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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

A. Fanouriakis¹, M. Kostopoulou², K. Cheema³, G. Bertsias⁴, D. Jayne³, D. Boumpas⁵. ¹University of Athens, Athens, Greece; ²"G. Gennimatas" General Hospital, Athens, Greece; ³University of Cambridge, Cambridge, United Kingdom; ⁴University of Crete Medical School, Heraklion, Greece; ⁵University of Athens Medical School, Athens, Greece

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

R. Furie¹, E. F. Morand², A. Askanase³, E. Vital^{4,5}, R. Kalyani⁶, G. Abreu⁷, L. Pineda⁸, R. Tummala⁹. ¹Zucker School of Medicine at Hofstra/Northwell, Great Neck, United States of America; ²Monash University, Melbourne, Australia; ³Columbia University College of Physicians and Surgeons, New York, United States of America; ⁴University of Leeds, Leeds, United Kingdom; ⁵NIHR Leeds Biomedical Research Centre at Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom; ⁶BioPharmaceuticals Medical, AstraZeneca, Gaithersburg, United States of America; ⁷BioPharmaceuticals Medical, AstraZeneca, Gothenburg, Sweden

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)