EULAR recommendations for the management of systemic lupus erythematosus: 2023 update

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Abstract

Objectives: To update the EULAR recommendations for the management of systemic lupus erythematosus (SLE) based on emerging new evidence.

Methods: An international Task Force formed the questions for the systematic literature reviews (01/2018-12/2022), followed by formulation and finalization of the statements after a series of meetings. A predefined voting process was applied to each overarching principle and recommendation. Levels of evidence and strengths of recommendation were assigned, and participants finally provided their level of agreement with each item.

Results: The Task Force agreed on 5 overarching principles and 13 recommendations, concerning the use of hydroxychloroquine (HCQ), glucocorticoids (GC), immunosuppressive drugs (ISD) (including methotrexate, mycophenolate, azathioprine, cyclophosphamide [CYC]), calcineurin inhibitors (CNIs, cyclosporine, tacrolimus, voclosporin) and biologics (belimumab, anifrolumab, rituximab). Advice is also provided on treatment strategies and targets of therapy, assessment of response, combination and sequential therapies, and tapering of therapy. HCQ is recommended for all lupus patients at a target dose 5mg/kg real body weight/day, considering the individual's risk for flares and retinal toxicity. GC are used as 'bridging therapy' during periods of disease activity; for maintenance treatment, they should be minimized to equal or less than 5 mg/day (prednisone equivalent) and, when possible, withdrawn. Prompt initiation of ISDs (methotrexate, azathioprine, mycophenolate) and/or biologic agents (anifrolumab, belimumab) should be considered to control the disease and facilitate GC tapering/discontinuation. CYC and rituximab should be considered in organ-threatening and refractory disease, respectively. For active lupus nephritis, GC, mycophenolate or low-dose IV CYC are recommended as anchor drugs, and add-on therapy with belimumab or CNIs (voclosporin or tacrolimus) should be considered. Updated specific recommendations are also provided for cutaneous, neuropsychiatric and haematological disease, SLE-associated antiphospholipid syndrome, kidney protection, as well as preventative measures for infections, osteoporosis, cardiovascular disease.

Conclusion: The updated recommendations provide consensus guidance on the management of SLE, combining evidence and expert-opinion.

Keywords: Systemic lupus erythematosus, treatment, lupus nephritis, recommendations

Introduction

Since 2008, when the first EULAR recommendations for the management of systemic lupus erythematosus (SLE) were published and widely adopted,[1] a series of specific recommendations on disease monitoring, neuropsychiatric SLE and lupus nephritis (LN), pregnancy and women's health issues in SLE have been developed.[2–5]. More recently, updated recommendations on the management of general SLE and LN were published in 2019 and 2020, respectively, the latter jointly with the European Renal Association/European Dialysis and Transplant Association (ERA/EDTA).

Since the 2019 update, the pace of new developments in SLE has accelerated. A second biologic drug, anifrolumab, has been approved for the management of SLE, while the field of LN has also witnessed major breakthroughs; the approval of belimumab and voclosporin, a novel calcineurin inhibitor (CNI), for patients with active LN has inspired discussions on a "paradigm shift" in the treatment of LN, moving from the traditional "induction-maintenance" regimen to the early use of combination therapies.[6,7] These advances created the impetus for an update of the recommendations, to provide guidance on an evolving landscape and capitalize on the experience gained thus far. Given the drug pipeline and lessons learnt regarding trial design from previous trial failures, it is likely that new therapeutic options will continue to emerge, and SLE may finally enter the era of more frequent updates of its management recommendations, similar to other diseases.[8,9]

Methods

Per the EULAR standard operating procedures (SOPs) [10] and the AGREE II document,[11] the convenor (DTB) submitted a proposal for an update of the recommendations for the management of SLE, which was approved by the EULAR Quality of Care Subcommittee and the EULAR Council. Following approval, a Task Force was assembled to form the research questions for the systematic literature review (SLR), that consisted of 35 rheumatologists, 5 nephrologists, and 2 patient representatives (JA, MKou), also including 2 methodologists (GB, CBM) and 2 fellows responsible for the SLR (AF, MK). Importantly, the Task Force also included non-European experts, 4 from the Americas (2 from the USA [RF, MP], 1 from Canada [DDG], 1 from Argentina [BAPE]), 4 from Asia [SCB, CCM, SVN, YT] and 1 from Australia [EM]. EMEUNET (EMerging EUlar NETwork) was also represented by 2 members (JM, CW). All members completed a COI form.

Before the first meeting, an outline of the proposed methodology, a set of the main research questions and the respective PICOs (Population, Intervention, Comparison and Outcomes) were circulated among the panellists, who were encouraged to comment, edit, and propose additional topics for the SLR. Through this process, it was decided that the SLRs would focus on five domains: 1) management of general and organ-specific SLE, 2) targets of treatment, 3) tapering/withdrawal of treatment, 4) management of patients with SLE and APS, and 5) the efficacy and safety of vaccination against herpes zoster and SARS-CoV2 viruses (a general SLR for infection prevention was not decided, as there are dedicated

EULAR recommendations on this topic). Separate PICOs and search strings were developed for each domain, resulting in five SLRs. The two fellows, supervised by the methodologists, performed the PICO-based SLRs using two different databases (PubMed and Central). Importantly, since the previous recommendations on general SLE had included papers through 12/2017, the current SLRs were limited to English language publications published between 1/2018 and 12/2022. Pertinent articles, identified by manual search within the reference list of the originally retrieved publications, were also included. A risk of bias assessment was performed using the Cochrane Risk of Bias tool and Newcastle-Ottawa scale for randomized controlled trials (RCT) and observational studies, respectively. The final level of evidence and grading of recommendations, according to the Oxford Evidence-based Medicine grading levels,[12] considered also the body of evidence that had informed the 2019 EULAR recommendations.[13]

The results of the SLRs, focusing on new evidence and data quality, were presented during the first meeting (29 April 2023), held virtually to facilitate the attendance of the international Task Force members. The participants reviewed the evidence, and an initial draft of the statements/recommendations was formulated following open deliberations. Then, suggestions and edits by all members were incorporated by the convenor, methodologists and the fellows responsible for the SLR to a new modified set of recommendations, which was again circulated to the panel members to propose any additional changes. To achieve consensus, a second meeting was held (7 May 2023), in which panellists discussed in detail each overarching principle and recommendation and came up with the final version which served as basis for the voting. During the third and last meeting (14 May 2023), all Task Force members who were present, were asked to vote per bullet point whether they agreed or not in principle with the respective statement. As per the EULAR SOPs, a recommendation was immediately accepted if more than 75% of those present voted in favour. In cases where consensus was not met, possible causes of disagreement were discussed, amendments to the statements were made, and a second round of voting requiring more than 66% agreement from participants took place. Following approval of the recommendation, every Task Force member provided their level of agreement (LoA) for each statement in a scale from 0 (no agreement at all) to 10 (100% agreement).

Of note, the 2019 recommendations counted a total of 33 recommendations belonging to 4 domains (goals of treatment, general principles of treatment, specific manifestations, and comorbidities). The current update aligns with the EULAR SOPs to include a maximum 15 bullet-point statements. To this end, recommendations from the previous set were either omitted or merged, and new recommendations were formulated. Because of this change from the previous update, all overarching principles and individual recommendations are hereby presented as new, even for individual recommendations where the essence has remained unchanged, because a detailed description of “merged”, “omitted”, “rephrased” statements was considered impractical.

Results

Following the meetings mentioned above, the Task Force formulated a final number of 5 overarching principles and 13 recommendations (**Table 1**). The detailed results of the SLR are summarized in the Appendix, however, parts of the data are also presented herein, to provide an explanation of the results.

Table 1. EULAR Recommendations for the management of patients with systemic lupus erythematosus – 2023 update

Overarching principles	**Level of agreement**	
	Mean (SD)	**% with score ≥ 8**
1. SLE requires multidisciplinary, individualized management with patient education and shared decision-making, taking into consideration the costs to patient and society.	**9.88 (0.40)**	**100**
2. SLE disease activity should be assessed at each clinic visit (the frequency depending on physician's discretion), with evaluation of organ damage (at least annually), using validated instruments.	**9.74 (0.63)**	**100**
3. Non-pharmacologic interventions, including sun protection, smoking cessation, healthy, balanced diet, regular exercise, and measures to promote bone health are important to improve long-term outcomes	**9.90 (0.37)**	**100**
4. Pharmacological interventions are directed by patient characteristics, type and severity of organ involvement, treatment-related harms, comorbidities, risk for progressive organ damage, and patient preferences.	**10 (0)**	**100**
5. Early SLE diagnosis (including serological assessment), regular screening for organ involvement (especially nephritis), prompt initiation of treatment aiming at remission (or low disease activity if remission is not possible), and strict adherence to treatment, are essential to prevent flares and organ damage, improve prognosis, and enhance quality of life.	**9.81 (0.51)**	**100**
Recommendation/Statement		
1. Hydroxychloroquine is recommended for all patients (**1b/A**), unless contraindicated, at a target dose of 5 mg/kg real body weight/day (**2b/B**) but individualized based on risk for flare (**2b/B**) and retinal toxicity.	**9.21 (1.35)**	**90.4**
2. Glucocorticoids, if needed, are dosed based upon the type and severity of organ involvement (**2b/C**), and should be reduced to maintenance dose of ≤5 mg/day (prednisone equivalent) (**2a/B**) and, when possible, withdrawn; in patients with	**9.57 (0.77)**	**97.6**

moderate to severe disease, pulses of intravenous methylprednisolone (125–1000 mg per day, for 1–3 days) (**3b/C**) can be considered.		
3. In patients not responding to hydroxychloroquine (alone or in combination with glucocorticoids) or patients unable to reduce glucocorticoids below doses acceptable for chronic use, addition of immunomodulating/immunosuppressive agents (for example methotrexate [**1b/B**], azathioprine **2b/C**] or mycophenolate [**2a/B**]) and/or biologic agents (for example, belimumab [**1a/A**] or anifrolumab [**1a/A**]) should be considered.	**9.32 (0.91)**	**95.2**
4. In patients with organ- or life-threatening disease, intravenous cyclophosphamide (**2b/C**) should be considered; in refractory cases rituximab (**2b/C**) may be considered.	**9.38 (0.99)**	**95.2**
5. Treatment of active skin disease should include topical agents (glucocorticoids, calcineurin inhibitors) (**2b/B**), antimalarials (hydroxychloroquine, chloroquine) (**1a/A**), and/or systemic glucocorticoids (**4/C**) as needed, with methotrexate (**1b/B**), mycophenolate (**4/C**), anifrolumab (**1a/A**), or belimumab (**1a/B**), considered as second-line therapy.	**9.35 (1.06)**	**95.2**
6. In active neuropsychiatric disease attributed to SLE, glucocorticoids and immunosuppressive agents for inflammatory manifestations (**1b/A**) and antiplatelet agents/anticoagulants for atherothrombotic/aPL-related manifestations (**2b/C**) should be considered.	**9.68 (0.81)**	**97.6**
7. For acute treatment of severe autoimmune thrombocytopenia, high-dose glucocorticoids (including pulses of intravenous methylprednisolone) (**4/C**), with or without intravenous immunoglobulin G (**4/C**), and/or rituximab (**2b/B**), and/or high-dose intravenous cyclophosphamide (**4/C**), followed by maintenance therapy with rituximab (**2b/B**), azathioprine (**2b/C**), mycophenolate (**2b/C**), or cyclosporine (**4/C**), should be considered.	**9.48 (0.86)**	**97.6**
8. Patients with active proliferative lupus nephritis should receive low-dose (EuroLupus) intravenous cyclophosphamide (**1a/A**) or mycophenolate (**1a/A**) and glucocorticoids (pulses of intravenous methylprednisolone followed by lower oral doses); combination therapy with belimumab (either with cyclophosphamide or mycophenolate (**1b/A**)) or calcineurin inhibitors (especially voclosporin or tacrolimus, combined with mycophenolate, **1b/A**) should be considered.	**9.36 (1.06)**	**92.8**
9. Following renal response, treatment of lupus nephritis should continue for at least three years (**2b/B**); patients initially treated with mycophenolate alone or in combination with belimumab or a calcineurin inhibitor should remain on these drugs (**1a/A**), whereas azathioprine or mycophenolate should replace cyclophosphamide for those initially	**9.56 (0.81)**	**95.2**

treated with cyclophosphamide alone (**1a/A**) or in combination with belimumab (**1a/A**).		
10. In patients at high-risk for renal failure (defined as reduced GFR, histological presence of cellular crescents or fibrinoid necrosis, or severe interstitial inflammation), high-dose (NIH regimen) intravenous cyclophosphamide (**1a/A**) in combination with pulse intravenous methylprednisolone, can be considered.	**9.57 (0.86)**	**95.2**
11. In SLE patients achieving sustained remission, gradual tapering of treatment should be considered, with withdrawal of glucocorticoids first (**2a/B**).	**9.89 (0.38)**	**100**
12. SLE associated with thrombotic antiphospholipid syndrome (APS) should be managed with long-term vitamin K antagonists after the first arterial or unprovoked venous thrombotic event (**1b/B**); low dose aspirin (75-100 mg/day) should be considered in SLE patients without APS but with high-risk aPL profile (**2a/B**).	**9.57 (0.83)**	**97.6**
13. Immunizations for the prevention of infections (HZV, HPV, influenza, COVID-19 and pneumococcus), management of bone health, renoprotection and cardiovascular risk, and screening for malignancies, should be performed (**5/D**).	**9.85 (0.36)**	**100**

Levels of evidence according to the Oxford Evidence-based Medicine grading levels ((https://www.cebm.net/wp-content/uploads/2014/06/CEBM-Levels-of-Evidence-2.1.pdf))

Overarching principles

The overarching principles contain general information on the management of SLE, reflect common sense and are not accompanied by a respective level of evidence. They are nevertheless important to set an overall framework for the approach to a patient with SLE and highlight the role of physician-patient interaction. The overarching principles were voted as a group of principles (i.e., not individually) and agreement was 100%.

1. SLE requires multidisciplinary, individualized management with patient education and shared decision-making, taking into consideration the costs to patient and society.

While rheumatologists are the specialists who should primarily care for SLE patients, the multisystem nature of the disease often mandates the involvement of other disciplines (e.g., nephrologists, dermatologists etc), and treatment decisions should be individualized considering patient preferences and patient education. Comparative costs of different treatments should be weighed against the cost of illness and the societal impact of SLE, in terms of social and work participation. Mean (SD) LoA was 9.88 (0.40).

2. SLE disease activity should be assessed at each clinic visit (the frequency depending on physician's discretion), with evaluation of organ damage (at least annually), using validated instruments.

Task Force members agreed on the need to formally assess lupus disease activity at each visit for the need of therapy adaptation. The phrasing "frequency depending on physician's discretion" was decided following deliberations, in which it became clear that optimal frequency of patient visits may vary, from a few days in a patient with active LN to up to 6 months in patients with long-standing quiescent disease; thus, judgment of the treating physician cannot be substituted by a fixed range of intervals. The most frequently used validated instruments for measuring disease activity are the various versions of the SLE disease activity index (SELENA-SLEDAI or SLEDAI-2K) and the British Isles Lupus Assessment Group (BILAG). Annual assessment of irreversible damage is important because damage accrual has significant prognostic value. Mean (SD) LoA for this principle was 9.74 (0.63).

3. Non-pharmacologic interventions, including sun protection, smoking cessation, healthy, balanced diet, regular exercise, and measures to promote bone health are important to improve long-term outcomes.

These interventions are not specific to SLE and pertain also to the general population, although patients with lupus should particularly avoid sun exposure due to the characteristic photosensitivity of the disease. The importance of smoking cessation should be emphasized, as smoking may also interfere with the efficacy of antimalarials [14] and biologics (belimumab) [15] among its other detrimental sequelae. Importantly, a dedicated set of EULAR recommendations on non-pharmacological management of SLE and systemic sclerosis were published very recently; the reader is referred there for more relevant information.[16] Mean (SD) LoA was 9.90 (0.37).

4. Pharmacological interventions are directed by patient characteristics, type and severity of organ involvement, treatment-related harms, comorbidities, risk for progressive organ damage, and patient preferences.

The phenotypic heterogeneity and variable severity of organ involvement, as well as differential response to drugs based on patient characteristics, mandate an individualized approach. Pharmacological treatment of lupus may range from hydroxychloroquine (HCQ) monotherapy for patients with mild skin and/or joint symptoms, to highly potent immunosuppressive medications like high-dose glucocorticoids (GC) and cyclophosphamide (CYC) in patients with organ- or life-threatening disease. When choosing therapy, immutable characteristics, such as race and ethnicity, as well as socioeconomic determinants and access to different drugs should be taken into account. For example, black patients with LN may be more responsive to mycophenolate than cyclophosphamide.[17] Patient research partners in the Task Force highlighted the importance of patient preferences in the treatment decisions, which form the basis of shared decision making. This principle received the highest mean LoA, mean (SD) 10 (0), indicating complete agreement of all individual panellists.

5. Early SLE diagnosis (including serological assessment), regular screening for organ involvement (especially nephritis), prompt initiation of treatment aiming at remission (or low disease activity if this is not possible), and strict adherence to treatment, are essential to prevent flares and organ damage, improve prognosis, and enhance quality of life.

The final overarching principle highlights four pillars in the management of SLE: i) need for early diagnosis, because despite increased awareness in combination with the new, more sensitive classification criteria,[18] recent studies support that SLE patients still face diagnostic delay (median 2 years from onset of symptoms)[19,20]; ii) vigilant monitoring for new organ involvement, mainly LN, especially during the first years of the disease, but also thereafter. This need for increased awareness for signs of new-onset kidney involvement was emphasized by several Task Force members, because LN represents a major milestone in the natural history of the disease and delaying its diagnosis has profound prognostic repercussions; iii) pursuing a treatment target, which should ideally be remission, as defined by the recent DORIS criteria,[21] or alternatively, a state of low disease activity, such as the Lupus Low Disease Activity state (LLDAS).[22] Both remission and LLDAS have been extensively validated and proven to reduce the risk for damage and other adverse outcomes in patients with SLE (a detailed analysis of the favourable outcomes associated with remission and LLDAS is given in the Appendix); and iv) the importance of patient adherence to treatment. Specific reference to the issue of adherence in the overarching principles was emphasized by several panellists, including the patient research partners, because medication non-adherence, despite reported wide variations, is considered a major cause of treatment failure.[23] A trusting relationship between the physician and patient forms the basis for the minimization of the risk of non-adherence. Mean (SD) LoA for the final overarching principle was 9.81 (0.51).

Individual recommendations

1. Hydroxychloroquine is recommended for all patients (1b/A), unless contraindicated, at a target dose of 5 mg/kg real body weight/day (2b/B), but individualized based on risk for flare (2b/B) and retinal toxicity.

HCQ is the mainstay of treatment for patients with SLE and the current SLR extended the existing body of evidence regarding the multiple beneficial effects of HCQ in various aspects of the disease. In the 2019 recommendations, emphasis was placed upon the specification that HCQ dose "*should not exceed 5 mg/kg real body weight/day*", in view of data which suggested a higher than previously thought risk for retinal toxicity by the use of more sensitive screening techniques.[24] A recent observational study assessed the risk for flares in relation to HCQ dose during the previous 6-month period and found an almost 2-fold risk for any flare for doses ≤ 5 mg/kg per day (vs > 5 mg/kg per day), increased to more than 6-fold for moderate or severe flares, with a threshold dose calculated near 5 mg/kg/day.[25] Until more data become available regarding benefit-risk relationship of different doses, it was decided that the

HCQ target dose remains at 5 mg/kg/day; however, this should be individualized based on risk for flare and retinal toxicity, with patients at higher risk for retinal toxicity (kidney disease, preexisting macular or retinal disease, tamoxifen use) being candidates for closer ophthalmologic follow-up. In selected patients and circumstances (e.g., moderate or severe disease), initial HCQ dose higher than 5 mg/kg/day (but not exceeding 400 mg/day) may be used, followed by lowering of the dose to within range once the patient has improved. In addition, Task Force members suggested the use of monitoring HCQ blood levels to guide the optimal dose for each patient and assess for possible non-adherence to therapy, based on studies suggesting that HCQ whole blood levels may reflect patient adherence to treatment.[26] Although a universal recommendation for HCQ blood level monitoring would be impractical, it can nevertheless be used to guide dosage adaptations, in settings where it is available. Finally, the use of antimalarials other than HCQ was discussed mainly by non-European panellists, to address the issue of potential limited availability or higher cost of HCQ in some countries. In such settings, chloroquine may be used as an alternative, bearing in mind that it may be more toxic than HCQ (mainly for retinal toxicity)[27]. Finally, quinacrine can be considered in patients with cutaneous manifestations and HCQ-induced retinopathy. The statement on HCQ was agreed on by 77.8% of participants following one round of amendments (the only statement where this was needed) and mean (SD) LoA was 9.21 (3.35).

2. Glucocorticoids, if needed, are dosed based upon the type and severity of organ involvement (2b/C), and should be reduced to maintenance dose of ≤5 mg/day (prednisone equivalent) (2a/B) and, when possible, withdrawn; in patients with moderate to severe disease, pulses of intravenous methylprednisolone (125–1000 mg per day, for 1–3 days) (3b/C) can be considered.

Minimization of GC use, in view of their detrimental effects, was a major theme of discussion during the Task Force meetings. Numerous studies in the current SLR confirmed associations of different cut-offs for daily prednisone dose with adverse outcomes, most of which pointed to the threshold of 5 mg/day. Although a controlled trial of different GC tapering regimens or maintenance doses is still lacking in SLE, the Task Force elected to lower the "acceptable" threshold of daily prednisone dose for maintenance treatment to maximum 5 mg/day prednisone equivalent, as compared to 7.5 mg/day in the 2019 recommendations. Ideally, one could envision the use of GC only as "bridging therapy" in SLE, similar to rheumatoid arthritis (lowest possible dose for the shortest possible period), and the complete withdrawal of GC is the optimal target.

Intravenous pulses of methylprednisolone (MP) of various doses (depending on disease severity and patient weight) capitalize on the immediate non-genomic effects of GC,[28] and may allow for a faster tapering of per os (PO) GC.[29] Importantly, pulse IV MP has not been linked to certain established GC-related harms, like avascular necrosis.[30] Initial PO dose also depends on disease severity; a retrospective study in 206 patients with LN using propensity score matching found higher rates of 1-year complete response in patients who started with ≥ 40 mg/day compared to those who started with ≤ 30 mg/day, without increased risk for GC-related damage.[31] A smaller study in non-renal lupus had found similar reduction in disease

activity at 1 year and higher risk of damage with starting dose > 30 mg/day versus ≤ 30 mg/day.[32] Despite these discrepancies, most panellists agreed that it is the chronic exposure to GC that confers the major risk, and the statement received 96.3% agreement and mean (SD) LoA was 9.57 (0.77).

3. In patients not responding to hydroxychloroquine (alone or in combination with glucocorticoids) or patients unable to reduce glucocorticoids below doses acceptable for chronic use, addition of immunomodulating/immunosuppressive agents (for example methotrexate [1b/B], azathioprine 2b/C] or mycophenolate [2a/B]) and/ or biologic agents (for example, belimumab [1a/A] or anifrolumab [1a/A]) should be considered.

This statement emphasizes the value of conventional and biologic immunomodulatory/immunosuppressive drugs for the control of the disease and facilitation of GC tapering and withdrawal. Since no new, high-quality data emerged in the past four years regarding conventional immunosuppressive drugs, deliberations regarding this statement focused on two main issues: i) inclusion of anifrolumab, following its approval in 2021 [33,34], as well as belimumab,[35] as biologic agents with proven efficacy in controlling disease activity, reducing flares, and allowing for GC dose reduction. In the recommendation, there is no hierarchy in the choice between anifrolumab and belimumab, as the two drugs have not been compared in a head-to-head trial and their approval was the result of RCTs in similar extrarenal SLE populations. The panel noted that there are more than 10 years of real-life clinical experience with belimumab, while no real-life data for anifrolumab had been published by the time of the SLR completion. ii) The positioning of biologic agents in relation to conventional immunosuppressive drugs for the treatment of SLE. For the latter point, while considerations from specific countries, healthcare settings and biologic reimbursement policies have to be taken into account, most panellists agreed that prior use of a conventional immunosuppressive drug (methotrexate [MTX], azathioprine [AZA], mycophenolate mofetil or mycophenolic acid, [henceforth combined referred to as "mycophenolate", see **Supplementary Table 1** for details] leflunomide,[36] or others) should not be mandatory for initiating anifrolumab or belimumab. Of note, this is unchanged from the 2019 recommendations. The rationale driving this statement was that, despite their substantially higher cost, approved biologic drugs have proven their efficacy in high-quality RCTs, while such data are lacking for conventional immunosuppressive drugs, which continue to be used based on rheumatologists' long-term real-life experience. This recommendation received 84.6% agreement and mean (SD) LoA was 9.32 (0.91).

4. In patients with organ- or life-threatening disease, intravenous cyclophosphamide (2b/C) should be considered; in refractory cases, rituximab (2b/C) may be considered.

Due to its gonadal toxicity, high-dose IV CYC is reserved for severe cases of lupus, in which it may be considered owing to its high efficacy. Rituximab (RTX) is used off-label in SLE and is recommended in circumstances[37] where other drugs have failed, with notable exceptions (e.g. immune cytopenias, see

below) where it can be used earlier. Although a universal definition of refractory disease is lacking in SLE, it is conceived as disease not responding to different classes of immunosuppressive medications. The combination of RTX with CYC had been used in early studies of RTX,[38] but additional benefit has not been confirmed [39] and this combination comes at the expense of an increased risk for infections. Sequential strategies of RTX followed by belimumab are being explored, but more data are needed.[40,41]

Patients not responding to any of the aforementioned therapies might be offered other options, such as plasma exchange,[42] haematopoietic stem cell transplantation,[43] or experimental therapies. In 2022, the use of CAR T-cells in 5 patients with severe, refractory SLE was published with encouraging results, yet RCTs and more long-term data are needed.[44] Agreement for this recommendation was 100%, with mean (SD) LoA 9.38 (0.99).

5. Treatment of active skin disease should include topical agents (glucocorticoids, calcineurin inhibitors) (2b/B), antimalarials (hydroxychloroquine, chloroquine) (1a/A), and/or systemic glucocorticoids (4/C) as needed, with anifrolumab (1a/A), belimumab (1a/B), methotrexate (1b/B), or mycophenolate (4/C), considered as second-line therapy.

For the treatment of active skin disease in SLE, few new data have emerged since the 2019 recommendations, and a significant body of evidence continues to originate from studies in patients with cutaneous lupus erythematosus. Recommended first-line treatment (topical agents, antimalarials and/or systemic GC) has not changed in the statement. HCQ is the antimalarial of choice, but chloroquine may be used in the settings discussed earlier.[45] Quinacrine (mepacrine) may also be used in cases of inadequate response or toxic retinopathy, as add-on to HCQ or alternative therapy, respectively,[46] but its use is limited by frequent intolerance and unavailability in many countries.

For the ~40% of patients not responding to first-line therapy,[47] comparative studies among existing immunosuppressive drugs are lacking. Despite this paucity, recommended second-line drugs have partly changed from 2019, because the Task Force decided to recommend drugs more familiar to rheumatologists (such as MTX or mycophenolate, instead of dapsone or retinoids). A small retrospective study in 73 patients with refractory CLE to first-line therapy found similar response rates (~65%) between MTX and mycophenolate.[48] Anifrolumab and belimumab have both shown efficacy in mucocutaneous manifestations of SLE, [49,50] although only anifrolumab has used the Cutaneous Lupus Area and Severity Index (CLASI) in its clinical programme, whereas belimumab has reported responses according to the general instruments SLEDAI and BILAG, hence the designation B in the Grading of Recommendation (despite positive RCT data). Importantly, the list of recommended drugs is indicative and other treatment may be considered as second- or third-line options, including dapsone, retinoids, calcineurin inhibitors (CNI), azathioprine (AZA), CYC and RTX, ideally in collaboration with dermatologists experienced in the treatment of CLE. Finally, thalidomide and, more recently, lenalidomide, are effective in various subtypes of cutaneous lupus,[51,52] and lenalidomide has a lower

risk for polyneuropathy than thalidomide; however, they should both be reserved for patients that have failed multiple previous agents, and with the utmost caution in women of reproductive age. This recommendation was agreed on by 96.3%, mean LoA (SD) was 9.35 (1.06).

6. In active neuropsychiatric disease attributed to SLE, glucocorticoids and immunosuppressive agents for inflammatory manifestations (1b/A) and antiplatelet agents/anticoagulants for atherothrombotic/aPL-related manifestations (2b/C) should be considered.

This recommendation has remained unchanged, since no new data have emerged during the last five years that would deem a modification of the recommendation appropriate. [53] Approach to a patient with possible neuropsychiatric SLE should follow the general principles as in the general population and symptomatic treatment as per individual manifestation should be considered. Attribution of a neuropsychiatric manifestation to SLE and published attribution models may be used in doubtful cases.[54,55] For severe inflammatory manifestations (e.g. myelopathy, acute confusional state), potent immunosuppressive agents, like CYC or RTX [56] should be preferred. For the approved biologic drugs anifrolumab and belimumab, there is a paucity of evidence regarding their efficacy in neuropsychiatric manifestations, because patients with active, severe forms of such manifestations were excluded from the RCTs of both drugs, and underrepresented in real-life use of belimumab. Anticoagulant treatment is mainly indicated in cases of cerebrovascular disease, such as ischemic stroke associated with antiphospholipid antibodies (aPL), because its value in other manifestations is not clear. Agreement on this recommendation was 96.3% and mean (SD) LoA was 9.68 (0.81).

7. For acute treatment of severe autoimmune thrombocytopenia, high-dose glucocorticoids (including pulses of intravenous methylprednisolone) (4/C), with or without intravenous immunoglobulin G (4/C), and/or rituximab (2b/B), and/or high-dose intravenous cyclophosphamide (4/C), followed by maintenance therapy with rituximab (2b/B), azathioprine (2b/C), mycophenolate (2b/C), or cyclosporine (4/C), should be considered.

Similar to neuropsychiatric SLE, treatment of autoimmune thrombocytopenia in SLE also did not witness major developments since 2019, thus the current recommendation reflects the principles outlined in the previous update. A platelet number of 20-30,000/mm^3 is typically used as the cut-off, below which therapy is indicated. Therapy includes: i) acute phase treatment with GC (including pulses of intravenous methylprednisolone, followed by 0.5-0.7 mg/kg/day prednisone equivalent with tapering) with or without intravenous immunoglobulin (IVIG); RTX may also be used early in this setting,[57] based also on the drug's documented efficacy in idiopathic immune thrombocytopenia, ii) early use of immunosuppressive medications as GC-sparing agents; a small retrospective study showed that SLE patients with immune cytopenias who relapsed had less often received concomitant immunosuppressive agents following treatment of the initial episode.[58] More importantly, mycophenolate was shown to reduce relapse when used as first-line in a RCT in patients with immune thrombocytopenia.[59] While a similar RCT has not

been performed in SLE, this study provided proof-of-concept for the first-line use of immunosuppressive medications in immune thrombocytopenia, a practice commonly followed by most rheumatologists in real-life practice. Regarding choice of drug for maintenance therapy, there is no hierarchy between the recommended drugs, and this is left to the treating physician's discretion. In cases refractory to these drugs, thrombopoietin receptor (TPO) agonists and splenectomy are options; although the two modalities have not been formally compared in SLE and data mainly come from observational studies,[60] it seems reasonable to use TPO agonists prior to splenectomy, given the possible complications and long-term sequelae of the latter. In addition, it should be considered that TPO agonists have been associated with a higher risk of thromboembolic events, therefore their use should be avoided in aPL positive patients.[61] Fostamatinib, a spleen tyrosine kinase inhibitor, is approved for the treatment of chronic immune thrombocytopenia, but has not been tested in SLE. Similar treatment options (excluding TPO agonists) pertain to SLE autoimmune haemolytic anaemia.

This recommendation received 92.6% agreement and mean (SD) LoA was 9.48 (0.86).

8. Patients with active proliferative lupus nephritis should receive low-dose (EuroLupus) intravenous cyclophosphamide (1a/A) or mycophenolate (1a/A) and glucocorticoids (pulses of intravenous methylprednisolone followed by lower oral doses); combination therapy with belimumab (either with cyclophosphamide or mycophenolate (1b/A)) or calcineurin inhibitors (especially voclosporin or tacrolimus, combined with mycophenolate, 1b/A) should be considered.

The recommendation regarding treatment of active LN received the highest attention in light of the recent approvals of belimumab and voclosporin. Discussions revolved mainly around the position of these drugs in the therapeutic algorithm of LN, i.e., whether they should be used upfront in an early combination therapy with standard-of-care (SoC, low-dose CYC [62] or mycophenolate in combination with GC, see **Supplementary Table 1** for usual drug doses in SLE), or whether they should be reserved for non-responding or relapsing disease. In this regard, deliberations towards the formulation of this recommendation focused on the following facts: i) LN is by default severe disease, accompanied by increased morbidity and mortality, and leading to gradual nephron loss and chronic kidney disease (CKD),[63] ii) rates of complete response at 1-2 years with SoC therapy (i.e., control arms) in recent clinical trials (including the phase 3 BLISS-LN and AURORA trials of belimumab and voclosporin, respectively)[64,65] are consistently low, in the range of 20-30%, and iii) both belimumab and voclosporin based on their RCTs have been approved for *all patients with active LN*, meaning that all patients can potentially receive them, including as first-line. Of note, in a *post-hoc* analysis of the BLISS-LN, belimumab in combination with SoC was found to reduce the risk for flares by 55% compared to SoC alone, and preserve glomerular filtration rate (GFR) better than SoC.[66,67] To this end, the possibility for a universal recommendation of early combination therapy aiming to increase renal response rates was intensively discussed among panellists. Counterarguments included the high cost of these therapies and the potential of overtreating some patients who would otherwise respond to treatment

with mycophenolate or low-dose IV CYC alone and respective cost or risk considerations, particularly relevant for long-term use of a CNI. Indeed, some patients with LN present with clinically and histologically milder disease, while others with risk factors for progression to end-stage kidney disease; at present it is unclear which patients will benefit more from early combination therapies. Of note, recent real-life studies have reported higher response rates with SoC, compared to rates reported in RCTs.[68,69] Based on all the above, it was proposed that early combination therapy "*should be considered*" in all adult patients with active LN, emphasizing the fact that treating physicians have the option to decide if and when combination therapy should be used. In the case of CNIs, combination refers to voclosporin, as well as tacrolimus (TAC), since the current SLR confirmed the superiority of TAC + mycophenolate over SoC (mainly high-dose CYC), although based on evidence exclusively from Asian populations.[70]

Additional points regarding the recommendation for LN warrant further clarification: first, no distinction between LN histological classes is made in the recommendation. It should be noted that neither belimumab nor voclosporin induced higher renal response rates versus placebo in a *post-hoc* RCT analysis of the small subgroup of patients with class V LN.[66,71] Nevertheless, patients with pure class V were underrepresented in these trials (less than 20%), and also there were fewer flares with belimumab in the pure V subgroup. Collectively, the Task Force opined that more data are needed to decide on the optimal treatment of class V LN; to provide a succinct message, it was elected that the statement considers patients with *any* class of LN that needs treatment. Of note, the recommended proteinuria cut-off for immunosuppressive treatment in class V LN remains 1 g/day, as per the 2019 EULAR/ERA-EDTA recommendations.[72] Second, the secondary analysis of the BLISS-LN trial found that belimumab was more efficacious in patients with baseline proteinuria below 3 gr/day.[66] Third, voclosporin provided a rapid reduction in proteinuria, which may be preferable in patients with a high baseline urine protein in the nephrotic range.[65] Fourth, in AURORA-1, patients with baseline GFR < 45 ml/min were excluded, thus the safety of voclosporin in patients with a low baseline GFR (30-45 ml/min) is as yet unclear. The final decision for the treatment of active LN should depend on the individual patient characteristics as outlined above (histologic class, baseline GFR, proteinuria), presence of extra-renal manifestations, comorbidities, risk for toxicity, access to drugs and cost issues, and patient preferences. If a combination therapy is not opted for in treatment-naïve LN patients, add-on treatment with belimumab or voclosporin should be considered in patients with inadequate response by three to six months, or those who flare. In these cases, physicians should consider to acquire expert consultation.

Regarding dosing of GC, pulses of IV MP (e.g 250-1000 mg for 1-3 days) are recommended as part of the initial (or "remission induction") regimen unless there are major safety concerns (e.g., infection). For oral therapy, large controlled trials comparing different GC regimens have not been performed in LN. The 2019 EULAR/ERA-EDTA recommendations endorsed a lower dose GC regimen for initial therapy compared to traditional practices (starting dose 0.3-0.5 mg/kg/day and 20 mg/day for proliferative classes and class V, respectively), though acknowledging that this was not based on high-quality data.[73] In the current version of recommendations, the principle for lower cumulative GC exposure was maintained.

Importantly, belimumab demonstrated superior GC-sparing potential than SoC in the BLISS-LN study, while the AURORA study of voclosporin used significantly lower GC doses than earlier studies (20–25 mg/d starting oral prednisone rapidly tapered to 5 mg by 12 weeks), lending further support to their use in LN. A recommended GC initial dose and tapering strategy is shown in Supplementary Table 1. The overall agreement for this recommendation was 92.8%, with a mean (SD) LoA of 9.36 (1.06).

Thrombotic microangiopathy (TMA) may be evident in up to 20% of LN biopsies, particularly in the presence of aPL, and is associated with an adverse impact on prognosis. Although not mentioned in the statement, treatment options in TMA-LN were discussed, even though high-quality data are lacking. In addition to anticoagulation therapy,[74] there is emerging evidence for the use of eculizumab, a monoclonal antibody against complement protein C5 which is efficacious in cases of complement-mediated TMA, for patients with LN and histologic evidence of TMA.[75]

9. Following renal response, treatment of lupus nephritis should continue for at least three years (2b/B); patients initially treated with mycophenolate alone or in combination with belimumab or a CNI should remain on these drugs (1a/A), whereas mycophenolate or azathioprine should replace cyclophosphamide for those initially treated with cyclophosphamide alone (1a/A) or in combination with belimumab (1a/A).

Following the choice of initial treatment, renal response should be monitored according to the 2019 EULAR/ERA-EDTA targets (reduction in proteinuria ≥25% and 50% at 3 and 6 months, respectively, and below 500-700 mg/day at 12 months, all with GFR within 10% from baseline). These therapeutic goals have now been validated.[76] Provided that response is achieved, subsequent (or "maintenance") therapy should depend on the initial regimen. If the initial regimen included mycophenolate (either monotherapy or in combination with belimumab or voclosporin), then the same regimen should continue for at least 3 years; on the other hand, if low-dose CYC had been initially used, alone or in combination with belimumab, it should be replaced by mycophenolate or AZA while belimumab should be continued (if used initially).

Duration of immunosuppressive therapy was also intensively discussed. Immunosuppressive treatment in LN, particularly in proliferative classes, should continue for at least 3 years.[77] Of note, in case of initial therapy with mycophenolate/CNI combination, there is a concern regarding the duration of therapy, as long-term use of "legacy" CNIs (tacrolimus, cyclosporine A) has been associated with nephrotoxicity and GFR decline. Several Asian RCTs have investigated CNI combination therapy as remission induction, but not as a long-term maintenance therapy.[78,79] In this regard, it is reassuring that the long-term AURORA-2 study extending to 3 years use of voclosporin/mycophenolate combination recently reported stable levels of GFR throughout the 3-year period.[80] This recommendation was agreed on by 96.4% of participants and mean (SD) LoA was 9.56 (0.81).

10. In patients at high-risk for kidney failure (defined as reduced glomerular filtration rate, histological presence of cellular crescents or fibrinoid necrosis, or severe interstitial inflammation), high-dose (NIH regimen) intravenous cyclophosphamide (1a/A) in combination with pulse intravenous methylprednisolone, can be considered.

A subset of patients with LN present with baseline clinical and histologic characteristics associated with an adverse long-term prognosis. Such patients can still be treated as in recommendation nr. 9, but it should be noted that patients with such characteristics are underrepresented or excluded in all recent trials in LN, (eg. the BLISS-LN and AURORA-1 excluded patients with GFR < 30 and ≤ 45 ml/min/1.73 m^2, respectively). Thus, the relative efficacy of these regimens in patients at high risk for kidney failure is currently unclear. A small (32 patients) *post hoc* analysis of the Aspreva Lupus Management Study (ALMS) found similar response rates (proteinuria and serum creatinine) between mycophenolate and high-dose IV CYC).[81] Thus, for patients presenting with impaired kidney function or histologic evidence of crescentic glomerulonephritis and/or severe interstitial inflammation, the traditional high-dose IV CYC regimen (0.5–0.75 g/m^2 monthly for 6 months) can also be considered, since it is the most extensively studied therapeutic regimen in severe LN, in the early studies from the National Institutes of Health. Importantly, this recommendation received 100% agreement among Task Force members, and a mean (SD) LoA of 9.57 (0.86)

Figures 1 and 2 outline the existing treatment options for the management of extrarenal SLE and LN, respectively.

11. In SLE patients achieving sustained remission, gradual tapering of treatment should be considered, with withdrawal of glucocorticoids first (2a/B).

The possibility of tapering immunosuppressive treatment in SLE patients with quiescent disease was a specific research question for the SLR, and concerned GC, immunosuppressive drugs (conventional and biologic), and finally, HCQ (in this sequence). Regarding GC, a meta-analysis calculated a 24% pooled incidence of SLE flares following GC discontinuation, but relative risk for major flares was not increased compared to patients who continued GC.[82] In the investigator-initiated CORTICOLUP study, discontinuation of prednisone in patients who had clinically quiescent disease for more than 1 year and received stable 5 mg/day proved inferior to continuation of the same dose, in terms of risk of disease flares.[83] Caveats of this study were discussed between Task Force members, mainly the abrupt discontinuation of prednisone and the fact that biologic agents like belimumab were not received by any patient. It was decided that these limitations, together with observational studies that have shown no increased risk of flares with gradual tapering of GC to complete withdrawal [84,85] and the detrimental effects of long-term GC use, allow for a recommendation that gradual GC tapering to discontinuation should be attempted in SLE, in line with current recommendation 2.

Regarding immunosuppressive agents, a second investigator-initiated RCT (WIN-Lupus) tested whether withdrawal of mycophenolate or AZA after 2-3 years of therapy in LN would be non-inferior to

continuation for the occurrence of renal relapses. The study failed to show non-inferiority, as patients in the discontinuation group had more relapses of LN and more extrarenal flares.[77] On the contrary, similar to GC, uncontrolled observational studies have reported successful withdrawal of immunosuppressive therapy in LN. Of note, the total duration of therapy, as well as of remission prior to discontinuation of immunosuppressive drugs is particularly important in the LN setting;[86,87] patients should have received at least 3 to 5 years of therapy and be in remission for at least 2 years before withdrawal can be attempted. Prior to withdrawal, tapering should be undertaken very gradually. A repeat kidney biopsy-guided decision for therapy withdrawal in patients in clinical remission, in order to assess for residual histologic activity predictive of a subsequent flare, is supported by recent observational studies and could be considered, although this has not been formally tested in a RCT.[88,89]

Contrary to GC and immunosuppressive drugs, HCQ should not be discontinued in SLE patients in the absence of unacceptable side-effects; in addition to its multiple benefits including survival,[90] the SLR concluded that HCQ discontinuation is associated with increased risk for flares (data from observational studies).[91–93] Additionally, HCQ therapy is a protective factor against disease relapse in patients discontinuing GC or immunosuppressive agents.[86,94] Although complete discontinuation is discouraged (with the exception of adverse effects), data on tapering/dose reduction are equivocal,[91,92] thus a decision for HCQ dose reduction in patients in remission should be taken on an individualised basis.

Importantly, the statement on tapering treatment in quiescent SLE received the highest level of agreement between members, 100%, and mean (SD) LoA 9.89 (0.38).

12. SLE associated with thrombotic antiphospholipid syndrome (APS) should be managed with long-term vitamin K antagonists after the first arterial or unprovoked venous thrombotic event (1b/B); low dose aspirin (75-100 mg/day) should be considered in SLE/non-APS patients with high-risk aPL profile (2a/B).

SLE patients with concomitant antiphospholipid syndrome (APS) represent a challenging endotype of the lupus spectrum. To this end, although EULAR has published specific recommendations for the management of APS in 2019,[95] it was decided that the significance of SLE-APS merits a specific question for the SLR. Management of definite SLE-aPL/APS should follow the same principles of therapy as primary APS, including the long-term use of vitamin K antagonists in patients with unprovoked venous and those with arterial thrombotic events.[95] After the first RCT on novel direct oral anticoagulants (DOACs) in APS (TRAPS trial), based on which the 2019 EULAR recommendations for the management of APS recommended against their use in patients with triple aPL positivity or prior arterial thrombosis, three additional RCTs compared vitamin K antagonists versus DOACs in patients with thrombotic APS.[95] A recent meta-analysis of these trials showed that DOAC use was associated with increased risk of subsequent arterial thrombotic events (OR: 5.43), especially stroke (OR: 10.74), and the composite of arterial or venous thrombotic events (OR: 4.46).[96] In patients who have not

experienced a thrombotic event, primary prophylaxis with low-dose aspirin should be considered in those with a high risk aPL profile, defined as lupus anticoagulant positivity, or double (any combination of lupus anticoagulant, anticardiolipin antibodies or anti-beta2glycoprotein I antibodies) or triple aPL (all three aPL). Apart from its other beneficial effects, HCQ has also potential antithrombotic effects and may reduce aPL levels,[97] and is particularly recommended in patients with SLE-aPL or SLE/APS.[98,99]
Catastrophic APS (CAPS) is a rare complication of APS, with concomitant or successive thrombosis in ≥ 3 organs. Although a detailed overview of the therapeutic options for CAPS was outside the scope of the SLR, several Task Force members deemed it important to cover this issue in the manuscript text. High-quality studies for the treatment of CAPS in SLE are lacking. Precipitating conditions (e.g infections) should be aggressively sought for and treated, to minimize the risk for the development of CAPS. Triple therapy with full anticoagulation, high-dose glucocorticoids and plasma exchange and/or IVIG is recommended for patients with CAPS; more recently, the complement inhibitor eculizumab has shown promise, especially in CAPS patients with features of complement-mediated TMA (microangiopathic hemolytic anemia, thrombocytopenia, acute kidney injury). The 2019 EULAR recommendations for the management of APS stated that complement inhibitors or rituximab may be considered in refractory CAPS. [100] Agreement for this recommendation was 96.4% and mean (SD) LoA was 9.57 (0.83).

13. Immunizations for the prevention of infections (HZV, HPV, influenza, COVID-19 and pneumococcus), management of bone health, renoprotection and cardiovascular risk, and screening for malignancies, should be performed (5/D).

The final recommendation is a statement regarding major comorbidities in SLE, reflecting expert opinion based on the evidence for the general benefit of the mentioned measures. As on APS, EULAR has issued specific recommendations regarding vaccinations[101] and cardiovascular risk management[102] in patients with autoimmune rheumatic diseases, including SLE, and the reader is referred to the respective manuscripts for further details. In view of the COVID pandemic and the burden of herpes zoster in lupus patients,[103] the current SLR included a research question regarding the efficacy and safety of vaccines against SARS-CoV2 and HZV in lupus. Both the live attenuated and the more efficacious recombinant zoster vaccine have been used in patients with SLE and, although studies are limited, they are considered safe.[104,105] Similarly, several observational studies have proven the immunogenicity and safety of SARS-CoV2 vaccines, which are recommended for SLE patients.[106] Prompt identification and management of infections/sepsis is essential in SLE, and vigilant monitoring for opportunistic infections is warranted in selected patients receiving potent immunosuppressive drugs (e.g high-dose GC, CYC, RTX).[107] In patients with LN, adjunct treatment with nephroprotective agents is of utmost importance to decelerate nephron loss, in combination with immunosuppressive therapy. Renin-angiotensin-aldosterone blockade is required, unless not tolerated, to control hypertension (target level below 130/80 mm Hg).[108] More recently, novel classes of agents, mainly sodium glucose transport 2 (SGLT-2) inhibitors (“flozins”) have gained attention as kidney protective drugs for any case of chronic kidney

disease; SGLT-2 is expressed in kidney biopsies of patients with LN,[109] and its targeting seems reasonable. A preliminary study of dapagliflozin in a small number of SLE patients (18 with LN) found no difference in proteinuria following therapy.[110] Until more data are available, SGLT-2 inhibitors may be considered in LN patients with reduced GFR below 60 -90 ml/min or proteinuria more than 0.5-1 g/day, on top of ACE/ARBi during the maintenance phase.

The final recommendation received 92.8% agreement and mean (SD) LoA was 9.85 (0.36).

Discussion

For these recommendations, we assembled a Task Force of world-leading experts in the field of SLE from four continents, to assure the widest possible representation and broad expertise. This is particularly important, because SLE across the world is very different in terms of presentation and severity. To this end, the current set of recommendations sought to ensure a fair balance and guarantee equal representation of mild, moderate, and severe disease, the relative frequency of which may well vary between different countries and continents.

A major modification to the previous sets of EULAR recommendations for SLE was the reduction of the number of individual recommendations. Indeed, to align with the EULAR SOPs, but also streamline and simplify the recommendations and facilitate their dissemination, the Task Force managed to condense the recommendations to 13 (with 5 overarching principles). Similar to the 2019 version, the first recommendations (1-4) refer to optimal use of commonly used drugs, recommendations 5-12 deal with specific organ manifestations, and the final recommendation covers the issue of adjunct treatments and comorbidities.

Regarding the use of individual drugs, the emphasis on a more restricted use of GC evolved further from the 2019 recommendations. Thus, GC should be used only if needed, as for mild forms of SLE HCQ alone may suffice. A maximum recommended maintenance dose of 5 mg/day prednisone equivalent is now recommended, stricter than the 7.5 mg/day in the previous recommendations. Of note, this change did not come in view of new high-quality data or RCTs, although we found observational studies linking mean prednisone doses 5 mg/day with adverse sequelae. Nevertheless, there was unanimous agreement among Task Force members that a strong recommendation for a lower dose of GC should be given in view of the detrimental effects of their long-term use and the approval of new agents with GC-sparing effects.

To avoid long-term exposure to GC, early use of immunosuppressive drugs is recommended in SLE. The sequence between conventional and biologic drugs was a matter of extensive debate within the Task Force. Nevertheless, in 2019 it was already stated that add-on treatment with belimumab (then the only approved biologic) “should be considered in patients not responding to combinations of HCQ and GC with or without immunosuppressive agents”. Thus, it was agreed that placing biologic drugs (now, belimumab and anifrolumab) after failure of conventional drugs would constitute a step backwards from 2019. To this end, the current recommendations do not require prior failure to one or more conventional

drugs before initiating a biologic agent, although for the majority cases it may be prudent to try at least one conventional immunosuppressive.

Since 2019, anifrolumab was approved for the treatment of extrarenal SLE in 2021. On the other hand, there is now more than 10 years real-life experience with belimumab, with results confirming good control of disease activity, reduction of flares and halting of damage accrual.[111,112] The two drugs have a different mechanism of action and have not been directly compared. Two indirect treatment comparison studies (each supported by each one of the manufacturing companies and using a different patient database) reported conflicting results at very low levels of evidence and high risk of bias and, therefore, cannot be interpreted as comparative efficacy studies.[113,114] Thus, with current evidence, the two drugs are recommended with no hierarchy between them. Of note, both drugs seem to have better efficacy in serologically active patients at baseline, although this should not limit their use to this subset of patients.[115,116]

Undoubtedly, the most expected outcome of the current update was the verdict regarding the positioning of belimumab and voclosporin in the treatment of LN. The rationale behind the phrasing that early combination therapy with either belimumab or a CNI "should be considered" reflects the fact that world-wide treatment recommendations for SLE should take into account different patient characteristics, but also variable access to drugs in high- versus low-income countries. If an early combination therapy is chosen, specific patient characteristics may favour belimumab over a CNI or vice versa, for instance, presence of extrarenal disease activity for belimumab, or nephrotic-range proteinuria for CNI. Importantly, an update of dedicated EULAR recommendations for the management of LN is currently being scheduled.

Patients with SLE experience a wide variety of symptoms, which extend beyond the classical manifestations that require immunosuppressive therapy. Indeed, symptoms such as fatigue, non-inflammatory pain, mood disturbance and cognitive dysfunction are among the ones most frequently referred and valued by patients. A recently proposed system categorized symptoms of SLE in two types, the typical inflammatory symptoms ("type 1") requiring immunosuppression, and symptoms such as those mentioned above ("type 2"), which do not respond to immunosuppressive therapy, yet often dominate patient-reported outcomes.[117] We acknowledge that the current recommendations mainly address classic inflammatory SLE manifestations, in part because the Task Force felt that the data on type 2 symptoms are not so robust to justify specific management recommendations. Nevertheless, a holistic care of patients with SLE should value and address all symptoms mentioned by patients, both those requiring immunosuppressive therapy, as well as those in need of complimentary approaches.[118]

A crucial point pertaining to any set of management recommendations is their implementation in real-life clinical practice, often not self-explanatory because recommendations by definition cannot capture all aspects of everyday clinical practice. To tackle this need, the EULAR SOPs suggest the definition of quality indicators in tabular form, at least for the most relevant recommendations, to serve as a checklist for treating physicians and facilitate rate of adherence after a reasonable period of time, Importantly,

following the issue of the 2019 EULAR recommendations for the management of SLE, such a set of quality indicators was published,[119] and subsequently tested independently in relation to quality of life of patients.[120] A similar initiative for the current recommendations would be valuable for their wider dissemination and implementation.

In conclusion, the 2023 recommendations for the management of SLE provide current state-of-the-art guidance for treating physicians around the world. Further issues for the future research agenda in SLE are shown in **Table 2**. This updated version will inform rheumatologists and nephrologists, health professionals, patients, regulators, payers and other stakeholders on the way modern treatment of SLE is perceived from experts in the field spanning four continents. It is the hope of this Task Force that the developments in the treatment of SLE will continue at such pace to mandate a new update of the EULAR recommendations within the next 3 years.

Table 2. Future research agenda in SLE

Existing therapies • Utility of measurement of drug blood levels (HCQ, MMF etc) • Randomized trials testing different initial glucocorticoid doses and different tapering regimens • Optimal duration of therapy and timing of immunosuppression discontinuation (both for renal and extrarenal disease) • Value of repeat kidney biopsy prior to immunosuppression discontinuation • Value of per-protocol repeat kidney biopsy after one year of treatment to guide further treatment • Prediction of flare in patients who taper drugs • Prediction of flare in patients who attain the treatment target • Use of statins, low-dose ASA and other conventional therapies to prevent cardiovascular disease
Pathophysiology and Biomarkers • Pre-SLE cohort initiatives delineating who is at risk to develop SLE and what are the sequential "hits" that lead to disease development (pre-SLE cohort initiatives) • Involvement of particular organ systems over others, multisystem versus organ-dominant disease • Prediction of response to specific therapies (by clinical, cellular and/or molecular markers) • Biomarkers for response to different biologic drugs (pharmacogenetics, transcriptomics etc)

Clinical trial design and new drug development

- Optimization of clinical trial design and study endpoints to maximize probability of new drug approval in SLE
- Handling of background medication to avoid polypharmacy and "dilution" of positive effects of drugs under study
- Inclusion of organ-specific endpoints and better disease activity measures
- Increase in number of adequately trained trial sites (recruitment, infrastructure and training)
- Academia versus industry-driven clinical trials
- Better and more sensitive measurements of disease activity
- Evaluation and standardization of patient-reported measures of disease activity/outcomes

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Figure legends

Figure 1. Treatment of non-renal systemic lupus erythematosus

Top-to bottom sequence does not imply order of preference (e.g. MTX, AZA and MMF are equal options for 2nd line therapy in mild disease or 1st line therapy in moderate disease).

*Mild disease: Constitutional symptoms; mild arthritis; rash ≤9% BSA; platelet count (PLTs) 50-100 x 10^9/L; SLEDAI≤6; BILAG C or ≤1 BILAG B manifestation

*Moderate disease: Moderate-severe arthritis (”RA-like”; rash 9-18% BSA; PLTs 20-50 x10^9/L; serositis; SLEDAI 7-12; ≥2 BILAG B manifestations

*Severe disease: Major organ threatening disease (cerebritis, myelitis, pneumonitis, mesenteric vasculitis); thrombocytopenia with platelets <20x10^9/L; TTP-like disease or acute hemophagocytic syndrome; rash > 18% BSA SLEDAI>12; ≥1 BILAG A manifestations

†Recommendation of belimumab and anifrolumab as first-line therapy in severe disease refers to cases of extrarenal SLE with non-major organ involvement, but extensive disease from skin, joints etc. The use of anifrolumab as add-on therapy in severe disease refers mainly to severe skin disease. For patients with severe neuropsychiatric disease, anifrolumab and belimumab are not recommended.

VKA: Vitamin K antagonists; aPL: Antiphospholipid antbodies; APS: Antiphospholipid syndrome; HCQ: Hydroxychloroquine; GC: Glucocortocoids; PO: Per os; IV: Intravenous; MTX: Methotrexate; AZA: Azathioprine; BEL: Belimumab; ANI: Anifrolumab; CNI: Calcineurin inhibitor; MMF: Mycophenolate mofetil; CYC: Cyclophosphamide; RTX: Rituximab; SLEDAI: SLE Disease Activity Index

Figure 2. Treatment of lupus nephritis

Top-to bottom sequence does not imply order of preference (similar to Figure 1).

In addition to general protective measures, as outlined in Figure 1

§ BEL should always be given in combination with MMF or low-dose CYC as initial therapy, and with MMF or AZA as maintenance therapy

^ CNIs should be given in combination with MMF

* Particularly recommended in the presence of poor prognostic factors: Reduced eGFR, histological presence of cellular crescents or fibrinoid necrosis, or severe interstitial inflammation

¶ Extension of high-dose CYC to subsequent phase refers to severe LN Cases, in which bimonthly or quarterly CYC pulses may be given following 6 monthly pulses

† In relapsing/refractory disease, especially after failure to CYC-based regimens

ACEi: Angiotensin-converting enzyme inhibitors; ARB: Angiotensin receptor blockers; SGLT2i: Sodium glucose transporter 2 inhibitors; eGFR: Estimated glomerular filtration rate; VKA: Vitamin K antagonists; APS: Antiphospholipid syndrome; HCQ: Hydroxychloroquine; GC: Glucocortocoids; PO: Per os; IV: Intravenous; MP: Methylprednisolone; MMF: Mycophenolate mofetil; CYC: Cyclophosphamide; AZA: Azathioprine; BEL: Belimumab; CNI: Calcineurin inhibitor; VOC: Voclosporin; TAC: Tacrolimus; RTX: Rituximab; Upr: Urine protein

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