SAT0173

A SYSTEMATIC LITERATURE REVIEW INFORMING THE 2019 UPDATE OF THE JOINT EUROPEAN LEAGUE AGAINST RHEUMATISM AND EUROPEAN RENAL ASSOCIATION–EUROPEAN DIALYSIS AND TRANSPLANT ASSOCIATION (EULAR/ERA-EDTA) RECOMMENDATIONS FOR THE MANAGEMENT OF LUPUS NEPHRITIS

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Background: Lupus nephritis (LN) affects ~ 40% of patients with systemic lupus erythematosus (SLE) and is associated with significant morbidity. New data has emerged since the publication of the EULAR/ERA-EDTA recommendations for the management of LN, involving a multidisciplinary panel of experts.

Objectives: To analyze the current evidence, in order to inform the 2019 update of the EULAR/ERA-EDTA recommendations for the management of LN.

Methods: According to the EULAR standardised operating procedures, a Medline systematic literature review (SLR) was performed, from January 2012 until 31 December 2018. The final level of evidence (LoE) and grading of recommendations considered the total body of evidence, including the LoE of the 2012 recommendations.

Results: We identified 542 relevant articles. High-quality evidence supports the use of immunosuppressive treatment for class III and IV LN (LoE 1a) there is moderate quality evidence for immunosuppression in pure class V LN, with nephrotic-range proteinuria (LoE 2b). Treatment should aim for a 25% reduction in proteinuria at 3 months, 50% at 6 months and complete renal response (< 500-700mg/day) at 12 months (LoE 2a-2b). Strong evidence supports the use of mycophenolate mofetil/mycophenolic acid (MMF/MPA) or low-dose intravenous cyclophosphamide (CY) for the initial treatment of class III/IV LN (LoE 1a, **Table**); Combination of tacrolimus with MMF/MPA and high-dose CY are alternatives in specific circumstances (LoE 1a, **Table**). There is little evidence to guide optimal duration of immunosuppression in LN (LoE 3). In end-stage kidney disease due to LN, all methods of kidney replacement treatment have been used, but transplantation is accompanied by the most favourable outcomes (LoE 2b).

Conclusion: There is high-quality evidence to guide the initial and subsequent phases of class III/IV LN treatment. There is low quality evidence to guide treatment of class V, monitoring and optimal duration of immunosuppression.

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FLARE ASSESSMENTS IN PATIENTS WITH ACTIVE SYSTEMIC LUPUS ERYTHEMATOSUS TREATED WITH ANIFROLUMAB IN 2 PHASE 3 TRIALS

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Background: Anifrolumab treatment resulted in improved British Isles Lupus Assessment Group (BILAG)-based Composite Lupus Assessment (BICLA) response rates in patients with systemic lupus erythematosus (SLE) in the phase 3 TULIP-2 and TULIP-1 trials.^{1,2} In addition, annualized flare rates were lower among the groups treated with anifrolumab compared with placebo.^{1,2}

Objectives: TULIP-2 and TULIP-1 data were analyzed to assess the effects of anifrolumab on the number of SLE flares and time to first flare during 52 weeks of treatment.

Methods: The randomized, double-blind, placebo-controlled TULIP-2 and TULIP-1 trials evaluated efficacy and safety of intravenous anifrolumab 300mg vs placebo every 4 weeks for 48 weeks, with the primary endpoints assessed at Week 52, in patients with moderate to severe SLE despite standard-of-care treatment. Flares were defined as ≥1 new BILAG-2004 A or ≥2 new (worsening) BILAG-2004 B domain scores compared with the prior month's visit. Time to first flare was evaluated using a Cox proportional hazards model. Annualized flare rate was analyzed using a negative binomial regression model.

Table. Randomized trials for induction therapy in LN

Reference	n	Intervention	Control	Prednisone dosing	End-point	Results	Overall risk of bias*
MMF vs CY Mendonca et al (2017)	40 (1:1)	MMF + Pz	CY + Pz	0.5 mg/kg/d	24w CR PR	CR: CY vs MMF 47.82% vs 52.94% p=0.861 PR: CY vs MMF 39.13% vs 35.3% p=ns	High
Sun et al (2015)	82 (1:1)	MMF + CYC + Pz	CY + Pz	1.0 mg/kg/d for 4-8w and tapering	6m RR	RR: CY vs CY+MMF 77.5% vs 88.1% p=0.2	High
Rathi et al (2016)	100 (1:1)	MMF + Pz	CY + Pz	1 mg/kg/d for 8w and tapering	24w TRR	TRR: CY vs MMF 75.0% vs 76.3% p=0.91	Some concerns
Sedhain et al (2018)	42(1:1)	MMF + Pz	CY + Pz	1 mg/kg/d for 4w and tapered to 5-7.5mg/d	6m TR	TR: MMF vs CY 28.6% vs 19% p=0.57	Some concerns
Sahay et al (2018)	144 (1:1:1)	MMF + Pz	NIH regimen vs Eurolupus (ELNT)regimen	1 mg/kg/d and tapered to 10mg/d	6m RR	RR: NIH:71.4% ELNT: 65% MMF:72.9% p=0.9	High
Low vs high CY Mehra et al (2018)	77 (1:1)	CY 6 x 500mg fortnightly + Pz	CY 6x750 mg/m ² four-weekly	1 mg/kg/d for 4w and tapered to 5-7.5 mg/d	52w CR PR	CR: low vs high 44% vs 65% p=0.08 CR/PR: low vs high 50% vs 73% p=0.04	Some concerns
Multitarget vs SoC Liu et al (2015)	362 (1:1)	MMF + TAC + Pz	CY + Pz	0.6 mg/kg/d for 4w and tapered to 10 mg/d	24w CR PR	CR: Multitarget vs CY 45.9% vs 25.6% p<0.001 CR+PR: Multitarget vs CY 83.5% vs 63.0% p<0.001	Some concerns
Rovin et al (2019)	265	Voclosporin (low or high dose) + MMF + Pz	MMF + Pz	20-25mg/d and tapered to 2.5 mg/d at 16w	48w CRR	CRR: low dose multitarget vs MMF OR = 3.21 p<0.001 High dose multitarget vs MMF OR=2.10 p=0.026	Low

Abbreviations: MMF Mycophenolate mofetil, CY cyclophosphamide, Pz Prednisone, CR complete response, PR partial response, RR renal response,

TRR treatment response rate, SoC standard of care, OR odds ratio.

*Overall risk of bias was assessed using the Revised Cochrane risk-of-bias tool (ROB2)

Results: In TULIP-2 (anifrolumab, n=180; placebo, n=182) and TULIP-1 (anifrolumab, n=180; placebo, n=184), fewer patients experienced ≥ 1 BILAG-2004 flare in the anifrolumab groups (TULIP-2: 31.1%, n=56; TULIP-1: 36.1%, n=65) compared with the placebo groups (TULIP-2: 42.3%, n=77; TULIP-1: 43.5%, n=80; Figure 1). Results favoring anifrolumab were observed in time to first flare (TULIP-2: hazard ratio [HR] 0.65, 95% confidence interval [CI] 0.46–0.91 and TULIP-1: HR 0.76, 95% CI 0.55–1.06; Figure 2) and BILAG-based annualized flare rates (TULIP-2: adjusted rate ratio 0.67, 95% CI 0.48–0.94 and TULIP-1: rate ratio 0.83, 95% CI 0.60–1.14) across both trials.

Conclusion: Across 2 phase 3 trials, we observed reductions in the total number of flares and annualized flare rates, as well as prolongation of time to first flare with anifrolumab treatment compared with placebo. These results support the potential of anifrolumab to reduce disease activity and reduce flares, benefiting patients with SLE.

References:

- [1] Morand EF, et al. *N Engl J Med*. 2020;382:211–221.
- [2] Furie RA, et al. *Lancet Rheumatol*. 2019;1:e208–e219.

Figure 1. Flares Assessed Using BILAG-2004 in Patients Treated With Anifrolumab Compared With Placebo in TULIP-2 and TULIP-1

BILAG, British Isles Lupus Assessment Group.

Note: Flare defined as ≥ 1 new (worsening) BILAG-2004 B domain scores as compared with the prior month's visit.

Figure 2. Time to First Flare in TULIP-2 and TULIP-1

Number at risk in TULIP-2													
Anifrolumab 300 mg	180	179	175	158	153	147	141	138	130	124	118	116	114
Placebo	182	181	167	159	149	137	120	113	107	98	97	95	77

Number at risk in TULIP-1													
Anifrolumab 300 mg	180	180	171	162	151	139	131	124	117	114	105	101	87
Placebo	184	181	170	159	149	132	123	120	111	103	96	91	70

BILAG, British Isles Lupus Assessment Group.

Note: Flare defined as ≥ 1 new (worsening) BILAG-2004 A or ≥ 2 new (worsening) BILAG-2004 B domain scores as compared with the prior month's visit. Time to first flare is derived as date of first flare minus date of first administration of investigational product. If the patient did not have a flare, the time to flare is censored at the end of the exposure time.

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SAT0175

IMPACT OF ANTIMALARIAL ADHERENCE ON MORTALITY AMONG PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS: A POPULATION-BASED COHORT STUDY

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Background: Evidence has consistently shown that adherence to AM is poor in systemic lupus erythematosus (SLE) patients. However, data on the impact of adherence to AM on mortality is scarce.

Objectives: To assess the effect of AM adherence on all-cause mortality in SLE patients from the general population.

Methods: This study used administrative databases from British Columbia, Canada. We created an incident SLE cohort between January 01, 1997, and March 31, 2015, using the physician billing data and a 7-year washout period. The inclusion criteria were at least two physician visits, at least two months apart, within two years, with an ICD-9 code (710.0) or ICD-10 code (M32.1, M32.8, M32.9) for SLE. Follow-up started at the first day of having both SLE and AM, i.e., at the SLE index date (second ICD code) for those whose first AM use occurred before the SLE index date, or the date of the first AM use if otherwise. Our outcome was all-cause mortality, obtained from the vital statistics registry. In the analysis, the follow-up time was divided into 30-days windows, for a total of 293,190 person-months. For each window, a measure of adherence, the proportion of days covered (PDC), was calculated and categorized as adherent (PDC $\geq$ 0.90), non-adherent (0<PDC<0.90), and discontinuer (no drug or PDC = 0). We used both Cox's proportional hazards models and marginal structural models (MSM) to estimate the effect of AM adherence on all-cause mortality. Both analysis controlled for baseline demographics (age, sex, residence, income quintile), as well as the following baseline and time-varying covariates: immunosuppressive and other medications, hospitalizations, inpatient, and other visits, and Charlson comorbidity index. To account for the possibility of a few time-varying covariates being mediators in the causal pathway from AM adherence to mortality, which may cause the Cox model to yield biased estimates of the adherence effects, we conducted the MSM analysis that can produce valid estimates as it balances the distributions of time-varying confounders among the three adherence groups via inverse probability weighting. **Results:** We identified 3,385 individuals with incident SLE (mean age 47.3 years, 89% were women) who had at least one filled AM prescription. Over the mean follow-up of 6.66 years, 288 (8.5%) incident SLE patients died. The incidence rate (IR) of mortality for AM adherent, non-adherent, and discontinuer patients were 4.31, 11.86, and 19.51 per 1000 person-years, respectively. Using the Cox model, the adjusted hazard ratio (HRs) obtained for AM adherent and non-adherent SLE patients were 0.20 and 0.66, respectively, compared to discontinuer SLE patients (Table 1). Using MSM, those adjusted HRs were found as 0.18 and 0.64. Also, the adjusted HRs for adherers compared to the non-adherers were 0.30 (Cox) and 0.28 (MSM). A statistically significant linear trend in the HRs of mortality risk over the adherence levels was found (Table 1, Linear Trend).

Table 1.

Adherence Levels	No. of Deaths	IR Ratios (95%CI)	Adjusted Cox HRs (95%CI)	Adjusted MSM HRs (95%CI)
Discontinuer (Reference)	198			
Non-adherent	47	0.61(0.44-0.84)	0.66(0.47-0.93)	0.64(0.46-0.89)
Adherent	43	0.22(0.16-0.31)	0.20(0.14-0.28)	0.18(0.12-0.25)
Contrast: Partial vs. Full		0.36(0.24-0.55)	0.30(0.19-0.46)	0.28(0.18-0.42)
Linear Trend			0.32(0.25-0.41)	0.29(0.23-0.37)

Conclusion: SLE patients that adhere to AM therapy have a lower risk of death than patients who do not adhere or who discontinue AM (5 and 3 times, respectively) in both the MSM and Cox analysis. Our findings support the importance of AM adherence to prevent premature deaths in SLE patients.

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SAT0176

THERAPEUTIC APHERESIS DURING PREGNANCY IN RHEUMATIC DISEASES

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