**Supplementary Table 3.** Results from the systematic literature research to inform the SLE recommendations

|  |  |
| --- | --- |
| **Topic** | **Evidence base** |
|  |  |
| **Q1. Benefits and harms of GC in treating SLE** |  |
| Comparable efficacy and less toxicity of lower-dose versus high-dose GC regimens |  |
| GC exposure and increased risk for infections |  |
| GC exposure and increased risk for organ damage |  |
| Pulse IV-MP and increased risk for infections |  |
|  |  |
| **Q2. Benefits and harms of HCQ in SLE** |  |
| Association of HCQ blood levels / compliance with outcome |  |
| Association of HCQ use with favourable outcome(s) |  |
| HCQ cumulative exposure and retinal toxicity |  |
|  |  |
| **Q3. Benefits and harms of immunosuppressive agents in SLE** |  |
| Efficacy of MTX |  |
| Efficacy of AZA |  |
| Efficacy of MMF |  |
| Efficacy of CYC |  |
| MTX and harms (infections) |  |
| AZA and harms (infections) |  |
| MMF and harms (infections) |  |
| CYC and harms (infections) |  |
| CYC and harms (gonadal toxicity) |  |
|  |  |
| **Q4. Benefits and harms of calcineurin inhibitors in SLE** |  |
| Efficacy of CNIs in extra-renal SLE |  |
|  |  |
| **Q5. Benefits and harms of biologics in SLE** |  |
| Efficacy of RTX in refractory SLE (general) |  |
| Efficacy of RTX in refractory SLE cytopenias |  |
| RTX and harms (infections) in SLE |  |
| Efficacy of belimumab in SLE |  |
| Safety of belimumab in SLE |  |
|  |  |
| **Q6. Management of skin involvement in SLE** |  |
| Antimalarials |  |
| Systemic GC |  |
| MMF (refractory skin disease) |  |
| MTX |  |
| Dapsone |  |
| Thalidomide (refractory skin disease) |  |
| Lenalidomide (refractory skin disease) |  |
| CYC (refractory skin disease) |  |
| IVIG (refractory skin disease) |  |
| Retinoids |  |
| Rituximab (refractory skin disease) |  |
| Belimumab (refractory skin disease) |  |
|  |  |
| **Q7. Management of renal involvement in SLE** |  |
| ***Use of CNIs*** |  |
| Similar efficacy in inducing remission (renal response) compared to SoC (CYC/MMF) |  |
| Similar efficacy in sustaining remission (no flares) compared to SoC (AZA/MMF) |  |
| Similar safety profile (infections) |  |
| Similar safety profile (mortality) |  |
| Similar safety profile (elevation of serum creatinine) |  |
| ***Multitarget*** |  |
| Superior efficacy in inducing remission (renal response) compared to SoC |  |
| Similar efficacy in sustaining remission (no flares) compared to SoC |  |
| Similar safety profile (infections) |  |
| Similar safety profile (mortality) |  |
| ***RTX*** |  |
| Similar efficacy in inducing remission (renal response) compared to SoC |  |
| Similar safety profile (infections) |  |
| ***Belimumab*** |  |
| Anti-proteinuric effect |  |
| Superior efficacy in sustaining remission (no flares) compared to SoC |  |
| ***MMF*** |  |
| **Induction** |  |
| Similar efficacy in inducing remission (renal response) compared to CYC |  |
| Similar efficacy in sustaining remission (no flares) compared to CYC |  |
| Similar efficacy in long term outcome (CKD, ESRD, treatment failure) compared to CYC |  |
| **Maintenance** |  |
| Superior efficacy in sustaining remission (no flares) compared to AZA |  |
| Similar efficacy in long term outcome (CKD, ESRD, treatment failure) compared to AZA |  |
| **Safety** |  |
| Similar safety profile (infections) |  |
| Superior safety profile (leukopenia) |  |
| Superior safety profile (ovarian failure/amenorrhea) |  |
| Inferior safety profile (GI symptoms / mostly diarrhea) |  |
| **CYC** |  |
| Similar safety profile of low versus at least standard dose of CYC |  |
| Similar efficacy of low versus at least standard dose of CYC in inducing remission (renal response) |  |
|  |  |
| **Q8. Management of neuropsychiatric involvement in SLE** |  |
| Performance of attribution models for NPSLE |  |
| Efficacy of CYC in NPSLE |  |
| Efficacy of MMF in NPSLE |  |
| Efficacy of rituximab in (refractory) NPSLE |  |
| Treatment of myelopathy with immunosuppression |  |
| Treatment of cerebrovascular disease with immunosuppression |  |
|  |  |
| **Q9. Management of APS in SLE** |  |
| Association of aPL with thrombosis, pregnancy, morbidity and organ damage |  |
| Low-dose ASA for 1ary prevention of thrombosis |  |
| HCQ for 1ary prevention of thrombosis |  |
| Warfarin for 2ary prevention of thrombosis |  |
|  |  |
| **Q10. Prevention of SLE flares** |  |
| Impact of disease flares on adverse outcomes (damage, mortality etc) |  |
| Efficacy of HCQ to prevent SLE flares |  |
| Efficacy of MMF to prevent SLE flares |  |
| Efficacy of rituximab to prevent SLE flares |  |
| Efficacy of belimumab to prevent SLE flares |  |
|  |  |
| **Q11. Assessment of activity and damage in SLE** |  |
| *Not applicable – See Supplementary Table 2 for detailed SLR results* | |
|  |  |
| **Q12. Treatment goals in SLE** |  |
| Correlation of disease activity with damage |  |
| Remission correlates with less damage accrual |  |
| Low disease activity state correlates with less damage accrual and risk for future flares |  |
| Correlation of flares with damage |  |
|  |  |
| **Q13. Duration of immunosuppressive treatment/biologic treatment in SLE** |  |
| *Not applicable – See Supplementary Table 2 for detailed SLR results* | |
|  |  |
| **Q14. Management of comorbidities in SLE** |  |
| ***Prevention of CVD in SLE*** |  |
| HCQ |  |
| Statins |  |
| ASA |  |
| ***Prevention of infections in SLE*** |  |
| HCQ (protective effect) |  |
| Vaccination (influenza) |  |
| Vaccination (pneumococcal) |  |
| Safety of vaccination (AE) |  |
| Safety of vaccination (flares) |  |

LoE: Level of Evidence; GC: Glucocorticoids; IV: Intravenous; MP: Methylprednizolone; HCQ: Hydroxychloroquine; MTX: Methotrexate; AZA: Azathioprine; MMF: Mycophenolate mofetil; CYC: Cyclophosphamide; CNI: Calcineurin inhibitors; RTX: Rituximab; IVIG: Intravevous immunoglobulin; SoC: Standard of care; CKD: Chronic kidney disease; ESRD: End-stage renal disease; GI: Gastrointestinal; NPSLE: Neuropsychiatric SLE; APS: Antiphospholipid syndrome; aPL: Antiphospholipid antibodies; ASA: Acetylsalicylic acid; CVD: Cardiovascular disease; AE: Adverse events

**Supplementary Table 4.** Level of evidence and grading of recommendations

|  |  |  |
| --- | --- | --- |
| **Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (LoE)** | | |
| **LoE** | **Therapy/Prevention/Etiology/Harm** | **Risk factors/Prognosis** |
| **1a** | Systematic reviews of RCT | Systematic review of inception cohort studies |
| **1b** | Individual, high-quality RCT | Individual inception cohort study (high quality) |
| **2a** | Systematic reviews of cohort studies | Systematic review of retrospective cohort studies or data from RCT |
| **2b** | Cohort study or low quality RCT | Retrospective cohort study or data from RCT |
| **2c** | "Outcomes" research studies | "Outcomes" research studies |
| **3a** | Systematic review of case-control studies |  |
| **3b** | Case-control studies |  |
| **4** | Case-series (and poor-quality cohort and case-control studies) | Case-series (and poor-quality prognostic cohort) studies) |
| **5** | Expert opinion | Expert opinion |
| **Grading of recommendations, assessment, development and evaluations (GRADE)** | | |
| **A** | Consistent level 1 studies | |
| **B** | Consistent level 2 or 3 studies; or extrapolations from level 1 studies | |
| **C** | Level 4 studies; or extrapolations from level 2 or 3 studies | |
| **D** | Level 5 evidence; or very inconsistent or inconclusive studies of any level | |

RCT: Randomized controlled trials

**Supplementary Table 5.** Recommended doses of drugs mentioned in the EULAR recommendations

|  |  |  |
| --- | --- | --- |
| **Drug** | **Recommended dose** | **Dose adjustment needed in CKD** |
| **Glucocorticoids** | *Mild-Moderate disease*: Start with ≤ 0.5 mg/Kg/day with gradual tapering  *Severe/Organ-threatening disease*: Consider IV MP pulses 250-1000 mg/day for 1-3 days - Continue with PO 0.5-0.7 mg/Kg/day with tapering  *All circumstances*: Avoid starting with 1 mg/Kg/day oral prednisone - Keep maintenance prednisone dose at ≤ 7.5 mg/day | No |
| **Hydroxychloroquine** | ≤ 5 mg/Kg/day (usually 300-400 mg/day)  In patients in remission, consider tapering to 200 mg/day | Yes |
| **Methotrexate** | 10-25 mg/week in 1-2 doses | Yes |
| **Azathioprine** | 2-3 mg/Kg/day in 2-3 doses  In patients in remission, consider tapering to < 2 mg/day | Yes |
| **Mycophenolate mofetil** | *Severe/Organ-threatening disease or “Induction” therapy in LN*: 3 g/day in 2 doses  *Mild-Moderate disease or “Maintenance therapy” in LN:* 1-2 g/day in 2 doses | Yes |
| **Cyclophosphamide** | *“Induction” therapy in LN*: IV 500 mg on weeks 0, 2, 4, 6, 8 and 10 (Euro-Lupus regimen)  *Organ- or life-threatening disease*: IV 0.75-1 g/m2 BSA/month for 6 months (NIH regimen) - Avoid continuation after this period | Yes |
| **Cyclosporine A** | 1-3 mg/Kg/day or 100-400 mg/day in 2 doses | Avoid overall |
| **Tacrolimus** | 0.05 to 0.1 mg/Kg/day or 2-4 mg/day in 2 doses - Titrate to target blood concentration 4-6 ng/ml 12 hours after dose | Yes |
| **Intravenous immunoglobulin** | 1 g/Kg/day for 1-2 days | No |
| **Rituximab** | 1000 mg on days 1 and 15 - *re-administration every 6 months or “on-demand”* | No |
| **Belimumab** | IV: 10 mg/Kg on weeks 0, 2, 4, then every 4 weeks  SC: 200 mg weekly | No |

IV: Intravenous; MP: Methylprednizolone; PO: Per os; LN: Lupus nephritis; BSA: Body surface area; NIH: National Institutes of Health; SC: Subcutaneous