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CLINICAL SCIENCE

Management of systemic lupus erythematosus: a systematic literature review informing the 2023 update of the EULAR recommendations

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Handling editor Kimme L Hyrich

► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/ard-2023-225319).

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Received 27 November 2023
Accepted 10 May 2024

To cite: Kostopoulou M, Mukhtyar CB, Bertsias G, *et al*. *Ann Rheum Dis* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/ard-2023-225319

ABSTRACT

Objectives To analyse the new evidence (2018–2022) for the management of systemic lupus erythematosus (SLE) to inform the 2023 update of the European League Against Rheumatism (EULAR) recommendations.

Methods Systematic literature reviews were performed in the Medline and the Cochrane Library databases capturing publications from 1 January 2018 through 31 December 2022, according to the EULAR standardised operating procedures. The research questions focused on five different domains, namely the benefit/harm of SLE treatments, the benefits from the attainment of remission/low disease activity, the risk/benefit from treatment tapering/withdrawal, the management of SLE with antiphospholipid syndrome and the safety of immunisations against varicella zoster virus and SARS-CoV2 infection. A Population, Intervention, Comparison and Outcome framework was used to develop search strings for each research topic.

Results We identified 439 relevant articles, the majority being observational studies of low or moderate quality. High-quality randomised controlled trials (RCTs) documented the efficacy of the type 1 interferon receptor inhibitor, anifrolumab, in non-renal SLE, and belimumab and voclosporin, a novel calcineurin inhibitor, in lupus nephritis (LN), when compared with standard of care. For the treatment of specific organ manifestations outside LN, a lack of high-quality data was documented. Multiple observational studies confirmed the beneficial effects of attaining clinical remission or low disease activity, reducing the risk for multiple adverse outcomes. Two randomised trials with some concerns regarding risk of bias found higher rates of relapse in patients who discontinued glucocorticoids (GC) or immunosuppressants in SLE and LN, respectively, yet observational cohort studies suggest that treatment withdrawal might be feasible in a subset of patients.

Conclusion Anifrolumab and belimumab achieve better disease control than standard of care in extrarenal SLE, while combination therapies with belimumab and voclosporin attained higher response rates in high-quality RCTs in LN. Remission and low disease activity are associated with favourable long-term outcomes. In patients achieving these targets, GC and immunosuppressive therapy may gradually be tapered. Cite Now

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Since the 2019 European League Against Rheumatism (EULAR) recommendations for the management of systemic lupus erythematosus (SLE), several studies have been published providing data on alternative therapeutic options and treatment targets. A systematic literature review (SLR) focusing on recent advances was performed to inform the 2023 update of EULAR recommendations for the management of SLE.

WHAT THIS STUDY ADDS

⇒ In extrarenal disease, anifrolumab and belimumab were superior to standard of care treatment in a number of high-quality randomised controlled trials.

⇒ High-quality evidence points towards better efficacy of combination treatments with belimumab or voclosporin compared with standard of care in patients with lupus nephritis.

⇒ Both remission and low disease activity have been associated with lower risk of adverse outcomes in observational studies.

⇒ Although treatment discontinuation increases the risk of flares, successful glucocorticoid withdrawal was accomplished in patients with SLE in remission in several cohort studies.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This SLR provided a systematic update of current evidence regarding the management of patients with SLE, to inform the 2023 update of the EULAR recommendations.

INTRODUCTION

Management of systemic lupus erythematosus (SLE) is challenging, owing to the heterogeneity of disease phenotype, the variable severity of involvement even within the same organ manifestation, and the different efficacy of drugs in different patient subgroups and disease manifestations.[1] Patients with SLE will frequently require multiple drugs during the course of their disease to achieve and maintain sufficient control. To this end, it is important that recent years have witnessed significant progress in the form of introduction of new drugs to treat the disease. Anifrolumab, an anti-type 1 interferon receptor inhibitor, was approved in 2021 for the treatment of moderate-to-severe extrarenal SLE.[2 3]

Belimumab and voclosporin (a novel calcineurin inhibitor (CNI)) were also approved by the European Medicines Agency in 2021 and 2022, respectively, for the treatment of lupus nephritis (LN), a cardinal manifestation of the disease affecting up to 40%–50% of patients, with significant impact on morbidity and survival.[4 5]

These important advances provided the ground for an update of the European League Against Rheumatism (EULAR) recommendations for the management of SLE, which was published recently.[6] To this end, we performed structured systematic literature reviews (SLRs), aiming to update the evidence for the efficacy and safety of different therapies, as well as try to define the optimal therapy of different organ manifestations of the disease. The results of these SLRs were presented to the Task Force members during dedicated meetings to form the current evidence base, on which the formulation of the current recommendations was based. The current manuscript presents in detail the results of these SLRs.

METHODS

We followed the standardised operating procedures for the development of EULAR-endorsed recommendations and employed the Appraisal of Guidelines Research and Evaluation instrument. Following assembly of the Task Force, the convenor (DTB), one methodologist (GB), one co-methodologist (CBM), and two fellows responsible for the SLR (AF and MK) created an outline of the proposed methodology, as well as the main research questions in the form of Population, Intervention, Comparison and Outcomes (PICOs), which were circulated among Task Force members. A Delphi-based methodology within the Task Force finally identified five research questions: (1) management of general and organ-specific SLE (divided in six subquestions regarding drug efficacy and safety in patients with active SLE, active mucocutaneous, musculoskeletal, haematological, neuropsychiatric and kidney involvement, respectively), (2) targets of treatment, (3) management of patients with SLE and antiphospholipid syndrome, (4) tapering/withdrawal of treatment in SLE and (5) efficacy and safety of vaccination against varicella zoster virus (VZV) reactivation and SARS-CoV2 infection (a generic SLR for infection risk and prevention in SLE was not performed, because there are specific EULAR recommendations on this topic).[7] Separate search strings were developed for each PICO (1–5), resulting in five separate SLRs (the six subquestions of PICO 1 (PICO 1a–f) were examined with a single search string) (online supplemental file 1 and 2, tables S1.1–S1.10).

Under the supervision of the methodologists, AF and MK performed the SLRs independently in two different databases (MEDLINE through PubMed and the Cochrane Library), with additional inclusion of *Lancet Rheumatology* (due to non-inclusion of the latter in PubMed). Since this was an update of the 2019 recommendations on general SLE, the current SLRs evaluated all English language publications published between January 2018 and December 2022. All study designs were included (meta-analyses, randomised controlled trials (RCTs), quasi-RCTs, cohort studies, case–control studies, cross–sectional studies) while narrative reviews, case series, case reports, conference abstracts, animal studies, trials in non-English language, trials with population<20 and trials on paediatric populations were excluded. In case a study was captured as an original publication and was also included in a meta-analysis, then only the meta-analysis data were used, to avoid duplicating the evidence from that particular study. Eligible studies were reviewed for snowball references and relevant articles, identified by manual search within the reference list of the originally retrieved publications, were also included. For each research question, a predefined extraction form was used to capture the population set, all relevant interventions, their duration of use, route of administration, dosage, follow-up time and the respective effect estimates, including incidence rate, mean difference, risk difference, correlation coefficient, odds ratio (OR) and relative risk. For each research question, results were synthesised and presented according to the interventions used and the respective outcomes.

Risk of bias (RoB) was assessed using the revised Cochrane Risk of Bias Assessment Tool for RCTs (ROB V.2), the Newcastle-Ottawa scale for observational studies, and the AMSTAR V.2 tool for meta-analyses (online supplemental file 3). In case of disagreements, these were internally discussed until achievement of consensus, and one methodologist was involved when deemed necessary. A Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist was completed and has been submitted along with the manuscript.

RESULTS

We screened a total of 10 889 articles, of which 578 were selected for full-text review, and 439 were finally included for data extraction (see figure 1 for a detailed flow diagram of the selection process). The results below are presented in terms of general efficacy of drugs in SLE, followed by treatment of specific manifestations, with a focus on LN.

Efficacy and safety of hydroxychloroquine (HCQ) in SLE

Between January 2018 and December 2022, a total of 39 studies (all observational) evaluated and confirmed the association of HCQ with various favourable outcomes (online supplemental file 4, table S4.1). A total of 10 studies reported a negative association between HCQ use and mortality in SLE; a meta-analysis of 21 studies (26 037 patients) found a pooled HR 0.46 for death in patients with SLE receiving HCQ (consistent results in all geographic regions).[8] Fewer (or individual) studies showed a positive effect of HCQ on various outcomes (reduced rate of disease flares, thrombosis, osteonecrosis, infections, among others). Regarding safety of HCQ, the focus was on retinal toxicity.[9 10] The current SLRs identified 10 studies (mostly of poor or fair quality) (table 1); two retrospective cohort studies of good quality (ie, lower RoB) reported retinopathy rates of 0.8% and 4.3%, respectively. Longer duration of HCQ intake and a higher cumulative dose were confirmed as risk factors for retinal toxicity. Regarding other safety issues, a concern for corrected QT (QTc) prolongation was raised when HCQ was used during the early phases of the COVID-19 pandemic; however, a total of six studies found no clinically relevant QTc prolongation with HCQ use.

The recommended dose of 5 mg/kg in the 2023 recommendations was based on (1) an observational study of good quality, which calculated the threshold for an increased risk of flares near 5 mg/kg/day of HCQ dose,[11] (2) older evidence of good quality, suggesting that risk of toxicity is low for doses below 5 mg/kg real body weight[10] and (3) indirect evidence for a slightly increased risk of flares in patients who taper HCQ versus those who continue (see below, Safety of treatment tapering in SLE).

Efficacy and safety of glucocorticoids (GC) in SLE

Although GC are widely used in SLE, high-quality RCTs assessing the efficacy of different schemes and tapering strategies are still lacking. A single, retrospective study of good quality in 206 patients with LN found higher rates of 1-year complete

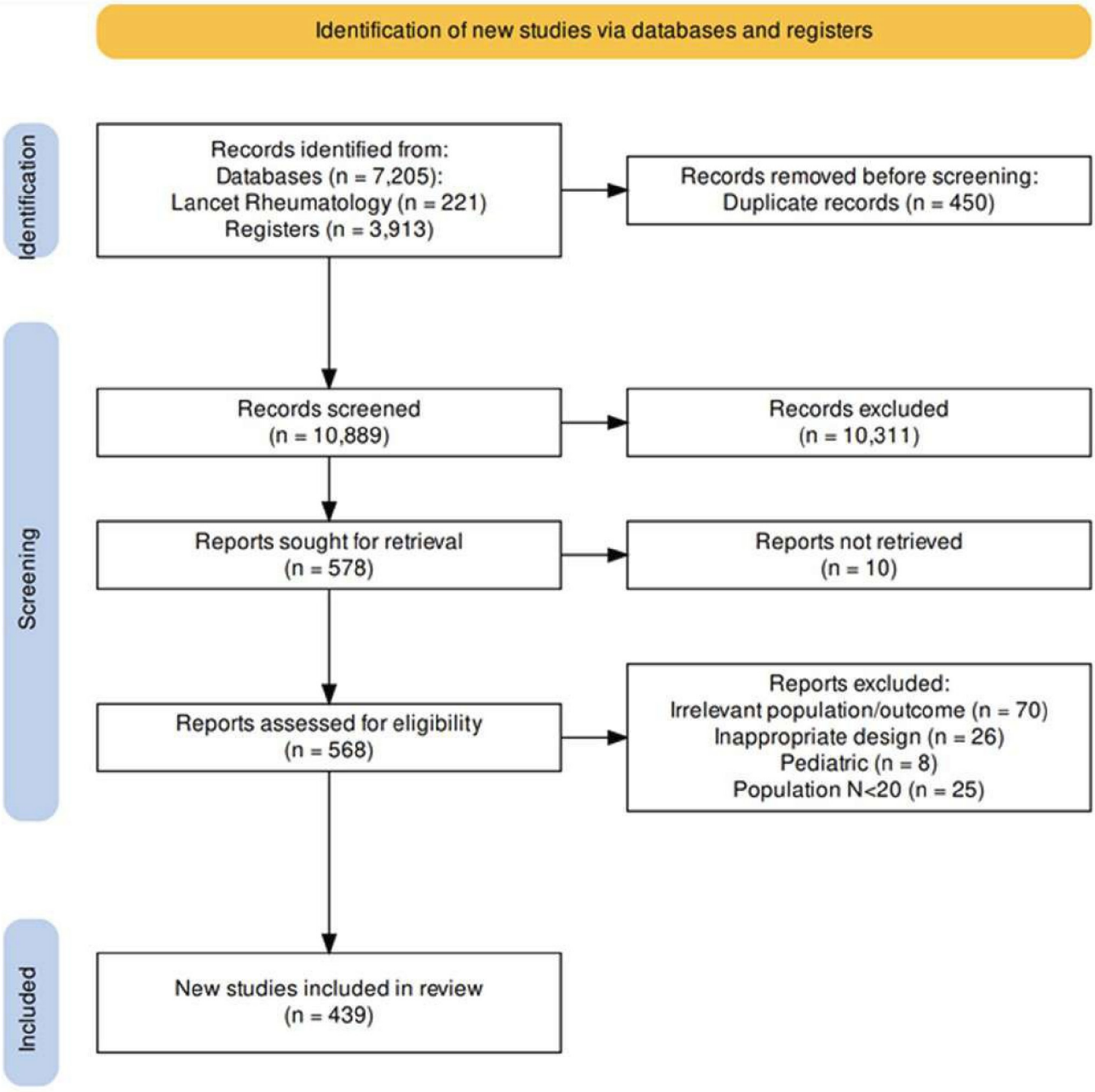

Figure 1 Flow diagram of the study selection process.

response in patients who started with ≥40 mg/day compared with those who started with ≤30 mg/day, without increased risk for GC-related damage.[12] Two small RCTs (one with 32 and one with 20 patients, both with high RoB) compared different doses of GC with same background immunosuppression (cyclophosphamide (CYC) and mycophenolate mofetil (MMF), respectively) and found discordant results; one showed equal response rates and the other higher rates in the high-dose GC arm.[13 14]

For safety, the SLRs identified a large number of studies examining different cut-offs of average prednisone doses in association with different adverse effects (online supplemental file 4, tableS4.2 for association with infections and online supplemental table S4.3 for associations with other harms). Most studies pointed towards thresholds of mean 5–7.5 mg/day prednisone, associated with a variety of GC-related side effects in multivariable associations.

Efficacy and safety of immunosuppressive drugs in extrarenal SLE

Immunosuppressive therapies used to treat extrarenal manifestations of SLE include both conventional drugs (azathioprine (AZA), methotrexate (MTX), MMF, CNIs, among others), as well as biologic agents (approved therapies belimumab and anifrolumab, and drugs used off-label, such as rituximab (RTX)). During the period captured by the SLRs, no new head-to-head comparisons between conventional immunosuppressive drugs were identified, rather only limited observational studies (mainly of-low quality) reporting efficacy in selected manifestations (mainly LN). To this end, this part will focus on new data regarding approved biologics.

We retrieved a total of 53 publications of belimumab in SLE, published between 2018 and 2022 (among them, 6 RCTs, 7 open-label extensions of previous RCTs, 11 post hoc analyses of

Table 1 Prevalence of HCQ retinopathy in observational studies and associations

Study	Design, n	Screening test	HCQ dose	Duration of HCQ treatment	Frequency of retinopathy	Factors associated with retinopathy	Study quality
Abdelbaky *et al*[70]	Cross-sectional, 80	10–2 VF, FAF	Mean (SD) 4.89 (1.01) mg/kg	Range 0.3–15 years	6.3%	Duration of HCQ use (10 vs 5 years, p=0.003) Cumulative HCQ dose (mean 661.9 vs 1489.2 g, p<0.001)	Poor
Petri *et al*[71]	Retro cohort, 537	Funduscopy +1 of: SD-OCT, mfERG, MP1, FAF		Range 0–48 years	4.3%	Age (p<0.0001), BMI (p=0.0160), and duration of HCQ use (p=0.0024)	Good
Ototake *et al*[72]	Retro cohort, 35 (6 CLE)	NS	≤5 mg/kg/day	Mean 32 weeks	0%		Poor
Martín-Iglesias *et al*[73]	Retro cohort, 110	SD-OCT in 2012 and 2017	Median (IQR) 3.22 (2.78–3.85) mg/kg/day and 3.12 (2.55–3.53) mg/kg/day, respectively	Median (IQR) 69 (37.75–104.50) months and 133 (101.75–170.25) months, respectively	0%		Poor
Lenfant *et al*[74]	Case control, 570	≥2 of: 10–2 VF, mfERG, SD-OCT and FAF				Cumulative HCQ dose (p=0.012), duration of HCQ use (p=0.033), CrCl (p=0.001), and geographical origin from West Indies or sub-Saharan Africa (p<0.001)	Fair
Kao *et al*[75]	Retro cohort, 92	≥2 of: 10–2 VF, mfERG, SD-OCT and FAF	Median (IQR) 6.9 (6.1–7.7) mg/kg/day	Median (IQR) 11.2 (9.4–12.7) years	10.9%	Lower body weight (OR 0.88; 95% CI 0.78 to 0.97 and presence of high myopia (OR 5.03; 95% CI 1.29 to 24.79 (univariate)	Poor
Almeida-Brasil *et al*[76]	Retro cohort, 1460	SDI retinal item—test NS		Mean (SD) 7.4 (4.4) years	0.8%	High HCQ dose (> 5 mg/kg/day) HR 2.35, p=ns	Good
Araujo *et al*[77]	Retro cohort, 539	Not specified		Median 19 years	15.3%		Poor
Lee *et al*[78]	Retro, 235	Not specified	Median 400 mg/day		0.8%		Poor
Spinelli *et al*[79]	Retro cohort, 504	Funduscopy +1 of: SD-OCT, mfERG		Mean (SD) 82.5 (77.4) months	5.5%		Fair

BMI, body mass index; CLE, cutaneous lupus erythematosus; CrCl, creatinine clearance; FAF, fundus autofluorescence; HCQ, hydroxychloroquine; mfERG, multifocal electroretinogram; MP1, microperimetry; NS, not specified; SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Damage Index; SD-OCT, spectral domain optical coherence tomography; VF, visual field.

previously published RCTs, 7 meta-analyses and 18 real-world observational studies), overall confirming efficacy of the drug in extrarenal lupus. A Cochrane SLR including 6 RCTs of belimumab in SLE found belimumab to be associated with a pooled risk ratio of 1.33 (95% CI 1.22 to 1.45) and 1.59 (95% CI 1.17 to 2.15) for Safety of Estrogen in Lupus National Assessment—Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI) reduction by four points and reduction of GC dose by 50%, respectively.[15] Importantly, after the publication of the 2019 recommendations, belimumab has been tested in phase III RCTs in specific ethnic/racial populations, the Efficacy and Safety of Belimumab in Black Race Patients with SLE (EMBRACE) RCT in 448 African-Americans,[16] and the Belimumab in Subjects with SLE-North East Asia (BLISS-NEA) in 707 patients from North-East Asia.[17] Although in both studies, SLE Responder Index (SRI)-4 responses at 52 weeks were higher with belimumab versus placebo, the EMBRACE did not reach statistical significance (SRI response at week 52 48.7% with belimumab versus 41.6% with placebo (OR 1.40, 95% CI 0.93 to 2.11)). On the contrary, in BLISS-NEA, more patients treated with belimumab were SRI-4 responders at week 52 (53.8% vs 40.1% with placebo, OR 1.99, 95% CI 1.40 to 2.82). Regarding safety of belimumab, a phase IV RCT (BASE, 4003 patients) designed to test safety issues, found slightly higher rates of serious depression (0.35% vs 0.05%; Δ 0.15%, 95% CI 0.02% to 0.58%), treatment-emergent suicidality (1.42% vs 1.16%; Δ 0.26%, 95% CI −0.44% to 0.96%) and sponsor-adjudicated serious suicide or self-injury (0.75% vs 0.25%; post hoc Δ 0.50%, 95% CI 0.06% to 0.94%) with belimumab compared with placebo.[18] Similarly, a pooled post hoc analysis of one phase II and five phase III RCTs of belimumab (total 4170 patients) reported that serious depression was more common with belimumab (0.2% vs 0.1%) although suicide/self-injury was similar (0.3% in each group).[19] Incidence of all other adverse events and mortality was also similar between belimumab and placebo.

In addition to the Treatment of Uncontrolled Lupus via the Interferon Pathway (TULIP) trials, the SLR retrieved a total of 17 publications related to the use of anifrolumab in SLE: 2 phase II RCTs (one was in LN), 2 open-label extension studies, 7 post hoc analyses of previous RCTs, and 4 meta-analyses. Despite the discordant SRI-4 data of the two TULIP trials, both studies found significantly greater British Isles Lupus Assessment Group (BILAG)-based Composite Lupus Assessment (BICLA) response rates with anifrolumab compared with placebo (pooled OR 2.25, 95% CI 1.72 to 2.95, in a meta-analysis).[20] A post hoc analysis of the TULIP trials found that anifrolumab was associated with lower annualised disease flare rates (rate ratio 0.75, 95% CI 0.60 to 0.95), prolonged time to first flare (HR 0.70, 95% CI 0.55 to 0.89) and fewer patients with ≥1 flare (Δ −9.3%, 95% CI −16.3% to −2.3%), compared to placebo.[21] Regarding GC-sparing potential, another post hoc analysis of both TULIP trials reported sustained reduction to ≤7.5 mg/day prednisone

in patients on ≥10 mg/day at baseline in 50.5% for anifrolumab versus 31.8% for placebo (Δ 18.7%, p<0.001),[22] while the above-mentioned meta-analysis (including also the MUSE phase II study of the drug) calculated the respective pooled OR at 2.45 (95% CI 1.69 to 3.54) compared to placebo.[20] In terms of safety, in general, adverse events and serious adverse events were similar between anifrolumab and placebo in RCTs, with the exception of VZV infection; analysis of the TULIP trials found a higher incidence of VZV in anifrolumab-treated patients versus placebo (6.4% vs 1.4%), evident in both interferon-high and interferon-low patients,[22] and confirmed in meta-analyses.[20 23] On the other hand, in the long-term extension of the TULIP studies (placebo controlled, 369 patients), VZV rates by year decreased over time and were lower during the long-term extension period than during the first year of TULIP (6.8 for year 1, dropping to 2.9 in year 4).[24]

In RCTs, both belimumab and anifrolumab showed better clinical responses in patients who had abnormal serological markers at baseline (low C3/C4 levels and/or high antidouble-stranded DNA antibodies).[22 25 26]

Treatment of specific extrarenal manifestations of SLE

Subquestions 1b–1f of PICO 1 were focused on the efficacy of different immunosuppressive treatments in various organ manifestations of SLE (mucocutaneous, musculoskeletal, haematological, neuropsychiatric and kidney involvement). The results on LN are presented in a separate section. Regarding other manifestations, the SLRs confirmed the paucity of high-quality data for their treatment. For skin disease, belimumab and anifrolumab have documented efficacy in RCTs of their clinical programme; however, belimumab has used the skin component from BILAG, while the more recent TULIP trials of anifrolumab have used the skin-specific Cutaneous Lupus Activity and Damage Index (CLASI) (table 2).

A meta-analysis of six RCTs focusing on skin efficacy of belimumab found a pooled OR of clinical response (BILAG defined) at 52 weeks of 1.44 (95% CI 1.20 to 1.74, I^2=0%).[27] Clinical response was first noted after 20 weeks of treatment (OR 1.35, 95% CI 1.01 to 1.81, I^2=0%), sustained through 1 year. In addition, CLASI data for belimumab have been reported in three observational studies (including 62, 67 and 466 patients, respectively), all showing significant reductions from baseline, ranging from 4 to 6 units (table 2).[28–30] Anifrolumab RCTs have used CLASI to assess response; post hoc analyses of both TULIP phase III and the phase II MUSE trial have shown percentage differences in CLASI-A 50 (ie, 50% reduction from baseline) response more than 20% from placebo, almost reaching 30% in MUSE.[22 31 32]

Efficacy data on arthritis were more scarce, available only from RCT of belimumab and anifrolumab. The post hoc analysis of the TULIP studies found that anifrolumab was associated with greater percentage of patients achieving ≥50% reduction in active swollen and tender joints (treatment Δ: 12.6% (95% CI 2.4% to 22.9%)).[22] Significant reduction was also noted in a similar analysis of the MUSE phase II study (mean (SD) swollen and tender joint reductions –5.5 (6.3) vs –3.4 (5.9) for placebo, p=0.004).[32] For belimumab, only two small observational, uncontrolled studies (n=81 and 20, respectively) specifically reported a reduction in the number of swollen and tender joints.[33 34]

The SLR retrieved very few studies regarding haematological and neuropsychiatric manifestations. For neuropsychiatric SLE (NPSLE), a single meta-analysis on the efficacy of RTX in refractory SLE (including NPSLE) reported a pooled complete response rate of 90% for neuropsychiatric manifestations (95% CI 53% to 99%).[35] No other relevant studies were identified. For immune cytopenias, post hoc analysis of the TULIP trials found a 25% difference in response rate in haematological manifestations, in favour of anifrolumab (56% vs 31% for placebo), but with no further details.[31] A similar analysis of the BLISS trials (published in 2012, thus not included in the current SLR) had not found a difference of belimumab over placebo for haematological manifestations.

Treatment of LN

The SLR identified 98 studies evaluating the efficacy and safety of various treatments in LN. These included 14 meta-analyses (1 of high quality, 9 of low or critically low quality and 4 network meta-analyses), 15 RCTs (5 of low RoB, 6 with some concerns and 4 with high RoB) and 69 studies with other study designs (2 open-label extension studies of RCTs, 2 post hoc studies, 1 integrated analysis and 64 observational studies including 8 prospective cohorts, 53 retrospective cohorts, 2 cross-sectional and 1 case–control study) and varied quality.

Table 2 Efficacy of belimumab and anifrolumab on skin disease in SLE

Study	Design, n	Intervention	Control	Outcome definition	Follow-up	Result	
RCTs							**Risk of bias**
Vital *et al*[22]	RCT (pooled phase III), 726	Anifrolumab	Placebo	≥50% CLASI-A reduction in pts with bsl CLASI-A≥10	12 weeks	ANI versus PBO Δ: 21.0% (95% CI 8.1% to 34.0%); p<0.001	Low
Morand *et al*[31]	RCT (pooled phase III), 726	Anifrolumab	Placebo	≥50% CLASI-A reduction in pts with bsl CLASI-A≥10	52 weeks	Greater proportion of patients with ANI versus PBO achieved CLASI-A 50 (49/107 (46%) vs 24/94 (25%)	Low
Merrill *et al*[32]	Post hoc RCT (phase II), 201	Anifrolumab	Placebo	≥50% mCLASI reduction in pts with bsl mCLASI>0	52 weeks	More ANI-treated patients demonstrated mCLASI 50: 57/92 (62.0%) vs 30/89 (33.7%), OR (90% CI) 3.31 (1.97 to 5.55), p<0.001	Low
Observational Studies							**Study Quality**
Gatto *et al*[28]	Retrospective cohort, 466	Belimumab	–	CLASI reduction	48 months	Significant reduction from median 4 (IQR 2–7.5) to 0 (IQR 0–5), p<0.001	Good

ANI, anifrolumab; bsl, baseline; CLASI, Cutaneous Lupus Erythematosus Disease Area and Severity Index; CLASI-A, Cutaneous Lupus Erythematosus Disease Area and Severity Index Activity Score; PBO, placebo; pts, patients; RCT, randomised controlled trial; SLE, systemic lupus erythematosus.

14 RCTs (5 head-to-head, 2 dose-comparison and 7 add-on vs placebo trials) involving 2099 LN patients evaluated the efficacy and safety of various drugs as initial treatments for LN (table 3).

Regarding comparison of standard of care therapies (CYC and MMF), only two new RCTs, both in Asian LN populations, were identified from the SLR (one with high and one with low RoB). One small RCT of 49 LN patients with impaired kidney function (mean±SD baseline serum creatinine 1.58±1.38 mg/dL) showed similar efficacy between CYC (monthly pulses of 0.5–1 g/m^2 for 6 months) and low-dose MMF (1.5 g/day) after 24 weeks of treatment (19.0% vs 28.6%, p=0.572).[36] In a second RCT, a low versus high dose of intravenous CYC (low dose: six fortnightly intravenous CYC pulses of 500 mg, high dose: 4 weekly six cycles of 750 mg/m^2), both followed by AZA, were administered in 38 and 37 patients, respectively. After 52 weeks, patients in the high-dose group had significantly increased rates of complete/partial response (50% vs 73%, p=0.04) and fewer relapses (3% vs 24%, p=0.01) compared with the low-dose group, with no difference in infection rates and death.[37] Although this study was designated as low RoB, it was nevertheless open-label and the sample size was relatively small.

Five RCTs (2 with low RoB, 2 with some concerns and 1 with high RoB) explored the effect of CNIs, either as monotherapy or in combination with MMF, against CYC/MMF.[5 38–41] In an open-label non-inferiority (margin 15%) RCT of 299 LN patients, tacrolimus (TAC) was non-inferior to CYC in terms of complete and partial response after 24 weeks of treatment. When the individual components of response were investigated, TAC was associated with a significant decrease in estimated glomerular filtration rate (eGFR), counterbalanced by greater reductions in proteinuria compared with CYC.[38] Similarly, in another RCT of 83 patients with proliferative LN who received 1:1 TAC or MMF followed by AZA, both arms had comparable remission rates at 12 months (46.3% vs 57.1% p=0.3).[39] Regarding long-term outcomes, TAC was non-inferior to MMF in a study of 150 patients who were previously randomised to TAC or MMF as induction treatment and AZA as maintenance.[42] After 10 years, the TAC group had similar relapse rates compared with MMF and there was also no difference in a composite outcome (reduction in eGFR≥30%, chronic kidney disease stage 4/5 or death). As in the previous SLR, no RCT was identified assessing the role of CNI as monotherapy in proliferative LN in non-Asian populations. In a meta-analysis of trials in Asian populations, TAC outperformed CYC in terms of complete response (OR 2.41 95% CI 1.46 to 3.99, based on seven studies), but had a similar effect when compared with MMF (OR 0.95 95% CI 0.54 to 1.64, based on three studies).[43] Similar results were reported in two recent network meta-analyses.[44 45]

Three RCTs investigated the efficacy of multitarget therapy (CNI in combination with MMF, two using voclosporin and one using TAC) compared with MMF or CYC, all pointing towards better response rates with the multitarget treatment.[5 40 41] In AURA-LV, a phase II multicentre RCT, 267 patients were randomised 1:1:1 to receive either voclosporin (23.7 or 39.5 mg, each two times per day) or placebo, in combination with MMF (2 g/day) and low dose GC. At 24 weeks, patients on low-dose voclosporin had significantly increased complete response rates (defined as urine protein-to-creatinine ratio (UPCr) <0.5 mg/mg, an eGFR>60 mL/min/1.73 m^2 or no decrease of ≥20% of baseline eGFR, no administration of rescue medication and no more than 10 mg prednisone equivalent per day for 3 or more consecutive days or for 7 or more days during weeks 44–52) compared with placebo (OR 2.03, 95% CI 1.01 to 4.05); in terms of safety, voclosporin was associated with higher rates of adverse events and death.[41] The AURORA trial was a phase III multicentre RCT involving 357 LN patients with class III, IV, V or mixed classes. Patients were randomly assigned to voclosporin (23.7 mg two times per day) or placebo in addition to 2 g/day of MMF and low-dose GCs and were followed for 52 weeks. Complete renal response (defined as in AURA-LV) was achieved in significantly more patients in the voclosporin group than placebo (41% vs 23%, OR 2.65 95% CI 1.64 to 4.27), while both groups had similar eGFR and safety profile during follow-up. Importantly, subgroup analysis showed no benefit from the introduction of voclosporin in class V or when the dose of MMF exceeded 2 g/day.[5] An integrated analysis of pooled data from phases II and III voclosporin trials, as well as a long-term extension study of the AURORA trial (the latter published after the completion of the present SLR) corroborated the previous findings in efficacy and safety.[46 47] In another small (n=56), open-label RCT with longer follow-up (72 weeks), combination treatment with TAC (0.06–0.08 mg/kg/day) and MMF (20–30 mg/kg/day) was superior to intravenous CYC (0.5–0.75 g/m monthly for 6 months) in terms of renal response (81.5% vs 57.7%, p<0.05) and kidney function (mean ± SD serum creatinine 56.7±32.1 vs 72.5±32.5, p 0.019).[40]

Four RCTs evaluated the efficacy and safety of biologic agents added to background immunosuppressive therapy. Two phase III trials investigated the add-on effect of belimumab (one of low RoB and the other with some concerns), one phase II trial investigated the add-on effect of anifrolumab (RoB with some concerns) and another phase II RCT investigated the add-on effect of obinutuzumab (low RoB). In the Belimumab International Study in Lupus Nephritis (BLISS-LN), a phase III, double-blind, placebo-controlled trial, 448 patients were randomly assigned to intravenous belimumab (10 mg/kg/month) or placebo added to standard therapy (ie, six pulses of intravenous CYC 500 mg every 2 weeks followed by AZA, or MMF (3 g/day) plus GC 0.5–1 mg/kg/day as initial dose).[4] Patients were stratified according to induction treatment and race. The primary endpoint assessed at 104 weeks was the primary efficacy renal response (PERR) defined as UPCr≤0.7 g/g, eGFR no worse than 20% below the preflare value or at least 60 mL/min/1.73 m^2 and no use of rescue therapy. More patients in the belimumab group achieved PERR compared with placebo at 104 weeks (43% vs 32% OR 1.6 95%CI 1.0 to 2.3).[4] In a secondary analysis, patients with class 5 or with a UPCr>3 g/g did not benefit from the addition of belimumab, in terms of PERR. However, the risk of a 30% and 40% decline in eGFR and the risk of flare were significantly less in patients receiving belimumab.[48] The CALIBRATE study was a phase II open-label RCT in patients with refractory or relapsing LN, assessing the safety and potential benefit from the addition of belimumab to a background treatment of RTX and intravenous CYC.[49] Although the addition of belimumab did not increase adverse events, patients on belimumab and placebo had similar response rates (52% vs 41%, p=0.4). The phase II double-blinded TULIP-LN study randomised 147 patients with biopsy-proven proliferative LN in a 1:1:1 ratio to receive either monthly 300 mg of intravenous anifrolumab (basic regimen), 900 mg of intravenous anifrolumab for 3 doses and 300 mg thereafter (intensified regimen (IR)) or placebo on top of MMF (2 g/day) and GC.[50] The primary endpoint (change in UPCr at week 52 for combined anifrolumab vs placebo) was not met; however, when the two anifrolumab arms were analysed separately, more patients in the IR achieved complete response compared with placebo (45.5% and 31.1% respectively). Importantly, safety concerns were raised due to an increased incidence of VZV infection in the combined anifrolumab groups versus placebo (16.7% vs 8.2%). In another phase II RCT, 125 LN

Table 3 Efficacy of initial treatments for LN in RCTs 2018–2022

Study	N	Intervention	Control	Outcome definition	Follow-up	Efficacy outcome	RoB
Head to head							
CYC versus MMF							
Sedhain *et al*[36]	49	Intravenous CYC	MMF	TR : UPr<3.5 g/24 hours if baseline≥3.5 g or >50% decrease if baseline UPr<3.5 g; or stable (±25%) renal function	24 weeks	19.0% vs 28.6%*	High
CNI versus soc							
Zheng *et al*[38]	299	TAC	Intravenous CYC	CR+PR CR: UPr<0.5 g/24 hours, serum albumin≥3.5 g/dL and SCr in reference range or ≤115% from baseline; PR: UPr<3.5 g/24 hours and decreased by>50% from baseline, serum albumin≥3.0 g/dL and stable renal function	24 weeks	83.0% vs 75.0%†	Low
Kamanamool *et al*[39]	83	TAC	MMF	CR: return to baseline sCr and UPCr<500 mg/g (<50 mg/mmol)	12 months	46.3% vs 57.1%†	Some concerns
Ye *et al*[40]	56	TAC+MMF	Intravenous CYC	CR+PR CR:UPr<0.4 g/24 hours, urine RBC<3/HP, no WBC or tubular shape, normal albumin, normal SCr, anti-ds DNA negative PR: UPr decreased by ≥50%, but >0.4 g, albumin≥30 g/L but still not normal, SCr decreased by ≥50% but not to normal	72 weeks	81.5% vs 57.7%*	High
Leflunomide versus soc							
Zhang *et al*[80]	100	LEF	CYC	CR, PR CR: UPr<0.3 g/day, with normal urinary sediment, normal serum albumin and stable renal function PR: UPr decreased >50%, with a serum albumin≥30 g/L and stable renal function	24 weeks	CR: 23% vs 27%† PR: 56% vs 42%†	Some concerns
Dose comparison							
Low CYC versus high CYC							
Mehra *et al*[37]	75	Low intravenous CYC	High intravenous CYC	CR: UPCr<0.5 g and normal or stable (±10%) renal function and inactive urinary sediment PR: >50% reduction in proteinuria to subnephrotic levels and normal or stable (±10%) renal function and inactive urinary sediment	56 weeks	CR 44% vs 65%† CR/PR 50% vs 73%*	Low
Low GCs versus high GCs							
Bharati *et al*[14]	20	Low Pz	High Pz	TR: UPr<3 g/24 hours if baseline≥3 g or >50% decrease if baseline UPr<3 g, and stable (±25%) renal function	24 weeks	40% vs 100%*	High
Bandhan *et al*[13]	32	Low Pz	High Pz	CR, PR	24 weeks	CR 66.7% vs 66.7%† CR/PR 86.7% vs 83.3%†	High
Add-on versus placebo							
CNIs							
Rovin *et al*[5] (AURORA)	357	VCS+MMF	Placebo+MMF	CR: UPCr≤0.5 mg/mg, eGFR≥60 mL/min or no confirmed eGFR decrease >20% from baseline, no rescue treatment and no >10 mg Pz per day for ≥3 days or for ≥7 days in total during weeks 44–52	52 weeks	41% vs 23% OR 2.65*	Low
Rovin *et al*[41] (AURA-LV)	265	Low-dose VCS or high-dose VCS+MMF	Low-dose or high-dose matched placebo+MMF	CR: UPCr≤0.5 mg/mg, eGFR≥60 mL/min or no confirmed eGFR decrease >20% from baseline	24 weeks	Low 32.6% vs high 27.3% vs placebo 19.3% Low VCS versus placebo OR 2.03* High VCS versus placebo OR 1.59†	Some concerns
Biologics							
Belimumab							
Furie *et al*[4] (BLISS-LN)	448	Intravenous BLM+intravenous CYC/MMF	Placebo+intravenous CYC/MMF	PERR: UPCr≤0.7, eGFR≥80% preflare value or ≥60 mL/min/1.73 m^2, no use of rescue treatment)	104 weeks	43% vs 32% OR 1.6*	Low

Continued

Table 3 Continued

Study	N	Intervention	Control	Outcome definition	Follow-up	Efficacy outcome	RoB
Atisha-Fregoso *et al*[49] (CALIBRATE)	43	Intravenous BLM+RTX+ intravenous CYC	Placebo+RTX+ intravenous CYC	CR/PR CR: UPCr of <0.5, eGFR≥120 mL/min/1.73 m^2, or >80% of the baseline value and adherence to GCs dosing. PR: the same except that a UPCr>50% was accepted	48 weeks	52% vs 41%†	Some concerns
Anifrolumab							
Jayne *et al*[50] (TULIP-LN)	147	ANI basic regimen or ANI intensified regimen+MMF	Placebo+MMF	Reduction in baseline UPCr	52 weeks	69% vs 70%†	Some concerns
Obinutuzumab							
Furie *et al*[51]	125	OBI+MMF	Placebo+MMF	CR: UPCr<0.5, normal renal function without worsening of baseline SCr by >15% and inactive urinary sediment	52 weeks	35% vs 23%‡	Low

*Statistically significant p≤0.05.
†Statistically non-significant p>0.05.
‡Statistically significant p≤0.2.
ANI, anifrolumab; anti-ds DNA, antidouble-stranded DNA; BLISS-LN, Belimumab International Study in Lupus Nephritis; BLM, belimumab; CNI, calcineurin inhibitor; CR, complete response; CYC, cyclophosphamide; eGFR, estimated glomerular filtration rate; GCs, glucocorticoids; LEF, leflunomide; LN, lupus nephritis; MMF, mycophenolate mofetil; OBI, obinutuzumab; PERR, primary efficacy renal response; PR, partial response; Pz, prednisone; RBC, red blood cells; RCT, randomised controlled trials; RoB, risk of bias; RTX, rituximab; sCr, serum creatinine; TAC, tacrolimus; TR, treatment response; TULIP, Treatment of Uncontrolled Lupus via the Interferon Pathway; UPCr, urine protein-to-creatinine ratio; UPr, urine protein; VCS, voclosporin; WBC, white blood cells.

patients were randomly assigned to obinutuzumab, a humanised type 2 anti-CD20 monoclonal antibody, or placebo in addition to MMF and GC.[51] After 52 and 104 weeks significantly more patients in the obinutuzumab group achieved complete response (UPCr<0.5, normal renal function without worsening of baseline serum creatinine by >15% and inactive urinary sediment) compared with placebo (35% vs 23%, p=0.1 and 41% vs 23%, p=0.026, respectively).

This SLR identified only one trial (RoB with some concerns) that was specifically designed to compare different drugs as maintenance treatments. In this RCT, 215 patients with biopsy-proven LN who had previously received intravenous CYC plus GC and achieved remission were randomised 1:1 to leflunomide (20 mg/day) or AZA (100 mg/day) for 36 months. The primary endpoint, time to kidney flare, was similar between groups (16 vs 14 months, p=0.67), and there was no difference in safety profile.[52]

Remission, low disease activity and associations with favourable outcomes in SLE

PICO 2 focused on the short-term and long-term benefits of attainment of treatment targets, both in extrarenal SLE and LN. The current SLR identified observational studies in which both remission (defined either per the recent Definition of Remission in SLE (DORIS) definition[53] or earlier definitions) and low disease activity (mainly defined as the lupus low disease activity state (LLDAS)[54]) are associated with reduced risk for damage accrual (table 4), as well as disease flares and other adverse sequelae (death, serious infections and hospitalisations, online supplemental table S4.4). In studies of good quality, range of OR for an increase in SDI were 0.49–0.75 for remission and 0.19–0.88 for LLDAS, versus patients not attaining these targets. Similarly, observational studies in LN examining the association between complete remission at variable time-points and favourable long-term kidney outcomes are shown in online supplemental table S4.5

Safety of treatment tapering in SLE

PICO 4 addressed the issue of safety of tapering and/or withdrawal of immunosuppressive treatment in patients with SLE who have quiescent disease. Studies were categorised according to tapering of (1) GC, (2) immunosuppressive drugs and (3) antimalarials. For GC, a randomised study (CORTICOLUP) found higher rate of flares in patients with SLE on chronic prednisone 5 mg/day who discontinued GC, versus those who continued this dose.[55] A meta-analysis reported a pooled incidence of 24% (95% CI 21 to 27) and 13% (95% CI 8 to 18) for global and major flares, respectively, following GC withdrawal[56]; a different meta-analysis focusing on risk factors found an increased risk for flare in serologically active, clinically quiescent disease after GC withdrawal (OR 1.78, 95% CI 1.00 to 3.15), while HCQ use trended towards decreased risk of flare, however results were not statistically significant (OR 0.50, 95% CI 0.23 to 1.07). Individual observational studies of the current SLR are shown in table 5 and support that gradual tapering to discontinuation of GC may be achieved without increasing the risk for flares, especially with slow tapering and long-standing remission prior to complete withdrawal (although most of these did not have a control patient group which did not discontinue GC).

Contrary to GC, although a similar RCT of withdrawal versus continuation has not been performed, discontinuation of antimalarials is more frequently associated with increased risk of flares. Four observational studies addressed this issue. Large observational studies from the multicentre Systemic Lupus International Collaborating Clinics (SLICC) cohort,[57] the Toronto Lupus cohort,[58] as well as five other SLE cohorts in Canada,[59] reported higher rates of disease flares in patients with SLE who stopped HCQ compared with patients who continued, with HR ranging from 1.56[57] to 2.30.[58] Tapering HCQ to a lower dose seems to be associated with a lower risk for flare, as patients in the Toronto cohort who tapered had significantly fewer flares versus abrupt discontinuation (45.9% vs 72.6%; p=0.01),[58] while the respective risk for flare in the SLICC study for those with HCQ dose reduction was 1.20 (95% CI 1.04 to 1.38) compared with patients who continued.[57]

Finally, regarding withdrawal of synthetic immunosuppressive drugs, a limited number of studies have been published, mainly in LN. The Weaning of Immunosuppressive Therapy in Lupus Nephritis (WIN-Lupus) study randomised 96 patients with proliferative LN in remission after 2–3 years of immunosuppression to treatment discontinuation versus maintenance.[60] Relapses

Table 4 Association of attainment of remission or LLDAS with risk for damage accrual

Study	Design	Target	Association with SDI	Study quality
Kikuchi *et al*[81]	Prospective	LLDAS within 12 months	No association	Good
Hao *et al*[82]	Retrospective	LLDAS-50	OR=0.19, 95% CI 0.04 to 0.99	Good
Alarcon *et al*[83]	Retrospective	LLDAS; remission	Remission/LLDAS: 0.18, 95% CI 0.12 to 0.26	Poor
Ugarte-Gil *et al*[84] (SLICC)	Prospective	Remission off-Tx, remission on-Tx, LDA-TC and mLLDAS (per 25% increase in time spent in a specified state vs active state)	Remission off-Tx: IRR=0.75 95% CI 0.70 to 0.81 Remission on-Tx: IRR=0.68 95% CI 0.62 to 0.75 LDA-TC: IRR=0.79 95% CI 0.68 to 0.92 mLLDAS: IRR=0.76 95% CI 0.65 to 0.89	Good
Nikfar *et al*[85]	Retrospective	Remission on/off-Tx, sustained remission (≥5 years)	Sustained remission on-Tx: HR 0.62, 95% CI 0.38 to 0.98	Good
Jakez-Ocampo *et al*[86]	Cross-sectional	Remission	Remission group 0.68 (0.67), versus control group 1.05 (0.87) (p=0.016);	Good
Golder *et al*[87] (APLC)	Prospective	LLDAS-50	HR 0.59, 95% CI 0.45 to 0.76	Good
Golder *et al*[88] (APLC)	Prospective	Remission (various DORIS definitions); LLDAS	Remission: Adj. HR 0.49–0.65 LLDAS: Adj. HR 0.54	Good
Kang *et al*[89]	Retrospective	LLDAS, MDA, LDA (Toronto)	LLDAS associated with lower SDI (β 0.06, 95% CI: 0.13 to 0.002)—MDA and LDA (Toronto) showed no association	Good
Sharma *et al*[90]	Prospective	LLDAS-50	Adj. HR 0.37, 95% CI 0.19 to 0.73	Fair
Ugarte-Gil *et al*[91]	Prospective	LLDAS; DORIS remission	Remission at given visit: HR=0.46; 95% CI 0.26 to 0.82 LLDAS/remission: HR=0.50; 95% CI 0.26 to 0.97 LLDAS not remission: HR=0.88; 95% CI 0.367 to 2.09	Good
Petri *et al*[92]	Prospective	Clinical remission off-Tx; Clinical remission on-Tx LLDAS	LLDAS-50 rate ratio 0.39–0.47, p<0.0001 Clinical remission on Tx: rate ratio 0.54, p<0.0001	Good
Floris *et al*[93]	Prospective	LLDAS; clinical remission at 6 months	Clinical remission: OR 0.07 95% CI 0.01 to 0.59 LLDAS: 0.25 95% CI 0.06 to 0.99	Poor
Tani *et al*[94]	Prospective	Remission (DORIS), LLDAS	Sustained remission (whole f–u): ΔSLICC 0.12 vs 0.48, p=0.018 Sustained LLDAS (whole f–u): ΔSLICC 0.11 vs 0.63, p<0.001	Good
Kandane-Rathnayake *et al*[95] (APLC)	Prospective	LLDAS—never	adj. HR 1.46, 95% CI 1.26 to 1.69	Good
Tselios *et al*[96]	Prospective	Remission; LDA (clinical SLEDAI≤2)	Comparable for remission and LDA	Poor

Adj. HR, adjusted HR; APLC, Asia Pacific Lupus Collaboration; DORIS, Definition Of Remission In SLE; IRR, Incidence Rate Ratio; LDA, low disease activity; LLDAS, lupus low disease activity state; LLDAS-50, lupus low disease activity state for ≥50% of the observation time; MDA, minimal disease activity; SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Damage Index; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index; SLICC, Systemic Lupus International Collaborating Clinics; TC, Toronto cohort; Tx, treatment.

of LN (27.3% vs 12.5%), as well as severe disease flares (31.8% vs 12.5%), were significantly more common in the discontinuation group. An Italian uncontrolled observational study reported a 22.9% relapse rate (19/83 patients) in LN patients who discontinued immunosuppression. Antimalarial treatment and longer duration of remission (>3 years) at the time of therapy withdrawal were associated with lower risk of LN relapse.[61]

Safety of herpes zoster and SARS-CoV2 vaccination in SLE

The final PICO focused on prevention of specific infections in SLE, namely VZV and COVID-19, rather than on general preventive measures for infections (vaccinations, etc), for which specific EULAR recommendations exist and are regularly updated.[7] These particular infections were chosen, because of the impact of zoster on patients with SLE (in view also of the potential increased risk with new therapies, such as interferon inhibitors),[62] and the public health problem imposed by the COVID pandemic, most obvious in populations with immunosuppression.[63]

Regarding efficacy and safety of the zoster vaccine in patients with SLE, we identified three studies assessing the newer recombinant, adjuvanted vaccine (Shingrix) in patients with systemic autoimmune diseases, which also included a small subset with SLE. A study in 403 patients (16 with SLE) found a flare rate of 7.1% in the SLE group (all were mild), as well as one zoster breakthrough case.[64] Another study on 622 patients (24 with SLE) reported mild flares in 4/24 patients with SLE (17%), all treated only with GC.[65] The third, larger study, using two claims databases from the USA to estimate recombinant zoster vaccination among adults aged≥50 years with systemic autoimmune diseases and possible vaccine-related flares, found no statistically significant increase in flares for any autoimmune disease following either dose of recombinant vaccine (more than 4500 patients with SLE in the two databases, risk ratio for flare in the risk window vs control window 0.9–1.0 in this group).[66] Formerly, the live attenuated vaccine (Zostavax) was tested in a single, high-quality RCT in 90 quiescent patients with SLE (plus 10 healthy controls), testing VZV IgG reactivity and safety at 6 weeks.[67] Both anti-VZV IgG and T-cell spots increased significantly in herpes zoster-vaccinated patients, in a similar magnitude to healthy controls, while only two patients experienced a mild/moderate flare.

Regarding the immunogenicity and safety of SARS-CoV2 vaccination in patients with SLE, the SLR identified a significant number of studies (online supplemental table S4.6). A meta-analysis, including 32 studies and 8269 patients in total, tested clinical effectiveness (ie, prevention from COVID-19), immunogenicity and safety, and found a pooled seropositivity rate 81.1% following various anti-SARS-CoV2 vaccine formulations (higher with mRNA vaccines), very rare severe adverse events (<1%), as well as a cumulative flare rate 5.5%[68]; however, moderate or severe flares were reported only in 0%–2% of patients in all but one studies (online supplemental table S4.6). Additionally, seven studies addressed the influence of concomitant or background immunosuppression on vaccine immunogenicity (online supplemental table S4.7). As shown in these studies, concomitant use of

Table 5 Studies evaluating tapering and withdrawal of glucocorticoids in patients with SLE

Study	Design, n	Intervention	Control	Follow-up	Outcome	Result	
RCT							**Risk of bias**
Mathian *et al*[55]	RCT, 124	GCs maintenance	GCs withdrawal	52 weeks	Risk of flare	RR 0.2 95% CI 0.1 to 0.7	High
					Time to first flare	HR 0.2; 95% CI 0.1 to 0.6	
					Risk of moderate/ severe flares	RR 0.1 95% CI 0.1 to 0.9	
Observational							**Study quality**
Floris *et al*[97]	Prospective, 127	Pz tapering		2 years	Flare rate	Flares in pts with Pz≤5 mg/day 42.4% versus pts with Pz>5 mg/day 46.4%, p=0.706	Poor
Nakai *et al*[98]	Retrospective, 73	GCs withdrawal		52 weeks	Flare-free remission	80%	Poor
Ji *et al*[99]	Retrospective, 132	GCs withdrawal		Median 21.8 months	Flare rate	36.4%	Poor
Tselios *et al*[100]	Prospective, 204 propensity score-matching	GCs maintenance	GCs withdrawal	24 months	Flare rate	50% vs 33.3%; p=0.01	Good
					Damage accrual	17.6% vs 6.9%; p=0.022	
Fasano *et al*[101]	Prospective, 154	GCs maintenance	GCs withdrawal	Median 59 months	Flare rate	11.2% vs 12.5%; p=0.81	Fair
					Damage accrual	No difference	
Tani *et al*[102]	Retrospective, 148	GCs withdrawal		1 year	Flare rate	23.4%	Poor
Goswami *et al*[103]	Retrospective, 148	GCs withdrawal		Median 539 days, IQR 266–841	Flare rate	20.9%	Poor
					Renal flare	12.2%	
Hanaoka *et al*[104]	Retrospective, 73	Pz, IS or HCQ	No treatment	Mean 14.9 months	Flare rate	Higher in the no-drug group compared with any-drug group p<0.001	Poor

GC, glucocorticoids; HCQ, hydroxychloroquine; IS, immunosuppressants; pts, patients; Pz, prednisone; RCT, randomised controlled trial; RR, risk ratio; SACQ, serologically active clinically quiescent; SLE, systemic lupus erythematosus.

MMF, RTX and possible GC was associated with lower patient ability to mount immune responses to SARS-CoV2 vaccination.

DISCUSSION

For the recent update of the EULAR recommendations for the management of SLE, we performed five different SLRs based on respective PICOs, to cover the most important aspects in the treatment of this challenging disease.

HCQ is the backbone treatment for all patients with SLE, while GC are still used in the majority of patients. The current SLR confirmed the beneficial effects of HCQ in lupus, ranging from prevention of infections or thrombosis to improved survival. Regarding retinal toxicity, although studies seem to converge to longer duration of use and higher cumulative dose as major risk factors for this complication, the actual rate of this complication had wide variation among studies, possibly in part due to different screening techniques used and definitions applied. We did not document other major safety signals. On the contrary, the current SLR confirmed the correlation of chronic GC use with multiple adverse outcomes in SLE (eg, susceptibility to infections, osteonecrosis, irreversible damage, among others). It should be noted that the recommended lowering of the maximum maintenance dose to 5 mg/day (instead of 7.5 mg/day) was not based on a randomised trial comparing the safety of these two different maintenance doses. Nevertheless, most observational studies that tested threshold daily prednisone doses in relation to adverse events pointed to the 5 mg/day, as well as to a stronger association with increasing doses (see table 1).

For the use of conventional and biologic immunosuppressive drugs in extrarenal SLE, the approved biologics anifrolumab and belimumab have proven efficacy in the form of high-quality RCTs with low RoB, compared with standard of care. Importantly, RCTs have become more elaborate in recent years, because in the anifrolumab studies, organ-specific endpoints, such as the CLASI and tender/swollen joint counts, were applied (belimumab studies had used SLEDAI and BILAG domains). RCTs are not available for conventional immunosuppressive agents in extrarenal SLE and are unlikely to be performed in the future due to the long experience with the everyday use of the drugs. Additionally, there are very few comparative studies between different immunosuppressive agents, (MTX, AZA, MMF, etc) all prior to the starting date of the current SLR.

Regarding the treatment of LN, equal efficacy of standard of care treatment, MMF and CYC, was again confirmed in additional comparative studies, mainly of low quality. More importantly, two high-quality RCTs with low RoB led to the approval of belimumab and voclosporin for the treatment of active LN.[4 5] These RCTs were the largest that have been performed in LN to date, and the BLISS-LN additionally used a novel response definition (PERR) and used an extended time-point at 2 years (all other RCTs of 'induction' therapies in LN have tested efficacy at 6 or 12 months). Post hoc analyses of both BLISS-LN and AURORA did not find a statistically significant benefit of any of the drugs in class 5 LN, but patients with this histologic class represented less than 20% of the study population in both studies; belimumab was also found to perform better in patients with baseline proteinuria less than 3 g/day.

For treatment targets of SLE, our SLR provided robust evidence for the positive association of remission and LLDAS with lower risk for multiple adverse outcomes, including damage (table 4), flares, mortality and hospitalisation. Although the two states are comparable in terms of prognosis, data point towards slightly lower odds for damage accrual for remission over LLDAS; on the other hand, LLDAS is achieved more frequently than DORIS remission. The prognostic significance of both conditions has been tested in longitudinal cohorts of patients receiving routine

care. Interestingly, a randomised trial has been designed to test whether a 'treat-to-target' approach aiming at remission or LLDAS confers additional benefit over standard of care.[69]

Two randomised studies, CORTICOLUP and WIN-LUPUS, tested the discontinuation of prednisone (CORTICOLUP) and immunosuppressive agents (WIN-LUPUS) in extrarenal SLE and LN, respectively.[55 60] Although both studies found higher rates of relapse in patients that discontinued treatment, and withstanding their limitations (eg, CORTICOLUP was criticised for the abrupt—rather than more gradual—stopping of prednisone from 5 mg/day), they have opened the way for similar trials in SLE. A number of cohort studies have been reported with successful discontinuation, especially of GC, without an increased risk for flare in the majority of patients.

Some methodological considerations of our work merit explanation. Since high-quality studies are lacking for most organ manifestations of SLE, we adopted an inclusive approach during article screening and selection, in order to capture evidence from observational and non-controlled studies for topics where RCTs are absent or scarce. This led to inclusion of a large number of studies (n=439), many of which had limited contribution to the conclusions regarding drug efficacy for specific manifestations. This issue is particularly relevant for conventional immunosuppressive drugs, which are often used to treat extrarenal lupus manifestations, but lack support from randomised evidence. With improved trial design and approval of new drugs (mainly biologics), we anticipate that SLR for future updates of SLE recommendations will focus more on RCTs and high-quality observational studies with low RoB. Additionally, our SLR did not include the EMBASE database, and Medline was partially captured through PubMed. We acknowledge that this may have led to omission of some studies, nevertheless the multiple sources used for our SLR (PubMed, Cochrane, hand search of references of included studies) has reduced the possibility of leaving out significant studies.

In conclusion, the dedicated SLRs that supported the update of the EULAR recommendations for the management of SLE found high-quality data for the efficacy of biologic agents in treating the disease (anifrolumab and belimumab) and for the new treatment options in LN (RCT with low RoB for belimumab and voclosporin), but low-to-moderate quality concerning most other aspects of the disease. Additionally, treatment targets, such as remission and low disease activity, show a robust and consistent association with several favourable outcomes, supporting their establishment as the goal of therapy in SLE. Studies (some of them randomised) addressing the issue of treatment tapering in lupus patients in remission have also been published since the previous recommendations, following the paradigm of rheumatoid arthritis and spondylarthritis.

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Acknowledgements We wish to acknowledge the support of the EULAR Quality of Care Committee and express our sincere appreciation and gratitude to the EULAR Secretariat, especially Simona Lupatin, executive assistant and to Dora Togia for the outstanding organisation and coordination.

Contributors MK and AF drafted the manuscript, CBM, GB and DTB edited the manuscript, and AF provided the final version. AF acts as the guarantor responsible for the overall content of the manuscript.

Funding This study was supported by the European League Against Rheumatism (project number QoC015).

Competing interests AF reports honoraria and/or consulting fees from Lilly, Boehringer, Novartis, AbbVie, AstraZeneca, GSK, MSD, Pfizer, UCB, Amgen, Aenorasis, support for attending meetings from UCB. MK reports honoraria and/or consulting fees from GSK, participation in advisory boards from GSK, AstraZeneca, Amgen. GB reports grants from GSK, AstraZeneca, Pfizer, honoraria and/or consulting fees from Lilly, Aenorasis, Novartis, AstraZeneca, GSK, SOBI, Pfizer, participation in advisory boards from Novartis. DTB reports unrestricted investigational grants from GSK, honoraria and/or consulting fees from GSK, AstraZeneca, Pfizer. CBM declares no conflict of interest.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as online supplemental information.

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