15:62–8.

3.1.1

| **ABT compared to placebo for SLE with predominant musculoskeletal compromise** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| Outcome № of participants (studies) | Relative effect (95% CI) | **Anticipated absolute effects (95% CI)** | | | Quality | What happens |
| **Without ABT** | **With ABT** | **Difference** |
| Musculoskeletal flares assessed with: BILAG A follow up: 12 months № of participants: 95 (1 RCT) | **RR 0.58** (0.39 to 0.95) | 62.5% | **36.3%** (24.4 to 59.4) | **26.3% fewer** (38.1 fewer to 3.1 fewer) | ⨁⨁◯◯ LOW 1,2 | ABT may decrease flares |
| Musculoskeletal flares assessed with: BILAG A or B follow up: 12 months № of participants: 95 (1 RCT) | **RR 0.92** (0.78 to 1.19) | 84.4% | **77.6%** (65.8 to 100.0) | **6.7% fewer** (18.6 fewer to 16 more) | ⨁⨁◯◯  LOW 1,3 | ABT may decrease flares |
| Musculoskeletal flares assessed with: Physician evaluation follow up: 12 months № of participants: 95 (1 RCT) | **RR 0.68** (0.56 to 0.96) | 84.4% | **57.4%** (47.3 to 81.0) | **27.0% fewer** (37.1 fewer to 3.4 fewer) | ⨁⨁◯◯ LOW 1,2 | ABT may decrease flares |

1. Risk of bias
2. Optimal information size not met
3. Wide confidence intervals include significant benefit and harm

* Merrill JT, Burgos-Vargas R, Westhovens R, Chalmers A, D’Cruz D, Wallace DJ, et al. The efficacy and safety of abatacept in patients with non-life-threatening manifestations of systemic lupus erythematosus: results of a twelve-month, multicenter, exploratory, phase IIb, randomized, double-blind, placebo-controlled trial. Arthritis Rheum. 2010;62:3077–87.

3.1.2

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Atacicept 75 mg compared to placebo for SLE with predominant musculoskeletal compromise** | | | | | | |
| Outcome  № of participants  (studies) | Relative effect  (95% CI) | **Anticipated absolute effects (95% CI)** | | | Quality | What happens |
| **Without Atacicept 75mg** | **With Atacicept 75mg** | **Difference** |
| Musculoskeletal flares  assessed with: BILAG A and B  follow up: 52 weeks  № of participants: 316  (1 RCT) | **RR 1.19**  (0.74 to 1.94) | 17.8% | **21.2%**  (13.2 to 34.6) | **3.4% more**  (4.6 fewer to 16.8 more) | ⨁⨁◯◯  LOW 1 | Atacicept 75 mg may make no difference in reducing musculoskeletal flares |

1. Wide confidence interval includes significant benefit and harm

* Isenberg D, Gordon C, Licu D, Copt S, Rossi CP, Wofsy D. Efficacy and safety of atacicept for prevention of flares in patients with moderate-to-severe systemic lupus erythematosus (SLE): 52-week data (APRIL-SLE randomised trial). Ann Rheum Dis. 2015;74:2006–15.

3.1.3

| Belimumab **compared to placebo for SLE with predominant musculoskeletal compromise** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| Outcome  № of participants  (studies) | Relative effect  (95% CI) | **Anticipated absolute effects (95% CI)** | | | Quality | What happens |
| **Without** belimumab | **With** belimumab | **Difference** |
| Musculoskeletal BILAG improvement (≥2 level) any dose follow up: 1 year  № of participants: 1008 (2 RCTs) | **RR 1.19** (1.00 to 1.42) | 34.5% | **41.1%** (34.5 to 49.0) | **6.6% more** (0 fewer to 14.5 more) | ⨁⨁◯◯ LOW 1,3 | Belimumab may increase BILAG improvement |
| Any worsening in Musculoskeletal BILAG any dose follow up: 1 year  № of participants: 1558 (2 RCTs) | **RR 0.76** (0.47 to 1.23) | 5.0% | **3.8%** (2.4 to 6.2) | **1.2% fewer** (2.7 fewer to 1.2 more) | ⨁⨁◯◯ LOW 1,2 | Belimumab may make little or no difference to the risk of BILAG worsening |
| Any Musculoskeletal SELENA-SLEDAI improvement (NOT MID) any dose follow up: 1 year  № of participants: 1096 (2 RCTs) | **RR 1.16** (1.03 to 1.31) | 49.3% | **57.2%** (50.8 to 64.6) | **7.9% more** (1.5 more to 15.3 more) | ⨁⨁◯◯ LOW 1,2 | Belimumab may increase BILAG improvement |
| Any Musculoskeletal SELENA-SLEDAI worsening (NOT MID) any dose follow up: 1 year  № of participants: 582 (2 RCTs) | **RR 0.75** (0.38 to 1.47) | 6.8% | **5.1%** (2.6 to 10.1) | **1.7% fewer** (4.2 fewer to 3.2 more) | ⨁⨁◯◯  LOW 1,2 | Belimumab may make little or no difference to the risk of BILAG worsening |

1. Attrition bias
2. Wide confidence intervals include significant benefit and harm
3. Optimal information size not met

* Manzi S, Sánchez-Guerrero J, Merrill JT, Furie R, Gladman D, Navarra SV, et al. Effects of belimumab, a B lymphocyte stimulator-specific inhibitor, on disease activity across multiple organ domains in patients with systemic lupus erythematosus: combined results from two phase III trials. Ann Rheum Dis. 2012;71:1833–8.

3.1.4

| **CQ compared to placebo for SLE with predominant musculoskeletal compromise** | | |
| --- | --- | --- |
| Outcome № of participants (studies) | **Impact** | Quality |
| Flares  follow up: 1 year  № of participants: 23 (1 RCT) | At the beginning of the trial 3 patients in the chloroquine arm had arthritis, and all improved at the end of follow up. | ⨁◯◯◯  VERY LOW 1,2 |

1. Selective outcome reporting
2. Optimal information size not met

* Meinão IM, Sato EI, Andrade LE, Ferraz MB, Atra E. Controlled trial with chloroquine diphosphate in systemic lupus erythematosus. Lupus. 1996;5:237–41.

3.1.5

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **MTX compared to placebo for SLE with predominant musculoskeletal compromise** | | | | | | |
| Outcome  № of participants  (studies) | Relative effect  (95% CI) | **Anticipated absolute effects (95% CI)** | | | Quality | What happens |
| **Without MTX** | **With MTX** | **Difference** |
| Symptom persistence  follow up: 6 months  № of participants: 41  (1 RCT) | **RR 0.06**  (0.003 to 0.350) | 76.2% | **4.6%**  (0.2 to 26.7) | **71.6% fewer**  (76 fewer to 49.5 fewer) | ⨁⨁◯◯  LOW 1,2 | MTX may increase the probability of symptom resolution |

1. No blinding
2. Optimal information size not met

* Carneiro JR, Sato EI. Double blind, randomized, placebo controlled clinical trial of methotrexate in systemic lupus erythematosus. J Rheumatol. 1999;26:1275–9.

3.1.6

| **GCs compared to placebo for SLE with predominant musculoskeletal compromise** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| Outcome  № of participants  (studies) | Relative effect  (95% CI) | **Anticipated absolute effects (95% CI)** | | | Quality | What happens |
| **Without GCs** | **with GCs** | **Difference** |
| Clinical improvement (No Score) follow up: 28 days  № of participants: 16 (1 RCT) | **RR 0.60** (0.21 to 1.70) | 62.5% | **37.5%** (13.1 to 100.0) | **25.0% fewer**  (49.4 fewer to 43.8 more) | ⨁◯◯◯ VERY LOW 1,2 | It is uncertain whether GCs affect this outcome |
| Prevention of Flares follow up: 18 months  № of participants: 41 (1 RCT) | **RR 0.95** (0.22 to 4.18) | 15.0% | **14.2%** (3.3 to 62.7) | **0.8% fewer**  (11.7 fewer to 47.7 more) | ⨁⨁◯◯ LOW 1,2 | GCs may make little or no difference in the risk of flares |
| Prevention of Severe flares: follow up: 18 months  № of participants : 41 (1 RCT) | **RR 0.19** (0.01 to 3.75) | 10.0% | **1.9%** (0.1 to 37.5) | **8.1% fewer**  (9.9 fewer to 27.5 more) | ⨁⨁◯◯ LOW 1,2 | GCs may reduce severe flares |

1. Selective outcome reporting
2. Wide confidence intervals include significant benefit and harm

* Mackworth-Young CG, David J, Morgan SH, Hughes GR. A double blind, placebo controlled trial of intravenous methylprednisolone in systemic lupus erythematosus. Ann Rheum Dis. 1988;47:496–502.
* Tseng C-E, Buyon JP, Kim M, Belmont HM, Mackay M, Diamond B, et al. The effect of moderate-dose corticosteroids in preventing severe flares in patients with serologically active, but clinically stable, systemic lupus erythematosus: findings of a prospective, randomized, double-blind, placebo-controlled trial. Arthritis Rheum. 2006;54:3623–32.

3.2.1

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **MMF compared to CYC for SLE with predominant musculoskeletal compromise** | | | | | | |
| Outcome  № of participants  (studies) | Relative effect  (95% CI) | **Anticipated absolute effects (95% CI)** | | | Quality | What happens |
| **Without MMF** | **With MMF** | **Difference** |
| Response  assessed with: BILAG C or D  follow up: 24 weeks  № of participants: 49  (1 RCT) | **RR 0.95**  (0.87 to 1.09) | 138.5% | **100.0%**  (100.0 to 100.0) | **6.9% fewer**  (18 fewer to 12.5 more) | ⨁⨁◯◯  LOW 1 | MMF may make no difference to improve musculoskeletal symptoms related to CYC |

1. Wide confidence intervals include significant benefit and harm

* Ginzler EM, Wofsy D, Isenberg D, Gordon C, Lisk L, Dooley M-A, et al. Nonrenal disease activity following mycophenolate mofetil or intravenous cyclophosphamide as induction treatment for lupus nephritis: findings in a multicenter, prospective, randomized, open-label, parallel-group clinical trial. Arthritis Rheum. 2010;62:211–21.

3.2.2

| **MTX compared to CQ for SLE with predominant musculoskeletal compromise** | | |
| --- | --- | --- |
| Outcome № of participants (studies) | **Impact** | Quality |
| Number of swollen joints follow up: 6 months  № of participants: 41 (1 RCT) | The number of swollen joints in the Methotrexate group at the beginning of the study was 7.77 (SD 9.68) and at the end of the study was 0.77 (SD 1.74). In the chloroquine group, the number was at the beginning of the study of 2.7 (SD 4.6) and at the end of the study was 1.1 (SD 2.9) without intergroup difference in the number of swollen joints at the end of the study. | ⨁⨁◯◯  LOW 1,2 |
| Number of swollen joints  follow up: 6 months  № of participants: 41 (1 RCT) | The number of swollen joints in the Methotrexate group at the beginning of the study was 11.7 (SD 19.4) and at the end of the study was 1.4 (SD 3.1). In the chloroquine group, was at the beginning of the study of 3.4 (SD 5.7) and at the end of the study was 1.4 (SD 3.42) without intergroup difference in the swollen joints index at the end of the study. | ⨁⨁◯◯  LOW 1,2 |
| Number of tender joint follow up: 6 months  № of participants: 41 (1 RCT) | The number of tender joints in the Methotrexate group at the beginning of the study was 20.1 (SD 10.0) and at the end of the study was 3.3 (SD 5.3). In the chloroquine group, was at the beginning of the study of 15.2 (SD 11.2) and at the end of the study was 4.1 (SD 6.7) without intergroup difference in the number of tender joints at the end of the study. | ⨁⨁◯◯  LOW 1,2 |
| Tender joint index follow up: 6 months  № of participants: 41 (1 RCT) | The tender joint index in the Methotrexate group at the beginning of the study was 35.7 (SD 21.7) and at the end of the study was 4.5 (SD 9.1). In the chloroquine group was at the beginning of the study of 23.0 (SD 17.4) and at the end of the study was 4.8 (SD 9.8) without intergroup difference in the swollen joints index at the end of the study. | ⨁⨁◯◯  LOW 1,2 |
| VAS scale for pain  follow up: 6 months  № of participants: 41 (1 RCT) | The VAS scale for pain in the Methotrexate group at the beginning of the study was 5.4 (SD 2.3) and at the end of the study was 1.4 (SD 2.1). In the chloroquine group was at the beginning of the study of 4.5 (SD 2.6) and at the end of the study was 1.5 (SD 2.2) without intergroup difference in the VAS scale for pain at the end of the study. | ⨁⨁◯◯  LOW 1,2 |

1. Open label trial
2. Possible benefits or harms. Small number of events.

* Islam MN, Hossain M, Haq SA, Alam MN, Ten Klooster PM, Rasker JJ. Efficacy and safety of methotrexate in articular and cutaneous manifestations of systemic lupus erythematosus. Int J Rheum Dis. 2012;15:62–8.

4.1.1

| **ABT compared to placebo for lupus with predominant skin compromise** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| Outcome № of participants (studies) | Relative effect (95% CI) | **Anticipated absolute effects (95% CI)** | | | Quality | What happens |
| **Without ABT** | **With ABT** | **Difference** |
| Flares assessed with: BILAG A follow up: 12 months № of participants: 60 (1 RCT) | **RR 1.16** (0.63 to 2.50) | 42.1% | **48.8%** (26.5 to 100.0) | **6.7% more** (15.6 fewer to 63.2 more) | ⨁◯◯◯ VERY LOW 1,2 | We are uncertain whether ABT improves/reduces flares (BILAG A) as the quality of the evidence has been assessed as very low |
| Flares assessed with: BILAG A or B follow up: 12 months № of participants: 60 (1 RCT) | **RR 1.08** (0.86 to 1.48) | 78.9% | **85.3%** (67.9 to 100.0) | **6.3% more** (11.1 fewer to 37.9 more) | ⨁◯◯◯ VERY LOW 1,2 | We are uncertain whether ABT improves/reduces flares (BILAG A or B) as the quality of the evidence has been assessed as very low |
| Flares assessed with: Physician evaluation follow up: 12 months № of participants: 60 (1 RCT) | **RR 0.87** (0.67 to 1.31) | 78.9% | **68.7%** (52.9 to 100.0) | **10.3% fewer** (26.1 fewer to 24.5 more) | ⨁◯◯◯ VERY LOW 1,2 | We are uncertain whether ABT improves/reduces physician assessed flares as the quality of the evidence has been assessed as very low |

1. Risk of bias
2. Wide confidence intervals include significant benefit and harm

* Merrill JT, Burgos-Vargas R, Westhovens R, Chalmers A, D’Cruz D, Wallace DJ, et al. The efficacy and safety of abatacept in patients with non-life-threatening manifestations of systemic lupus erythematosus: results of a twelve-month, multicenter, exploratory, phase IIb, randomized, double-blind, placebo-controlled trial. Arthritis Rheum. 2010;62:3077–87.

4.1.2

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Atacicept 75 mg compared to placebo for lupus with predominant skin compromise** | | | | | | |
| Outcome  № of participants  (studies) | Relative effect  (95% CI) | **Anticipated absolute effects (95% CI)** | | | Quality | What happens |
| **Without Atacicept 75mg** | **With Atacicept 75mg** | **Difference** |
| Skin flares  assessed with: BILAG A and B  follow up: 52 weeks  № of participants: 316  (1 RCT) | **RR 1.2**  (0.7 to 1.9) | **Observed** | | | ⨁⨁OO  LOW 1 | Atacicept 75mg may make no difference in reducing skin flares |
| 17.5% | **21.0%**  (12.2 to 33.2) | **3.5% more**  (5.3 fewer to 15.7 more) |

1. CI95% including benefits and harms

* Isenberg D, Gordon C, Licu D, Copt S, Rossi CP, Wofsy D. Efficacy and safety of atacicept for prevention of flares in patients with moderate-to-severe systemic lupus erythematosus (SLE): 52-week data (APRIL-SLE randomised trial). Ann Rheum Dis. 2015;74:2006–15.

4.1.3

| Belimumab **compared to placebo for lupus with predominant skin compromise** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| Outcome  № of participants  (studies) | Relative effect  (95% CI) | **Anticipated absolute effects (95% CI)** | | | Quality | What happens |
| **Without** Belimumab | **With** Belimumab | **Difference** |
| BILAG improvement (2 levels) any dose follow up: 1 years  Number of participants: 971 (2 RCT) | **RR 1.41** (1.12 a 1.77) | 22.0% | **31.0%** (24.6 a 38.9) | **9.0% more**  (2.6 more to 16.9 more) | ⨁⨁⨁◯ MODERATE 2 | Belimumab probably increases clinical improvement |
| Any worsening in BILAG any dosefollow up: 1 years  Number of participants: 1610 (2 RCT) | **RR 1.09** (0.68 a 1.74) | 4.5% | **4.9%** (3.0 a 7.8) | **0.4% more**  (1.4 less to 3.3 more) | ⨁⨁◯◯ LOW 1 | Belimumab may reduce any worsening |
| Any SELENA-SLEDAI improvement (NOT MID) any dosefollow up: 1 years  Number of participants: 1055 (2 RCT]) | **RR 1.32** (1.12 a 1.57) | 33.1% | **43.6%** (37.0 a 51.9) | **10.6% more**  (4 more to 18.8 more) | ⨁⨁⨁◯ MODERATE 2 | Belimumab probably increases clinical improvement |
| Any SELENA-SLEDAI worsening (NOT MID) any dosefollow up: 1 years  Number of participants: 305 (2 RCT]) | **RR 1.02** (0.54 a 1.92) | 12.9% | **13.2%** (7.0 a 24.8) | **0.3% more**  (5.9 less a 11.9 more ) | ⨁⨁◯◯ LOW 1 | Belimumab may reduce any worsening |

1. Attrition bias and selective outcome reporting
2. 95% CI including significant benfits and harms
3. Optimal information size not met

* Manzi S, Sánchez-Guerrero J, Merrill JT, Furie R, Gladman D, Navarra SV, et al. Effects of belimumab, a B lymphocyte stimulator-specific inhibitor, on disease activity across multiple organ domains in patients with systemic lupus erythematosus: combined results from two phase III trials. Ann Rheum Dis. 2012;71:1833–8.

4.1.4

| **CQ compared to placebo for dermatological manifestations of lupus** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| Outcome  № of participants  (studies) | Relative effect  (95% CI) | **Anticipated absolute effects (95% CI)** | | | Quality | What happens |
| **Without Chloroquine** | **With Chloroquine** | **Difference** |
| Flares follow up: 1 years  Number of participants: 23 (1 RCT)) | **RR 0.22** (0.03 a 1.59) | 41.7% | **9.2%** (1.3 a 66.3) | **32.5% less**  (40.4 less to 24.6 more) | ⨁⨁◯◯ LOW 1,2 | Chloroquine may make little or no difference to avoid flares in patients with Lupus with predominant skin compromise |

1. Selective outcomes reporting
2. Optimal information size not met

* Meinão IM, Sato EI, Andrade LE, Ferraz MB, Atra E. Controlled trial with chloroquine diphosphate in systemic lupus erythematosus. Lupus. 1996;5:237–41.
* Williams HJ, Egger MJ, Singer JZ, Willkens RF, Kalunian KC, Clegg DO, et al. Comparison of hydroxychloroquine and placebo in the treatment of the arthropathy of mild systemic lupus erythematosus. J Rheumatol. 1994;21:1457–62.

4.1.5

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| --- | --- | --- | --- | --- | --- | --- |
| **MTX compared to placebo for lupus with predominant skin compromise** | | | | | | |
| Outcome  № of participants  (studies) | Relative effect  (95% CI) | **Anticipated absolute effects (95% CI)** | | | Quality | What happens |
| **Without MTX** | **With MTX** | **Difference** |
| Skin compromise  assessed with: Presence of skin compromise at the end of the study (24 weeks)  № of participants: 28  (1 RCT) | **RR 0.25**  (0.25 to 0.57) | 100.0% | **25.0%**  (25.0 to 57.0) | **75.0% fewer**  (75 fewer to 43 fewer) | ⨁⨁OO  LOW 1,2 | MTX may improve skin compromise |

1. No blinding

2. Optimal information size not met

* Islam MN, Hossain M, Haq SA, Alam MN, Ten Klooster PM, Rasker JJ. Efficacy and safety of methotrexate in articular and cutaneous manifestations of systemic lupus erythematosus. Int J Rheum Dis. 2012;15:62–8.

4.1.6

|  |  |  |  |
| --- | --- | --- | --- |
| **MMF compared to placebo for lupus with predominant skin compromise** | | |  |
| Outcome  № of participants  (studies) | **Impact** | Quality |  |
|  |
| Significant worsening of skin lesions  № of participants: 14  (1 RCT) | No patients presented skin lesion worsening | ⨁⨁◯◯  LOW 1,2 |  |
| Significant improvement of skin lesions (>20%)  № of participants: 15  (1 RCTs) | 2/8 patients in the MMF arm significantly improved vs no patients in the control arm | ⨁◯◯◯  VERY LOW 1,2 |  |

1. No blinding

2. Optimal information size not met

* Mok, C. C. “Mycophenolate Mofetil for Non-Renal Manifestations of Systemic Lupus Erythematosus: A Systematic Review.” Scandinavian Journal of Rheumatology 36, no. 5 (October 2007): 329–37. doi:10.1080/03009740701607042.

4.1.7

| **GCs compared to placebo for lupus with predominant skin compromise** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| Result  Number of participants (Studies ) | Relative effect (95% CI) | **Absolute Effect (95% CI)** | | | Quality | What happens |
| **Without GCs** | **With GCs** | **Difference** |
| Clinical improvement (No Score) follow up: 28 days  Number of participants: 15 (1 RCT) | **RR 0.73** (0.39 a 1.35) | 85.7% | **62.6%** (33.4 to 100.0) | **23.1% less**  (52.3 less to 30 more) | ⨁⨁◯◯ LOW 1,2 | GCs may have little or no effect in clinical improvement in patients with Lupus with predominant skin compromise |
| Flares follow up: 18 months  Number of participants: 41 (1 RCT) | **RR 0.63** (0.12 a 3.41) | 15.0% | **9.4%** (1.8 a 51.1) | **5.5% less**  (13.2 less a 36.1 more) | ⨁⨁◯◯ LOW 1,2 | GCs may slightly reduce flares |
| Severe flares follow up: 18 months  Number of participants: 41 (1 RCT) | **RR 0.19** (0.01 a 3.75) | 10.0% | **1.9%** (0.1 a 37.5) | **8.1% less**  (9.9 less a 27.5 more) | ⨁⨁◯◯ LOW 1,2 | GCs may reduce severe flares |

1. Selective outcome reporting
2. Possible benefits and harms

* Mackworth-Young CG, David J, Morgan SH, Hughes GR. A double blind, placebo controlled trial of intravenous methylprednisolone in systemic lupus erythematosus. Ann Rheum Dis. 1988;47:496–502.
* Tseng C-E, Buyon JP, Kim M, Belmont HM, Mackay M, Diamond B, et al. The effect of moderate-dose corticosteroids in preventing severe flares in patients with serologically active, but clinically stable, systemic lupus erythematosus: findings of a prospective, randomized, double-blind, placebo-controlled trial. Arthritis Rheum. 2006;54:3623–32.

4.2.1

| **Acitretin compared to HCQ for cutaneous lupus** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| Outcome № of participants (studies) | Relative effect (95% CI) | **Anticipated absolute effects (95% CI)** | | | Quality | What happens |
| **Without Acitretin** | **With Acitretin** | **Difference** |
| Complete clearing assessed with: scores for erythema, infiltration and scaling/hyperkeratosis follow up: 8 weeks № of participants: 58 (1 RCT) | **RR 0.77** (0.23 to 2.43) | 23.3% | **18.0%** (5.4 to 56.7) | **5.4% fewer** (18 fewer to 33.4 more) | ⨁⨁◯◯ LOW 1,2 | Acitretin may make little or no difference to complete clearing |
| Marked improvement assessed with: scores for erythema, infiltration and scaling/hyperkeratosis follow up: 8 weeks № of participants: 58 (1 RCT) | **RR 1.07** (0.41 to 2.79) | 26.7% | **28.5%** (10.9 to 74.4) | **1.9% more** (15.7 fewer to 47.7 more) | ⨁⨁◯◯ LOW 1,2 | Acitretin may slightly increase marked improvement |
| Deterioration assessed with: scores for erythema, infiltration and scaling/hyperkeratosis follow up: 8 weeks № of participants: 58 (1 RCT) | In Acitretin arm 6 patients worsened. No patient worsened in Hydroxychloroquine arm. | | | | ⨁◯◯◯ VERY LOW 1,2,3 |  |
| Adverse events requiring additional treatment follow up: 8 weeks № of participants: 58 (1 RCT) | **RR 1.50** (0.75 to 3.06) | 33.3% | **50.0%** (25.0 to 100.0) | **16.7% more** (8.3 fewer to 68.7 more) | ⨁⨁◯◯ LOW 1,2 | Acitretin may increase adverse events requiring additional treatment |

1. Risk of bias
2. Wide confidence intervals include significant benefit and harm
3. Very few events

* Ruzicka T, Sommerburg C, Goerz G, Kind P, Mensing H. Treatment of cutaneous lupus erythematosus with acitretin and hydroxychloroquine. Br J Dermatol. 1992;127:513–8.

4.2.2

| **CsA compared to AZA for dermatological manifestations of lupus** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| Result  Number of participants (Studies ) | Relative effect (95% CI) | **Absolute Effect(95% CI)** | | | Quality | What happens |
| **without Cyclosporine** | **with Cyclosporine** | **Difference** |
| Lupus Rash follow up: 1 year  Number of participants: 33 (1 RCT) | **RR 1.25** (0.43 a 3.62) | 26.7% | **33.3%** (11.5 a 96.5) | **6.7% more**  (15.2 less a 69.9 more ) | ⨁⨁◯◯ LOW 1,2 | Cyclosporine may have little or no effect in Lupus Rash improvement in patients with Lupus with predominant skin compromise |
| Mouth ulcers follow up: 1 year Number of participants: 33 (1 RCT) | **RR 0.14** (0.02 a 1.03) | 40.0% | **5.6%** (0.8 a 41.2) | **34.4% less**  (39.2 less a 1.2 more ) | ⨁⨁◯◯ LOW 1,2 | Cyclosporine may reduce mouth ulcers |

1. Open-label trial
2. Possible benefits or harms. Small number of participants

* Griffiths B, Emery P, Ryan V, Isenberg D, Akil M, Thompson R, et al. The BILAG multi-centre open randomized controlled trial comparing ciclosporin vs azathioprine in patients with severe SLE. Rheumatology. 2010;49:723–32.

4.2.3

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Clofazimine compared to CQ for lupus with predominant skin compromise** | | | | | | |
| Outcome  № of participants  (studies) | Relative effect  (95% CI) | **Anticipated absolute effects (95% CI)** | | | Quality | What happens |
| **Without Clofazimine** | **With Clofazimine** | **Difference** |
| Good response  assessed with: >5 in a score of improvement (range 0-6)  Follow up: 6 month  № of participants: 33  (1 RCT) | **RR 0.91**  (0.65 to 1.33) | 82.4% | **74.9%**  (53.5 to 100.0) | **7.4% fewer**  (28.8 fewer to 27.2 more) | ⨁⨁◯◯  LOW 1 | Clofazimine may make little or no difference compared with chloroquine |
| Complete response  assessed with: Score 6 Follow up:6 month  № of participants: 33  (1 RCT) | **RR 0.45**  (0.10 to 1.60) | 58.8% | **26.5%**  (5.9 to 94.1) | **32.4% fewer**  (52.9 fewer to 35.3 more) | ⨁⨁◯◯  LOW 1 | Clofazimine may reduce the probability of complete response compared with chloroquine |

1. CI95% that includes significant benefits and harms

* Bezerra ELM, Vilar MJP, da Trindade Neto PB, Sato EI. Double-blind, randomized, controlled clinical trial of clofazimine compared with chloroquine in patients with systemic lupus erythematosus. Arthritis Rheum. 2005;52:3073–8.

4.2.4

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **MMF compared to CYC for lupus with predominant skin compromise** | | | | | | |
| Outcome  № of participants  (studies) | Relative effect  (95% CI) | **Anticipated absolute effects (95% CI)** | | | Quality | What happens |
| **Without MMF** | **With MMF** | **Difference** |
| Response  assessed with: BILAG C or D  follow up: 24 weeks  № of participants: 107  (1 RCT) | **RR 1.13**  (0.89 to 1.42) | 70.6% | **79.8%**  (62.8 to 100.0) | **9.2% more**  (7.8 fewer to 29.6 more) | ⨁⨁◯◯  LOW 1 | MMF may increase the probability of response |

1. 95%CI that includes absence of benefits

* Isenberg D, Gordon C, Licu D, Copt S, Rossi CP, Wofsy D. Efficacy and safety of atacicept for prevention of flares in patients with moderate-to-severe systemic lupus erythematosus (SLE): 52-week data (APRIL-SLE randomised trial). Ann Rheum Dis. 2015;74:2006–15.

4.2.5

| **MTX compared to CQ for dermatological manifestations of lupus** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| Outcome  Number of participants (Studies ) | Relative effect (95% CI) | **Anticipated Absolute Effect(95% CI)** | | | Quality | What happens |
| **Without MTX** | **With MTX** | **Difference** |
| Proportion of patients with significant clinical improvement follow up: 6 months  Number of participants: 41 (1 RCT) | **RR 1.07** (0.82 a 1.41) | 80.8% | **86.4%** (66.2 a 100.0) | **5.7% more**  (14.5 less a 33.1 more ) | ⨁⨁◯◯ LOW 1,2 | MTX may have little or no effect in clinical improvement in patients with lupus with predominant skin compromise |

1. Open label study
2. Possible benefits or harms. Small number of events

* Islam MN, Hossain M, Haq SA, Alam MN, Ten Klooster PM, Rasker JJ. Efficacy and safety of methotrexate in articular and cutaneous manifestations of systemic lupus erythematosus. Int J Rheum Dis. 2012;15:62–8.

4.3.1

| **Active treatment compared to symptomatic treatment for chilblain SLE** | | |
| --- | --- | --- |
| Outcome № of participants (studies) | **Impact** | Quality |
| Survival № of participants: 133 (20 observational studies) | Considering patients with SLE diagnosis or who developed SLE during follow up:  In 45% (19 of 42) episodes were AMs2 were used, resulted in improvement of the lesions.  In 54% (7 of 13) episodes were systemic GCs3 were used, resulted in improvement of the lesions  In 26% (6 of 23) episodes were topical GCs were used, resulted in improvement of the lesions  Other interventions have been less reported in case reports and case series (i.e. lenalidomide, fumaric acid, dapsone, AZA, MMF)  In patients with diagnosis of sarcoidosis and lupus pernio, similar results were observed. | ⨁◯◯◯ VERY LOW 1 |

1. Case reports and case series
2. GCs doses were heterogeneous. More frequent initial doses were prednisolone 1 - 2 mg/kg/day.
3. Most frequent AMs was HCQ (200mg bid)

* Bansal S, Goel A. Chilblain lupus erythematosus in an adolescent girl. Indian Dermatology Online Journal. 2014;5:30.
* Boehm I, Bieber T. Chilblain lupus erythematosus Hutchinson: successful treatment with mycophenolate mofetil. Arch Dermatol. 2001;137:235–6.
* Bouaziz JD, Barete S, Le Pelletier F, Amoura Z, Piette JC, Francès C. Cutaneous lesions of the digits in systemic lupus erythematosus: 50 cases. Lupus. 2007;16:163–7.
* Cappel JA, Wetter DA. Clinical Characteristics, Etiologic Associations, Laboratory Findings, Treatment, and Proposal of Diagnostic Criteria of Pernio (Chilblains) in a Series of 104 Patients at Mayo Clinic, 2000 to 2011. Mayo Clinic Proceedings. 2014;89:207–15.
* Cavazzana I, Sala R, Bazzani C, Ceribelli A, Zane C, Cattaneo R, et al. Treatment of lupus skin involvement with quinacrine and hydroxychloroquine. Lupus. 2009;18:735–9.
* Chan Y, Tang WYM, Lam WY, Loo SKF, Li SPS, Au AWM, et al. A cluster of chilblains in Hong Kong. Hong Kong Med J. 2008;14:185–91.
* Cosnes A. Low Blood Concentration of Hydroxychloroquine in Patients With Refractory Cutaneous Lupus Erythematosus: A French Multicenter Prospective Study. Archives of Dermatology. 2012;148:479.
* Dalm VASH, van Hagen PM. Efficacy of Lenalidomide in Refractory Lupus Pernio. JAMA Dermatology. 2013;149:493.
* Doutre MS, Beylot C, Beylot J, Pompougnac E, Royer P. Chilblain lupus erythematosus: report of 15 cases. Dermatology (Basel). 1992;184:26–8.
* Fisher DA, Everett MA. Violaceous rash of dorsal fingers in a woman. Diagnosis: chilblain lupus erythematosus (perniosis). Arch Dermatol. 1996;132:459, 462.
* Günther C, Meurer M, Stein A, Viehweg A, Lee-Kirsch MA. Familial chilblain lupus; a monogenic form of cutaneous lupus erythematosus due to a heterozygous mutation in TREX1. Dermatology. 2009;219(2):162–6.
* Khaitan BK, Sood A, Mittal R, Singh YL, Singh MK. Chilblain lupus erythematosus mimicking acrofacial vitiligo. Indian J Dermatol Venereol Leprol. 2003;69:340–2.
* Lavigne C, Maillot F, Machet L, Lorette G, Vaillant L. Lethal pancytopenia associated with chilblain lupus erythematosus. Acta Derm Venereol. 2000;80:393.
* Millard LG, Rowell NR. Chilblain lupus erythematosus (Hutchinson). A clinical and laboratory study of 17 patients. Br J Dermatol. 1978;98:497–506.
* Mireku KA, Glover MHB, Davis L. Tender Macules and Papules on the Toes. JAMA Dermatology. 2014;150:329.
* Patel S, Hardo F. Chilblain lupus erythematosus. Case Reports. 2013 Nov 27;2013
* Pisoni CN, Obermoser G, Cuadrado MJ, Sanchez FJ, Karim Y, Sepp NT, et al. Skin manifestations of systemic lupus erythematosus refractory to multiple treatment modalities: poor results with mycophenolate mofetil. Clin Exp Rheumatol. 2005;23:393–6.
* Pock L, Petrovská P, Becvár R, Mandys V, Hercogová J. Verrucous form of chilblain lupus erythematosus. J Eur Acad Dermatol Venereol. 2001;15:448–51.
* Stagaki E, Mountford WK, Lackland DT, Judson MA. The Treatment of Lupus Pernio. Chest. 2009;135:468–76.
* Viguier M, Pinquier L, Cavelier-Balloy B, de la Salmonière P, Cordoliani F, Flageul B, et al. Clinical and histopathologic features and immunologic variables in patients with severe chilblains. A study of the relationship to lupus erythematosus. Medicine (Baltimore). 2001;80:180–8.

4.4.1

| **Flucinonide cream compared to hydrocortisone cream for discoid lupus** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| Outcome № of participants (studies) | Relative effect (95% CI) | **Anticipated absolute effects (95% CI)** | | | Quality | What happens |
| **Without Flucinonide** | **With Flucinonide** | **Difference** |
| Resolution of skin lesions № of participants: 78 (1 RCT) | **RR 2.77** (0.95 to 8.08) | 9.76% | **27.0%** (9.3 to 78.8) | **17.3% more** (0.5 fewer to 69.1 more) | ⨁⨁◯◯ LOW 1,2 | Flucinonide may increase the probability of skin lesions resolution |

1. Few patients and events
2. Risk of bias

* Roenigk HH, Martin JS, Eichorn P, Gilliam JN. Discoid lupus erythematosus. Diagnostic features and evaluation of topical corticosteroid therapy. Cutis. 1980;25:281–5.

4.4.2

| **Acitretin compared to HCQ for discoid lupus** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| Outcome № of participants (studies) | Relative effect (95% CI) | **Anticipated absolute effects (95% CI)** | | | Quality | What happens |
| **Without Acitretin** | **With Acitretin** | **Difference** |
| Resolution of skin lesions № of participants: 58 (1 RCT) | **RR 0.93** (0.54 to 1.59) | 45.5%1 | **42.3%** (24.6 to 72.3) | **3.2% fewer** (20.9 fewer to 26.8 more) | ⨁⨁◯◯ LOW 2,3,4 | Acitretin may make little or no difference to the probability of skin lesions resolution |

1. Basal risk provided by: Wahie, S., and S.J. Meggitt. 2013. “Long-Term Response to Hydroxychloroquine in Patients with Discoid Lupus Erythematosus.” British Journal of Dermatology 169 (3): 653–59.
2. Few patients and events
3. Risk of bias
4. Other types of CLE were included in the trial

* Ruzicka T, Sommerburg C, Goerz G, Kind P, Mensing H. Treatment of cutaneous lupus erythematosus with acitretin and hydroxychloroquine. Br J Dermatol. 1992;127:513–8.
* Wahie S, Daly AK, Cordell HJ, Goodfield MJ, Jones SK, Lovell CR, et al. Clinical and Pharmacogenetic Influences on Response to Hydroxychloroquine in Discoid Lupus Erythematosus: A Retrospective Cohort Study. Journal of Investigative Dermatology. 2011;1311981–6.

4.5.1

| **AZA for resistant SLE** | | |
| --- | --- | --- |
| Outcome № of participants (studies) | **Impact** | Quality |
| Response № of participants: 9 (observational studies) | In 9 cases (5 subacute and 4 discoid) 5 achieved complete response and 2 partial response | ⨁◯◯◯ VERY LOW 1 |

1. Case reports and case series
2. Doses ranged between 100mg and 150 mg/day

* Ashinoff R, Werth VP, Franks AG. Resistant discoid lupus erythematosus of palms and soles: successful treatment with azathioprine. J Am Acad Dermatol. 1988;19:961–5.
* Callen JP, Spencer LV, Burruss JB, Holtman J. Azathioprine. An effective, corticosteroid-sparing therapy for patients with recalcitrant cutaneous lupus erythematosus or with recalcitrant cutaneous leukocytoclastic vasculitis. Arch Dermatol. 1991;127:515–22.
* Shehade S. Successful treatment of generalized discoid skin lesions with azathioprine. Arch Dermatol. 1986;122:376–7.
* Tsokos GC, Caughman SW, Klippel JH. Successful treatment of generalized discoid skin lesions with azathioprine. Its use in a patient with systemic lupus erythematosus. Arch Dermatol. 1985;121:1323–5.

4.5.2

| **CYC for resistant SLE** | | |
| --- | --- | --- |
| Outcome № of participants (studies) | **Impact** | Quality |
| Response № of participants: 8 (observational studies) | In 8 cases (6 subacute SLE, 2 discoid SLE) 4 achieved complete response and 2 partial response | ⨁◯◯◯ VERY LOW 1 |

1. Case reports and case series
2. Doses ranged between 100mg and 200 mg/day

* Klein A, Vogt T, Wenzel SM, Fleck M, Landthaler M. Cyclosporin combined with methotrexate in two patients with recalcitrant subacute cutaneous lupus erythematosus: Double immunosuppression in lupus disease. Australasian Journal of Dermatology. 2011;52:43–7.
* Raptopoulou A, Linardakis C, Sidiropoulos P, Kritikos H, Boumpas D. Pulse cyclophosphamide treatment for severe refractory cutaneous lupus erythematosus. Lupus. 2010;19:744–7.

4.5.3

| **Fumaric acid for resistant SLE** | | |
| --- | --- | --- |
| Outcome № of participants (studies) | **Impact** | Quality |
| Response № of participants: 11 (1 observational study) | In 11 cases (1 subacute SLE, 10 discoid SLE), after 24 weeks of treatment with FAEs, the total RCLASI activity score and the RCLASI activity score for skin lesions were still significantly decreased compared to the scores at baseline | ⨁◯◯◯ VERY LOW 1 |

1. Case series
2. Doses ranged between 100mg and 200 mg/day

* Kuhn A, Landmann A, Patsinakidis N, Ruland V, Nozinic S, Perusquia Ortiz AM, et al. Fumaric acid ester treatment in cutaneous lupus erythematosus (CLE): a prospective, open-label, phase II pilot study. Lupus. Oct 1;25:1357–64.

4.5.4

| **HCQ incremental dose for resistant SLE** | | |
| --- | --- | --- |
| Outcome № of participants (studies) | **Impact** | Quality |
| Response № of participants: 34 (1 observational study) | In 34 patients, increasing the dose to reach blood concentrations greater than 750 ng/mL, produced improvement of CLASI score of 4 points or 20%, in 26 (81%) of them. | ⨁◯◯◯ VERY LOW 1 |

1. Case series
2. Doses ranged between 100mg and 200 mg/day

* Chasset F, Arnaud L, Costedoat-Chalumeau N, Zahr N, Bessis D, Francès C. The effect of increasing the dose of hydroxychloroquine (HCQ) in patients with refractory cutaneous lupus erythematosus (CLE): An open-label prospective pilot study. Journal of the American Academy of Dermatology. 2016;74:693–699.e3.

4.5.5

| **Isotretinoin for resistant SLE** | | |
| --- | --- | --- |
| Outcome № of participants (studies) | **Impact** | Quality |
| Response № of participants: 7 (2 observational studies) | In 7 cases (1 subacute SLE, 5 discoid SLE) 2 achieved complete response | ⨁◯◯◯ VERY LOW 1 |

1. Case series
2. Dose: 1mg/kg

* D’Erme AM, Milanesi N, Difonzo EM, Lotti T, Gola M. Treatment of refractory subacute cutaneous lupus erythematosus with oral isotretinoin: A valid therapeutic option. Dermatologic Therapy. 2012;25:281–2.
* Shornick JK, Formica N, Parke AL. Isotretinoin for refractory lupus erythematosus. J Am Acad Dermatol. 1991;24:49–52.

4.5.6

| **IVIG for resistant SLE** | | |
| --- | --- | --- |
| Outcome № of participants (studies) | **Impact** | Quality |
| Response № of participants: 26 (1 observational study) | In 26 cases (7 subacute SLE, 5 discoid SLE), 6 achieved complete response and 12 partial response | ⨁◯◯◯ VERY LOW 1 |

1. Case series
2. Dose: 400 mg/kg/day for 5 days

* Camara I, Sciascia S, Simoes J, Pazzola G, Salas V, Karim Y, et al. Treatment with intravenous immunoglobulins in systemic lupus erythematosus: a series of 52 patients from a single centre. Clin Exp Rheumatol. 2014;32:41–7.

4.5.7

| **Lenalidomide for resistant SLE** | | |
| --- | --- | --- |
| Outcome № of participants (studies) | **Impact** | Quality |
| Response № of participants: 38 (4 observational studies) | In 38 cases (16 subacute SLE, 14 discoid SLE), 15 achieved complete response and 18 partial response | ⨁◯◯◯ VERY LOW 1 |

1. Case reports and case series
2. Dose ranged between 5mg every other day and 10mg/day

* Braunstein I, Goodman NG, Rosenbach M, Okawa J, Shah A, Krathen M, et al. Lenalidomide therapy in treatment-refractory cutaneous lupus erythematosus: Histologic and circulating leukocyte profile and potential risk of a systemic lupus flare. Journal of the American Academy of Dermatology. 2012;66:571–82.
* Cortés-Hernández J, Ávila G, Vilardell-Tarrés M, Ordi-Ros J. Efficacy and safety of lenalidomide for refractory cutaneous lupus erythematosus. Arthritis Research & Therapy. 2012;14:R265.
* Fennira F, Chasset F, Soubrier M, Cordel N, Petit A, Francès C. Lenalidomide for refractory chronic and subacute cutaneous lupus erythematosus: 16 patients. Journal of the American Academy of Dermatology. 2016;74:1248–51.
* Shah A, Albrecht J, Bonilla-Martinez Z, Okawa J, Rose M, Rosenbach M, et al. Lenalidomide for the Treatment of Resistant Discoid Lupus Erythematosus. Archives of Dermatology [Internet]. 2009 Mar 1 [cited 2016 Nov 18];145(3). Available from: http://archderm.jamanetwork.com/article.aspx?doi=10.1001/archdermatol.2009.30

4.5.8

| **Mepacrine / Quinacrine for resistant SLE** | | |
| --- | --- | --- |
| Outcome № of participants (studies) | **Impact** | Quality |
| Response № of participants: 44 (4 observational studies) | In 44 cases (13 subacute SLE, 28 discoid SLE) 18 achieved complete response and 14 partial response | ⨁◯◯◯ VERY LOW 1 |

1. Case reports and case series
2. Dose ranged between 100mg and 200mg/day

* Benoit, S, and M Goebeler. 2015. “Mepacrine in Recalcitrant Cutaneous Lupus Erythematosus: Old-Fashioned or Still Useful?” Acta Dermato Venereologica 95 (5): 596–99. doi:10.2340/00015555-2031.
* Feldmann, R., D. Salomon, and J. H. Saurat. 1994. “The Association of the Two Antimalarials Chloroquine and Quinacrine for Treatment-Resistant Chronic and Subacute Cutaneous Lupus Erythematosus.” Dermatology (Basel, Switzerland) 189 (4): 425–27.
* González-Sixto, B., I. García-Doval, R. Oliveira, C. Posada, M. A. García-Cruz, and M. Cruces. 2010. “[Quinacrine in the treatment of cutaneous lupus erythematosus: practical aspects and a case series].” Actas Dermo-Sifiliograficas 101 (1): 54–58.
* Lipsker, D., J. C. Piette, P. Cacoub, P. Godeau, and C. Frances. 1995. “Chloroquine-Quinacrine Association in Resistant Cutaneous Lupus.” Dermatology (Basel, Switzerland) 190 (3): 257–58.

4.5.9

| **MMF for resistant SLE** | | |
| --- | --- | --- |
| Outcome № of participants (studies) | **Impact** | Quality |
| Response № of participants: 49 (6 observational studies) | In 49 cases (5 subacute SLE, 21 discoid SLE) 24 achieved complete response and 17 partial response | ⨁◯◯◯ VERY LOW 1 |

1. Case reports and case series
2. Dose ranged between 500 mg and 1gr

* Gammon B, Hansen C, Costner MI. Efficacy of mycophenolate mofetil in antimalarial-resistant cutaneous lupus erythematosus. Journal of the American Academy of Dermatology. 2011;65:717–721.e2.
* Goyal S, Nousari HC. Treatment of resistant discoid lupus erythematosus of the palms and soles with mycophenolate mofetil. Journal of the American Academy of Dermatology. 2001;45:142–4.
* Hanjani NM, Nousari CH. Mycophenolate mofetil for the treatment of cutaneous lupus erythematosus with smoldering systemic involvement. Arch Dermatol. 2002;138:1616–8.
* Kreuter A, Tomi NS, Weiner SM, Huger M, Altmeyer P, Gambichler T. Mycophenolate sodium for subacute cutaneous lupus erythematosus resistant to standard therapy. British Journal of Dermatology. 2007;156:1321–7.
* Pisoni CN, Obermoser G, Cuadrado MJ, Sanchez FJ, Karim Y, Sepp NT, et al. Skin manifestations of systemic lupus erythematosus refractory to multiple treatment modalities: poor results with mycophenolate mofetil. Clin Exp Rheumatol. 2005;23:393–6.
* Schanz S, Ulmer A, Rassner G, Fierlbeck G. Successful treatment of subacute cutaneous lupus erythematosus with mycophenolate mofetil. Br J Dermatol. 2002;147:174–8.

4.5.10

| **MTX for resistant SLE** | | |
| --- | --- | --- |
| Outcome № of participants (studies) | **Impact** | Quality |
| Response № of participants: 57 (4 observational studies) | In 57 cases (26 subacute SLE, 11 discoid SLE) 8 achieved complete response and 46 partial response | ⨁◯◯◯ VERY LOW 1 |

1. Case reports and case series
2. Doses ranged between 12.5 and 25mg/week.

* Boehm IB, Boehm GA, Bauer R. Management of cutaneous lupus erythematosus with low-dose methotrexate: indication for modulation of inflammatory mechanisms. Rheumatol Int. 1998;18:59–62.
* Böhm L, Uerlich M, Bauer R. Rapid improvement of subacute cutaneous lupus erythematosus with low-dose methotrexate. Dermatology (Basel). 1997;194:307–8.
* Kuhn A, Specker C, Ruzicka T, Lehmann P. Methotrexate treatment for refractory subacute cutaneous lupus erythematosus. J Am Acad Dermatol. 2002;46:600–3.
* Wenzel J, Brahler S, Bauer R, Bieber T, Tuting T. Efficacy and safety of methotrexate in recalcitrant cutaneous lupus erythematosus: results of a retrospective study in 43 patients. British Journal of Dermatology. 2005;153:157–62.

4.5.11

| **Topical calcineurin inhibitors or topical GCs for resistant SLE** | | |
| --- | --- | --- |
| Outcome № of participants (studies) | **Impact** | Quality |
| Response № of participants: 20 (1 RCT) | In a randomized trial of TAC 0.1% vs clobetasol 0.05%, there was no significant difference between TAC and clobetasol. However, compared with TAC, 11 patients (61%) developed telangiectasia on the clobetasol side as early as week 3 (P < 0.05)  Similar results were seen in observational studies | ⨁◯◯◯ VERY LOW 1,2 |
| Response № of participants: 92585 (1 observational study) | In a cohort of 92585 pimecrolimus users, no increase in the risk of lymphoma was observed compared to other topical agents. | ⨁⨁◯◯ LOW |

1. Risk of bias
2. Wide confidence intervals include benefit and harm

* Böhm M, Gaubitz M, Luger TA, Metze D, Bonsmann G. Topical tacrolimus as a therapeutic adjunct in patients with cutaneous lupus erythematosus. A report of three cases. Dermatology (Basel). 2003;207:381–5.
* de la Rosa Carrillo D, Christensen OB. Treatment of chronic discoid lupus erythematosus with topical tacrolimus. Acta Derm Venereol. 2004;84:233–4.
* Drüke A, Gambichler T, Altmeyer P, Freitag M, Kreuter A. 0.1% Tacrolimus ointment in a patient with subacute cutaneous lupus erythematosus. Journal of Dermatological Treatment. 2004;15:63–4.
* Heffernan MP, Nelson MM, Smith DI, Chung JH. 0.1% Tacrolimus Ointment in the Treatment of Discoid Lupus Erythematosus. Archives of Dermatology [Internet]. 2005 [cited 2016 Nov 18];141(9). Available from: http://archderm.jamanetwork.com/article.aspx?doi=10.1001/archderm.141.9.1170
* Lampropoulos CE. Topical tacrolimus therapy of resistant cutaneous lesions in lupus erythematosus: a possible alternative. Rheumatology. 2004;43:1383–5.
* Madan V, August PJ, Chalmers RJG. Efficacy of topical tacrolimus 0.3% in clobetasol propionate 0.05% ointment in therapy-resistant cutaneous lupus erythematosus: a cohort study: Efficacy of topical tacrolimus in clobetasol proprionate ointment for therapy-resistant LE. Clinical and Experimental Dermatology. 2010;35:27–30.
* Schneeweiss S, Doherty M, Zhu S, Funch D, Schlienger RG, Fernandez-Vidaurre C, et al. Topical Treatments with Pimecrolimus, Tacrolimus and Medium- to High-Potency Corticosteroids, and Risk of Lymphoma. Dermatology. 2009;219:7–21.
* Sugano M, Shintani Y, Kobayashi K, Sakakibara N, Isomura I, Morita A. Successful treatment with topical tacrolimus in four cases of discoid lupus erythematosus. The Journal of Dermatology. 2006;33:887–91.
* Tlacuilo-Parra A. Pimecrolimus 1% cream for the treatment of discoid lupus erythematosus. Rheumatology. 2005;44:1564–8.
* Tzung T-Y, Liu Y-S, Chang H-W. Tacrolimus vs. clobetasol propionate in the treatment of facial cutaneous lupus erythematosus: a randomized, double-blind, bilateral comparison study. British Journal of Dermatology. 2007;156:191–2.
* Walker SL, Kirby B, Chalmers RJG. The effect of topical tacrolimus on severe recalcitrant chronic discoid lupus erythematosus. Br J Dermatol. 2002;147:405–6.
* Yoshimasu T, Ohtani T, Sakamoto T, Oshima A, Furukawa F. Topical FK506 (tacrolimus) therapy for facial erythematous lesions of cutaneous lupus erythematosus and dermatomyositis. Eur J Dermatol. 2002;12:50–2.

4.5.12

| **RTX for resistant SLE** | | |
| --- | --- | --- |
| Outcome № of participants (studies) | **Impact** | Quality |
| Response № of participants: 87 (6 observational studies) | In 87 cases, 38 achieved complete response and 14 partial response | ⨁◯◯◯ VERY LOW 1 |

1. Case reports and case series
2. Dose: 375 mg/m2 was the more frequent

* Alsanafi S, Kovarik C, Mermelstein AL, Werth VP. Rituximab in the Treatment of Bullous Systemic Lupus Erythematosus: Journal of Clinical Rheumatology. 2011;17:142–4.
* Cieza-Díaz DE, Avilés-Izquierdo JA, Ceballos-Rodríguez C, Suárez-Fernández R. Lupus eritematoso cutáneo subagudo refractario tratado con rituximab. Actas Dermo-Sifiliográficas. 2012;103:555–7.
* Kieu V, O’Brien T, Yap L-M, Baker C, Foley P, Mason G, et al. Refractory subacute cutaneous lupus erythematosus successfully treated with rituximab. Australasian Journal of Dermatology. 2009 Aug;50(3):202–6.
* Ramos-Casals M, García-Hernández FJ, de Ramón E, Callejas JL, Martínez-Berriotxoa A, Pallarés L, et al. Off-label use of rituximab in 196 patients with severe, refractory systemic autoimmune diseases. Clin Exp Rheumatol. 2010;28:468–76.
* Terrier B, Amoura Z, Ravaud P, Hachulla E, Jouenne R, Combe B, et al. Safety and efficacy of rituximab in systemic lupus erythematosus: Results from 136 patients from the French autoimmunity and rituximab registry. Arthritis & Rheumatism. 2010;62:2458–66.
* Uthman I, Taher A, Abbas O, Menassa J, Ghosn S. Successful Treatment of Refractory Skin Manifestations of Systemic Lupus Erythematosus with Rituximab: Report of a Case. Dermatology. 2008;216:257–9.

4.5.13

| **Thalidomide for resistant SLE** | | |
| --- | --- | --- |
| Outcome № of participants (studies) | **Impact** | Quality |
| Response № of participants: 238 (7 observational studies) | In 238 cases (78 subacute SLE, 84 discoid SLE) 172 achieved complete response and 27 partial response  In considered cases, discontinuation due to adverse events was reported in up to 20% of the cases, and some degree of sensory axonal polyneuropathy in up to 71.4% | ⨁◯◯◯ VERY LOW 1 |

1. Case reports and case series
2. Doses ranged between 12.5 mg and 100 mg/day

* Baret I, De Haes P. Thalidomide: Still an important second-line treatment in refractory cutaneous lupus erythematosus? Journal of Dermatological Treatment. 2015;26:173–7.
* Briani C, Zara G, Rondinone R, Iaccarino L, Ruggero S, Toffanin E, et al. Positive and negative effects of thalidomide on refractory cutaneous lupus erythematosus. Autoimmunity. 2005;38:549–55.
* Coelho A, Souto MID, Cardoso CRL, Salgado DR, Schmal TR, Waddington Cruz M, et al. Long-term thalidomide use in refractory cutaneous lesions of lupus erythematosus: a 65 series of Brazilian patients. Lupus. 2005;14:434–9.
* Cortés-Hernández J, Torres-Salido M, Castro-Marrero J, Vilardell-Tarres M, Ordi-Ros J. Thalidomide in the treatment of refractory cutaneous lupus erythematosus: prognostic factors of clinical outcome: Thalidomide in refractory CLE. British Journal of Dermatology. 2012;166:616–23.
* Housman TS, Jorizzo JL, McCarty MA, Grummer SE, Fleischer AB, Sutej PG. Low-dose thalidomide therapy for refractory cutaneous lesions of lupus erythematosus. Arch Dermatol. 2003;139:50–4.
* Ordi-Ros J, Cortés F, Cucurull E, Mauri M, Buján S, Vilardell M. Thalidomide in the treatment of cutaneous lupus refractory to conventional therapy. J Rheumatol. 2000;27:1429–33.
* Sato EI, Assis LS, Lourenzi VP, Andrade LE. Long-term thalidomide use in refractory cutaneous lesions of systemic lupus erythematosus. Rev Assoc Med Bras (1992). 1998;44:289–93.

5.1.1

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| --- | --- | --- | --- |
| **AZA compared to placebo for neuropsychiatric SLE** | | |  |
| Outcome  № of participants  (studies) | **Impact** | Quality |  |
|  |
| Long term benefit  № of participants: 54  (1 observational study) | Significantly less patients treated with AZA died or were hospitalized | ⨁◯◯◯  VERY LOW 2 |  |
| Short term benefit  № of participants: 24  (1 RCT) | No benefit was observed with the indication of AZA | ⨁◯◯◯  VERY LOW 1,2 |  |

1. Inappropriate allocation concealment

2. Optimal information size not met

* Hahn BH, Kantor OS, Osterland CK. Azathioprine plus prednisone compared with prednisone alone in the treatment of systemic lupus erythematosus. Report of a prospective controlled trial in 24 patients. Ann Intern Med. 1975;83:597–605.
* Ginzler E, Sharon E, Diamond H, Kaplan D. Long-term maintenance therapy with azathioprine in systemic lupus erythematosus. Arthritis Rheum. 1975;18:27–34.

5.1.2

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| --- | --- | --- | --- | --- | --- | --- |
| Belimumab **compared to placebo for neuropsychiatric lupus** | | | | | | |
| Outcome  № of participants  (studies) | Relative effect  (95% CI) | **Anticipated absolute effects (95% CI)** | | | Quality | What happens |
| **Without** belimumab | **With** belimumab | **Difference** |
| Improvement  Assessed with: BILAG  Follow up: 52 weeks  № of participants: 21  (1 RCT) | **RR 0.72**  (0.42 to 1.24) | 83.3% | **60.0%**  (35.0 to 100.0) | **23.3% fewer**  (48.3 fewer to 20 more) | ⨁◯◯◯  VERY LOW 1,2 | It is uncertain if belimumab improves neuropsychiatric lupus symptoms |
| Improvement  Assessed with: SLEDAI  follow up: 52 weeks  № of participants: 21  (1 RCT) | Improvement rates were 20.0% for placebo arm and 100%/69.2% for belimumab arms | | | | ⨁◯◯◯  VERY LOW 1,2 | It is uncertain if belimumab improves neuropsychiatric lupus symptoms |

1. Patients with serious neurological symptoms were excluded

2. 95%CI including benefits and harms

* Manzi S, Sánchez-Guerrero J, Merrill JT, Furie R, Gladman D, Navarra SV, et al. Effects of belimumab, a B lymphocyte stimulator-specific inhibitor, on disease activity across multiple organ domains in patients with systemic lupus erythematosus: combined results from two phase III trials. Ann Rheum Dis. 2012;71:1833–8..

5.1.3

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **CYC compared to placebo for neuropsychiatric lupus** | | | | | | |
| Outcome  № of participants  (studies) | Relative effect  (95% CI) | **Anticipated absolute effects (95% CI)** | | | Quality | What happens |
| **Without CYC** | **With CYC** | **Difference** |
| Treatment failure  № of participants: 92  (2 RCTs) | **RR 0.28**  (0.05 to 1.56) | 66.7% | **18.7%**  (3.3 to 100.0) | **48.0% fewer**  (63.3 fewer to 37.3 more) | ⨁⨁◯◯  LOW 1,2 | CYC may decrease the risk of treatment failure |
| Relapse  № of participants: 60  (1 RCT) | **RR 0.51**  (0.32 to 0.83) | 73.9% | **37.7%**  (23.7 to 61.3) | **36.2% fewer**  (50.3 fewer to 12.6 fewer) | ⨁⨁◯◯  LOW 2,3 | CYC may decrease the risk of relapse |
| EEG improvement  № of participants: 43  (1 RCT) | **RR 4.13**  (1.16 to 14.68) | 18.2% | **75.1%**  (21.1 to 100.0) | **56.9% more**  (2.9 more to 248.7 more) | ⨁⨁◯◯  LOW 2,3 | CYC may increase the risk of EEG improvement |

1. 95%CI includes benefits and absence of benefits

2. One of the studies had adequate sequence generation, but the allocation concealment was not considered to be adequate. Blinding was not reported. Incomplete data were not addressed adequately. The study was not considered to be free from other bias as only 32 patients were randomised in blocks of 10 and the trial stopped recruiting early due to apparent benefit. The other study did not reported sequence generation nor blinding.

3. Optimal information size not met

* Barile-Fabris L, Ariza-Andraca R, Olguín-Ortega L, Jara LJ, Fraga-Mouret A, Miranda-Limón JM, et al. Controlled clinical trial of IV cyclophosphamide versus IV methylprednisolone in severe neurological manifestations in systemic lupus erythematosus. Ann Rheum Dis. 2005;64:620–5.
* Stojanovich L, Stojanovich R, Kostich V, Dzjolich E. Neuropsychiatric lupus favourable response to low dose i.v. cyclophosphamide and prednisolone (pilot study). Lupus. 2003;12:3–7.

5.1.4

|  |  |  |  |
| --- | --- | --- | --- |
| **IVIG compared to placebo for neuropsychiatric SLE** | | |  |
| Outcome  № of participants  (studies) | **Impact** | Quality |  |
|  |
| Clinical response  № of participants: 17  (2 observational studies) | 6 Patients presented total remission and 8 patients partial remission | ⨁◯◯◯  VERY LOW 1 |  |

1. Optimal information size not met

* Camara I, Sciascia S, Simoes J, Pazzola G, Salas V, Karim Y, et al. Treatment with intravenous immunoglobulins in systemic lupus erythematosus: a series of 52 patients from a single centre. Clin Exp Rheumatol. 2014;32:41–7.
* Milstone AM, Meyers K, Elia J. Treatment of acute neuropsychiatric lupus with intravenous immunoglobulin (IVIG): a case report and review of the literature. Clin Rheumatol. 2005;24:394–7.

5.1.5

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **TPE compared to reinfusion apheresis or placebo for neuropsychiatric lupus** | | | | | | |
| Outcome  № of participants  (studies) | Relative effect  (95% CI) | **Anticipated absolute effects (95% CI)** | | | Quality | What happens |
| **Without TPE** | **With TPE** | **Difference** |
| Clinical improvement  № of participants: 18  (1 RCT) | **RR 4.00**  (0.64 to 25.02) | 16.7% | **66.7%**  (10.7 to 100.0) | **50.0% more**  (6 fewer to 400.3 more) | ⨁◯◯◯  VERY LOW 1,2 | There is uncertainty about the effect of TPE |
| Clinical improvement  № of participants: 39  (2 Observational studies) | Informed complete remission were 54-74%, partial remission 13 - 46% and no response 0-13%. | | | | ⨁◯◯◯  VERY LOW 1,2 | There is uncertainty about the effect of TPE |

1. Randomization issues

2. 95%CI includes benefits and harms

* Wei N, Klippel JH, Huston DP, Hall RP, Lawley TJ, Balow JE, et al. Randomised trial of plasma exchange in mild systemic lupus erythematosus. Lancet. 1983;1:17–22.
* Neuwelt CM. The role of plasmapheresis in the treatment of severe central nervous system neuropsychiatric systemic lupus erythematosus. Ther Apher Dial. 2003;7:173–82.
* Bartolucci P, Bréchignac S, Cohen P, Le Guern V, Guillevin L. Adjunctive plasma exchanges to treat neuropsychiatric lupus: a retrospective study on 10 patients. Lupus. 2007;16:817–22.

5.1.6

|  |  |  |  |
| --- | --- | --- | --- |
| **RTX compared to placebo for neuropsychiatric SLE** | | |  |
| Outcome  № of participants  (studies) | **Impact** | Quality |  |
|  |
| Clinical response  № of participants: 102  (10 observational studies) | The observed response rate was 75 to 100%. In one of the publications, 45% relapsed at 17 months. | ⨁⨁◯◯  LOW |  |

* Tokunaga M, Saito K, Kawabata D, Imura Y, Fujii T, Nakayamada S, et al. Efficacy of rituximab (anti-CD20) for refractory systemic lupus erythematosus involving the central nervous system. Ann Rheum Dis. 2007;66:470–5.
* Narvaez J, Rios-Rodriguez V, de la Fuente D, Estrada P, Lopez-Vives L, Gomez-Vaquero C, et al. Rituximab therapy in refractory neuropsychiatric lupus: current clinical evidence. Semin Arthritis Rheum. 2011;41:364–72.
* Farinha F, Abrol E, Isenberg DA. Biologic therapies in patients with neuropsychiatric systemic lupus erythematosus. Lupus. 2016;25:1278–9.

5.2.1

|  |  |  |  |
| --- | --- | --- | --- |
| **CYC compared to GCs for SLE relates seizures** | | |  |
| Outcome  № of participants  (studies) | **Impact** | Quality |  |
|  |
| Seizures  follow up: 24 weeks  № of participants: 11  (1 RCT) | Adequate response was observed in 6/6 patients treated with CYC and 2/5 patients treated with GCs | ⨁◯◯◯  VERY LOW 1,2 |  |

1. Inadequate allocation concealment

2. CI95% including benefits and harms

* Barile-Fabris L, Ariza-Andraca R, Olguín-Ortega L, Jara LJ, Fraga-Mouret A, Miranda-Limón JM, et al. Controlled clinical trial of IV cyclophosphamide versus IV methylprednisolone in severe neurological manifestations in systemic lupus erythematosus. Ann Rheum Dis. 2005;64:620–5.

5.2.2

|  |  |  |  |
| --- | --- | --- | --- |
| **TPE compared to placebo for SLE relates seizures** | | |  |
| Outcome  № of participants  (studies) | **Impact** | Quality |  |
|  |
| Clinical response  № of participants: 4  (1 observational study) | 100% improved | ⨁◯◯◯  VERY LOW 1 |  |

1. Optimal information size not met

* Neuwelt CM. The role of plasmapheresis in the treatment of severe central nervous system neuropsychiatric systemic lupus erythematosus. Ther Apher Dial. 2003;7:173–82.

5.2.3

|  |  |  |  |
| --- | --- | --- | --- |
| **RTX compared to placebo for SLE relates seizures** | | |  |
| Outcome  № of participants  (studies) | **Impact** | Quality |  |
|  |
| Clinical response  № of participants: 9  (3 observational studies) | The observed response rate was 100%. | ⨁◯◯◯  VERY LOW 1 |  |

1. Optimal information size not met

* Farinha F, Abrol E, Isenberg DA. Biologic therapies in patients with neuropsychiatric systemic lupus erythematosus. Lupus. 2016;2:1278–9.

5.3.1

|  |  |  |  |
| --- | --- | --- | --- |
| **AZA compared to placebo for SLE relates psychosis** | | |  |
| Outcome  № of participants  (studies) | **Impact** | Quality |  |
|  |
| Clinical response  № of participants: 4  ( 1 observational study) | 4/7 long term remission of psychosis | ⨁◯◯◯  VERY LOW 1 |  |

1. Optimal information size not met

* Pego-Reigosa JM, Isenberg DA. Psychosis due to systemic lupus erythematosus: characteristics and long-term outcome of this rare manifestation of the disease. Rheumatology (Oxford). 2008;47:1498–502.

5.3.2

|  |  |  |  |
| --- | --- | --- | --- |
| **TPE compared to placebo for neuropsychiatric SLE** | | |  |
| Outcome  № of participants  (studies) | **Impact** | Quality |  |
|  |
| Clinical response  № of participants: 4  (1 observational study) | The observed response rate was 3/4. | ⨁◯◯◯  VERY LOW 1 |  |

1. Optimal information size not met

* Neuwelt CM. The role of plasmapheresis in the treatment of severe central nervous system neuropsychiatric systemic lupus erythematosus. Ther Apher Dial. 2003;7:173–82

5.3.3

|  |  |  |  |
| --- | --- | --- | --- |
| **RTX compared to placebo for SLE related psychosis** | | |  |
| Outcome  № of participants  (studies) | **Impact** | Quality |  |
|  |
| Clinical response  № of participants: 10  (2 observational studies) | The observed response rate was 100%. | ⨁◯◯◯  VERY LOW 1 |  |

1. Optimal information size not met

* Farinha F, Abrol E, Isenberg DA. Biologic therapies in patients with neuropsychiatric systemic lupus erythematosus. Lupus. 2016;2:1278–9.
* Tokunaga M, Saito K, Kawabata D, Imura Y, Fujii T, Nakayamada S, et al. Efficacy of rituximab (anti-CD20) for refractory systemic lupus erythematosus involving the central nervous system. Ann Rheum Dis. 2007;66:470–5.

5.4.1

|  |  |  |  |
| --- | --- | --- | --- |
| **CYC compared to GCs for SLE related myelitis** | | |  |
| Outcome  № of participants  (studies) | **Impact** | Quality |  |
|  |
| Symptoms  follow up: 24 weeks  № of participants: 11  (1 RCT) | Adequate response was observed in 2/3 patients treated with CYC and 1/2 patients treated with GCs | ⨁◯◯◯  VERY LOW 1,2 |  |

1. Inadequate allocation concealment

2. CI95% including benefits and harms

* Barile-Fabris, L., R. Ariza-Andraca, L. Olguín-Ortega, L. J. Jara, A. Fraga-Mouret, J. M. Miranda-Limón, J. Fuentes de la Mata, P. Clark, F. Vargas, and J. Alocer-Varela. “Controlled Clinical Trial of IV Cyclophosphamide versus IV Methylprednisolone in Severe Neurological Manifestations in Systemic Lupus Erythematosus.” Annals of the Rheumatic Diseases 64, no. 4 (April 2005): 620–25. doi:10.1136/ard.2004.025528.

5.4.2

|  |  |  |  |
| --- | --- | --- | --- |
| **MMF compared to placebo for SLE related myelitis** | | |  |
| Outcome  № of participants  (studies) | **Impact** | Quality |  |
|  |
| Clinical response  № of participants: 4  (1 observational study) | 1/4 presented complete response, 2/4 partial response and 1/4 no response | ⨁◯◯◯  VERY LOW 1 |  |

1. Optimal information size not met

* Mok, C. C. “Mycophenolate Mofetil for Non-Renal Manifestations of Systemic Lupus Erythematosus: A Systematic Review.” Scandinavian Journal of Rheumatology 36, no. 5 (October 2007): 329–37. doi:10.1080/03009740701607042.

5.4.3

|  |  |  |  |
| --- | --- | --- | --- |
| **RTX compared to placebo for SLE related myelitis** | | |  |
| Outcome  № of participants  (studies) | **Impact** | Quality |  |
|  |
| Clinical response  № of participants: 15  (3 observational studies) | The observed response rate was 83 - 100%. | ⨁◯◯◯  VERY LOW 1 |  |

1. Optimal information size not met

* Farinha, F., E. Abrol, and D. A. Isenberg. “Biologic Therapies in Patients with Neuropsychiatric Systemic Lupus Erythematosus.” Lupus 25, no. 11 (October 1, 2016): 1278–79. doi:10.1177/0961203316631636.

5.5.1

|  |  |  |  |
| --- | --- | --- | --- |
| **CYC compared to GCs for SLE peripheral neuropathy** | | |  |
| Outcome  № of participants  (studies) | **Impact** | Quality |  |
|  |
| Symptoms  Follow up: 24 weeks  № of participants: 11  (1 RCT) | Adequate response was observed in 3/4 patients treated with CYC and 0/3 patients treated with GCs | ⨁◯◯◯  VERY LOW 1,2 |  |

1. Inadequate allocation concealment

2. CI95% including benefits and harms

* Barile-Fabris L, Ariza-Andraca R, Olguín-Ortega L, Jara LJ, Fraga-Mouret A, Miranda-Limón JM, et al. Controlled clinical trial of IV cyclophosphamide versus IV methylprednisolone in severe neurological manifestations in systemic lupus erythematosus. Ann Rheum Dis. 2005;64:620–5.

5.5.2

|  |  |  |  |
| --- | --- | --- | --- |
| **RTX compared to placebo for SLE related peripheral neuropathy** | | |  |
| Outcome  № of participants  (studies) | **Impact** | Quality |  |
|  |
| Clinical response  № of participants: 6  (4 observational studies) | The observed response rate was 100%. | ⨁◯◯◯  VERY LOW 1 |  |

1. Optimal information size not met

* Farinha, F., E. Abrol, and D. A. Isenberg. “Biologic Therapies in Patients with Neuropsychiatric Systemic Lupus Erythematosus.” Lupus 25, no. 11 (October 1, 2016): 1278–79. doi:10.1177/0961203316631636.

5.6.1

|  |  |  |  |
| --- | --- | --- | --- |
| **CYC compared to GCs for SLE related optic neuritis** | | |  |
| Outcome  № of participants  (studies) | **Impact** | Quality |  |
|  |
| Clinical response  follow up: 24 weeks  № of participants: 11  (1 RCT) | Adequate response was observed in 4/4 patients treated with CYC and 0/1 patients treated with GCs | ⨁◯◯◯  VERY LOW 1,2 |  |

1. Inadequate allocation concealment

2. CI95% including benefits and harms

* Barile-Fabris L, Ariza-Andraca R, Olguín-Ortega L, Jara LJ, Fraga-Mouret A, Miranda-Limón JM, et al. Controlled clinical trial of IV cyclophosphamide versus IV methylprednisolone in severe neurological manifestations in systemic lupus erythematosus. Ann Rheum Dis. 2005;64:620–5.

5.6.2

|  |  |  |  |
| --- | --- | --- | --- |
| **TPE compared to placebo for SLE related optic neuritis** | | |  |
| Outcome  № of participants  (studies) | **Impact** | Quality |  |
|  |
| Clinical response  № of participants: 4  (1 observational study) | 4/4 patients presented partial response | ⨁◯◯◯  VERY LOW 1 |  |

1. Optimal information size not met

* Man BL, Mok CC, Fu YP. Neuro-ophthalmologic manifestations of systemic lupus erythematosus: a systematic review. Int J Rheum Dis. 2014;17:494–501.

6.1.1

| **Active treatment (GCs\* / CYC / TPE / RTX) compared to best support treatment for diffuse alveolar hemorrhage** | | |
| --- | --- | --- |
| Outcome № of participants (studies) | **Impact** | Quality |
| Survival № of participants: 226 (59 observational studies) | 252 (93%) of 270 were treated with GCs.1 Overall survival was 60%.  87 (70%) of 125 episodes where CYC was used resulted in survival.  38 (45%) of 85 episodes where TPE was used resulted in survival.  18 (75%) of 24 episodes where RTX was used resulted in survival. In 9 episodes RTX and CYC were used together. | ⨁◯◯◯ VERY LOW1 |
| \* GCs doses were heterogeneous. More frequent initial doses were prednisolone 1 - 2 mg/kg/day and intravenous pulse methylprednisolone 500 - 1000 mg/day for 3 days or equivalent | | |

1. Uncontrolled observational studies

* Andrade C, Mendonça T, Farinha F, Correia J, Marinho A, Almeida I, et al. Alveolar hemorrhage in systemic lupus erythematosus: a cohort review. Lupus. 2016;25:75–80.
* Cañas C, Tobón GJ, Granados M, Fernández L. Diffuse alveolar hemorrhage in Colombian patients with systemic lupus erythematosus. Clin Rheumatol. 2007;26:1947–9.
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6.1.2

| **RTX compared to CYC for diffuse alveolar hemorrhage** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| Outcome № of participants (studies) | Relative effect (95% CI) | **Anticipated absolute effects (95% CI)** | | | Quality | What happens |
| **Without RTX** | **With RTX** | **Difference** |
| Response to treatment assessed with: BVAS/WG of 0 and successful completion of the prednisone taper at 6 months. № of participants: 55 (1 RCT) | **RR 1.4** (0.7 to 2.6) | 40.7% | **57.0%** (28.5 to 100.0) | **16.3% more** (12.2 fewer to 65.2 more) | ⨁◯◯◯ VERY LOW 1,2 | It is uncertain whether RTX improves treatment response |
| Severe adverse effects assessed with: defined as death (from any cause), cancer, grade 2 or higher leukopenia or thrombocytopenia, grade 3 or higher infections, drug-induced cystitis, venous thromboembolic events, stroke, hospitalization, and infusion reactions leading to the discontinuation of further infusions № of participants: 197 (1 RCT) | **RR 0.93** (0.60 to 1.40) | 33.7% | **31.3%** (20.2 to 47.1) | **2.4% fewer** (13.5 fewer to 13.5 more) | ⨁⨁◯◯ LOW 2 | RTX may make little or no difference in severe adverse effects |

1. Indirect evidence: The studies included patients that had alveolar hemorrhage secondary to ANCA associated vasculities

2. 95%CI includes significant benefits and harms

* Stone, John H., Peter A. Merkel, Robert Spiera, Philip Seo, Carol A. Langford, Gary S. Hoffman, Cees G. M. Kallenberg, et al. “Rituximab versus Cyclophosphamide for ANCA-Associated Vasculitis.” The New England Journal of Medicine 363, no. 3 (July 15, 2010): 221–32. doi:10.1056/NEJMoa0909905.

6.2.1

| **Colchicine plus NSAIDs or prednisone compared to NSAIDs or prednisone for acute pericarditis** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| Outcome № of participants (studies) | Relative effect (95% CI) | **Anticipated absolute effects (95% CI)** | | | Quality | What happens |
| **Without Colchicine** | **With Colchicine** | **Difference** |
| Recurrence rate follow up: mean 6 months № of participants: 360 (2 RCTs) | **RR 0.36** (0.23 to 0.58) | 30.6% | **11.0%** (7.0 to 17.7) | **19.6% fewer** (23.5 fewer to 12.8 fewer) | ⨁⨁⨁◯ MODERATE 1,2 | Colchicine probably improves recurrence rate at 6 months |
| Recurrence rate follow up: mean 12 months № of participants: 360 (2 RCTs) | **RR 0.40** (0.26 to 0.61) | 33.3% | **13.3%** (8.7 to 20.3) | **20.0% fewer** (24.7 fewer to 13 fewer) | ⨁⨁⨁◯ MODERATE 1,2 | Colchicine probably improves recurrence rate at 12 months |
| Recurrence rate follow up: mean 18 months № of participants: 360 (2 RCTs) | **RR 0.41** (0.28 to 0.61) | 36.7% | **15.0%** (10.3 to 22.4) | **21.6% fewer** (26.4 fewer to 14.3 fewer) | ⨁⨁⨁◯ MODERATE 1,2 | Colchicine probably improves recurrence rate at 18 months |
| Total adverse effects assessed with: Patient report follow up: median 18 months № of participants: 804 (5 RCTs) | **RR 1.30** (0.84 to 2.00) | 8.2% | **10.7%** (6.9 to 16.4) | **2.5% more** (1.3 fewer to 8.2 more) | ⨁⨁◯◯ LOW 1,3 | Colchicine may slightly increase the risk of total adverse effects |
| Adverse events leading to discontinuation assessed with: Patient reported follow up: median 18 months № of participants: 804 (5 RCTs) | **RR 1.46** (0.86 to 2.48) | 5.2% | **7.6%** (4.5 to 13.0) | **2.4% more** (0.7 fewer to 7.7 more) | ⨁⨁◯◯ LOW 1,3 | Colchicine may slightly increase the risk of total adverse effects |

1. Risk of bias
2. Not SLE population
3. Wide confidence intervals include benefit and harm

* Imazio M, Bobbio M, Cecchi E, Demarie D, Demichelis B, Pomari F, et al. Colchicine in addition to conventional therapy for acute pericarditis: results of the COlchicine for acute PEricarditis (COPE) trial. Circulation. 2005;112:2012–6.
* Imazio M, Bobbio M, Cecchi E, Demarie D, Pomari F, Moratti M, et al. Colchicine as first-choice therapy for recurrent pericarditis: results of the CORE (COlchicine for REcurrent pericarditis) trial. Arch Intern Med. 2005;165:1987–91.
* Imazio M, Brucato A, Cemin R, Ferrua S, Maggiolini S, Beqaraj F, et al. A randomized trial of colchicine for acute pericarditis. N Engl J Med.;369:1522–8.
* Imazio M, Cecchi E, Ierna S, Trinchero R, CORP Investigators. CORP (COlchicine for Recurrent Pericarditis) and CORP-2 trials--two randomized placebo-controlled trials evaluating the clinical benefits of colchicine as adjunct to conventional therapy in the treatment and prevention of recurrent pericarditis: study design and rationale. J Cardiovasc Med (Hagerstown). 2007;8:830–4.
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6.2.2

| **Colchicine compared to placebo for multiple recurrent pericarditis** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| Outcome № of participants (studies) | Relative effect (95% CI) | **Anticipated absolute effects (95% CI)** | | | Quality | What happens |
| **Without Colchicine** | **With Colchicine** | **Difference** |
| Recurrence rate follow up: mean 18 months № of participants: 240 (1 RCT) | **RR 0.51** (0.33 to 0.77) | 42.5% | **21.7%** (14.0 to 32.7) | **20.8% fewer** (28.5 fewer to 9.8 fewer) | ⨁⨁⨁◯ MODERATE 1,2 | Colchicine probably improves recurrence rate at 6 months |
| Total adverse effects assessed with: Patient report follow up: median 18 months № of participants: 804 (5 RCTs) | **RR 1.30** (0.84 to 2.00) | 8.2% | **10.7%** (6.9 to 16.4) | **2.5% more** (1.3 fewer to 8.2 more) | ⨁⨁◯◯ LOW 1,3 | Colchicine may slightly increase the rate of total adverse effects |
| Adverse events leading to discontinuation assessed with: Patient report follow up: median 18 months № of participants: 804 (5 RCTs) | **RR 1.46** (0.86 to 2.48) | 5.2% | **7.6%** (4.5 to 13.0) | **2.4% more** (7 fewer to 7.7 more) | ⨁⨁◯◯ LOW 1,3 | Colchicine may slightly increase the rate of total adverse effects |

1. Risk of bias
2. Not SLE population
3. Wide confidence intervals include benefit and harm

* Imazio M, Bobbio M, Cecchi E, Demarie D, Demichelis B, Pomari F, et al. Colchicine in addition to conventional therapy for acute pericarditis: results of the COlchicine for acute PEricarditis (COPE) trial. Circulation. 2005;112:2012–6.
* Imazio M, Bobbio M, Cecchi E, Demarie D, Pomari F, Moratti M, et al. Colchicine as first-choice therapy for recurrent pericarditis: results of the CORE (COlchicine for REcurrent pericarditis) trial. Arch Intern Med. 2005;165:1987–91.
* Imazio M, Brucato A, Cemin R, Ferrua S, Maggiolini S, Beqaraj F, et al. A randomized trial of colchicine for acute pericarditis. N Engl J Med.;369:1522–8.
* Imazio M, Cecchi E, Ierna S, Trinchero R, CORP Investigators. CORP (COlchicine for Recurrent Pericarditis) and CORP-2 trials--two randomized placebo-controlled trials evaluating the clinical benefits of colchicine as adjunct to conventional therapy in the treatment and prevention of recurrent pericarditis: study design and rationale. J Cardiovasc Med (Hagerstown). 2007;8:830–4.
* Alabed S, Cabello JB, Irving GJ, Qintar M, Burls A. Colchicine for pericarditis. Cochrane Database Syst Rev. 2014;28

6.2.3

| **GCs compared to placebo for acute pericarditis** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| Outcome № of participants (studies) | Relative effect (95% CI) | **Anticipated absolute effects (95% CI)** | | | Quality | What happens |
| **Without GCs** | **With GCs** | **Difference** |
| Recurrence rate № of participants: 31 (2 Observational study) | **OR 7.50** (0.62 to 90.65) | 45.5% | **86.2%** (34.1 to 98.7) | **40.8% more** (1.,4 fewer to 53.2 more) | ⨁◯◯◯ VERY LOW 1,2,3 | It is uncertain if GCs affects this outcome |
| Treatment failure № of participants: 15 (1 Observational study) | No events reported in treatment or control arms | | | | ⨁◯◯◯ VERY LOW 1,2,4 |  |

1. Risk of bias
2. Not SLE population
3. Wide confidence intervals include benefit and harm
4. Few patients / events

* Farinha NJ, Bartolo A, Trindade L, Vaz T, Monterroso J, Areias JC, et al. [Acute pericarditis in childhood. The 9-year experience of a tertiary referral center]. Acta Med Port. 1997;10:157–60.
* Raatikka M, Pelkonen PM, Karjalainen J, Jokinen EV. Recurrent pericarditis in children and adolescents: report of 15 cases. J Am Coll Cardiol.;42:759–64.

6.2.4

| **AZA plus GCs compared to placebo for acute recurrent pericarditis** | | |
| --- | --- | --- |
| Outcome № of participants (studies) | **Impact** | Quality |
| Recurrence № of participants: 40 (1 observational study) | 29 of 46 (63%) did not experience recurrence since AZA was started. 27 of 46 (58.6%) did not experience recurrence after discontinuation of AZA. | ⨁◯◯◯ VERY LOW 1 |
| Adverse effects № of participants: 40 (1 observational study) | Transient hepatotoxicity was observed in 5 patients (10.8%) and leucopenia in 3 patients (6.5%). | ⨁◯◯◯ VERY LOW 1 |

1. Few patients / events

* Vianello F, Cinetto F, Cavraro M, Battisti A, Castelli M, Imbergamo S, et al. Azathioprine in isolated recurrent pericarditis: A single centre experience. International Journal of Cardiology. 2011;147:477–8.

6.3.1

| **Belimumab compared to placebo for SLE with predominant cardiopulmonary compromise** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| Outcome № of participants (studies) | Relative effect (95% CI) | **Anticipated absolute effects (95% CI)** | | | Quality | What happens |
| **Without** belimumab | **With** belimumab | **Difference** |
| Improvement BILAG assessed with: BILAG cardiovascular / Respiratory domain. Down from an A or B score to a B, C or D score. follow up: mean 52 weeks № of participants: 61 (2 RCTs) | **RR 1.31** (0.77 to 1.82) | 38.1% | **49.9%** (29.3 to 69.3) | **11.8% more** (8.8 fewer to 31.2 more) | ⨁⨁◯◯ LOW 1,2 | Belimumab may improve cardiovascular / respiratory symptoms |
| Improvement SELENA-SLEDAI assessed with: Serosal domain.  follow up: mean 52 weeks № of participants: 105 (2 RCTs) | **RR 0.90** (0.62 to 1.42) | 56.3% | **50.6%** (34.9 to 79.9) | **5.6% fewer** (21.4 fewer to 23.6 more) | ⨁⨁◯◯ LOW 1,2 | Belimumab may make little or no difference to SELENA-SLEDAI improvement |
| Serious adverse events follow up: mean 52 weeks № of participants: 2133 (3 RCTs) | **RR 0.97** (0.79 to 1.20) | 16.0% | **15.5%** (12.6 to 19.2) | **0.5% fewer** (3.4 fewer to 3.2 more) | ⨁⨁⨁◯ MODERATE 2 | Belimumab probably makes little or no difference to serious adverse effects |

1. Risk of bias
2. Wide confidence intervals include potential benefit and harm

* Manzi S, Sánchez-Guerrero J, Merrill JT, Furie R, Gladman D, Navarra SV, et al. Effects of belimumab, a B lymphocyte stimulator-specific inhibitor, on disease activity across multiple organ domains in patients with systemic lupus erythematosus: combined results from two phase III trials. Ann Rheum Dis. 2012;71:1833–8.
* Navarra SV, Guzmán RM, Gallacher AE, Hall S, Levy RA, Jimenez RE, et al. Efficacy and safety of belimumab in patients with active systemic lupus erythematosus: a randomised, placebo-controlled, phase 3 trial. Lancet. 2011 Feb 26;377(9767):721–31.
* Furie R, Petri M, Zamani O, Cervera R, Wallace DJ, Tegzová D, et al. A phase III, randomized, placebo-controlled study of belimumab, a monoclonal antibody that inhibits B lymphocyte stimulator, in patients with systemic lupus erythematosus. Arthritis Rheum. 2011;63:3918–30.
* Wallace DJ, Stohl W, Furie RA, Lisse JR, McKay JD, Merrill JT, et al. A phase II, randomized, double-blind, placebo-controlled, dose-ranging study of belimumab in patients with active systemic lupus erythematosus. Arthritis Rheum. 2009;61:1168–78.

7.1.1

| **AZA compared to AZA plus GCs for hematological manifestations of lupus** | | | | |
| --- | --- | --- | --- | --- |
| Result  Number of participants (Studies ) | | **Impact** | Certainty | |
|
|  |
| General hematological manifestations follow-up: 24 months  (1 observational study) | In a randomized trial (data not shown in publication) that randomly divided patients to AZA plus GCs vs GCs during a mean follow-up period of 18 to 24 months, there were no significant differences in the Coombs' antibodies dosing.  A Latin-American cohort reported a negative association with the treatment with AZA and the appearance of hemolytic anemia in patients without previous hematological manifestations (multivariate analysis: OR 0.46 CI95% 0.24–0.89 (Very low certainty: High risk of bias and imprecision) | | | ⨁⨁◯◯  LOW 1,2 |

1. Unclear randomization and allocation concealment
2. Small number of events

* Hahn BH, Kantor OS, Osterland CK. Azathioprine plus prednisone compared with prednisone alone in the treatment of systemic lupus erythematosus. Report of a prospective controlled trial in 24 patients. Ann Intern Med. 1975;83:597–605.
* González-Naranjo LA, Betancur OM, Alarcón GS, Ugarte-Gil MF, Jaramillo-Arroyave D, Wojdyla D, et al. Features associated with hematologic abnormalities and their impact in patients with systemic lupus erythematosus: Data from a multiethnic Latin American cohort. Semin Arthritis Rheum. 2016;45:675–83.

7.1.2

| **Belimumab (1 mg/kg and 10 mg/kg) compared to placebo for hematological manifestations of lupus** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| Result  Number of participants (Studies ) | Relative effect (95% CI) | **Absolute Effect(95% CI)** | | | Certainty | What happens |
| **Without** belimumab | **With** belimumab | **Difference** |
| Improvement in BILAG score **any doses** follow-up: 52 weeks Number of participants: 272 (1 RCT) | **RR 0.68** (0.40 a 1.15) | 21.6% | **14.7%** (8.6 a 24.8) | **6.9% less**  (13 less to 3.2 more) | ⨁⨁◯◯ LOW 1,2 | Belimumab any dose may make little or no difference to improvement of BILAG score domain in patients with Lupus with hematological manifestations |
| Worsening in BILAG **any doses** follow-up: 52 weeks Number of participants: 1677 (1 RCT) | **RR 0.37** (0.25 a 0.56) | 9.1% | **3.4%** (2.3 a 5.1) | **5.7% less**  (6,8 less to 4 less) | ⨁⨁◯◯ LOW 1,2 | Belimumab (any dose) may prevent deterioration of BILAG score in patients with Lupus with hematological manifestations |
| Worsening in SLEDAI **any doses** follow-up: 52 weeks Number of participants: 1555 (1 RCT) | **RR 0.61** (0.39 a 0.95) | 6.5% | **4.0%** (2.5 a 6.2) | **2.5% less**  (4 less to 0,3 less) | ⨁⨁◯◯ LOW 1,2 | Belimumab any dose may slightly prevent deterioration of SLEDAI score in patients with Lupus with hematological manifestations |

1. Selective outcome reporting (not MID), lost to follow up
2. Small number of events

* Manzi S, Sánchez-Guerrero J, Merrill JT, Furie R, Gladman D, Navarra SV, et al. Effects of belimumab, a B lymphocyte stimulator-specific inhibitor, on disease activity across multiple organ domains in patients with systemic lupus erythematosus: combined results from two phase III trials. Ann Rheum Dis. 2012;71:1833–8.

7.1.3

| **AMs compared to placebo for hematological lupus** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| Result  Number of participants (Studies ) | Relative effect (95% CI) | **Absolute Effect(95% CI)** | | | Certainty | What happens |
| **Without AMs for hematological lupus** | **With AMs for hematological lupus** | **Difference** |
| Hematological flares follow-up: 1 years  Number of participants: 23 (1 RCT) | **RR 0.22** (0.01 a 4.07) | 16.7% | **3.7%** (0.2 a 67.8) | **13.0% less**  (16.5 less to 51.2 more ) | ⨁⨁◯◯ LOW 1,2 | AMs may prevent flares in patients with hematological manifestations of Lupus |
| Incidence of hematological involvement in chronically treated lupus follow-up: Retrospective (1 observational study) | The identified cohort reported a negative association between the treatment with AMs and the occurrence of hematological manifestations in patients without previous hematological manifestations (OR 0.61 95% CI 43–0.85) in a univariate analysis (Very low certainty in the effect estimate due to high risk of bias and imprecision). Specifically regarding hemolytic anemia,the results showed a negative association with the treatment with AMs in a multivariate analysis: OR 0.6 - 95% CI 0.45–0.80 | | | | ⨁◯◯◯ VERY LOW 2 |  |

1. Selective outcome reporting (SLEDAI without MID)
2. Small number of events

* Catoggio LJ, Soriano ER, Imamura PM, Wojdyla D, Jacobelli S, Massardo L, et al. Late-onset systemic lupus erythematosus in Latin Americans: a distinct subgroup? Lupus. 2015;24:788–95.
* Meinão IM, Sato EI, Andrade LE, Ferraz MB, Atra E. Controlled trial with chloroquine diphosphate in systemic lupus erythematosus. Lupus. 1996;5:237–41.

7.1.4

| **CYC compared to placebo for hematological manifestations of lupus** | | |
| --- | --- | --- |
| Result  Number of participants (Studies ) | **Impact** | Certainty |
|
|  |
| TTP follow-up: 3 years  (2 observational studies) | Two case report mentioned the use of CYC as a maintenance therapy after TPE with fresh frozen plasma with adequate response (Very low certainty in the effect, high risk of bias, imprecision). | ⨁◯◯◯ VERY LOW 1,2 |
| Evans syndrome follow-up: 30 months  (1 observational study) | A case series with patients with Evans syndrome reported that CYC was the most commonly used immunosuppressant (74%, 20/27). Treatment effectiveness was not reported. | ⨁◯◯◯ VERY LOW 1,2 |
| Aplastic anemia  follow-up: 6 months  (1 observational study) | A literature review found 5 case reports of patients with aplastic anemia treated with CYC, 4 of them showing adequate response and 1 with poor response (Very low certainty in the effect, high risk of bias, imprecision). | ⨁◯◯◯ VERY LOW 1,2 |

1. Not randomized
2. Small number of events

* Blum D, Blake G Lupus-associated thrombotic thrombocytopenic purpura-like microangiopathy World J Nephrol 2015;4: 528-531
* Mashhadi MA, Bari Z Thrombotic thrombocytopenic purpura and deep vein thrombosis as the presenting manifestations of systemic lupus erythematosus: A case report and review of literature J Res Med Sci. 2011;16:1082–1088.
* Zhang L, Wu X, Wang L, Li J, Chen H, Zhao Y, et al. Clinical Features of Systemic Lupus Erythematosus Patients Complicated With Evans Syndrome: A Case-Control, Single Center Study. Medicine (Baltimore). 2016;95:e3279.
* Alishiri G-H, Saburi A, Bayat N, Saadat A-R, Saburi E. The initial presentation of systemic lupus erythematosis with aplastic anemia successfully treated with rituximab. Clinical Rheumatology. 2012;31:381–4.

7.1.5

| **CsA compared to placebo for hematological manifestations of lupus** | | |
| --- | --- | --- |
| Result  Number of participants (Studies ) | **Impact** | Certainty |
|
|  |
| Evans syndrome follow-up: 5 years  (1 observational study) | A case series with patients with Evans syndrome reported the use of CsA (37%, 10/27) as an immunosuppressant. No incidence of treatment failure was reported. | ⨁◯◯◯ VERY LOW 1,2 |
| Aplastic anemia (1 observational study) | A literature review found 2 case reports of patients with aplastic anemia treated with CsA both of them showing adequate response | ⨁◯◯◯ VERY LOW 1,2 |

1. Case series
2. Small number of events

* Zhang L, Wu X, Wang L, Li J, Chen H, Zhao Y, et al. Clinical Features of Systemic Lupus Erythematosus Patients Complicated With Evans Syndrome: A Case-Control, Single Center Study. Medicine (Baltimore). 2016;95:e3279.
* Alishiri G-H, Saburi A, Bayat N, Saadat A-R, Saburi E. The initial presentation of systemic lupus erythematosis with aplastic anemia successfully treated with rituximab. Clinical Rheumatology. 2012;31:381–4.

7.1.6

| **Danazol compared to placebo for hematological manifestations of lupus** | | |
| --- | --- | --- |
| Result  Number of participants (Studies ) | **Impact** | Certainty |
|
|  |
| Evans syndrome and hemolytic anemia follow-up: 8 months  (1 observational study) | 18 patients (1 case series and 2 case reports) showed that danazol proved to be effective added to GCs in Evan’s syndrome , autoimmune hemolytic anemia (AIHA) | ⨁◯◯◯ VERY LOW 2,3 |
| Red cell aplasia follow-up: 6 weeks (1 observational study) | A case report showed that danazol proved to be effective in red cell aplasia. | ⨁◯◯◯ VERY LOW 2,3 |
| Thrombocytopenia follow-up: 8 weeks (2 Randomized trials) | Danazol has been used successfully in the treatment of thrombocytopenia (2 Controlled trials with 47 patients) showing increase in platelet count. A case of SLE thrombocytopenia in pregnancy that failed GCs therapy showed adequate response to danazol added at the 36th week. | ⨁⨁◯◯ LOW 1,2 |

1. Unclear randomization, lost to follow up
2. Small number of events
3. Case series

* Letchumanan P, Thumboo J Danazol in the Treatment of Systemic Lupus Erythematosus: A Qualitative Systematic Review Semin Arthritis Rheum 2011 40:298-306

7.1.7

| **DHEA compared to placebo for hematological manifestations of lupus** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| Result  Number of participants (Studies ) | Relative effect (95% CI) | **Absolute Effect(95% CI)** | | | Certainty | What happens |
| **Without DHEA** | **With DHEA** | **Difference** |
| Platelet count improvement follow-up: 3 months  Number of participants: 28 (1 RCT) | - | Mean difference in platelet count was **16.55** +/- **8.76** | Mean difference in platelet count was **-25.0** *+/-* **8.63** | MD **41.55 less**  (47.99 less to 35.11 less) | ⨁◯◯◯ VERY LOW 1,2,3 | It is uncertain whether DHEA affects platelet count in patients with SLE with predominant hematological manifestations |
| Hematocrit improvement follow-up: 3 months  Number of participants: 28 (1 RCT) | - | Mean difference in hematocrit was **0.18** +/- **0.99** | Mean difference in hematocrit was **1.46** +/- **0.53** | MD **15.09 higher**  (15.37 higher a 14.81 higher) | ⨁◯◯◯ VERY LOW 1,2,3 | It is uncertain whether DHEA affects hematocrit in patients with SLE with predominant hematological manifestations |
| Hematological flares follow-up: 3 months  Number of participants: 28 (1 RCT) | **RR 0.38** (0.12 a 1.13) | 57.1% | **21.7%** (6.9 a 64.6) | **35.4% less**  (50.3 less a 7.4 more) | ⨁◯◯◯ VERY LOW 1,2,3 | It is uncertain whether DHEA affects hematological flares in patients with SLE with predominant hematological manifestations |

1. Unclear concealed allocation, selective outcomes reporting
2. Small number of events
3. Most of the included patients didn't have hematological manifestations of SLE

* van Vollenhoven RF, Engleman EG, McGuire JL. Dehydroepiandrosterone in systemic lupus erythematosus. Results of a double-blind, placebo-controlled, randomized clinical trial. Arthritis Rheum. 1995;38:1826–31.

7.1.8

| **Eltrombopag compared to placebo for hematological manifestations of lupus** | | |
| --- | --- | --- |
| Result  Number of participants (Studies ) | **Impact** | Certainty |
|
|  |
| Autoimmune thrombocytopenia follow-up: 100 days  (1 observational study) | A case report informed adequate response of a patient with thrombotic thrombocytopenia purpura treated with eltrombopag. | ⨁◯◯◯ VERY LOW 1,2 |

1. Not randomized
2. Small number of events

* Scheinberg P, Singulane CC, Barbosa LSG, Scheinberg M. Successful platelet count recovery in lupus-associated thrombocytopenia with the thrombopoietin agonist eltrombopag. Clinical Rheumatology. 2014;33:1347–9.

7.1.9

| **Epratuzumab compared to placebo for hematological manifestations of lupus** | | |
| --- | --- | --- |
| Result  Number of participants (Studies ) | **Impact** | Certainty |
|
|  |
| Grade III hematological toxicity (lymphopenia) follow-up: 6 months  (1 observational study) | A prospective cohort reported that 2 out of 14 patients presented episodes of leucopenia (threshold not reported) | ⨁◯◯◯ VERY LOW 1,2 |
| Any adverse event follow-up: 6 months  (1 observational study) | A prospective cohort reported that 10 out of 14 patients presented any adverse event | ⨁◯◯◯ VERY LOW 1,2 |
| Infections follow-up: 6 months  (1 observational study) | A prospective cohort reported that 5 out of 14 patients presented any infection | ⨁◯◯◯ VERY LOW 1,2 |
| Clinical improvement follow-up: 6 months  (1 observational study) | A prospective cohort reported that 0 out of 14 patients showed clinical improvement (BILAG SCALE MID not reported) | ⨁◯◯◯ VERY LOW 1,2 |

1. Not randomized
2. Small number of events

* Dörner T, Kaufmann J, Wegener WA, Teoh N, Goldenberg DM, Burmester GR. Initial clinical trial of epratuzumab (humanized anti-CD22 antibody) for immunotherapy of systemic lupus erythematosus. Arthritis Res Ther. 2006;8:R74.

7.1.10

| **MMF (1500 - 2000 mg) compared to placebo for hematological manifestations of lupus** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| Result  Number of participants (Studies ) | Relative effect (95% CI) | **Absolute Effect(95% CI)** | | | Certainty | What happens |
| **Pre MMF** | **Post MMF** | **Difference** |
| Hemoglobin (g/dl) follow-up: 1 year  Number of participants: 10 (1 observational study) | - | The mean Hb post treatment (g/dl) was 11.3 +/- 1.6 | The mean Hb post? treatment (g/dl) was 11.5 +/- 1.5 | MD **0.2 lower**  (2.12 lower a 1.72 higher) | ⨁◯◯◯ VERY LOW 1 | MMF may make little or no difference in increasing Hb levels |
| Thrombocytes (x1000 /ml) follow-up: 1 years  Number of participants: 10 (1 observational study) | - | The mean thrombocyte count post? treatment (/dl) was 244 +/- 104 | The mean thrombocyte count post? treatment (/dl) was 242+/- 85 | MD **2 higher.** (115.73 lower a 119.73 higher.) | ⨁◯◯◯ VERY LOW 1 | MMF may make little or no difference in increasing thrombocyte count |
| Leucocytes (/ml) follow-up: 1 year  Number of participants: 10 (1 observational study) | - | The mean leucocyte count post? treatment (/dl) was 5230 +/- 2356 | The mean leucocyte count post? treatment (/dl) was 4821 +/- 1762 | MD **409 higher.** (2169.73 lower to 2987.73 higher.) | ⨁◯◯◯ VERY LOW 1 | MMF may make little or no difference in increasing leucocytes count |
| Lymphocytes (/ml) follow-up: 1 year  Number of participants: 10 (1 observational study) | - | The mean lymphocyte count pre treatment (/dl) was **0** | - | MD **39 higher.** (491.3 lower to 569.3 higher.) | ⨁◯◯◯ VERY LOW 1 | MMF may make little or no difference increase lymphocytes count with hematological manifestations of Lupus |

1. Small number of events

* Gaubitz M, Schorat A, Schotte H, Kern P, Domschke W. Mycophenolate mofetil for the treatment of systemic lupus erythematosus: an open pilot trial. Lupus 1999;8:731–6.

7.1.11

| **TPE\* compared to placebo for hematological manifestations of lupus** | | |
| --- | --- | --- |
| Result  Number of participants (Studies ) | **Impact** | Certainty |
|
|  |
| Aplastic anemia (1 observational study) | A literature review found 4 case reports of patients with aplastic anemia treated with TPE, all of them showing adequate response | ⨁◯◯◯ VERY LOW 1 |
| Evans syndrome follow-up: 5 years  (1 observational study) | A case series with patients with Evans syndrome reported that TPE was exceptionally used in Evans syndrome (2 patients out of 27). Treatment failure was not reported. | ⨁◯◯◯ VERY LOW 1 |
| TTP follow-up: 18 months  (5 observational studies) | A case series of 6 patients with TTP associated to SLE reported the use of TPE in 5 of them (all of them combined with GC). From the 5 patients receiving TPE, two patients had manifestations of active lupus and three were inactive at the end of follow up. Three further case reports showed positive results after treatment with TPE. A case of a successful pregnancy outcome with the use of antepartum GCs and monthly prophylactic TPE in a woman with a history of systemic lupus erythematosus (SLE) and severe refractory thrombotic thrombocytopenic purpura (TTP) was reported. | ⨁◯◯◯ VERY LOW 1 |
| \* Median of 8 sessions | | |

1. Small number of events

* Aleema A, Al-Sugairb S Thrombotic Thrombocytopenic Purpura Associated with Systemic Lupus Erythematosus Acta Haematol 2006;115:68–73.
* Zhang L, Wu X, Wang L, Li J, Chen H, Zhao Y, et al. Clinical Features of Systemic Lupus Erythematosus Patients Complicated With Evans Syndrome: A Case-Control, Single Center Study. Medicine (Baltimore). 2016;95:e3279.
* Gholam-Hossein A, Saburi A, Bayat N, Saadat AR, Saburi E The initial presentation of systemic lupus erythematosus with aplastic anemia successfully treated with rituximab Clin Rheumatol (2012) 31:381–384
* Blum D, Blake G, Lupus-associated thrombotic thrombocytopenic purpura-like microangiopathy World J Nephrol 2015;4:528-531
* Guvenc B, Unsal C, Gurkan E, Canataroğlu A, Saritas B, Evran M. Systemic lupus erythematosus and thrombotic thrombocytopenic purpura: a case report. Transfus Apher Sci. 2004;31:17–20.
* Ali Mashhadi M, Bari Z Thrombotic thrombocytopenic purpura and deep vein thrombosis as the presenting manifestations of systemic lupus erythematosus: A case report and review of literature J Res Med Sci. 2011; 16: 1082–1088.
* Abou-Nassar K, Karsh J, Giulivi A, Allan D. Successful prevention of thrombotic thrombocytopenic purpura (TTP) relapse using monthly prophylactic plasma exchanges throughout pregnancy in a patient with systemic lupus erythematosus and a prior history of refractory TTP and recurrent fetal loss. Transfus Apher Sci. 2010;43:29–31.

7.1.12

| **RTX\* compared to placebo for SLE related hematologic manifestations** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| Outcome № of participants (studies) | Relative effect (95% CI) | **Anticipated absolute effects (95% CI)** | | | Quality | What happens |
| **Without RTX** | **With RTX** | **Difference** |
| Autoimmune thrombocytopenia, platelet count complete response № of participants: 463 (5 RCTs) | **RR 1.42** (1.13 to 1.77) | 30.5% | **43.4%** (34.5 to 54.0) | **12.8% more** (4 more to 23.5 more) | ⨁⨁⨁◯ MODERATE 1 | RTX probably increases platelet count |
| Autoimmune thrombocytopenia, bleeding events № of participants: 362 (4 RCTs) | **RR 1.34** (0.63 to 2.87) | 4.9% | **6.6%** (3.1 to 14.2) | **1.7% more** (1.8 fewer to 9.2 more) | ⨁⨁◯◯ LOW 1,2 | RTX may make little or no difference to bleeding |
| Anemia, leucopenia and thrombocytopenia Infection № of participants: 362 (4 RCTs) | **RR 1.40** (0.87 to 2.26) | 13.2% | **18.5%** (11.5 to 29.8) | **5.3% more** (1.7 fewer to 16.6 more) | ⨁⨁⨁◯ MODERATE 2 | RTX probably increase infections |
| Autoimmune Hemolityc anemia, complete response at 6 months № of participants: 64 (1 RCT) | **RR 1.6** (0.9 to 2.9) | 37.5% | **60.0%** (33.8 to 100.0) | **22.5% more** (3.7 fewer to 71.2 more) | ⨁⨁◯◯ LOW 2,3 | RTX may increase complete response |
| Autoimmune hemolityc anemia, relapse or death № of participants: 64 (1 RCT) | **HR 0.33** (0.12 to 0.88) | **Observed** | | | ⨁⨁◯◯ LOW 3,4 | RTX may decrease relapse or death |
| 60.0% | **26.1%** (10.4 to 55.4) | **33.9% fewer** (49.6 fewer to 4.6 fewer) |
| Anemia, leucopenia and thrombocytopenia follow up: 10 months (1 observational study) | A German cohort of 67 patients treated with RTX reported that major disease manifestations (Including hematological ones) significantly improved upon RTX treatment. Specifically, the presence of the following signs and symptoms decreased significantly: anemia (38.8% to 23.5%), leucopenia (20.5% to 9.1%) and thrombocytopenia (32.9% to 11.8%) with p < 0.05 each. | | | | ⨁◯◯◯ VERY LOW 5 |  |
| Autoimmune Thrombocytopenia follow up: 20 months (1 observational study) | A cohort that included one hundred and thirty-one patients with refractory lupus that were treated with RTX reported adequate response regarding thrombocytopenia (Patients with platelets count < 60000/ml, 16.4% at the beginning of the study and 2.6 % at 3 month follow up (p < 0.001)) and lack of response regarding hemolytic anemia (Patients with hemolytic anemia at beginning of the study 4.7% and 1.0% at 3 month follow up) (Very low certainty in the effect estimate: High risk of bias, imprecision) | | | | ⨁◯◯◯ VERY LOW 5 |  |
| Hematological manifestations not specified follow up: 12 (2 observational studies) | An Italian cohort of 25 patients treated with RTX informed that14 patients had a complete response and 10 a partial response of hematological manifestations. Another Korean cohort reported adequate response of 10 patients out of 11 patients after RTX treatment | | | | ⨁◯◯◯ VERY LOW 5 |  |
| TTP follow up: 8 months (1 observational study) | A case report informed adequate response of a patient with thrombotic thrombocytopenia purpura treated with RTX | | | | ⨁◯◯◯ VERY LOW 5 |  |
| Aplastic anemia follow up: 3 months (1 observational study) | A case report informed adequate response of a patient with aplastic anemia after 3 months treated with RTX and antithymocyte globulin. | | | | ⨁◯◯◯ VERY LOW 5 |  |
| Refractory thrombocytopenia follow up: 28 months (1 observational study) | In a case series of 16 patients with refractory thrombocytopenia, RTX was added to ongoing treatment with methylprednisolone and/or IVIG. 5 of them presented flares and 14 achieved remission. (Very low certainty in the effect estimate: High risk of bias, imprecision) | | | | ⨁◯◯◯ VERY LOW 5 |  |
| \* Most frequent dose: 375 mg/m2 QWK | | | | | | |

1. No SLE patients
2. 95%CI includes benefits and harms
3. No blinding
4. Optimal information size not met
5. Small number of events

* Fernández-Nebro A, de la Fuente JLM, Carreño L, Izquierdo MG, Tomero E, Rúa-Figueroa I, et al. Multicenter longitudinal study of B-lymphocyte depletion in refractory systemic lupus erythematosus: the LESIMAB study. Lupus. 2012;21:1063–76.
* Iaccarino L, Bartoloni E, Carli L, Ceccarelli F, Conti F, De Vita S, et al. Efficacy and safety of off-label use of rituximab in refractory lupus: data from the Italian Multicentre Registry. Clin Exp Rheumatol. 2015;33:449–56.
* Bang S-Y, Lee CK, Kang YM, Kim H-A, Suh C-H, Chung WT, et al. Multicenter retrospective analysis of the effectiveness and safety of rituximab in korean patients with refractory systemic lupus erythematosus. Autoimmune Dis. 2012;2012:565039.
* Niaz FA, Aleem A. Response to rituximab in a refractory case of thrombotic thrombocytopenic purpura associated with systemic lupus erythematosus. Saudi J Kidney Dis Transpl. 2010;21:109–12.
* Witt M, Grunke M, Proft F, Baeuerle M, Aringer M, Burmester G, et al. Clinical outcomes and safety of rituximab treatment for patients with systemic lupus erythematosus (SLE) - results from a nationwide cohort in Germany (GRAID). Lupus. 2013;22:1142–9.
* Liu W, Hu Z, Lin S, He J, Zhou Y Systemic lupus erythematosis with severe aplastic anemia successfully treated with rituximab and antithymocyte globulinantithymocyte globulin. Pak J Med Sci 2014;30:449-451.
* Jovancevic B, Lindholm C, Pullerits R. Anti B-cell therapy against refractory thrombocytopenia in SLE and MCTD patients: long-term follow-up and review of the literature. Lupus. 2013;22:664–74.
* Chugh S, Darvish-Kazem S, Lim W, Crowther MA, Ghanima W, Wang G, et al. Rituximab plus standard of care for treatment of primary immune thrombocytopenia: a systematic review and meta-analysis. Lancet Haematol. 2015;2:e75-81.
* Birgens H, Frederiksen H, Hasselbalch HC, Rasmussen IH, Nielsen OJ, Kjeldsen L, et al. A phase III randomized trial comparing glucocorticoid monotherapy versus glucocorticoid and rituximab in patients with autoimmune haemolytic anaemia. British Journal of Haematology. 2013;163:393–9.

7.1.13

| **GCs\* compared to placebo for hematological manifestations of lupus** | | |
| --- | --- | --- |
| Result  Number of participants (Studies ) | **Impact** | Certainty |
|
|  |
| General hematological manifestations follow-up: 4 years  (1 observational study) | A Latin-American cohort reported a negative association with the treatment with GCs and hemolytic anemia in an univariate analysis, not confirmed in the multivariate analysis. | ⨁◯◯◯ VERY LOW 1 |
| Evans syndrome follow-up: 30 months  Number of participants:  (1 observational study) | A case series with patients with Evans syndrome reported that GCs were used in the majority of patients (60%, 16/27). | ⨁◯◯◯ VERY LOW 1 |
| Myelofibrosis follow-up: 6 years  (1 observational study) | A case report informed the efficacy of GCs therapy (methylprednisolone pulse therapy) in the treatment of lupus associated myelofibrosis showing response in the WBC count, platelet count and Hb level. | ⨁◯◯◯ VERY LOW 1 |
| Aplastic anemia follow-up: 6 months  (1 observational study) | A literature review found 5 case reports of patients with aplastic anemia treated with GCs, 4 of them showing adequate response and 1 with poor response (Very low certainty in the effect high risk of bias, imprecision). | ⨁◯◯◯ VERY LOW 1 |
| \* Most frequent dose: methylprednisolone 1 g/three times | | |

1. Small number of events

* González-Naranjo LA, Betancur OM, Alarcón GS, Ugarte-Gil MF, Jaramillo-Arroyave D, Wojdyla D, et al. Features associated with hematologic abnormalities and their impact in patients with systemic lupus erythematosus: Data from a multiethnic Latin American cohort. Semin Arthritis Rheum. 2016;45:675–83.
* Zhang L, Wu X, Wang L, Li J, Chen H, Zhao Y, et al. Clinical Features of Systemic Lupus Erythematosus Patients Complicated With Evans Syndrome: A Case-Control, Single Center Study. Medicine (Baltimore). 2016;95:e3279.
* Pundole X, Konoplev S, Oo TH, Lu H. Autoimmune myelofibrosis and systemic lupus erythematosus in a middle-aged male presenting only with severe anemia: a case report. Medicine (Baltimore). 2015;94:e741.
* Alishiri G-H, Saburi A, Bayat N, Saadat A-R, Saburi E. The initial presentation of systemic lupus erythematosis with aplastic anemia successfully treated with rituximab. Clinical Rheumatology. 2012 Feb;31(2):381–4.

7.1.14

| **TAC / Sirolimus\* compared to placebo for hematological manifestations of lupus** | | |
| --- | --- | --- |
| Result  Number of participants (Studies ) | **Impact** | Certainty |
|
|  |
| Evans syndrome follow-up: 1 years  (1 observational study) | A publication reported the case of a patients with ES that reached durable complete response by 12 months on therapy | ⨁◯◯◯ VERY LOW 1 |
| Toxicity follow-up: 1 year  (1 observational study) | The most common adverse effect was grade 1 to 2 mucositis (N = 10 of 30). One subject developed posterior multifocal leukoencephalopathy and stopped sirolimus. | ⨁◯◯◯ VERY LOW 1 |
| Hemophagocytic syndrome follow-up: 5 months  (1 observational study) | A case report informed the efficacy of low dose TAC in the treatment of refractory hemophagocytic syndrome showing response in the WBC count, Platelet count and Hb level. | ⨁◯◯◯ VERY LOW 1 |
| Multilineage cytopenia follow-up: 1 years  (1 observational study) | A cohort of 30 patients (12 with hematological manifestations of lupus) reported the following results: A total of 8 of 12 patients with multilineage autoimmune cytopenias obtained a CR by 1 year on therapy. Two patients achieved a PR and the remaining 2 of 12 were nonresponders. | ⨁◯◯◯ VERY LOW 1 |
| \* Tacrolimus at 2–3 mg/day, Sirolimus 2-2.5 mg/m2 | | |

1. Small number of events

* Bride KL, Vincent T, Smith-Whitley K, Lambert MP, Bleesing JJ, Seif E, et al Sirolimus is effective in relapsed/refractory autoimmune cytopenias: results of a prospective multi-institutional trial Blood 2016;127: 17–28.
* Watanabe H, Hirase N, Goda H, Nishikawa H, Ikuyama S Oral low-dose tacrolimus therapy for refractory hemophagocytic syndrome associated with systemic lupus erythematosus Mod Rheumatol 2012;22:284–289.

7.1.15

| **IVIG compared to placebo for Immune thrombocytopenia** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| Outcome № of participants (studies) | Relative effect (95% CI) | **Anticipated absolute effects (95% CI)** | | | Quality | What happens |
| **Without IVIG** | **With IVIG** | **Difference** |
| Effective rate № of participants: 469 (8 RCTs) 1 | Efficacy rate range reported in the included RCT was 69 to 100%. IVIG is probably effective for treating immune thrombocytopenia. Subgroup analysis did not revealed differences between pediatric and adult patients | | | | ⨁⨁⨁◯ MODERATE 2 | - |
| Platelet count < 20000 assessed with: GCs vs IVIG № of participants: 401 (6 RCTs) | **RR 0.74** (0.65 to 0.85) | 82.0% | **60.6%** (53.3 to 69.7) | **21.3% fewer** (28.7 fewer to 12.3 fewer) | ⨁⨁⨁◯ MODERATE 2 | IVIG probably increases the chance of platelet > 20000 |

1. Marked effect – platelet count less than 100109/l for 2 months, cessation of bleeding; well effect – platelet count from 50 to 100109/l for 2 months, cessation of bleeding; improvement – increasing the platelet count, improving the bleeding symptoms; invalid – no improvement of platelet and bleeding symptoms. The number of patients getting a good therapeutic effect was calculated as marked effect with well effect.

2. Risk of bias: mean Jadad score was 2

* Qin Y-H, Zhou T-B, Su L-N, Lei F-Y, Zhao Y-J, Huang W-F. The efficacy of different dose intravenous immunoglobulin in treating acute idiopathic thrombocytopenic purpura: a meta-analysis of 13 randomized controlled trials. Blood Coagul Fibrinolysis. 2010;21:713–21.
* Beck CE, Nathan PC, Parkin PC, Blanchette VS, Macarthur C. Corticosteroids Versus Intravenous Immune Globulin for the Treatment of Acute Immune Thrombocytopenic Purpura in Children: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. The Journal of Pediatrics. 2005;147:521–7.

7.2.1

| **CsA\* compared to AZA for hematological manifestations of lupus** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| Result  Number of participants (Studies ) | Relative effect (95% CI) | **Absolute Effect (95% CI)** | | | Certainty | What happens |
| **Without CsA** | **With CsA** | **Difference** |
| Resolution of anemia follow-up: 12 months  Number of participants: 89 (1 RCT) | **RR 1.79** (0.90 a 3.54) | 21.4% | **38.4%** (19.3 a 75.9) | **16.9% more**  (2.1 less a 54.4 more) | ⨁⨁◯◯ LOW 1,2 | CsA may increase resolution of anemia |
| Resolution of leucopenia follow-up: 12 months  Number of participants: 89 (1 RCT) | **RR 0.38** (0.20 a 0.74) | 50.0% | **19.0%** (10.0 a 37.0) | **31.0% less**  (40 less a 13 less) | ⨁⨁◯◯ LOW 1,2 | Cyclosporine may have little or no effect in resolution of leucopenia |
| Resolution of thrombocytopenia follow-up: 12 months  Number of participants: 89 (1 RCT) | **RR 0.13** (0.01 a 2.41) | 7.1% | **0.9%** (0.1 a 17.2) | **6.2% less**  (7.1 less a 10.1 more) | ⨁⨁◯◯ LOW 1,2 | Cyclosporine may have little or no effect in resolution of thrombocytopenia |
| \* Cyclosporine was commenced at 1.0 mg/kg/day in two divided doses and increased at 2 weekly intervals by 0.5 mg/kg/day, aiming for a dose of 2.5 mg/kg/day. The maximum permissible dose was 3.5 mg/kg/day. AZA was started at 0.5 mg/kg/day in two divided doses, and increased by 0.5 mg/kg/day at 2 weekly | | | | | | |

1. Selective reporting (laboratory results without clear explanation of thresholds)
2. Low number of events

* Griffiths B, Emery P, Ryan V, Isenberg D, Akil M, Thompson R, et al. The BILAG multi-centre open randomized controlled trial comparing ciclosporin vs azathioprine in patients with severe SLE. Rheumatology. 2010;49:723–32.

7.2.2

| **Danazol\* compared to cytotoxic drugs for hematological manifestations of lupus** | | |
| --- | --- | --- |
| Result  Number of participants (Studies ) | **Impact** | Certainty |
|
|  |
| Thrombocytopenia, Evan’s syndrome and hemolytic anemia follow-up: 8 weeks  (1 observational study) | Multiple case series showed that danazol has been used successfully in the treatment of thrombocytopenia (115 patients - efficacy rate not shown), Evan’s syndrome (59 patients - efficacy rate not shown), autoimmune hemolytic anemia | ⨁◯◯◯ VERY LOW 1,2 |
| Discontinuation due to adverse events follow-up: 8 weeks (1 observational study) | Overall, there were only 6 patients (about of 115 patients) who discontinued danazol due to adverse reactions, which included 4 patients with hepatitis and 2 patients with rash and menstrual disturbances. | ⨁◯◯◯ VERY LOW 1,2 |
| \* Doses between 200 to1200 mg/d | | |

1. Retrospective
2. Small number of participants

* Letchumanan P, Thumboo J Danazol in the Treatment of Systemic Lupus Erythematosus: A Qualitative Systematic Review Semin Arthritis Rheum 2011;40:298-306

7.2.3

| **MMF\* compared to CYC (IV) for hematological manifestations of lupus** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| Result  Number of participants (Studies ) | Relative effect (95% CI) | **Absolute Effect(95% CI)** | | | Certainty | What happens |
| **Without MMF** | **With MMF** | **Difference** |
| BILAG improvement follow-up: 24 weeks Number of participants: 102 (1 RCT) | **RR 0.89** (0.66 a 1.19) | 67.3% | **59.9%** (44.4 a 80.1) | **7.4% less**  (22.9 less a 12.8 more ) | ⨁⨁◯◯ LOW 1,2 | MMF may have little or no effect on BILAG improvement |
| BILAG deterioration follow-up: 24 weeks Number of participants: 136 (1 RCT) | **RR 1.19** (0.68 a 2.09) | 24.3% | **28.9%** (16.5 a 50.8) | **4.6% more**  (7.8 less a 26.5 more ) | ⨁⨁◯◯ LOW 1,2 | MMF may have little or no effect on BILAG deterioration |
| \* MMF: initial dose, 1000 mg per day, increased to 3000 mg per day. CYC: 0.5 g per square meter of body-surface area, increased to 1.0 g per square meter | | | | | | |

1. Open label
2. Small number of events

* Ginzler EM, Wofsy D, Isenberg D, Gordon C, Lisk L, Dooley MA. Nonrenal disease activity following mycophenolate mofetil or intravenous cyclophosphamide as induction treatment for lupus nephritis: findings in a multicenter, prospective, randomized, open-label, parallel-group clinical trial. Arthritis Rheum 2010;62:211-21.

8.1.1

| **AZA plus GCs compared to GCs for gastrointestinal manifestations of lupus** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| Result  Number of participants (Studies ) | Relative effect (95% CI) | **Absolute Effect (95% CI)** | | | Certainty | What happens |
| **Without AZA plus GCs** | **With AZA plus GCs** | **Difference** |
| Relapse follow up: 3 weeks Number of participants: 50 (1 RCT) | **RR 9.39** (1.27 a 69.61) | 3.7% | **34.8%** (4.7 a 100.0) | **31.1% more**  (1 more a 254.1 more ) | ⨁◯◯◯ LOW 1,2,5 | AZA may have little or no effect on relapses |
| Recurrence  follow up: 3 years Number of participants: 50 (1 RCT) | **RR 0.13** (0.04 a 0.86) | 4.3% | **0.6%** (0.2 a 3.7) | **3.8% less**  (4.2 less a 0.6 less ) | ⨁⨁◯◯ LOW 1,2,3,5 | AZA may have little or no effect on recurrence after relapse |
| Pseudo-obstruction (1 observational study) | AZA was used as maintenance therapy in 6/18 patients after GCs induction with good effects. | | | | ⨁◯◯◯ VERY LOW 2,4 | We are uncertain if AZA may have little or no effect on intestinal Pseudo-obstruction |
| Protein loosing enteropathy  (5 observational studies ) | Twenty cases (20/61, 33%) responded to AZA; two of them supported by HCQ (all patients received also GCs). One of these patients was refractory to AZA and was succesfully trated with cyclophosphamide. Four 4/61 (7%) cases responded to both AZA and CYC, and one patient responded to CsA and HCQ. The treatment regime consisted of high-dose prednisolone (0.8–1 mg/kg/day for 6 weeks, then tapered to 10 mg/day or less) and AZA (up to 2 mg/kg/day). | | | | ⨁◯◯◯ VERY LOW 2,4 | We are uncertain if AZA may have little or no effect on Protein loosing enteropathy |

1. Important lost to follow up (5 patients)
2. Small number of events
3. Non randomized trials proved similar results showing that during follow-up, 61 of 131 (47%) patients relapsed and 56 out of 131 (42%) had a loss of remission. One year after drug withdrawal, 59% of the patients required retreatment, increasing to 73% and 81% after 2 and 3 years, respectively J Hepatol. 2013 Jan;58(1):141-7. doi: 10.1016/j.jhep.2012.09.009. Epub 2012 Sep 16. Relapse is almost universal after withdrawal of immunosuppressive medication in patients with autoimmune hepatitis in remission. van Gerven, Verwer BJ, Witte BI, van Hoek B, Coenraad MJ, van Erpecum KJ, Beuers U, van Buuren HR, de Man RA, Drenth JP, den Ouden JW, Verdonk RC, Koek GH, Brouwer JT, Guichelaar MM, Mulder CJ, van Nieuwkerk KM, Bouma G; Dutch Autoimmune Hepatitis Working Group.
4. Case reports
5. Indirect evidence (patients with autoimmune hepatitis without LES).

* Stellon AJ, Hegarty JE, Portmann B, Williams R. Randomised controlled trial of azathioprine withdrawal in autoimmune chronic active hepatitis. Lancet. 1985;1:668–70.
* Mok MY, Wong RW, Lau CS. Intestinal pseudo-obstruction in systemic lupus erythematosus: an uncommon but important clinical manifestation. Lupus. 2000;9:11-8.
* Sultan M. Al-Mogairen Lupus protein-losing enteropathy (LUPLE): A systematic review. Rheumatol Int 2011:31:995–1001.
* Mok CC, Ying KY, Mak A, To CH, Szeto ML. Outcome of protein-losing gastroenteropathy in systemic lupus erythematosus treated with prednisolone and azathioprine. Rheumatology (Oxford). 2006;45:425–9.
* Zheng WJ, Tian XP, Li L, Jing HL, Li F, Zeng XF, et al. Protein-losing enteropathy in systemic lupus erythematosus: analysis of the clinical features of fifteen patients. J Clin Rheumatol. 2007;13:313–316

| 8.1.2 | | | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| **Belimumab compared to placebo for Lupus for gastrointestinal manifestations of lupus** | | | | | | |
| Result  Number of participants (Studies ) | Relative effect (95% CI) | **Absolute Effect (95% CI)** | | | Certainty | What happens |
| **Without** belimumab | **With** belimumab | **Difference** |
| Proportion of patients with significant clinical improvement BILAG **(any dose)** follow up: 1 year  Number of participants: 151 (2 RCT) | **RR 1.16** (0.69 a 1.92) | 28.8% | **33.5%** (19.9 a 55.4) | **4.6% more**  (8.9 less a 26.5 more ) | ⨁⨁◯◯ LOW1,2 | Belimumab (any dose) may make little or no difference to improvement of BILAG score domain in patients with lupus with gastrointestinal manifestations |
| Worsening in BILAG **(any dose)** follow up: 1 year  Number of participants: 1573 (2 RCT) | **RR 1.25** (0.24 a 6.43) | 0.4% | **0.5%** (0.1 a 2.4) | **0.1% more**  (0.3 less a 2.1 more ) | ⨁⨁⨁◯ MODERATE 1 | Belimumab (any dose) probably makes little or no difference to worsening of BILAG score domain in patients with lupus with gastrointestinal manifestations |
| Worsening in SLEDAI **(any dose)** follow up: 1 year  Number of participants: 1635 (2 RCT) | **RR 0.28** (0.09 a 0.83) | 1.6% | **0.5%** (0.1 a 1.4) | **1.2% less**  (1.5 less a 0.3 less ) | ⨁⨁⨁◯ MODERATE 2 | Belimumab (any dose) probably makes little or no difference to worsening of BILAG score domain in patients with lupus with gastrointestinal manifestations |

1. Small numbar of events, possible benefits and harms
2. Small number of events

* Manzi S, Sánchez-Guerrero J, Merrill JT, Furie R, Gladman D, Navarra SV, et al. Effects of belimumab, a B lymphocyte stimulator-specific inhibitor, on disease activity across multiple organ domains in patients with systemic lupus erythematosus: combined results from two phase III trials. Ann Rheum Dis. 2012;71:1833–8.

8.1.3

| **CsA compared to placebo for gastrointestinal manifestations of lupus** | | |
| --- | --- | --- |
| Result  Number of participants (Studies ) | **Impact** | Certainty |
|
|  |

|  |  |  |
| --- | --- | --- |
| Pseudo-obstruction follow up: 11 years (1 observational study) | CsA was reported as a second line choice for pseudo-obstruction after GCs induction. | ⨁◯◯◯ VERY LOW 1,2 |

1. Case reports
2. Small number of events

* Zhang, Mengtao Li and Xiaofeng Zeng Lingling Zhang, Dong Xu, Hong Yang, Xinping Tian, Qian Wang, Yong Hou, Na Gao, Li The Journal of Rheumatology in Systemic Lupus Erythematosus: A Retrospective Case-control Study Clinical Features, Morbidity, and Risk Factors of Intestinal Pseudo-obstruction http://www.jrheum.org/content/early/2016/01/02/jrheum.150074

8.1.4

| **CYC compared to GCs for gastrointestinal manifestations** | | |
| --- | --- | --- |
| Result  Number of participants (Studies ) | **Impact** | Certainty |
|
|  |
| Enteritis/vasculitis (3 observational studies (Case reports)) | Immunosuppressive treatment is usually reserved for severe cases or those with recurrent enteritis. Successful treatment of gastrointestinal vasculitis with CYC in patients with SLE has been reported. | ⨁◯◯◯ VERY LOW 1,2 |
| Pseudo-obstruction (1 observational study) | Intravenous CYC was described as a second line therapy after GCs in patients with pseudo-obstruction. CYC was used in 8 out of 40 cases in combination with GCs. Two patients who received only CYC had a good response. | ⨁◯◯◯ VERY LOW 1 |
| Protein loosing enteropathy (1 observational study) | 61 patients received CYC. Twenty-eight (28/61, 46%) patients remitted with IV CYC. Four 4/61 (7%) cases responded to both AZA and CYC, and one patient responded to CsA and HCQ. Three patients were refractory to CYC, two died, and one responded to etanercept. | ⨁◯◯◯ VERY LOW 1 |

1. Low number of events
2. Case series

* Grimbacher B, Huber M, von Kempis J, Kalden P, Uhl M, Köhler G, et al. Successful treatment of gastrointestinal vasculitis due to systemic lupus erythematosus with intravenous pulse cyclophosphamide: a clinical case report and review of the literature. Br J Rheumatol. 1998;37:1023–8.
* Laing TJ. Gastrointestinal vasculitis and pneumatosis intestinalis due to systemic lupus erythematosus: successful treatment with pulse intravenous cyclophosphamide. Am J Med. 1988;85:555–8.
* Alves SC, Fasano S, Isenberg DA. Autoimmune gastrointestinal complications in patients with systemic lupus erythematosus: case series and literature review. Lupus. 2016;25:1509–19.
* Kwok S-K, Seo S-H, Ju JH, Park K-S, Yoon C-H, Kim W-U, et al. Lupus enteritis: clinical characteristics, risk factor for relapse and association with anti-endothelial cell antibody. Lupus. 2007;16:803–9.
* Wang J, Liu G, Liu T, Wei J. Intestinal pseudo-obstruction in systemic lupus erythematosus: a case report and review of the literature. Medicine (Baltimore). 201;93:e248.
* Werner de Castro GR, Appenzeller S, Bértolo MB, Costallat LTL. Protein-losing enteropathy associated with systemic lupus erythematosus: response to cyclophosphamide. Rheumatol Int. 2005;25:135–8.
* Al-Mogairen SM. Lupus protein-losing enteropathy (LUPLE): a systematic review. Rheumatol Int. 2011;31:995–1001.

8.1.5

| **MMF compared to placebo for Lupus with gastrointestinal manifestations** | | |
| --- | --- | --- |
| Result  Number of participants (Studies ) | **Impact** | Certainty |
|
|  |

|  |  |  |
| --- | --- | --- |
| Lupus enteritis follow up: 12 months  (1 observational study) | 136 patients with diagnosis of Lupus enteritis were treated with MMF after at least 12 months of treatment with GCs. At the 12-month follow-up, 63 patients (46%) were good responders, 18 (13%) had partial response, and 42 (31%) were non responders. There was a 10% missing data. At the one-month follow-up, 33% of all the patients from baseline experienced AES; 26% of them discontinued their treatment. The certainty in the effect estimate is very low due to high risk of bias and imprecision. | ⨁◯◯◯ VERY LOW 1 |

1. Low number of participants and events

* Lourdudoss C, Vollenhoven R van. Mycophenolate mofetil in the treatment of SLE and systemic vasculitis: experience at a single university center. Lupus. 2014 Mar;23(3):299–304.

8.1.6

| **RTX compared to GCs for lupus enteritis (vasculitis)** | | |
| --- | --- | --- |
| Result  Number of participants (Studies ) | **Impact** | Certainty |
|
|  |

|  |  |  |
| --- | --- | --- |
| Lupus enteritis (vasculitis) (1 observational study) | Beneficial effects of RTX in SLE patients with diffuse involvement of the GI tract have been described. Very low certainty: Information obtained from 3 case reports | ⨁◯◯◯ VERY LOW 1 |

1. Case reports

* Ju JH, Min J-K, Jung C-K, Oh SN, Kwok S-K, Kang KY, et al. Lupus mesenteric vasculitis can cause acute abdominal pain in patients with SLE. Nat Rev Rheumatol. 2009;5:273–81.
* Waite L, Morrison E. Severe gastrointestinal involvement in systemic lupus erythematosus treated with rituximab and cyclophosphamide (B-cell depletion therapy). Lupus. 2007;16:841–2.
* Alves SC, Fasano S, Isenberg DA. Autoimmune gastrointestinal complications in patients with systemic lupus erythematosus: case series and literature review. Lupus. 2016;25:1509–19.

8.1.7

| **GCs compared to placebo for gastrointestinal manifestations of lupus** | | |
| --- | --- | --- |
| Result  Number of participants (Studies ) | **Impact** | Certainty |
|
|  |
| Hepatitis  (3 observational studies) | The recommended treatment for both autoimmune hepatitis (AIH) and Lupus is immunosuppressive therapy. The standard treatment for AIH comprises high dose of prednisone. High risk of bias studies evaluating the response of chronic active liver disease proved remission rates of 65–80%. Approximately 13% of patients discontinued therapy because of intolerable prednisone-related side effects.  AZA should be added to the therapeutic regimen as a GCs-sparing agent or in refractory cases.  Previous guidelines on autoimmune hepatitis recommend (all recommendations based in low certainty - observational studies, indirect evidence studies including mainly infants):  1. Prednisone in combination with AZA or a higher dose of prednisone alone is the appropriate treatment for severe AIH in adults (Strong recommendation)  2. Prednisone in combination with AZA is the preferred initial treatment because of its lower frequency of side effects (Optional recommendation).  3. All patients treated with prednisone alone or in combination with AZA must be monitored for the development of drug-related side effects (Optional recommendation).  4. AZA or 6-mercaptopurine is preferred as a GCs-sparing agent in children, especially when high doses of prednisone are required for disease control (Optional recommendation). | ⨁◯◯◯ VERY LOW 1,2 |
| Peritonitis (4 observational studies) | Mild cases of lupus peritonitis may be treated with NSAIDs alone. However, 4 case reports show rapid response with GCs. The same case reports support the use of high-dose GCs in the form of pulse methylprednisolone (as well as additional immunosuppressive agents such as AZA, CsA and CYC) in patients presenting with massive ascites and in those with recurrent or refractory peritonitis. | ⨁◯◯◯ VERY LOW 1,2 |
| Lupus enteritis - GI vasculitis  (5 observational studies) | Lupus enteritis is typically responsive to high dose of GCs (2 case series 41 and 14 patients were treated with EV methylprednisolone 1 mg/k/d and then tapered to oral meprednisone with good response). Very low certainty: Information obtained from case reports, small case series and physicians surveys | ⨁◯◯◯ VERY LOW 1 |
| Pancreatitis (2 observational studies) | GCs have been suggested to be the cause of pancreatitis. However, pancreatitis has been described in patients with SLE on no GCs. On the other hand, GCs were shown to decrease mortality. Mortality was decreased in patients who were treated with GCs after the onset of pancreatitis 13 out of 64 patients that received GCs died (20%), compared to 8 out of 13 patients (61%) among those who were not treated with GCs for their pancreatitis. Different doses of GCs were reported ranging from an increase of 10 mg/day of prednisone, to pulsed-dose methylprednisolone at 1 g IV every day for 3 consecutive days. | ⨁◯◯◯ VERY LOW 1 |
| Pseudo-obstruction  (3 observational studies) | 17/18 patients required the use of high dose systemic GCs therapy with good response. Similar results were obtained in case reports. The initial dose was 500 mg or 1000 mg/day of methylprednisolone followed by 1 to 2 mg/kg/day or prednisolone. The use of AZA or TAC was mentioned as second line therapy. | ⨁◯◯◯ VERY LOW 1 |
| Protein loosing enteropathy  (3 observational studies) | In this review, the details of therapy were reported for 93 patients. All lupus patients (93/93, 100%) were treated with GCs. Thirty-two of 93 (34%) responded to GCs alone, and 61/93 (66%) were also started with other immunosuppressive therapy. | ⨁◯◯◯ VERY LOW 1 |

1. Small number of participants
2. Information provided from observational trial

* Autoimmune Hepatitis: Clinical Review with Insights into the Purinergic Mechanism of Disease. Journal of Clinical and Translational Hepatology. 2016 Dec 15 [cited 2017 Dec 11];1(2). Available from: http://www.xiahepublishing.com/ArticleFullText.aspx?sid=2&jid=1&id=10.14218%2fJCTH.2013.00015
* Mok CC. Investigations and management of gastrointestinal and hepatic manifestations of systemic lupus erythematosus. Best Practice & Research Clinical Rheumatology. 2005;19:741–66.
* Andoh A, Fujiyama Y, Kitamura S, Ihara T, Ueda K, Miyagawa A, et al. Acute lupus peritonitis successfully treated with steroid pulse therapy. J Gastroenterol. 1997;32:654–7.
* Kaklamanis P, Vayopoulos G, Stamatelos G, Dadinas G, Tsokos GC. Chronic lupus peritonitis with ascites. Ann Rheum Dis. 1991;50:176–7.
* Andoh A, Fujiyama Y, Kitamura S, Ihara T, Ueda K, Miyagawa A, Hodohara K, et al. Acute lupus peritonitis successfully treated with steroid pulse therapy J Gastroenterol. 1997;32:654-7.
* Nesher G, Breuer GS, Temprano K, Moore TL, Dahan D, Baer A, et al. Lupus-associated pancreatitis. Semin Arthritis Rheum. 2006;35:260–7.
* Derk CT, DeHoratius RJ. Systemic lupus erythematosus and acute pancreatitis: a case series. Clin Rheumatol. 2004 Apr;23(2):147–51.
* Mok M, Wong RWS, Lau CS. Intestinal pseudo-obstruction in systemic lupus erythematosus: an uncommon but important clinical manifestation. Lupus. 2000;9:11–8.
* Wang J, Liu G, Liu T, Wei J. Intestinal pseudo-obstruction in systemic lupus erythematosus: a case report and review of the literature. Medicine (Baltimore). 2014;93:e248.
* Park F-D, Lee J-K, Madduri G-D, Ghosh P. Generalized megaviscera of lupus: refractory intestinal pseudo-obstruction, ureterohydronephrosis and megacholedochus. World J Gastroenterol. 2009;15:3555–9.
* Al-Mogairen SM. Lupus protein-losing enteropathy (LUPLE): a systematic review. Rheumatol Int. 201;31:995–1001.
* Zheng W, Tian X, Li L, Jing H, Li F, Zeng X, et al. Protein-losing enteropathy in systemic lupus erythematosus: analysis of the clinical features of fifteen patients. J Clin Rheumatol. 2007;13:313–6.

8.1.8

| **Early surgical intervention (< 48 hours) compared to late surgical intervention for gastrointestinal manifestations of lupus** | | |
| --- | --- | --- |
| Result  Number of participants (Studies ) | **Impact** | Certainty |
|
|  |

|  |  |  |
| --- | --- | --- |
| Gastrointestinal manifestations of lupus (Lupus enteritis)  (1 observational study) | When a rapid response to immunosuppressive therapy is not achieved, surgical intervention for possible bowel perforation or large area of ischemia should be considered. Early laparotomy within 24 to 48 h is critical for improving the prognosis of patients with acute abdomen It was found that 10 of 11 patients with this condition who underwent surgery after 48 h died, while none of 33 patients who were operated on within 24-48 h died. | ⨁◯◯◯ VERY LOW 1 |

1. Small number of events

* Medina F, Ayala A, Jara LJ, Becerra M, Miranda JM, Fraga A. Acute Abdomen in Systemic Lupus Erythematosus. The American Journal of Medicine. 1997;103:100–5.

8.1.9

| **TAC compared to placebo for gastrointestinal manifestations of lupus** | | |
| --- | --- | --- |
| Result  Number of participants (Studies ) | **Impact** | Certainty |
|
|  |

|  |  |  |
| --- | --- | --- |
| Pseudo-obstruction (1 observational study) | TAC was reported as a second line choice for pseudo-obstruction after GCs induction. | ⨁◯◯◯ VERY LOW 1,2 |

1. Case reports
2. Small number of reports

* Zhang, Mengtao Li and Xiaofeng Zeng Lingling Zhang, Dong Xu, Hong Yang, Xinping Tian, Qian Wang, Yong Hou, Na Gao, Li The Journal of Rheumatology in Systemic Lupus Erythematosus: A Retrospective Case-control Study Clinical Features, Morbidity, and Risk Factors of Intestinal Pseudo-obstruction <http://www.jrheum.org/content/early/2016/01/02/jrheum.150074>

| 8.2.1 | | | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| **CsA compared to AZA for gastrointestinal manifestations of lupus** | | | | | | |
| Result  Number of participants (Studies ) | Relative effect (95% CI) | **Absolute Effect(95% CI)** | | | Certainty | What happens |
| **Without Cyclosporine** | **With Cyclosporine** | **Difference** |
| Raised liver function tests follow up: 6 months Number of participants: 89 (1 RCT)) | **RR 0.60** (0.23 a 1.53) | 21.4% | **12.9%** (4.9 a 32.8) | **8.6% less**  (16.5 less a 11.4 more ) | ⨁◯◯◯ VERY LOW 1,2,3 | CsA may make little or no difference to treat raised liver function tests |
| Jaundice follow up: 6 months Number of participants: 89 (1 RCT) | **RR 0.13** (0.01 a 2.41) | 7.1% | **0.9%** (0.1 a 17.2) | **6.2% less**  (7.1 less a 10.1 more ) | ⨁◯◯◯ VERY LOW 1,2,3 | CsA may make little or no difference to treat jaundice |

1. Selective outcomes reporting, not clear thresholds
2. Unclear randomization and allocation
3. Small number of events with possible benefits and harms

* Griffiths B, Emery P, Ryan V, Isenberg D, Akil M, Thompson R, et al. The BILAG multi-centre open randomized controlled trial comparing ciclosporin vs azathioprine in patients with severe SLE. Rheumatology. 2010;49:723–32.

8.2.2

| **MMF compared to CYC for gastrointestinal manifestations of lupus** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| Result  Number of participants (Studies ) | Relative effect (95% CI) | **Absolute Effect(95% CI)** | | | Certainty | What happens |
| **Sin MMF** | **Con MMF** | **Difference** |
| Significant improvement in intestinal manifestations (vasculitis) follow up: 1 Number of participants: 17 (1 RCT)) | **RR 1.00** (0.81 a 1.24) | 100.0% | **100.0%** (81.0 a 100.0) | **0.0% less**  (19 less a 24 more ) | ⨁⨁◯◯ LOW 1,2 | MMF may make little or no difference to treat intestinal vasculitis |

1. Unclear randomization and allocation
2. Small number of events and possible benefits and harms

* Ginzler EM, Wofsy D, Isenberg D, Gordon C, Lisk L, Dooley MA. Nonrenal disease activity following mycophenolate mofetil or intravenous cyclophosphamide as induction treatment for lupus nephritis: findings in a multicenter, prospective, randomized, open-label, parallel-group clinical trial. Arthritis Rheum 2010;62:211-21.

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| 9.1.1 | | |
| --- | --- | --- |
| **CYC compared to placebo for lupus nephritic in pediatric patients** | | |
| Result  Number of participants (Studies ) | **Impact** | Quality |
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|  |
| Death, response after AKI and progression of CKD  Follow up: 36 months  Number of participants: 108 patients  (1 Observational study) | A cohort included a total of 108 (19 male, 89 female) patients with a mean age at diagnosis of 11.4 ± 2.6 years (range 5.4–16.9) that received GCs treatment combined with IV CYC. At the end of the study, twenty-three patients had died (any cause). Thirty-two patients developed acute kidney injury (AKI), of whom 7 died, 18 resolved, and 7 progressed to CKD. | ⨁◯◯◯ VERY LOW 1,2 |
| Remission Follow up: 6 months  Number of participants: 29 patients  (1 Observational study) | Another cohort reported twenty nine patients with a mean age of 10.3 ± 2.6 year treated with a dose of 750 mg/m2 at the first month followed by six cycles of monthly cyclophosphamide (IVCY) at a dose of 1 g/m2. Twenty patients (69%) achieved remission at the end of induction therapy. | ⨁◯◯◯ VERY LOW 1,2 |
| Flares after remission  Follow up: 36 months  Number of participants: 21 patients  (1 Observational study) | A third cohort of 21 patients with lupus nephritis treated with Cyclophosphamide showed the following results: Five patients had six episodes of acute renal failure: one died, renal function returned to normal in two patients, two continued to chronic renal failure, and one died of chronic renal failure. | ⨁◯◯◯ VERY LOW 1,2 |

1. Case reports
2. Small number of reports
   * Opastirakul S, Chartapisak W. Pulse cyclophosphamide induction treatment in Thai children with diffuse proliferative lupus nephritis: Pulse IVCY in DPLN children. Nephrology. 2012;17:269–73.
   * Vachvanichsanong P, Dissaneewate P, Winn T. Intravenous cyclophosphamide for lupus nephritis in Thai children. Scand J Rheumatol. 2004;33:339-42.
   * Vachvanichsanong P, Dissaneewate P, McNeil E. Intravenous cyclophosphamide combined with steroids in pediatric onset severe lupus nephritis. Int Urol Nephrol. 2013;45:1301-8.
   * Paivi M Miettunen. Therapeutic approaches for the treatment of renal disease in juvenile systemic lupus erythematosus: an international multicentre PRINTO study. Ann Rheum Dis. 2013;72:1503-9.

9.1.2

| **Methylprednisolone plus MMF plus CsA compared to placebo for lupus nephritis in pediatric patients** | | |
| --- | --- | --- |
| Outcome № of participants (studies) | **Impact** | Certainty |
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|  |
| Remission follow up: 9 months № of participants: 22 patients  (2 observational studies) | A cohort of Six Japanese children treated with methylprednisolone pulse therapy (MPT) informed that complete remission was achieved in two patients. Another cohort of 16 patients with severe proliferative lupus nephritis informed that all patients achieved complete renal remission within a median of 8.7 months (4 - 24). | ⨁◯◯◯ VERY LOW 1,2 |
| Flares follow up: 10 years № of participants: 16 patients  (1 observational study) | The previously mentioned cohort of 16 patients with severe proliferative lupus nephritis showed that 12 patients remained free of flares after 10 years of follow up. | ⨁◯◯◯ VERY LOW 1,2 |
| End stage renal disease follow up: 53 months  (1 observational study ) | No patients developed end stage renal disease in 53 months of follow up. | ⨁◯◯◯ VERY LOW 1,2 |

1. Case series
2. Small amount of patients included

* Tanaka H, Tateyama T, Waga S. Methylprednisolone pulse therapy in Japanese children with severe lupus nephritis. Pediatr Nephrol. 2001;16:817-9.
* Aragon E, Resontoc LP, Chan YH, Lau YW, Tan PH, Loh HL, et al. Long-term outcomes with multi-targeted immunosuppressive protocol in children with severe proliferative lupus nephritis. Lupus. 2016;25:399-406.

9.1.3

| **Mizorbine compared to placebo for lupus nephritis in pediatric patients** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| Outcome № of participants (studies) | Relative effect (95% CI) | **Anticipated absolute effects (95% CI)** | | | Certainty | What happens |
| **Without Mizorbine** | **With Mizorbine** | **Difference** |
| Flare follow up: 1 years № of participants: 58 (1 RCT) | **RR 0.69** (0.40 to 1.21) | 56.7% | **39.1%** (22.7 to 68.6) | **17.6% fewer** (34 fewer to 11.9 more) | ⨁⨁◯◯ LOW 1,2 | Mizorbine may reduce flares in pediatric patients with Lupus nephritis |
| Dropout due to adverse events follow up: 1 years № of participants: 58 (1 RCT) | **RR 11.76** (0.68 to 203.37) | 0.0% | **(5 out of 28) 18%** (0.0 to 40) | **18% more** (0 fewer to 40 more) | ⨁⨁◯◯ LOW 1,2 | Mizorbine may increase Dropout due to adverse events in pediatric patients with Lupus nephritis |
| Dropout due to adverse events follow up: 1 year № of participants: 58 (1 RCT) | No difference in the severity of proteinuria or renal dysfunction at the end of the study was observed between the treatment groups | | | | ⨁◯◯◯ VERY LOW 2,3 |  |
| Proteinuria follow up: 2 years (1 observational study) | Observational trials that used Mizorbine associated with GCs pulse therapy show a possible decrease in proteinuria two years after the start of combination therapy (P = .0016) with stable serum creatinine levels of all patients. | | | | ⨁◯◯◯ VERY LOW 2,4 |  |

1. Important lost to follow up and unclear randomization and concealed allocation
2. Small amount of patients included
3. No numerical data provided for this outcome
4. Case series

* Kawasaki Y. Mizoribine: A New Approach in the Treatment of Renal Disease. Clinical and Developmental Immunology. 2009;2009:1–10.
* Tanaka Y, Yoshikawa N, Hattori S, Sasaki S, Ando T, Ikeda M, Honda M Combination therapy with steroids and mizoribine in juvenile SLE: a randomized controlled trial Pediatr Nephrol. 2010;25:877–882.

9.1.4

| **MMF compared to placebo for lupus nephritis in pediatric patients** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| Outcome № of participants (studies) | Relative effect (95% CI) | **Anticipated absolute effects (95% CI)** | | | Certainty | What happens |
| **Without MMF** | **With MMF** | **Difference** |
| Death follow up: 39 months (1 observational study) | not estimable | 42.1% | **0.0%** | **42.1% fewer** (42.1 fewer to 0 fewer) | ⨁◯◯◯ VERY LOW 1,2 | MMF may reduce death incidence in pediatric patients with lupus nephritis |
| Remission (partial or complete) follow up: 39 months № of participants: 52 (1 observational study) | **RR 2.30** (1.15 to 4.61) | 31.6% | **72.6%** (36.3 to 100.0) | **41.1% more** (4.7 more to 114 more) | ⨁◯◯◯ VERY LOW 1,2 | MMF may increase the remission rate in pediatric patients with Lupus nephritis |
| Flares follow up: 39 months № of participants: 16 patients (1 observational study) | Five girls with a mean age of 13.9 (range 12-15) years were treated with 1.2+/-0.20 g MMF daily. The number of flares decreased from 1.28 to 0.25 episodes per patient/year during a mean follow-up period of 39 (range 36-42) months after MMF initiation. | | | | ⨁◯◯◯ VERY LOW 1,2 | - |

1. Retrospective cohort
2. Small amount of patients included

* Chou HH, Chen MJ, Chiou YY. Enteric-coated mycophenolate sodium in pediatric lupus nephritis: a retrospective cohort study. Clin Exp Nephrol. 2016;20:628-36.
* Dittrich K, Ross S, Benz K, Amann K, Dötsch J. Experience with mycophenolate mofetil as maintenance therapy in five pediatric patients with severe systemic lupus erythematosus. Klin Padiatr. 2009;221:425-9.
* Buratti S, Szer IS, Spencer CH, Bartosh S, Reiff A. Mycophenolate mofetil treatment of severe renal disease in pediatric onset systemic lupus erythematosus. J Rheumatol. 2001;28:2103–8.
* Falcini F, Capannini S, Martini G, La Torre F, Vitale A, Mangiantini F, et al. Mycophenolate mofetil for the treatment of juvenile onset SLE: a multicenter study. Lupus. 2009;18:139–43.

9.1.5

| **Pentoxifylline compared to placebo for lupus nephritis in pediatric patients** | | |
| --- | --- | --- |
| Outcome № of participants (studies) | **Impact** | Certainty |
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|  |
| Laboratory results follow up: 1 years № of participants: 6 patients  (1 observational study) | A case series of 6 patients (mean 14.1 years) showed improvement in proteinuria, hematuria and creatinine. (Values not reported) | ⨁◯◯◯ VERY LOW 1,2,3 |

1. Case series
2. Laboratory results results (Surrogate outcome)
3. Small number of patients

* Vázquez García MJ, Vargas Camaño ME, Olalde Carmona R. Use of pentoxifylline in pediatric patients with grade IV (OMS) lupus nephropathy who have received multiple treatments. Rev Alerg Mex. 2000;47:109-14.

9.1.6

| **TPE compared to placebo for lupus nephritis in pediatric patients** | | |
| --- | --- | --- |
| Outcome № of participants (studies) | **Impact** | Certainty |
|
|  |
| Remission follow up: 1 year № of participants: 6 patients  (1 observational study) | An observational trial (6 patients) used TPE associated with pulse methylprednisolone therapy (three patients were also treated with cytotoxic drugs) for children with systemic lupus erythematosus (SLE) and glomerulonephritis. All patients had severe nephrotic syndrome and five of six experienced a complete and sustained (greater than 1 year) remission post-PE. | ⨁◯◯◯ VERY LOW 1,2 |
| End stage renal disease follow up: 1 year № of participants: 6 patients  (1 observational study) | In the study previously mentioned , one patient progressed to renal failure and dialysis more than 1 year post-PE. | ⨁◯◯◯ VERY LOW 1,2 |

1. case series
2. small number of patients

* Jordan SC, Ho W, Ettenger R, Salusky IB, Fine RN. Plasma exchange improves the glomerulonephritis of systemic lupus erythematosus in selected pediatric patients. Pediatr Nephrol. 1987;1:276-80.

9.1.7

| **RTX compared to placebo for lupus nephritis in pediatric patients** | | |
| --- | --- | --- |
| Outcome № of participants (studies) | **Impact** | Certainty |
|
|  |
| SLEDAI SCORE improvement follow up: 1 year № of participants: 4 patients  (1 observational study) | In a case series including 4 patients with lupus nephritis treated with RTX the SLEDAI score, for those patients, decreased from a median of 15.5 (11 - 18) to 3 (0 - 6). | ⨁◯◯◯ VERY LOW 1,2 |
| Maintenance after remission follow up: 1 year № of participants: 19 patients  (3 observational studies) | Of 19 patients that achieved remission included in 3 case series, 5 patients presented a flare and were successfully retreated with a second course of RTX. | ⨁◯◯◯ VERY LOW 1,2 |
| Lupus nephritis remission follow up: 6 months № of participants: 37 patients  (5 observational studies) | 5 case series reported LN response: 22 patients achieved response out 37of patients included. Mean follow-up: 6 months | ⨁◯◯◯ VERY LOW 1,2 |
| Adverse events follow up: 1 year № of participants: 30 patients  (3 observational studies) | Adverse events: In 3 case series including 30 patients with lupus nephritis treated with RTX, 8 patients had severe adverse events. | ⨁◯◯◯ VERY LOW 1,2 |

1. Case series
2. Small amount of patients included

* Reis J, Aguiar F, Brito I. Anti CD20 (Rituximab) therapy in refractory pediatric rheumatic diseases. Acta Reumatol Port. 2016;41:45-55.
* Trachana M, Koutsonikoli A, Farmaki E, Printza N, Tzimouli V, Papachristou F. Safety and efficacy of rituximab in refractory pediatric systemic lupus erythematosus nephritis: a single-center experience of Northern Greece. Rheumatol Int. 2013;33:809-13.
* Willems M, Haddad E, Niaudet P, Koné-Paut I, Bensman A, Cochat P, et al. Rituximab therapy for childhood-onset systemic lupus erythematosus. J Pediatr. 2006;148:623-627.
* Lau KK, Ault BH, Jones DP, Butani L. Induction therapy for pediatric focal proliferative lupus nephritis: cyclophosphamide versus mycophenolate mofetil. J Pediatr Health Care. 2008;22:282-8.
* Polido-Pereira J, Ferreira D, Rodrigues AM, Nascimento C, Costa P, Almeida M, et al. Rituximab use in pediatric autoimmune diseases: four case reports. Ann N Y Acad Sci. 2009;1173:712-20.
* Nwobi O, Abitbol CL, Chandar J, Seeherunvong W, Zilleruelo G. Rituximab therapy for juvenile-onset systemic lupus erythematosus. Pediatr Nephrol. 2008;23:413–9.
* Grajales C, Velásquez M. Rituximab en población pediátrica: experiencia en el tratamiento de enfermedades reumatológicas, en un hospital infantil de Medellín, Colombia. Rev Colomb Reumatol 2012;19: 201-207.

9.1.8

| **TAC compared to placebo for lupus nephritis in pediatric patients** | | |
| --- | --- | --- |
| Outcome № of participants (studies) | **Impact** | Certainty |
|
|  |
| Creatinine values follow up: 36 months № of participants: 19 patients  (1 observational study) | Creatinine values: in a cohort of 19 non adult patients (mean age 18 years from 9 to 34 years) treated for 36 months with TAC. All showed stable creatinine values (none duplicated or reduced 50% of creatinine levels). None of the patients died or presented end stage renal disease. | ⨁◯◯◯ VERY LOW 1,2 |
| Adverse events follow up: 1 year № of participants: 26 patients  (1 observational study) | Adverse events: 3 patients developed herpes zoster, 1 developed acute bronchitis.. None of the patients discontinued the treatment. | ⨁◯◯◯ VERY LOW 1,2 |

1. case series
2. small amount of patients included

* Tanaka H, Watanabe S, Aizawa-Yashiro T, Oki E, Kumagai N, Tsuruga K, et al. Long-term tacrolimus-based immunosuppressive treatment for young patients withlupus nephritis: a prospective study in daily clinical practice. Nephron Clin Pract. 2012;121:c165-73.
* Tanaka H, Aizawa T, Watanabe S, Oki E, Tsuruga K, Imaizumi T. Efficacy of mizoribine-tacrolimus-based induction therapy for pediatric lupus nephritis. Lupus. 2014;23:813–8.

9.1.9

| **Belimumab compared to placebo for lupus nephritis in pediatric patients** | | |
| --- | --- | --- |
| Result  Number of participants (Studies ) | **Impact** | Certainty |
|
|  |
| Disease activity  follow-up: 6 months  № of participants: 39 patients  (1 observational study) | In an observational cohort that included 39 patients treated with belimumab, GCs treatment was discontinued in 35% of patients 6 months after belimumab initiation. | ⨁◯◯◯ VERY LOW 1,2,3 |
| Proteinuria  № of participants:12 patients  (1 observational study) | In a cohort of 12 patients (6 of whom the follow-up was completed); 3/6 had >50% reduction in proteinuria | ⨁◯◯◯ VERY LOW 1,2,4 |

1. Small number of participants
2. Information provided from observational study with an important lost to follow up (50%)
3. Indirectness: Most of the pediatric patients with mucocutaneous or musculosqueletal manifestations
4. Indirectness: Adult patients

* Hui-Yuen JS, Reddy A, Taylor J, Li X, Eichenfield AH, Bermudez LM,et alSafety and Efficacy of Belimumab to Treat Systemic Lupus Erythematosus in Academic Clinical Practices. J Rheumatol. 2015;42:2288-95.

9.2.1

| **AZA compared to CYC for lupus nephritis in pediatric patients** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| Outcome № of participants (studies) | Relative effect (95% CI) | **Anticipated absolute effects (95% CI)** | | | Certainty | What happens |
| **Without AZA** | **With AZA** | **Difference** |
| End Stage renal disease  follow up: 8 years № of participants: 42 (1 observational study) | **RR 0.27** (0.02 to 3.95) | 11.1% | **3.0%** (0.2 to 43.9) | **8.1% fewer** (10.9 fewer to 32.8 more) | ⨁◯◯◯ VERY LOW 1 | AZA may make little or no difference to end Stage renal disease in pediatric patients with lupus nephritis |
| Renal flares follow up: 8 years № of participants: 42 (1 observational study) | **RR 1.02** (0.45 to 2.32) | 44.4% | **45.3%** (20.0 to 100.0) | **0.9% more** (24.4 fewer to 58.7 more) | ⨁◯◯◯ VERY LOW 1 | AZA may make little or no difference to Renal flares in pediatric patients with lupus nephritis |

1. Small amount of patients included

* Benseler SM, Bargman JM, Feldman BM, Tyrrell PN, Harvey E, Hebert D, et al. Acute renal failure in paediatric systemic lupus erythematosus: treatment and outcome. Rheumatology (Oxford). 2009;48:176-82.

9.2.2

| **CsA compared to prednisolone plus CYC for lupus nephritis in pediatric patients** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| Outcome № of participants (studies) | Relative effect (95% CI) | **Anticipated absolute effects (95% CI)** | | | Certainty | What happens |
| **Without CsA** | **With CsA** | **Difference** |
| CrCl >= 120 follow up: 1 year № of participants: 38 (1 RCT) | **RR 0.33** (0.11 to 1.02) | 50.0% | **16.5%** (5.5 to 51.0) | **33.5% fewer** (44.5 fewer to 1 more) | ⨁⨁◯◯ LOW 1,2 | CsA may decrease the probability of having a CrCl >=120 |
| Growth velocity >=8 cm/ year follow up: 1 year № of participants: 38 (1 RCT) | **RR 23.21** (1.46 to 369.79) | 0.0% | **55%** (0.0 to 55%) | **55% more** (0 more to 55% more) | ⨁⨁◯◯ LOW 1,2 | CsA may increase growth velocity |
| Dropout due to exacerbations follow up: 1 years № of participants: 38 (1 RCT) | **RR 5.53** (0.28 to 107.96) | 0.0% | **11%** (0.0 to 0.0) | **11% more** (0 more to 11% more) | ⨁⨁◯◯ LOW 1,2 | CsA may increase dropout due to adverse events |

1. Optimal information size not met
2. No blinding

* Fu LW, Yang LY, Chen WP, Lin CY. Clinical efficacy of cyclosporin a neoral in the treatment of pediatric lupus nephritis with heavy proteinuria. Br J Rheumatol. 1998;37:217-21.

9.2.3

| **MMF compared to CYC plus AZA for lupus nephritis in pediatric patients** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| Result  Number of participants (Studies ) | Relative effect (95% CI) | **Absolute Effect(95% CI)** | | | Certainty | What happens |
| **Without MMF** | **With MMF** | **Difference** |
| Remission Follow up: 24 weeks Number of participants: 24 (1 RCT) | **RR 1.23** (0.67 a 2.25) | 57.1% | **70.3%** (38.3 a 100.0) | **13.1% more**  (18.9 less a 71.4 more ) | ⨁⨁◯◯ LOW 1 | MMF may increase remission |
| Death Follow up: 36 months  Number of participants: 16 (1 RCT) | No t measureable | 0.0% (0 out of 8 patients) | **0.0%** (0.0 a 0.0) (0 out of 8 patients) | **0.0% less**  (0 less a 0 less ) | ⨁⨁◯◯ LOW 1,2 | - |
| End stage renal disease Follow up: 36 months  Number of participants: 16 (1 RCT) | **RR 0.20** (0.01 a 3.61) | 25.0% | **5.0%** (0.3 a 90.3) | **20.0% less**  (24.8 less a 65.3 more ) | ⨁⨁◯◯ LOW 1,2 | MMF may decrease ESRD |
| Doubling serum creatinine Follow up: 36 months  Number of participants: 16 (1 RCT) | **RR 0.33** (0.02 a 7.14) | 12.5% | **4.1%** (0.3 a 89.3) | **8.4% less**  (12.3 less a 76.8 more ) | ⨁⨁◯◯ LOW 1 | MMF may decrease creatinine doubling |
| Renal flare Follow up: 36 months  Number of participants: 16 (1 RCT) | **RR 0.20** (0.03 a 1.35) | 62.5% | **12.5%** (1.9 a 84.4) | **50.0% less**  (60.6 less a 21.9 more ) | ⨁⨁◯◯ LOW 1 | MMF may decrease renal flare |
| Withdrawal due to adverse events Follow up: 36 months  Number of participants: 16 (1 RCT) | **RR 0.20** (0.03 a 1.35) | 62.5% | **12.5%** (1.9 a 84.4) | **50.0% less**  (60.6 less a 21.9 more ) | ⨁⨁◯◯ LOW 1,2 | MMF may reduce adverse effects |

1. Small number of participants/ 95%CI includes benefits and harms
2. Important lost to follow-up (only patients in the maintenance group considered)

* Sundel R, Solomons N, Lisk L, Aspreva Lupus Management Study (ALMS) Group. Efficacy of mycophenolate mofetil in adolescent patients with lupus nephritis: evidence from a two-phase, prospective randomized trial. Lupus. 2012;21:1433–43.
* Lau KK, Ault BH, Jones DP, Butani L. Induction therapy for pediatric focal proliferative lupus nephritis: cyclophosphamide versus mycophenolate mofetil. J Pediatr Health Care. 2008;22:282-8.

10.1.1

| **LDA compared to placebo for patients with antiphospholipid antibodies and no history of thrombosis** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| Outcome № of participants (studies) | Relative effect (95% CI) | **Anticipated absolute effects (95% CI)** | | | Quality | What happens |
| **Without ASA** | **With ASA** | **Difference** |
| Thromboembolic event at 5 years № of participants: 98 (1 RCT) | **HR 1.04** (0.69 to 1.56) | **Moderate** | | | ⨁◯◯◯ VERY LOW 3,6 | ASA may have little or no effect in preventing thromboembolic events |
| 10.0% 1 | **10.4%** (7.0 to 15.2) | **0.4% more** (3 fewer to 5.2 more) |
| **High** | | |
| 16.7% 2 | **17.3%** (11.8 to 24.8) | **0.6% more** (4.9 fewer to 8.1 more) |
| Thromboembolic event at 5 years № of participants: 1110 (10 observational studies) | **RR 0.51** (0.35 to 0.76) | **Moderate** | | | ⨁◯◯◯ VERY LOW 4 | It is uncertain if ASA reduces thrombotic risk |
| 10.0% 1 | **5.1%** (3.5 to 7.6) | **4.9% fewer** (6.5 fewer to 2.4 fewer) |
| **High** | | |
| 16.7% 2 | **8.5%** (5.8 to 12.7) | **8.2% fewer** (10.9 fewer to 4 fewer) |
| Major gastrointestinal bleeding at 1 year follow up: 3.8 - 10.1 years № of participants: 94307 (7 RCTs) | **OR 1.59** (1.32 to 1.91) | **Low** | | | ⨁⨁⨁⨁ HIGH | ASA increases the risk of major gastrointestinal bleeding |
| 2 per 10000 5 | **3 per 10000** (2 to 4) | **1 more per 10000** (0 more to 2 more) |
| **High** | | |
| 10 per 10000 5 | **16 per 10000** (13 to 19) | **6 more per 10000** (3 more to 9 more) |
| Intracranial hemorrhage, including hemorrhagic stroke at 1 year follow up: 3.8 - 10.1 years № of participants: 114540 (10 RCTs) | **OR 1.34** (1.07 to 1.70) | **Low** | | | ⨁⨁⨁⨁ HIGH | ASA increases the risk of intracranial hemorrhage |
| 3 per 10000 | **4 per 10000** (3 to 5) | **1 more per 10000** (0 fewer to 2 more) |

1. Petri, M. “Thrombosis and Systemic Lupus Erythematosus: The Hopkins Lupus Cohort Perspective.” Scandinavian Journal of Rheumatology 25, no. 4 (1996): 191–93.
2. Arnaud, Laurent, Alexis Mathian, Amelia Ruffatti, Doruk Erkan, Maria Tektonidou, Ricard Cervera, Ricardo Forastiero, et al. “Efficacy of Aspirin for the Primary Prevention of Thrombosis in Patients with Antiphospholipid Antibodies: An International and Collaborative Meta-Analysis.” Autoimmunity Reviews 13, no. 3 (March 2014): 281–91. doi:10.1016/j.autrev.2013.10.014.
3. 95% CI includes benefits and harms
4. Most studies reportes unadjusted estimates
5. Whitlock, Evelyn P., Brittany U. Burda, Selvi B. Williams, Janelle M. Guirguis-Blake, and Corinne V. Evans. “Bleeding Risks With Aspirin Use for Primary Prevention in Adults: A Systematic Review for the U.S. Preventive Services Task Force.” Annals of Internal Medicine 164, no. 12 (June 21, 2016): 826–35. doi:10.7326/M15-2112.
6. Indirectness because inadecuate follow up lenght

* Erkan D, Harrison MJ, Levy R, Peterson M, Petri M, Sammaritano L, et al. Aspirin for primary thrombosis prevention in the antiphospholipid syndrome: a randomized, double-blind, placebo-controlled trial in asymptomatic antiphospholipid antibody-positive individuals. Arthritis Rheum. 2007;56:2382–91.
* Whitlock EP, Burda BU, Williams SB, Guirguis-Blake JM, Evans CV. Bleeding Risks With Aspirin Use for Primary Prevention in Adults: A Systematic Review for the U.S. Preventive Services Task Force. Ann Intern Med. 2016 21;164:826–35.
* Arnaud L, Mathian A, Ruffatti A, Erkan D, Tektonidou M, Cervera R, et al. Efficacy of aspirin for the primary prevention of thrombosis in patients with antiphospholipid antibodies: an international and collaborative meta-analysis. Autoimmun Rev. 2014;13:281–91.

10.1.2

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **LDA plus warfarin (INR 1.5) compared to LDA for patients with SLE and antiphospholipid antibodies without history of thrombosis** | | | | | | |
| Outcome  № of participants  (studies) | Relative effect  (95% CI) | **Anticipated absolute effects (95% CI)** | | | Quality | What happens |
| **LDA Without warfarin** | **LDA plus warfarin** | **Difference** |
| Thrombotic events  follow up: 2.7 years  № of participants: 166  (1 RCT) | **HR 1.07**  (0.27 to 4.20) | **Study population** | | | ⨁⨁◯◯  LOW 1,2 | Warfarin may have little or no effect on thrombotic risk |
| 4.9% | **5.2%**  (1.3 to 18.9) | **0.3% more**  (3.5 fewer to 14.1 more) |
| **High** | | |
| 10.0% | **10.7%**  (2.8 to 35.8) | **0.7% more**  (7.2 fewer to 25.8 more) |
| Bleeding  follow up: 2.7 years  № of participants: 166  (1 RCT) | The risk difference for bleeding episodes was 13% (CI 5.9, 20) and NNH = 7.6 (CI 4.9, 17.0) (P=0.0007) by Fisher’s exact test. NNH here refers to the number of patients to be treated with LDA plus Warfarin rather than LDA for 3 years (the median length of follow-up) in order to cause one extra case of bleeding. | | | | ⨁⨁⨁◯  MODERATE 1 |  |

1. No blinding

2. 95% CI includes benefits and harms

* Cuadrado MJ, Bertolaccini ML, Seed PT, Tektonidou MG, Aguirre A, Mico L, et al. Low-dose aspirin vs low-dose aspirin plus low-intensity warfarin in thromboprophylaxis: a prospective, multicentre, randomized, open, controlled trial in patients positive for antiphospholipid antibodies (ALIWAPAS). Rheumatology (Oxford). 2014;53:275–84.

10.2.1

| **Extended anticoagulation compared to no extended anticoagulation for patient with SLE, APS and VTE** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| Outcome № of participants (studies) | Relative effect (95% CI) | **Anticipated absolute effects (95% CI)** | | | Quality | What happens |
| **Without extended anticoagulation** | **With extended anticoagulation** | **Difference** |
| Mortality follow up: 10 - 36 months № of participants: 1184 (4 RCTs) | **RR 0.57** (0.31 to 1.03) | **4 years** | | | ⨁⨁◯◯ LOW 2,3,4 | Extended anticoagulation may reduce mortality |
| 15.0% 1 | **8.5%** (4.7 to 15.4) | **6.5% fewer** (10.3 fewer to 0.5 more) |
| Recurrent VTE at 1 year follow up: 10 - 36 months № of participants: 1184 (4 RCTs) | **RR 0.12** (0.09 to 0.38) | **First unprovoked VTE** | | | ⨁⨁⨁⨁ HIGH 1,6 | Extended anticoagulation significantly reduces VTE recurrence |
| 10.0% | **1.2%** (0.9 to 3.8) | **8.8% fewer** (9.1 fewer to 6.2 fewer) |
| **First unprovoked VTE with APS** | | |
| 14.1% 5 | **1.7%** (1.3 to 5.4) | **12.4% fewer** (12.8 fewer to 8.7 fewer) |
| **First unprovoked VTE with LA** | | |
| 28.3% 5 | **3.4%** (2.5 to 10.8) | **24.9% fewer** (25.8 fewer to 17.5 fewer) |
| Major bleeding at 1 year follow up: 10 - 36 months № of participants: 1184 (4 RCTs) | **RR 2.63** (1.02 to 6.76) | **Low** | | | ⨁⨁⨁◯ MODERATE 3 | Extended anticoagulation probably increases major bleeding |
| 0.3% 7 | **0.8%** (0.3 to 2.0) | **0.5% more** (0 fewer to 1.7 more) |
| **Moderate** | | |
| 0.6% | **1.6%** (0.6 to 4.1) | **1.0% more** (0 fewer to 3.5 more) |
| **High** | | |
| 2.5% | **6.6%** (2.6 to 16.9) | **4.1% more** (0.1 more to 14.4 more) |
| Recurrent VTE at 5 years follow up: 10 - 36 months № of participants: 1184 (4 RCTs) | **RR 0.12** (0.09 to 0.38) | **First unprovoked VTE** | | | ⨁⨁⨁⨁ HIGH 6 | Extended anticoagulation significantly reduces VTE recurrence |
| 30.0% | **3.6%** (2.7 to 11.4) | **26.4% fewer** (27.3 fewer to 18.6 fewer) |
| **First unprovoked VTE with APLA** | | |
| 42.3% 5 | **5.1%** (3.8 to 16.1) | **37.2% fewer** (38.5 fewer to 26.2 fewer) |
| **First unprovoked VTE with LA** | | |
| 84.9% 5 | **10.2%** (7.6 to 32.3) | **74.7% fewer** (77.3 fewer to 52.6 fewer) |
| Major bleeding at 5 years follow up: 10 - 36 months № of participants: 1184 (4 RCTs) | **RR 2.63** (1.02 to 6.76) | **Low** | | | ⨁⨁⨁◯ MODERATE 3 | Extended anticoagulation probably increases major bleeding |
| 1.5% 7 | **3.9%** (1.5 to 10.1) | **2.4% more** (0 fewer to 8.6 more) |
| **Moderate** | | |
| 3.0% 7 | **7.9%** (3.1 to 20.3) | **4.9% more** (0.1 more to 17.3 more) |
| **High** | | |
| 12.5% 7 | **32.9%** (12.8 to 84.5) | **20.4% more** (0.3 more to 72 more) |

1. Schulman, S., E. Svenungsson, and S. Granqvist. “Anticardiolipin Antibodies Predict Early Recurrence of Thromboembolism and Death among Patients with Venous Thromboembolism Following Anticoagulant Therapy. Duration of Anticoagulation Study Group. The American Journal of Medicine 104, no. 4 (April 1998): 332–38.
2. Estimate of effect is based on studies that included patients with and without APS. The effect of the intervention could be different in the subgroup of patients with APS
3. CI includes both values suggesting no effect and values suggesting either appreciable harms or appreciable benefit.
4. Small number of events. Decision to rate down also takes into account that two studies were stopped early for benefit.
5. Basal risk calculated using the RR informed by "Garcia, David, Elie A. Akl, Richard Carr, and Clive Kearon. “Antiphospholipid Antibodies and the Risk of Recurrence after a First Episode of Venous Thromboembolism: A Systematic Review.” Blood 122, no. 5 (August 1, 2013): 817–24. and the original risk informed in the adapted table
6. We decided not to rate down for indirectness because there is evidence of similar effect in patients with and without APS.
7. Annual risk of major bleeding is based on three risk levels: low, intermediate, and high. The corresponding 0.3%, 0.6%, and 1.2% risks are estimates based on control arms of included studies

* Table adapted from: Kearon C, et al. Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines, table 18.
* Garcia D, Akl EA, Carr R, Kearon C. Antiphospholipid antibodies and the risk of recurrence after a first episode of venous thromboembolism: a systematic review. Blood. 2013;122:817–24.

10.2.2

| **High intensity anticoagulation (INR 3 - 4.5) compared to moderate intensity anticoagulation (INR 2 - 3) for patient with SLE and APS** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| Outcome № of participants (studies) | Relative effect (95% CI) | **Anticipated absolute effects (95% CI)** | | | Quality | What happens |
| **Without High intensity anticoagulation (INR 3 - 4.5)** | **With High intensity anticoagulation (INR 3 - 4.5)** | **Difference** |
| Thrombotic events follow up: 3 years № of participants: 223 (2 RCTs) | **RR 2.44** (0.88 to 6.71) | **Observed** | | | ⨁◯◯◯ VERY LOW 2,9 | It is uncertain if high intensity anticoagulation affects this outcome |
| 4.0% | **9.8%** (3.5 to 26.8) | **5.8% more** (0.5 fewer to 22.8 more) |
| **High** | | |
| 30.0% 1 | **73.2%** (26.4 to 100.0) | **43.2% more** (3.6 fewer to 171.3 more) |
| Major bleeding at 3 years follow up: 1.8 years № of participants: 76646 (17 RCTs) 3 | **RR 2.7** (1.8 to 3.9) | **Low** | | | ⨁⨁⨁⨁ HIGH 6,7,8 | High intensity anticoagulation increases the risk of major bleeding |
| 4.5% 4 | **12.2%** (8.1 to 17.5) | **7.6% more** (3.6 more to 13.1 more) |
| **Moderate** | | |
| 7.5% 5 | **20.3%** (13.5 to 29.3) | **12.8% more** (6 more to 21.8 more) |
| Death follow up: 3 years № of participants: 223 (2 RCTs) | **RR 1.36** (0.31 to 5.90) | 2.7% | **3.6%** (0.8 to 15.7) | **1.0% more** (1.8 fewer to 13 more) | ⨁◯◯◯  VERY LOW 2,9 | It is uncertain if high intensity anticoagulation affects this outcome |
| Thrombosis (16 observational studies) | Multiple observational studies included in a systematic review reported: Thrombosis risk 23% (INR <3), 3.8% (INR >3) 10. | | | | ⨁◯◯◯ VERY LOW 11 | - |

1. Khamashta, M. A., M. J. Cuadrado, F. Mujic, N. A. Taub, B. J. Hunt, and G. R. Hughes. “The Management of Thrombosis in the Antiphospholipid-Antibody Syndrome.” The New England Journal of Medicine 332, no. 15 (April 13, 1995): 993–97. doi:10.1056/NEJM199504133321504.
2. 95%CI includes benefits and harms
3. Eleven studies had a observational design
4. Oake, Natalie, Alison Jennings, Alan J. Forster, Dean Fergusson, Steve Doucette, and Carl van Walraven. “Anticoagulation Intensity and Outcomes among Patients Prescribed Oral Anticoagulant Therapy: A Systematic Review and Meta-Analysis.” CMAJ: Canadian Medical Association Journal = Journal de l’Association Medicale Canadienne 179, no. 3 (July 29, 2008): 235–44. doi:10.1503/cmaj.080171.
5. Lopes, L. C., F. A. Spencer, I. Neumann, M. Ventresca, S. Ebrahim, Q. Zhou, N. Bhatnaga, S. Schulman, J. Eikelboom, and G. Guyatt. “Bleeding Risk in Atrial Fibrillation Patients Taking Vitamin K Antagonists: Systematic Review and Meta-Analysis.” Clinical Pharmacology and Therapeutics 94, no. 3 (September 2013): 367–75. doi:10.1038/clpt.2013.99.
6. We decided not to rate down for risk of bias because the results of the observational studies were consistent with the RCT
7. We decided not to rate down for indirectness because we found no evidence of different bleeding risk in patients with APS
8. Bleeding rate increased with anticoagulation target (2 > 2-3 > 3-5)
9. Patients in the INR 3.0 groups were frequently below the intended intensity of anticoagulation.
10. Ruiz-Irastorza, Guillermo, Beverley J. Hunt, and Munther A. Khamashta. “A Systematic Review of Secondary Thromboprophylaxis in Patients with Antiphospholipid Antibodies.” Arthritis and Rheumatism 57, no. 8 (December 15, 2007): 1487–95. doi:10.1002/art.23109.
11. No adjustment for possible confounders

* Oake N, Jennings A, Forster AJ, Fergusson D, Doucette S, van Walraven C. Anticoagulation intensity and outcomes among patients prescribed oral anticoagulant therapy: a systematic review and meta-analysis. CMAJ. 2008;179:235–44.
* Silva FF da, Carvalho JF de. Intensity of anticoagulation in the treatment of thrombosis in the antiphospholipid syndrome: a meta-analysis. Rev Bras Reumatol. 2015;55:159–66.
* Crowther MA, Ginsberg JS, Julian J, Denburg J, Hirsh J, Douketis J, et al. A comparison of two intensities of warfarin for the prevention of recurrent thrombosis in patients with the antiphospholipid antibody syndrome. N Engl J Med. 2003;349:1133–8.
* Finazzi G, Marchioli R, Brancaccio V, Schinco P, Wisloff F, Musial J, et al. A randomized clinical trial of high-intensity warfarin vs. conventional antithrombotic therapy for the prevention of recurrent thrombosis in patients with the antiphospholipid syndrome (WAPS). J Thromb Haemost. 2005;3:848–53.

10.2.3

| **Rivaroxaban compared to warfarin for anticoagulation in patients with APS and VTE** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| Outcome № of participants (studies) | Relative effect (95% CI) | **Anticipated absolute effects (95% CI)** | | | Quality | What happens |
| **With Warfarin** | **With Rivaroxaban** | **Difference** |
| New thrombotic events follow up: 210 days № of participants: 115 (1 RCT) | No thrombotic events occurred in any treatment arm suggesting that rivaroxaban is at least as effective as warfarin. | | | | ⨁⨁OO LOW 1,2 |  |
| New thrombotic events  assessed with: Indirect evidence in a study that used dabigatran follow up: 18 months № of participants: 2856 (1 RCT) | **HR 1.44** (0.78 to 2.64) | **Observed** | | | ⨁⨁OO LOW 2,4 | Direct acting oral anticoagulants may marginally increase the risk of new thrombotic events |
| 5.0% 3 | **7.1%** (3.9 to 12.7) | **2.1% more** (1.1 fewer to 7.7 more) |
| Major gastrointestinal bleeding at 1 year № of participants: 78166 (4 observational studies) | **RR 1.09** (0.92 to 1.30) | **Observed** | | | ⨁⨁OO LOW | Rivaroxaban may not significantly increase the risk of GI bleeding |
| 6.5% | **7.1%** (6.0 to 8.5) | **0.6% more** (0.5 fewer to 2 more) |

1. No blinding
2. Optimal information size not met
3. Basal risk based on: Wa ̊ hlander K, Eriksson H, Lundstro ̈ m T, et al; THRIVE III Investigators. Risk of recurrent venous thromboembolism or bleeding in relation to thrombophilic risk factors in patients receiving ximelagatran or placebo for long-term secondary prevention of venous thromboembolism. Br J Haematol. 2006;133(1):68-77 and Schulman, S., E. Svenungsson, and S. Granqvist. “Anticardiolipin Antibodies Predict Early Recurrence of Thromboembolism and Death among Patients with Venous Thromboembolism Following Anticoagulant Therapy. Duration of Anticoagulation Study Group.” The American Journal of Medicine 104, no. 4 (April 1998): 332–38.
4. Estimate of effect extracted from a study that compared dabigatran with warfarin in patients with VTE but without APS

* Cohen H, Hunt BJ, Efthymiou M, Arachchillage DRJ, Mackie IJ, Clawson S, et al. Rivaroxaban versus warfarin to treat patients with thrombotic antiphospholipid syndrome, with or without systemic lupus erythematosus (RAPS): a randomised, controlled, open-label, phase 2/3, non-inferiority trial. Lancet Haematol. 2016;3:e426-436.
* Schulman S, Kearon C, Kakkar AK, Schellong S, Eriksson H, Baanstra D, et al. Extended use of dabigatran, warfarin, or placebo in venous thromboembolism. N Engl J Med. 2013;368:709–18.
* He Y, Wong ICK, Li X, Anand S, Leung WK, Siu CW, et al. The association between non-vitamin K antagonist oral anticoagulants and gastrointestinal bleeding: a meta-analysis of observational studies. Br J Clin Pharmacol. 2016;82:285–300.

10.3.1

| **Warfarin compared to LDA for patients with SLE, APS and stroke** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| Outcome № of participants (studies) | Relative effect (95% CI) | **Anticipated absolute effects (95% CI)** | | | Quality | What happens |
| **Without Warfarin** | **With Warfarin** | **Difference** |
| Death or thrombosis assessed with: \* follow up: 2 years № of participants: 720 (1 RCT) | **RR 1.18** (0.90 to 1.55) | **Observed** | | | ⨁⨁◯◯ LOW 1,2,3 | Warfarin may not reduce death or thrombosis |
| 22.7% | **26.8%** (20.4 to 35.2) | **4.1% more** (2.3 fewer to 12.5 more) |
| Death or thrombosis (La+/aCL+) assessed with: \* follow up: 2 years № of participants: 120 (1 RCT) | **RR 1.34** (0.74 to 2.46) | **Observed** | | | ⨁⨁◯◯ LOW 1,3 | Warfarin may not reduce death or thrombosis |
| 26.7% | **35.8%** (19.8 to 65.7) | **9.1% more** (6.9 fewer to 39 more) |
| Non fatal major extracranial hemorrhage at 2 years follow up: 0 - 5 years № of participants: 3194 (4 RCTs) 4 | **RR 3.60** (2.29 to 5.66) | **Observed** | | | ⨁⨁⨁⨁ HIGH 6 | Warfarin increases the risk of bleeding |
| 1.0% 5 | **3.6%** (2.3 to 5.7) | **2.6% more** (1.3 more to 4.7 more) |
| Thrombosis (16 Observational studies) | Multiple observational studies included in a systematic review reported: Thrombosis risk 23% (INR <3), 3.8% (INR >3) 7. One observational study not included in the mentioned systematic review reported: Thrombosis risk 2.5% (Warfarin) and 5% (ASA) 8 | | | | ⨁◯◯◯ VERY LOW 9 | - |
| \* Death from any cause or ischemic stroke, myocardial infarction, transient ischemic attack, deep venous thrombosis, pulmonary embolism, systemic visceral arterial embolism, or peripheral arterial embolism | | | | | | |

1. Although the ASA dose was 325mg, we decided not to rate down for indirectness because there is evidence of similar effect with doses between 75 - 325mg (Antithrombotic Trialists’ Collaboration. Collaborative meta- analysis of randomised trials of antiplatelet therapy for pre- vention of death, myocardial infarction, and stroke in high risk patients. BMJ. 2002;324(7329):71-86.)
2. Patients were labeled as aPL positive, despite only a single test, if they had aCL (including IgA isotype) at any level. Moreover, low titers of aCL were included and LAC testing was not performed according to international recommendations.
3. 95%CI includes benefits and harms
4. Garde (1983), SPIRIT (1997), WASID (2000), and ESPRIT (2007).
5. Baseline event rates based on aspirin arm of the CAPRIE trial and adjusted for 2-y time frame
6. We decided not to rate down for indirectness because we found no evidence of different bleeding risk in APS patients (Bazzan, M., A. Vaccarino, S. Stella, M. T. Bertero, R. Carignola, B. Montaruli, D. Roccatello, Y. Shoenfeld, and Piedmont APS Consortium. “Thrombotic Recurrences and Bleeding Events in APS Vascular Patients: A Review from the Literature and a Comparison with the APS Piedmont Cohort.” Autoimmunity Reviews 12, no. 8 (June 2013): 826–31. doi:10.1016/j.autrev.2012.11.007)
7. Ruiz-Irastorza, Guillermo, Beverley J. Hunt, and Munther A. Khamashta. A systematic review of secondary thromboprophylaxis in patients with antiphospholipid antibodies.” Arthritis and Rheumatism 2007;58: 1487–95.
8. Bertero MT, Bazzan M, Carignola R, Montaruli B, Silvestro E, Sciascia S, et al. Antiphospholipid syndrome in northwest Italy (APS Piedmont Cohort): demographic features, risk factors, clinical and laboratory profile. Lupus. 2012;2:806–9.
9. No adjustment for possible confounders

* Table adapted from: Lansberg M, et al. Antithrombotic and thrombolytic therapy for ischemic stroke: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. CHEST 2012; 141(Suppl):e601S–e636S. Table 22.
* Levine SR, Brey RL, Tilley BC, Thompson JLP, Sacco RL, Sciacca RR, et al. Antiphospholipid antibodies and subsequent thrombo-occlusive events in patients with ischemic stroke. JAMA. 2004;291:576–84.

10.3.2

| **Warfarin plus LDA compared to LDA for patient with SLE, APS and stroke** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| Outcome № of participants (studies) | Relative effect (95% CI) | **Anticipated absolute effects (95% CI)** | | | Quality | What happens |
| **ASA Without Warfarin** | **ASA With Warfarin** | **Difference** |
| Major bleeding at 4 years № of participants: 7374 (14 RCTs) | **RR 5.0** (2.8 to 8.9) 1 | **Observed** | | | ⨁⨁⨁◯ MODERATE 1 | Warfarin plus ASA probably significantly increases the risk of major bleeding |
| 2.0% 2 | **10.0%** (5.6 to 17.8) | **8.0% more** (3.6 more to 15.8 more) |
| Stroke recurrence  follow up: 4 years № of participants: 20 (1 RCT) | **RR 0.25** (0.04 to 0.91) | **Observed** | | | ⨁◯◯◯ VERY LOW 4,5,6 | It is uncertain if Warfarin plus ASA reduces stroke recurrence |
| 53.4% 3 | **13.4%** (2.1 to 48.6) | **40.1% fewer** (51.3 fewer to 4.8 fewer) |

1. Indirect estimate of effect calculated using the Bucher method. Estimates of effect for warfarin vs. ASA based on 4. Garde (1983), SPIRIT (1997), WASID (2000), and ESPRIT (2007). Estmate of effect for Warafarin plus ASA vs Warfarin based on Dentali F, Douketis JD, Lim W, Crowther M. Combined aspirin-oral anticoagulant therapy compared with oral anticoagulant therapy alone among patients at risk for cardiovascular disease: a meta-analysis of randomized trials. Arch Intern Med. 2007;167:117–24.
2. Baseline event rates based on aspirin arm of the CAPRIE trial and adjusted for 2-y time frame
3. Levine SR, Brey RL, Tilley BC, Thompson JLP, Sacco RL, Sciacca RR, et al. Antiphospholipid antibodies and subsequent thrombo-occlusive events in patients with ischemic stroke. JAMA. 2004;291:576–84.
4. Randomization process, allocation concealment and blinding probably not explained and probably nor adequate.
5. Low number of events.
6. CI95% including marginal benefits

* .
* Okuma H, Kitagawa Y, Yasuda T, Tokuoka K, Takagi S. Comparison between single antiplatelet therapy and combination of antiplatelet and anticoagulation therapy for secondary prevention in ischemic stroke patients with antiphospholipid syndrome. Int J Med Sci. 2009;7:15–8.
* Dentali F, Douketis JD, Lim W, Crowther M. Combined aspirin-oral anticoagulant therapy compared with oral anticoagulant therapy alone among patients at risk for cardiovascular disease: a meta-analysis of randomized trials. Arch Intern Med. 2007;167:117–24

10.4.1

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| --- | --- | --- | --- | --- | --- | --- |
| **LDA compared to placebo for pregnant asymptomatic women with antiphospholipid antibodies** | | | | | | |
| Outcome № of participants (studies) | Relative effect (95% CI) | **Anticipated absolute effects (95% CI)** | | | Quality | What happens |
| **Without ASA** | **With ASA** | **Difference** |
| Spontaneous abortion and/or fetal death  № of participants: 67  (2 RCTs) | **RR 2.25**  (0.10 to 49.00) | **Observed risk** | | | ⨁◯◯◯  VERY LOW 1,2 | It is uncertain if ASA reduces the risk of spontaneous abortion and/or fetal death |
| 2.0% | **4.5%**  (0.2 to 98.0) | **2.5% more**  (1.8 fewer to 96 more) |
| Pregnancy complications  № of participants: 67  (2 RCTs) | **RR 2.07**  (0.45 to 9.59) | **Observed risk** | | | ⨁◯◯◯  VERY LOW 1,2 | It is uncertain if ASA reduces the risk of pregnancy complications |
| 6.5% | **13.5%**  (2.9 to 62.3) | **7.0% more**  (3.6 fewer to 55.8 more) |
| Preterm delivery  № of participants: 84  (2 RCTs) | **RR 2.88**  (0.85 to 23.50) | **Observed risk** | | | ⨁⨁◯◯  LOW 1,2 | ASA could increase the probability of preterm delivery |
| 2.0% | **5.8%**  (1.7 to 47.0) | **3.8% more**  (0.3 fewer to 45 more) |
| Low birth weight delivery  № of participants: 67  (2 RCTs) | **RR 0.98**  (0.07 to 13.50) | **Observed risk** | | | ⨁◯◯◯  VERY LOW 1,2 | It is uncertain if ASA reduces the risk of preterm delivery |
| 3.5% | **3.4%**  (0.2 to 47.3) | **0.1% fewer**  (3.3 fewer to 43.8 more) |

1. Randomization process not clear in both trials

2. 95%CI including benefits and harms

* Amengual O, Fujita D, Ota E, Carmona L, Oku K, Sugiura-Ogasawara M, et al. Primary prophylaxis to prevent obstetric complications in asymptomatic women with antiphospholipid antibodies: a systematic review. Lupus. 2015;24:1135–42.
* Cowchock S, Reece EA. Do low-risk pregnant women with antiphospholipid antibodies need to be treated? Organizing Group of the Antiphospholipid Antibody Treatment Trial. Am J Obstet Gynecol. 1997;176:1099–100.

10.5.1

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| --- | --- | --- | --- | --- | --- | --- |
| **Heparin plus LDA compared to LDA for pregnant with APS** | | | | | | |
| Outcome № of participants (studies) | Relative effect (95% CI) | **Anticipated absolute effects (95% CI)** | | | Quality | What happens |
| **ASA Without Heparin** | **ASA With Heparin** | **Difference** |
| Fetal Loss  № of participants: 352  (5 RCTs) | **RR 0.54**  (0.39 to 0.75) | 41.5% | **22.4%**  (16.2 to 31.1) | **19.1% fewer**  (25.3 fewer to 10.4 fewer) | ⨁⨁⨁◯  MODERATE 1,2 | Heparin probably reduces pregnancy loss |
| Premature delivery  № of participants: 310  (4 RCTs) | **RR 1.25**  (0.62 to 2.53) | 9.0% | **11.2%**  (5.6 to 22.7) | **2.2% more**  (3.4 fewer to 13.7 more) | ⨁⨁◯◯  LOW 1,3 | Heparin may make little or no difference to premature delivery |
| IUGR  № of participants: 140  (2 RCTs) | **RR 3.00**  (0.63 to 14.31) | 2.9% | **8.6%**  (1.8 to 40.9) | **5.7% more**  (1.1 fewer to 38 more) | ⨁◯◯◯  VERY LOW 1,3 | We are uncertain whether heparin improves/reduces IUGR as the quality of the evidence has been assessed as very low |

1. No blinding in most trials

2. Optimal information size not met

3. 95% CI including benefits and harms

* Farquharson RG, Quenby S, Greaves M. Antiphospholipid syndrome in pregnancy: a randomized, controlled trial of treatment. Obstet Gynecol. 2002;100:408–13.
* Goel N, Tuli A, Choudhry R. The role of aspirin versus aspirin and heparin in cases of recurrent abortions with raised anticardiolipin antibodies. Med Sci Monit. 2006;12:CR132-136.
* Kutteh WH. Antiphospholipid antibody-associated recurrent pregnancy loss: treatment with heparin and low-dose aspirin is superior to low-dose aspirin alone. Am J Obstet Gynecol. 1996;174:1584–9.
* Laskin CA, Spitzer KA, Clark CA, Crowther MR, Ginsberg JS, Hawker GA, et al. Low molecular weight heparin and aspirin for recurrent pregnancy loss: results from the randomized, controlled HepASA Trial. J Rheumatol. 2009;36:279–87.
* Rai R, Cohen H, Dave M, Regan L. Randomised controlled trial of aspirin and aspirin plus heparin in pregnant women with recurrent miscarriage associated with phospholipid antibodies (or antiphospholipid antibodies). BMJ. 1997;314:253–7.

10.5.2

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| --- | --- | --- | --- | --- | --- | --- |
| **GCs plus LDA compared to LDA for pregnant with SLE and APS (recurrent pregnancy loss)** | | | | | | |
| Outcome  № of participants  (studies) | Relative effect  (95% CI) | **Anticipated absolute effects (95% CI)** | | | Quality | What happens |
| **LDA Without GCs** | **LDA With GCs** | **Difference** |
| Fetal Loss  № of participants: 241  (2 RCTs) | **RR 0.80**  (0.56 to 1.13) | 35.8% | **28.6%**  (20.0 to 40.4) | **7.2% fewer**  (15.7 fewer to 4.7 more) | ⨁⨁◯◯  LOW 1 | GCs may slightly reduce fetal loss |
| Premature delivery  № of participants: 241  (2 RCTs) | **RR 5.01**  (2.66 to 9.44) | 8.1% | **40.7%**  (21.6 to 76.7) | **32.6% more**  (13.5 more to 68.6 more) | ⨁⨁⨁⨁  HIGH | GCs increase premature deliveries |
| Infant admission to neonatal ICU  № of participants: 106  (1 RCT) | **RR 9.35**  (2.28 to 38.30) | 3.7% | **34.6%**  (8.4 to 100.0) | **30.9% more**  (4.7 more to 138.1 more) | ⨁⨁⨁⨁  HIGH | GCs increase infant admission to neonatal ICU |

1. 95%CI including benefits and harms

* Laskin CA, Bombardier C, Hannah ME, Mandel FP, Ritchie JW, Farewell V, et al. Prednisone and aspirin in women with autoantibodies and unexplained recurrent fetal loss. N Engl J Med. 1997;337:148–53.
* Silver RK, MacGregor SN, Sholl JS, Hobart JM, Neerhof MG, Ragin A. Comparative trial of prednisone plus aspirin versus aspirin alone in the treatment of anticardiolipin antibody-positive obstetric patients. Am J Obstet Gynecol. 1993;169:1411–7.
* Lassere M, Empson M. Treatment of antiphospholipid syndrome in pregnancy--a systematic review of randomized therapeutic trials. Thromb Res. 2004;114:419–26.

10.5.3

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| --- | --- | --- | --- | --- | --- | --- |
| **GCs plus LDA compared to heparin plus LDA for pregnant with SLE and APS** | | | | | | |
| Outcome  № of participants  (studies) | Relative effect  (95% CI) | **Anticipated absolute effects (95% CI)** | | | Quality | What happens |
| **GCs plus LDA** | **Heparin plus LDA** | **Difference** |
| Pregnancy loss  № of participants: 20  (1 RCT) | **RR 1.0**  (0.6 to 1.8) | 25.0% | **25.0%**  (15.0 to 45.0) | **0.0% fewer**  (10 fewer to 20 more) | ⨁◯◯◯  VERY LOW 1,2 | We are uncertain whether GCs improves/reduces pregnancy loss as the quality of the evidence has been assessed as very low |
| Premature delivery  № of participants: 20  (1 RCT) | **RR 5.0**  (1.3 to 5.0) | 25.0% | **100.0%**  (32.5 to 100.0) | **75% more**  (7.5 more to 100 more) | ⨁⨁◯◯  LOW 1,3 | GCs may increase premature deliveries |

1. No blinding

2. 95%CI including benefits and harms

3. Optimal information size not met

* Cowchock FS, Reece EA, Balaban D, Branch DW, Plouffe L. Repeated fetal losses associated with antiphospholipid antibodies: a collaborative randomized trial comparing prednisone with low-dose heparin treatment. Am J Obstet Gynecol. 1992;166:1318–23.
* Lassere M, Empson M. Treatment of antiphospholipid syndrome in pregnancy--a systematic review of randomized therapeutic trials. Thromb Res. 2004;114:419–26.

10.5.4

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| --- | --- | --- | --- | --- | --- | --- |
| **IVIG compared to heparin plus LDA for pregnant with APS** | | | | | | |
| Outcome  № of participants  (studies) | Relative effect  (95% CI) | **Anticipated absolute effects (95% CI)** | | | Quality | What happens |
| **Heparin plus ASA** | **IVIG** | **Difference** |
| Fetal Loss  № of participants: 118  (2 RCTs) | **RR 2.29**  (1.38 to 3.81) | 23.7% | **54.3%**  (32.7 to 90.4) | **30.6% more**  (9 more to 66.7 more) | ⨁⨁◯◯  LOW 1,2 | IVIG may increase fetal losses compared to heparin plus ASA |
| Premature delivery  № of participants: 118  (2 RCTs) | **RR 0.95**  (0.14 to 6.28) | 3.4% | **3.2%**  (0.5 to 21.3) | **0.2% fewer**  (2.9 fewer to 17.9 more) | ⨁◯◯◯  VERY LOW 1,3 | We are uncertain whether IVIG increases or reduces premature deliveries as the quality of the evidence has been assessed as very low |

1. Lack of blinding

2. Optimal information size not met

3. 95% CI including benefits and harms

* Dendrinos S, Sakkas E, Makrakis E. Low-molecular-weight heparin versus intravenous immunoglobulin for recurrent abortion associated with antiphospholipid antibody syndrome. Int J Gynaecol Obstet. 2009;104:223–5.
* Triolo G, Ferrante A, Ciccia F, Accardo-Palumbo A, Perino A, Castelli A, et al. Randomized study of subcutaneous low molecular weight heparin plus aspirin versus intravenous immunoglobulin in the treatment of recurrent fetal loss associated with antiphospholipid antibodies. Arthritis Rheum. 2003;48:728–31.

10.5.5

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| --- | --- | --- | --- | --- | --- | --- |
| **IVIG plus heparin plus LDA compared to heparin plus LDA for pregnant with SLE and APS (recurrent pregnancy loss)** | | | | | | |
| Outcome  № of participants  (studies) | Relative effect  (95% CI) | **Anticipated absolute effects (95% CI)** | | | Quality | What happens |
| **Heparin plus ASA without IVIG** | **Heparin plus ASA plus IVIG** | **Difference** |
| Pregnancy loss  № of participants: 16  (1 RCT) | No pregnancy losses in any arm | | | | ⨁⨁◯◯  LOW 1 |  |
| Premature delivery  № of participants: 16  (1 RCT) | **RR 3.0**  (1.1 to 7.5) | 22.2% | **66.7%**  (24.4 to 100.0) | **44.4% more**  (2.2 more to 144.4 more) | ⨁⨁◯◯  LOW 1 | IVIG may increase premature delivery |

1. Optimal information size not met

* Branch DW, Peaceman AM, Druzin M, Silver RK, El-Sayed Y, Silver RM, et al. A multicenter, placebo-controlled pilot study of intravenous immune globulin treatment of antiphospholipid syndrome during pregnancy. The Pregnancy Loss Study Group. Am J Obstet Gynecol. 2000;182:122–7.
* Empson M, Lassere M, Craig J, Scott J. Prevention of recurrent miscarriage for women with antiphospholipid antibody or lupus anticoagulant. Cochrane Database Syst Rev. 2005;CD002859.

10.5.6

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| --- | --- | --- | --- | --- | --- | --- |
| **LMWH compared to UFH for pregnant with SLE and APS** | | | | | | |
| Outcome  № of participants  (studies) | Relative effect  (95% CI) | **Anticipated absolute effects (95% CI)** | | | Quality | What happens |
| **UFH** | **LMWH** | **Difference** |
| Fetal Loss  № of participants: 135  (3 RCTs) | **RR 0.55**  (0.32 to 0.95) | 36.8% | **20.2%**  (11.8 to 34.9) | **16.5% fewer**  (25 fewer to 1.8 fewer) | ⨁⨁◯◯  LOW 1,2 | LMWH may reduce fetal loss |
| Premature delivery  № of participants: 135  (3 RCTs) | **RR 2.04**  (0.46 to 9.04) | 2.9% | **6.0%**  (1.4 to 26.6) | **3.1% more**  (1.6 fewer to 23.6 more) | ⨁◯◯◯  VERY LOW 1,3 | We are uncertain whether LMWH reduces premature deliveries as the quality of the evidence has been assessed as very low |
| Infant admission to NEONATAL ICU  № of participants: 60  (1 RCT) | **RR 1.00**  (0.15 to 6.64) | 6.7% | **6.7%**  (1.0 to 44.3) | **0.0% fewer**  (5.7 fewer to 37.6 more) | ⨁◯◯◯  VERY LOW 1,3 | We are uncertain whether LMWH reduces infant admission to NEONATAL ICU as the quality of the evidence has been assessed as very low |
| IUGR  № of participants: 109  (2 RCTs) | **RR 0.68**  (0.12 to 4.04) | 5.5% | **3.7%**  (0.7 to 22.0) | **1.7% fewer**  (4.8 fewer to 16.6 more) | ⨁◯◯◯  VERY LOW 1,3 | We are uncertain whether LMWH reduces IUGR as the quality of the evidence has been assessed as very low |

1. No blinding

2. Optimal information size not met

3. 95%CI includes benefits and harms

* Fouda UM, Sayed AM, Abdou A-MA, Ramadan DI, Fouda IM, Zaki MM. Enoxaparin versus unfractionated heparin in the management of recurrent abortion secondary to antiphospholipid syndrome. Int J Gynaecol Obstet. 2011;112:211–5.
* Noble LS, Kutteh WH, Lashey N, Franklin RD, Herrada J. Antiphospholipid antibodies associated with recurrent pregnancy loss: prospective, multicenter, controlled pilot study comparing treatment with low-molecular-weight heparin versus unfractionated heparin. Fertil Steril. 2005;83:684–90.
* Stephenson MD, Ballem PJ, Tsang P, Purkiss S, Ensworth S, Houlihan E, et al. Treatment of antiphospholipid antibody syndrome (APS) in pregnancy: a randomized pilot trial comparing low molecular weight heparin to unfractionated heparin. J Obstet Gynaecol Can. 2004;26:729–34.

10.5.7

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| --- | --- | --- | --- | --- | --- | --- |
| **Enoxaparin 40 mg compared to enoxaparin 80 mg for pregnant with SLE and APS** | | | | | | |
| Outcome  № of participants  (studies) | Relative effect  (95% CI) | **Anticipated absolute effects (95% CI)** | | | Quality | What happens |
| **WithEnoxaparin 80mg** | **With Enoxaparin 40mg** | **Difference** |
| Fetal loss  № of participants: 180  (1 RCT) | **RR 0.73**  (0.41 to 1.25) | 71.4% | **52.1%**  (29.3 to 89.3) | **19.3% fewer**  (42.1 fewer to 17.9 more) | ⨁⨁◯◯  LOW 1,2 | Enoxaparin 40mg may reduce fetal losses |

1. No blinding

2. 95% CI includes benefits and harms

* Brenner B, Bar J, Ellis M, Yarom I, Yohai D, Samueloff A, et al. Effects of enoxaparin on late pregnancy complications and neonatal outcome in women with recurrent pregnancy loss and thrombophilia: results from the Live-Enox study. Fertil Steril. 2005;84:770–3.

10.5.8

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| --- | --- | --- | --- | --- | --- | --- |
| **HCQ compared to placebo for pregnant with SLE and APS** | | | | | | |
| Outcome  № of participants  (studies) | Relative effect  (95% CI) | **Anticipated absolute effects (95% CI)** | | | Quality | What happens |
| **Without Hydoxychloroquine** | **With Hydoxychloroquine** | **Difference** |
| Disease activity  assessed with: Patients with SLEDAI > 4 at delivery  № of participants: 20  (1 RCT) | not estimable | 50.0% | **0.0%** | **50.0% fewer**  (2.1 fewer to 50 fewer) | ⨁⨁⨁◯  MODERATE 1 | HCQ probably reduces SLE activity during pregnancy |
| Thrombotic event  № of participants: (5 observational studies) | The effect of AMs in preventing thrombotic events was consistently found in studies taking into account the exposure previous to the event. A dose effect was suggested by one study with a small sample size, which prevented the statistical significance of the results. The magnitude of the effect is high according to the only study with time-dependent analysis, however, confidence intervals were wide. | | | | ⨁⨁◯◯  LOW |  |
| Adverse pregnancy outcomes  № of participants: 311  (10 observational studies) | All the studies are concordant in showing the absolute safety of AMs during pregnancy: congenital malformations were not more frequent than in unexposed children and no cases of ocular, auditory or neurological toxicity were reported. | | | | ⨁⨁◯◯  LOW |  |

1. Optimal information size not met

* Levy RA, Vilela VS, Cataldo MJ, Ramos RC, Duarte JL, Tura BR, et al. Hydroxychloroquine (HCQ) in lupus pregnancy: double-blind and placebo-controlled study. Lupus. 2001;10:401–4.
* Ruiz-Irastorza G, Cuadrado MJ, Ruiz-Arruza I, Brey R, Crowther M, Derksen R, et al. Evidence-based recommendations for the prevention and long-term management of thrombosis in antiphospholipid antibody-positive patients: report of a task force at the 13th International Congress on antiphospholipid antibodies. Lupus. 2011;20:206–18.

10.6.1

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| --- | --- | --- | --- | --- | --- | --- |
| **Heparin plus LDA compared to placebo for SLE plus APS seeking pregnancy** | | | | | | |
| Outcome  № of participants  (studies) | Relative effect  (95% CI) | **Anticipated absolute effects (95% CI)** | | | Quality | What happens |
| **Without heparin plus ASA** | **With heparin plus ASA** | **Difference** |
| Live births  № of participants: 180  (1 RCT) | **RR 1.10**  (0.92 to 1.38) | 65.6% | **72.1%**  (60.3 to 90.5) | **6.6% more**  (5.2 fewer to 24.9 more) | ⨁⨁◯◯  LOW 1,2 | Thromboprophylaxis may increase live births |
| Pregnancy  follow up: 0 - 6 months  № of participants: 180  (1 RCT) | **RR 1.60**  (1.16 to 2.40) | 33.3% | **53.3%**  (38.7 to 80.0) | **20.0% more**  (5.3 more to 46.7 more) | ⨁⨁⨁◯  MODERATE 1 | Thromboprophylaxis probably increases pregnancies at 0 - 6 months |
| Pregnancy  follow up: 6 - 12 months  № of participants: 180  (1 RCT) | **RR 0.91**  (0.60 to 1.37) | 38.9% | **35.4%**  (23.3 to 53.3) | **3.5% fewer**  (15.6 fewer to 14.4 more) | ⨁⨁◯◯  LOW 1,2 | Thromboprophylaxis may make little or no difference to pregnancy at 6 to 12 months |
| IUGR  № of participants: 180  (1 RCT) | **RR 0.35**  (0.12 to 0.89) | 18.9% | **6.6%**  (2.3 to 16.8) | **12.3% fewer**  (16.6 fewer to 2.1 fewer) | ⨁⨁⨁◯  MODERATE 1 | Thromboprophylaxis probably reduces IUGR |
| Patient requiring transfusion  № of participants: 180  (1 RCT) | Four patients in the intervention arm required transfusion vs no patient in the control arm | | | | ⨁⨁◯◯  LOW 1,2 |  |

1. No blinding

2. 95%CI including benefits and harms

* Ismail AM, Hamed AH, Saso S, Abu-Elhasan AM, Abu-Elghar MM, Abdelmeged AN. Randomized controlled study of pre-conception thromboprophylaxis among patients with recurrent spontaneous abortion related to antiphospholipid syndrome. Int J Gynaecol Obstet. 2016;132:219–23.

11.1.1

| **GCs compared to placebo for ophthalmological manifestations of lupus** | | |
| --- | --- | --- |
| Outcome № of participants (studies) | **Impact** | Quality |
|
|  |
| Clinical improvement of scleritis follow up: 6 months (1 observational study) | In a case series of 3 patients with posterior scleritis, all patients showed improvement after treatment with GCs (2 of them systemic and 1 topical and periocular injections). | ⨁◯◯◯ VERY LOW 2,3 |
| Clinical improvement of uveitis follow up: 6 months (1 observational study) | In a korean cohort of 432 patients with uveitis, 33 were associated with autoimmune disease. For those, GCs were the important treatment drug, and high dose of systemic GCs therapy was applied in 22 (67%) patients. Combined CsA and topical GCs treatment was used in 20 patients (61%). The most frequent ocular complications were cataract 1 (3%) and retinal vacuities 1 (3%) (no association with treatment described). | ⨁◯◯◯ VERY LOW 1,2 |
| Clinical improvement of choroidopathy follow up: 6 months (1 observational study) | In a case series of 24 patients, 23 patients (82%) had resolution of their choroidopathy when their systemic disease was brought under control after treatment with systemic GCs. | ⨁◯◯◯ VERY LOW 2 |

1. Sampling not clearly described
2. Small number of events
3. Case series

* Lee SY, Chung WT, Jung WJ, Lee SW. Retrospective study on the effects of immunosuppressive therapy in uveitis associated with rheumatic diseases in Korea. Rheumatol Int. 2012;32:3903–8.
* Wong RW, Chan A, Johnson RN, McDonald HR, Kumar A, Gariano R, et al. Posterior scleritis in patients with systemic lupus erythematosus: Retinal Cases & Brief Reports. 2010;4:326–31.
* Nguyen QD, Uy HS, Akpek EK, Harper SL, Zacks DN, Foster CS. Choroidopathy of systemic lupus erythematosus. Lupus. 2000;9:288–98.

11.1.2

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| --- | --- | --- |
| **MMF compared to placebo for ophthalmologic manifestations of lupus** | | |
| Outcome № of participants (studies) | **Impact** | Quality |
|
|  |
| Recurrence of uveitis in maintenance follow up: 33 months (1 observational study) | In 95 patients MMF was combined with prednisolone in a dosage between 2.5 to 10 mg/day. In eight patients MMF was used as a monotherapy and in three cases one further systemic immunosuppressant was required. The frequency of recurrences was one or less in 92 patients, two in six cases and three or greater in eight patients. In four patients, treatment with MMF was discontinued as the drug was judged ineffective in controlling the disease. | ⨁◯◯◯ VERY LOW 1 |
| OCT/FA score in uveitis follow up: 33 months (1 observational study) | In a prospective pilot study diminishing ocular inflammation in 10 of the 11 patients examined over a period of four to nine months. Here, MMF was used as a third agent in patients who responded inadequately to either GCs at an unacceptably high dose or when combined with cyclosporine or was substituted for AZA as a second- or third-line drug. | ⨁◯◯◯ VERY LOW 1 |
| Adverse events follow up: 33 months (1 observational study) | In the previously mentioned cohort of 95 patients the most frequently observed side effects were gastrointestinal upset (15%), followed by headache (9.3%), fatigue (5.7%), eczema (5%), and hair loss (3.5%). | ⨁◯◯◯ VERY LOW 1 |
| Visual acuity in uveitis follow up: 33 months (1 observational study) | Lau et al. in an open-label retrospective series of 14 patients with refractory uveitis treated with MMF for a mean of 33 months showed that vision improved in seven eyes, did not change in 14 eyes and was reduced in seven eyes. | ⨁◯◯◯ VERY LOW 1 |

1. Non adjusted estimates

* Zierhut M, Stübiger N, Siepmann K, Deuter CME. MMF and eye disease. Lupus. 2005;14 Suppl 1:s50-54.

11.1.3

|  | | |
| --- | --- | --- |
| **TPE compared to placebo for ophthalmological manifestations of lupus** | | |
| Outcome № of participants (studies) | **Impact** | Quality |
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|  |
| Clinical improvement for choroidopathy follow up: 1 months (1 observational study) | TPE were successfully applied in this case, resulting in a disappearance of the retinal detachment due to immune complexes-mediated choroidopathy in one month. | ⨁◯◯◯ VERY LOW 1 |
| Clinical improvement for retinal vasculitis follow up: 5 days (1 observational study) | A patient with retinal vasculitis associated to SLE refractory to pulsed intravenous methylprednisolone, was treated with TPE for 5 days followed by a single intravenous infusion of cyclophosphamide (750 mg). The patient's overall medical status improved dramatically. | ⨁◯◯◯ VERY LOW 1 |

1. Non adjusted estimates

* Papadaki TG. Plasmapheresis for Lupus Retinal Vasculitis. Archives of Ophthalmology. 2006;124:1654.
* Hannouche D, Korobelnik JF, Cochereau I, Hayem G, Beaudreuil J, Meyer O, et al. Systemic lupus erythematosus with choroidopathy and serous retinal detachment. Int Ophthalmol. 1995;19:125-7.

11.1.4

| **Bevacizumab compared to placebo for ophthalmological manifestations in lupus** | | |
| --- | --- | --- |
| Outcome № of participants (studies) | **Impact** | Quality |
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| --- | --- | --- |
| Clinical improvement in uveitis follow up: 3 months (1 observational study) | A 15-years old patient with SLE and uveitis refractory to pulsed intravenous methylprednisolone and oral cyclophosphamide 100 mg daily , was treated with one dose of 1.25 mg intravitreal bevacizumab. On re-evaluation a week later, the VA (OD) was 20/20, the NVE had regressed and the vitreous haemorrhage had almost cleared. The patient was evaluated 3 months after the intravitreal injection, with no recurrence of bleeding from the NVE and stable VA. | ⨁◯◯◯ VERY LOW 1 |

1. Non adjusted estimates

* Kurup S, Lew J, Byrnes G, Yeh S, Nussenblatt R, Levy-Clarke G. Therapeutic efficacy of intravitreal bevacizumab on posterior uveitis complicated by neovascularization. Acta Ophthalmol. 2009;87:349–52.

11.1.5

|  | | |
| --- | --- | --- |
| **Infliximab compared to placebo for ophthalmological manifestations of lupus** | | |
| Outcome № of participants (studies) | **Impact** | Quality |
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|  |
| FA/OCT score for uveitis follow up: 3 months (1 observational study) | In a cohort of 23 patients with uveitis due to autoimmune diseases, 11 out of 23 patients (50%) had improvement in the FA/OCT score Very low certainty in the effect (Very serious risk of bias, Serious indirectness, Serious imprecision) | ⨁◯◯◯ VERY LOW 1,2,3 |
| Concomitant medication reduction for uveitis follow up: 3 months (1 observational study) | In the same cohort 10 out of 23 patients (44%) had reduction in the concomitant medication | ⨁◯◯◯ VERY LOW 1,2 |
| Discontinuation due to adverse event before week 10 (uveitis patients) follow up: 3 months (1 observational study) | In the same cohort 2 out of 23 patients (9%) needed to discontinue the medication due to adverse event before week 10 | ⨁◯◯◯ VERY LOW 1,2 |
| Visual acuity (uveitis patients) follow up: 3 months (1 observational study) | In a cohort of 23 patients with uveitis due to autoimmune disease (Not only SLE; the most comon causes were Behcet disease and Sarcoidosis), 8 patients (34%) achieved an improvement in visual acuity (Snellen charts from 2 to 8) | ⨁◯◯◯ VERY LOW 1,2 |
| Discontinuation due to adverse event (uveitis patients) follow up: 3 months (1 observational study) | In the same cohort 5 out of 23 patients (22%) discontinued the medication due to adverse event | ⨁◯◯◯ VERY LOW 1,2 |
| Improvement in visual acuity (1 line) in patients with scleritis follow up: 12 months (1 observational study) | In a case series of 10 patients, 2 patients presented improvement in visual acuity in 1 line in a 12-months follow up | ⨁◯◯◯ VERY LOW 1,2 |
| Deterioration in visual acuity (2 lines) in patients with scleritis follow up: 12 months (1 observational study) | In a case series of 10 patients, 2 patients presented improvement in visual acuity in 1 line in a 12-months follow up | ⨁◯◯◯ VERY LOW 1,2 |
| Recurrence follow up: 12 months (1 observational study) | In a case series of 10 patients, 6 patients presented recurrence in a 12-months follow up | ⨁◯◯◯ VERY LOW 1,2 |

1. Low number of patients/events
2. Case series

* Suhler EB, Smith JR, Wertheim MS, Lauer AK, Kurz DE, Pickard TD, et al. A prospective trial of infliximab therapy for refractory uveitis: preliminary safety and efficacy outcomes. Arch Ophthalmol. 2005;123:903–12.
* Doctor P, Sultan A, Syed S, Christen W, Bhat P, Foster CS. Infliximab for the treatment of refractory scleritis. British Journal of Ophthalmology. 2010 ;94:579–83.

11.1.6

|  | | |
| --- | --- | --- |
| **RTX compared to placebo for oftalmological manifestations of lupus** | | |
| Outcome № of participants (studies) | **Impact** | Quality |
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| --- | --- | --- |
| Visual acuity in uveitis follow up: 6-9 months (1 observational study) | Tappeiner and colleagues reported improvement of endogenous uveitis and associated cystoid macular edema in an adult patient treated with RTX; the treatment also displayed a GCs sparing effect. However, the B-cell depletion in the peripheral blood and the positive effect on uveitis were transient, since there was a recurrence of inflammation after 6 and 9 months from RTX treatment | ⨁◯◯◯ VERY LOW 1 |

1. Non adjusted estimates

* Tappeiner C, Heinz C, Specker C, Heilighenhaus A. Rituximab as a treatment option for refractory endogenous anterior uveitis. Ophthalmic Res 2007;39:184–6.

11.2.1

|  | | |
| --- | --- | --- |
| **RTX compared to CYC plus AZA for ophthalmological manifestations of lupus** | | |
| Outcome № of participants (studies) | **Impact** | Quality |
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| --- | --- | --- |
| Visual acuity in retinal vasculitis follow up: 3 months (1 RCT) | In a randomized trial that randomized 20 patients with retinal vasculitis due to Behcet`s disease to RTX vs CYC plus AZA the mean VA improved in two patients in the RTX group versus three in the CYC plus AZA group, remained unchanged in 1 (RTX) vs 1 (CYC plus AZA), and worsened in 7 (RTX) vs 6 (CYC plus AZA) patients | ⨁⨁◯◯ LOW 1,2 |

1. Non SLE patients (Behcet's disease)
2. Optimal information size not met

* Davatchi F, Shams H, Rezaipoor M, Sadeghi-Abdollahi B, Shahram F, Nadji A, et al. Rituximab in intractable ocular lesions of Behcet's disease; randomized single-blind control study (pilot study). Int J Rheum Dis 2010;13:246–52.

12.1

| **TPE compared to any for SLE** | | |
| --- | --- | --- |
| Outcome № of participants (studies) | **Impact** | Certainty |
|
|  |
| Complications  № of participants: 342563  (1 observational study) | Studies reported incidence: 1.2% | - |
| Complications leading to stopping the procedure including vasovagal reactions, hematoma, painful arm, citrate reaction № of participants: 342563  (1 observational study) | Studies reported incidence: 0.9% | - |
| Complications in elderly (2 observational studies) | Studies reported incidence: 4.57 – 13.3% | - |

* Wiersum-Osselton JC, Marijt-van der Kreek T, van Dongen R. Plasmapheresis in healthy donors in the Netherlands: Cohort study of risk factors for donor complications. Transfusion and Apheresis Science. 2013;48:163.
* Abdel-Rahman EM, Hayes J, Balogun RA. Therapeutic plasma exchange in the elderly: Experience at a tertiary center. Journal of Clinical Apheresis. 2012;27:108–11.
* Basic-Jukic N, Brunetta B, Kes P. Plasma Exchange in Elderly Patients. Therapeutic Apheresis and Dialysis. 2010;14:161–5.

12.2

| **AZA compared to any for SLE** | | |
| --- | --- | --- |
| Outcome № of participants (studies) | **Impact** | Certainty |
|
|  |
| Infections (7 RCTs) | Studies reported incidence: 2.4 – 42.4% | - |
| Amenorrhea and/or Ovarian complications: (10 Studies) | Studies reported incidence: 1.4 - 36% | - |
| Hematological (10 Studies) | Studies reported incidence: 6 - 50% | - |
| Treatment interruption because of AEs (15 Studies) | Studies reported incidence: 16 - 26% | - |
| Cancer (3 Observational studies) | An increase in cancer risk after 5 (OR 2.0, CI 0.4–0.1) and 10 years of continuous therapy (4.4, CI 0.9–20.9) and cumulative doses >600 g (OR 6.7, CI 1.2–36.1) has been reported. Previous studies with shorter follow up have found inconsistent results. | ⨁◯◯◯ VERY LOW 1,2 |

1. Confidence interval includes significant decrease and increase in the risk of cancer
2. Different estimates across studies

* Oglesby A, Shaul AJ, Pokora T, Paramore C, Cragin L, Dennis G, et al. Adverse event burden, resource use, and costs associated with immunosuppressant medications for the treatment of systemic lupus erythematosus: a systematic literature review. Int J Rheumatol. 2013;2013:347520.
* La Mantia L, Mascoli N, Milanese C. Azathioprine. Safety profile in multiple sclerosis patients. Neurological Sciences. 2007;28:299–303.

12.3

| Belimumab **compared to any for SLE** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| Outcome № of participants (studies) | Relative effect (95% CI) | **Anticipated absolute effects (95% CI)** | | | Certainty | What happens |
| **Without** belimumab | **With** belimumab | **Difference** |
| Progressive multifocal leukoencephalopathy № of participants: 2985 (1 observational) | **RR 4.5** (2.25 – 9) | 4 per 10000 | **27 per 10000** | **23 more per 10000** | ⨁⨁◯◯ LOW | Belimumab may increase the risk of Progressive multifocal leukoencephalopathy |
| Malignant neoplasms Follow up: 5-6 years  № of participants: 998 (1 observational) | Reported incidence: 2.6%. | | | | - |  |
| Infections  Follow up: 5-6 years № of participants: 998 (1 observational) | Reported incidence: 11.7% (all infections), 1.7% (Serious infections), 2.3% (opportunistic infections), 1.2% (sepsis) | | | | - |  |
| Depression Follow up: 5-6 years  № of participants: 998 (1 observational) | Reported incidence: Any (15.4%), suicide/self-injury (0.4%) | | | | - |  |
| Infusion reactions Follow up: 5-6 years № of participants: 998 (1 observational) | Reported incidence: 2.6% | | | |  |  |

1. Risk of bias

2. Wide confidence intervals include significant benefit and harm

* Raisch DW, Rafi JA, Chen C, Bennett CL. Detection of cases of progressive multifocal leukoencephalopathy associated with new biologicals and targeted cancer therapies from the FDA’s adverse event reporting system. Expert Opinion on Drug Safety. 2016;15:1003–11.
* Bruce IN, Urowitz M, van Vollenhoven R, Aranow C, Fettiplace J, Oldham M, et al. Long-term organ damage accrual and safety in patients with SLE treated with belimumab plus standard of care. Lupus. 2016;25:699–709.

12.4

| **MTX compared to any for SLE** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| Outcome № of participants (studies) | Relative effect (95% CI) | **Anticipated absolute effects (95% CI)** | | | Certainty | What happens |
| **Without Methotrexate** | **With Methotrexate** | **Difference** |
| Infections (1 RCT) | Studies reported incidence: 4.9% | | | | - |  |
| Hematological (1 RCTs) | Studies reported incidence: 26.8% | | | | - |  |
| Any hepatic adverse effect № of participants: 13177 (32 RCTs) | **RR 2.19** (1.73 to 2.79) | **Observed** | | | ⨁⨁⨁⨁ HIGH | Methotrexate increases the risk of hepatic adverse effects |
| 8.0% | **17.5%** (13.8 to 22.3) | **9.5% more** (5.8 more to 14.3 more) |
| Severe hepatic adverse effects assessed with: Liver failure, fibrosis, cirrhosis or death № of participants: 13177 (32 RCTs) | **RR 0.12** (0.01 to 1.09) | 48 per 100000 | **6 per 100000** (0 a 52) | **42 fewer per 100000 (**47 fewer a 4 more) | ⨁◯◯◯ VERY LOW 1,2 | It is uncertain if methotrexate increases the risk of severe hepatic adverse effects |
| Respiratory adverse events  assessed with: Infectious or non-infectious adverse events № of participants: 1630 (7 RCTs) | **RR 1.03** (0.90 to 1.17) | 30.7% | **31.6%** (27.6 to 35.9) | **0.9% more** (3.1 fewer to 5.2 more) | ⨁⨁◯◯ LOW 3,4 | Methotrexate may not significantly increase the risk of respiratory adverse events |

1. Follow up was not adequate
2. CI95% includes benefits and harms
3. Studies not included SLE patients
4. 95%CI includes significant harms

* Oglesby A, Shaul AJ, Pokora T, Paramore C, Cragin L, Dennis G, et al. Adverse event burden, resource use, and costs associated with immunosuppressant medications for the treatment of systemic lupus erythematosus: a systematic literature review. Int J Rheumatol. 2013;2013:347520.
* Conway R, Low C, Coughlan RJ, O’Donnell MJ, Carey JJ. Methotrexate use and risk of lung disease in psoriasis, psoriatic arthritis, and inflammatory bowel disease: systematic literature review and meta-analysis of randomised controlled trials. BMJ. 2015;350:h1269.
* Conway R, Low C, Coughlan RJ, O’Donnell MJ, Carey JJ. Risk of liver injury among methotrexate users: A meta-analysis of randomised controlled trials. Seminars in Arthritis and Rheumatism. 2015;45:156–62.

12.5

| **MMF compared to any for SLE** | | |
| --- | --- | --- |
| Outcome № of participants (studies) | **Impact** | Certainty |
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|  |
| Gastrointestinal symptoms (10 RCTs) | Studies reported incidence: 4.2 - 61.4% | - |
| Amenorrhea and/or ovarian complications (10 RCTs) | Studies reported incidence: 0 - 6% | - |
| Hematological complications (10 RCTs) | Studies reported incidence: 0 - 21.7% | - |
| Infections (10 RCTs) | Studies reported incidence: 2.7 - 68.5% | - |

* Oglesby A, Shaul AJ, Pokora T, Paramore C, Cragin L, Dennis G, et al. Adverse event burden, resource use, and costs associated with immunosuppressant medications for the treatment of systemic lupus erythematosus: a systematic literature review. Int J Rheumatol. 2013;2013:347520.
* Conti F, Ceccarelli F, Perricone C, Massaro L, Cipriano E, Pacucci VA, et al. Mycophenolate mofetil in systemic lupus erythematosus: results from a retrospective study in a large monocentric cohort and review of the literature. Immunol Res. 2014;60:270–6.

12.6

| **CYC compared to any for SLE** | | |
| --- | --- | --- |
| Outcome № of participants (studies) | **Impact** | Certainty |
|
|  |
| Infections (oral) (8 RCTs) | Studies reported incidence: 26 - 61% | - |
| Amenorrhea and/or ovarian complications (IV) (21 RCTs) | Studies reported incidence: 1.9 - 58% | - |
| Amenorrhea and/or ovarian complications (Oral) (8 RCTs) | Studies reported incidence: 28 - 71% | - |
| Hematological (IV) (21 RCTs) | Studies reported incidence: 1.4 - 38.7% | - |
| Infections (IV): (21 RCTs) | Studies reported incidence: 11.8 - 77% | - |
| Hematological (oral): (8 RCTs) | Studies reported incidence: 7 - 25.8% | - |
| Hemorrhagic Cystitis (oral) (10 observational studies) | In the studies in which the diagnosis was usually or always confirmed by cystoscopy, the incidence of hemorrhagic cystitis ranged from 12% to 41%. | - |
| Bladder cancer (oral) (11 observational studies) | A substantially elevated risk of bladder cancer associated with cyclophosphamide treatment was observed in all studies (OR range 3.6–100). Unselected patients with lupus do not appear to be at elevated risk of bladder cancer (OR 1.23, 95% CI 0.66–2.11), based on a multicenter cohort study of 9,547 patients followed up for an average of 8 years | ⨁◯◯◯ VERY LOW 1 |

* 1. Confidence interval includes significant increase in the risk of bladder cancer
* Oglesby A, Shaul AJ, Pokora T, Paramore C, Cragin L, Dennis G, et al. Adverse event burden, resource use, and costs associated with immunosuppressant medications for the treatment of systemic lupus erythematosus: a systematic literature review. Int J Rheumatol. 2013;2013:347520.
* Monach PA, Arnold LM, Merkel PA. Incidence and prevention of bladder toxicity from cyclophosphamide in the treatment of rheumatic diseases: A data-driven review. Arthritis & Rheumatism. 2010;62:9–21.

12.7

| **IVIG compared to any for SLE** | | |
| --- | --- | --- |
| Outcome № of participants (studies) | **Impact** | Certainty |
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|  |
| Severe adverse events follow-up: 1 year (1 observational study) | In a retrospective cohort of 2397 patients, 25 (1%) patients presented severe adverse events | - |
| Fever follow-up: 1 months  (1 observational study) | In a retrospective case series of 77 patients, 11 (14%) patients presented fever | - |
| Rash follow-up: 1 month  (1 observational study) | In a retrospective case series of 77 patients, 8 (10%) patients presented Rash | - |
| Cyanosis follow-up: 1 month  (1 observational study) | In a retrospective case series of 77 patients, 3 (3.8%) patients presented cyanosis | - |
| Hypotension follow-up: 1 month  (1 observational study) | In a retrospective case series of 77 patients, 2 (2.6%) patients presented hypotension | - |
| Any adverse event follow-up: 1 year  (1 observational study) | In a retrospective cohort of 2397 patients, 192 (8%) patients presented any adverse event | - |

* Frenzel W, Wietek S, Svae T-E, Debes A, Svorc D. Tolerability and safety of Octagam® (IVIG): a post-authorization safety analysis of four non-interventional phase IV trials. Int J Clin Pharmacol Ther. 2016;54:847–55.
* Palabrica FRR, Kwong SL, Padua FR. Adverse events of intravenous immunoglobulin infusions: a ten-year retrospective study. Asia Pac Allergy. 2013;3:249–56.

12.8

| **CsA compared to any for SLE** | | |
| --- | --- | --- |
| Outcome № of participants (studies) | **Impact** | Certainty |
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|  |
| Leucopenia follow-up: 6 months (10 RCT) | Leucopenia: 11 out of 189 patients (5.8%) | - |
| Menstrual disorder follow-up: 6 months : (10 RCT) | Menstrual disorder: 4 out of 96 patients (4%) | - |
| Liver dysfunction follow-up: 6 months (10 RCT) | Liver dysfunction: 4 out of 59 patients (6.8%) | - |
| Hyperglycemia follow-up: 6 months : (10 RCT) | Hyperglycemia: 14 out of 71 patients (20%) | - |
| Infections follow-up: 6 months (10 RCT) | Infections: 37 out of 196 patients (18.9%) | - |
| Nephrotoxicity follow-up: 2 years  N. of patients: 867 (13 RCT) | Nephrotoxicity was defined as an increase in serum creatinine level of 50% or more above baseline, at least once during the study period. In the CsA-treated group, 102 of 474 patients (21.5%) exhibited such a rise in serum creatinine, compared to 5 of 393 patients (1.3%) in the control group (Fig. 1). The weighted average risk difference in developing nephrotoxicity between CsA treatment and an alternative therapy was 15.4% (95% CI 11.8% to 18.8%) | ⨁⨁⨁⨁ HIGH |

* Zhang X, Ji L, Yang L, Tang X, Qin W. The effect of calcineurin inhibitors in the induction and maintenance treatment of lupus nephritis: a systematic review and meta-analysis. Int Urol Nephrol. 2016;48:731–43.
* Vercauteren SB, Bosmans JL, Elseviers MM, Verpooten GA, De Broe ME. A meta-analysis and morphological review of cyclosporine-induced nephrotoxicity in auto-immune diseases. Kidney Int. 1998;54:536–45.

12.9

| **RTX compared to placebo for Lupus** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| Outcome № of participants (studies) | Relative effect (95% CI) | **Anticipated absolute effects (95% CI)** | | | Certainty | What happens |
| **Without RTX** | **With RTX** | **Difference** |
| Serious AE follow up: 3 months № of participants: 3982 (16 RCTs) | **OR 1.10** (0.79 to 1.53) | **Observed** | | | ⨁⨁⨁◯ MODERATE 1 | RTX probably slightly increases the risk of severe adverse effects |
| 11.8% | **12.8%** (9.6 to 17.0) | **1.0% more** (2.2 fewer to 5.2 more) |
| Serious infections follow up: 3 months № of participants: 4485 (19 RCTs) | **RR 0.97** (0.64 to 1.48) | **Observed** | | | ⨁⨁◯◯ LOW 1,2 | RTX may no increase the risk of serious infections |
| 2.6% | **2.5%** (1.7 to 3.8) | **0.1% fewer** (0.9 fewer to 1.2 more) |
| Serum sickness follow up: 3 months № of participants: (1 RCT) | Serum sickness: RTX 4% vs. PCB 0%. 33 cases have been reported in the literature. | | | | ⨁⨁⨁◯ MODERATE 3 | RTX probably increases the risk of serum sickness |
| Neutropenia degree 3–4 follow up: 3 months № of participants: 100 (1 RCT) | **RR 2.265** (0.580 to 2.810) | 3.4% | **7.7%** (2.0 to 9.6) | **4.3% more** (1.4 fewer to 6.2 more) | ⨁⨁◯◯ LOW 1 | RTX may increase the risk of severe neutropenia |
| Progressive multifocal leukoencephalopathy № of participants: 2985 (1 observational) | 76 reported cases, 69 in oncology indications, one autoimmune hemolytic anemia, five in other autoimmune disorders, and one in an unknown indication. Estimated incidence 1 in 4000 | | | |  |  |

1. The 95% confidence interval around the pooled effect includes both no effect and appreciable benefit or harm

2. Risk of bias

3. Low event rate

* Singh JA, Wells GA, Christensen R, Tanjong Ghogomu E, Maxwell L, Macdonald JK, et al. Adverse effects of biologics: a network meta-analysis and Cochrane overview. Cochrane Database Syst Rev. 2011:CD008794.
* Karmacharya P, Poudel DR, Pathak R, Donato AA, Ghimire S, Giri S, et al. Rituximab-induced serum sickness: A systematic review. Semin Arthritis Rheum. 2015;45:334–40.
* Carson KR, Focosi D, Major EO, Petrini M, Richey EA, West DP, et al. Monoclonal antibody-associated progressive multifocal leucoencephalopathy in patients treated with rituximab, natalizumab, and efalizumab: a Review from the Research on Adverse Drug Events and Reports (RADAR) Project. Lancet Oncol. 2009;10:816–24.

12.10

| **AMs compared to placebo for SLE** | | |
| --- | --- | --- |
| Outcome № of participants (studies) | **Impact** | Quality |
|
|  |
| Retinal toxicity № of participants: 647 (4 observational studies) | In all, 4 studies, including 647 patients treated with CQ for a mean of 10 years, found that 16 (2.5%) patients were diagnosed as having definite retinal toxicity, in comparison with only 2 (0.1%) of 2043 patients taking HCQ for a similar period included in 6 studies. When patients classified as having probable retinal toxicity were added, there were 17/647 (2.6%) CQ users and 6/2043 (0.3%) HCQ users with toxicity (OR 9.16, 95% CI 3.42 to 28.47, p=0.001). | - |
| Cardiac toxicity № of participants: 70 (2 studies) | Cardiotoxicity of AMs in patients with SLE has been evaluated in 2 studies including 70 patients treated with HCQ and 28 patients treated with CQ, respectively. No cases of clinically relevant cardiotoxicity were reported. | - |
| Fetal adverse effects № of participants: 275 (10 observational studies) | All the studies are concordant in showing the absolute safety of AMs during pregnancy: congenital malformations were not more frequent than in unexposed children and no cases of ocular, auditory or neurological toxicity were reported. | - |
| Adverse effects leading to discontinuation № of participants: 647 (4 observational studies) | 15% presented AE leading to discontinuation | - |

* Ruiz-Irastorza G, Ramos-Casals M, Brito-Zeron P, Khamashta MA. Clinical efficacy and side effects of antimalarials in systemic lupus erythematosus: a systematic review. Ann Rheum Dis. 2010;69:20–8.