# The Asia-Pacific League of Associations for Rheumatology consensus statements on the management of systemic lupus erythematosus

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**Systemic lupus erythematosus (SLE) is prevalent in Asia and carries a variable prognosis among patients across the Asia-Pacific region, which could relate to access to health care, tolerability of medications, and adherence to therapies. Because many aspects of SLE are unique among patients from this region, the Asia-Pacific League of Associations for Rheumatology developed the first set of consensus recommendations on the management of SLE. A core panel of 13 rheumatologists drafted a set of statements through face-to-face meeting and teleconferences. A literature review was done for each statement to grade the quality of evidence and strength of recommendation. 29 independent specialists and three patients with SLE were then recruited for a modified Delphi process to establish consensus on the statements through an online voting platform. A total of 34 consensus recommendations were developed. Panellists agreed that patients with SLE should be referred to a specialist for the formulation of a treatment plan through shared decision making between patients and physicians. Remission was agreed to be the goal of therapy, but when it cannot be achieved, a low disease activity state should be aimed for. Patients should be screened for renal disease, and hydroxychloroquine is recommended for all Asian people with SLE. Major organ manifestations of SLE should be treated with induction immunosuppression and subsequently maintenance; options include cyclophosphamide, mycophenolate mofetil, azathioprine, and calcineurin inhibitors, in combination with glucocorticoids. Biologics, combination regimens, plasma exchange, and intravenous immunoglobulins should be reserved for cases of refractory or life-threatening disease. Anticoagulation therapy with warfarin is preferred to the direct oral anticoagulants for thromboembolic SLE manifestations associated with a high-risk antiphospholipid antibody profile.**

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## Introduction

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease characterised by periods of exacerbation and remission, with organ damage accrued as a result of disease activity and treatment complications, leading to impaired health-related quality of life and reduced life expectancy. Although the health and economic burden of SLE is substantial, the prevalence of SLE varies considerably worldwide. A population-based study in the USA showed an ethnic disparity in the burden of SLE, with highest prevalence among Black people, followed by Hispanic, Asian, and White people.[1]

The clinical manifestations of SLE in Asian populations are distinct in several ways. Renal disease is present in 40–82% of Asian patients compared with 30% of White patients with SLE[2] and more often leads to renal failure. In White people, the most common neuropsychiatric manifestations attributed to SLE are seizure disorders, cerebrovascular diseases, and an acute confusional state.[3] In contrast, psychosis, headache, and cognitive dysfunction are the most common neuropsychiatric events reported in Asian patients.[4,5]

The prognosis of SLE also varies among ethnic groups. In one US study, 73% of patients with lupus nephritis who developed end stage renal disease were African American or Hispanic American.[6] The poor prognosis of African American patients with lupus nephritis has been associated with the presence of the *APOL-1*G1/2* alleles.[7] Although similar genetic factors have not been reported in Asian patients with SLE, poor tolerance to immunosuppressive therapies has been reported in this group. In the Aspreva Lupus Management Study (ALMS), which compared the efficacy of mycophenolate mofetil with intravenous pulse cyclophosphamide for induction therapy in patients with lupus nephritis, a substantial proportion of Asian patients given mycophenolate mofetil developed serious adverse events.[8] A randomised controlled trial (RCT) of the B cell inhibitor ocrelizumab (anti-CD20), in conjunction with high-dose glucocorticoids and mycophenolate mofetil, in patients with lupus nephritis was prematurely terminated because of serious infections and mortality in Asian patients.[9] In a meta-analysis of 56 treatment trials for lupus nephritis, the rate of serious infections in Asian patients was higher than that in non-Asian patients (4·1–25·0% *vs* 4·4–8·5%), as was the rate of infection-related mortality (0·0–6·7% *vs* 0·0–2·1%).[10] In addition, mycophenolate mofetil was not associated with a lower infection risk than cyclophosphamide in Asian patients. Although pharmacogenetic data are not available, interethnic differences in the tolerability of medications, which affect their efficacy, highlights the importance of individualised therapy.

The worse prognosis of SLE in some Asian countries could be related to access to health care, delayed diagnosis, and poor treatment adherence. Asian patients reported being more concerned with the toxic effects of medicines, especially immunosuppressive drugs, when compared with White patients.[11,12] Despite the availability of

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guidelines from Europe and the USA for SLE management,[13–15] differences in clinical phenotypes, variations in health-care access, cultural background, drug adherence, infection risk, comorbidities, and the effectiveness and tolerance of medications influence therapeutic decisions among Asian patients. Consensus statements on SLE management are thus necessary to serve as a guide to specialists, family physicians, specialty nurses, and other health-care professionals in the Asia-Pacific region.

## Methods and data collection

### Participant selection

An SLE special interest group was established under the Scientific Committee of the Asia-Pacific League of Associations for Rheumatology (APLAR). The members, who are key opinion leaders in the region, were nominated by APLAR membership societies. A steering committee, consisting of four special interest group members (Chi Chiu Mok, Eric Morand, Sandra Navarra, and Yoshiya Tanaka), was established to formulate a set of consensus-statements for SLE management in the Asia-Pacific region. The steering committee, together with nine other members (the authors of this work), drafted the statements, which were categorised into overarching principles, general management, and specific treatment strategies for SLE.

At least two specialists (who were rheumatologists or nephrologists) from each APLAR region, who were not involved in drafting the statements but are actively involved in SLE care and research, were invited for a modified Delphi process. Three patients with SLE who were proficient in English, knowledgeable in the disease, and actively involved in SLE self-help groups and research were also involved. The purpose of the Delphi process and the consensus statements were fully explained to the patients by email communications, and they had support from core group members for clarification of the information from the literature.

### Consensus formation

A total of 35 statements were proposed by the core group after a face-to-face meeting in 2019, one teleconference, and email communications. These statements were selected on the basis of clinical practice, literature review, and suggestions from external non-APLAR experts.

All members involved in the Delphi process were provided with a reference list, evidence grading, and strength of recommendation for the statements, and were asked to indicate anonymously the amount of agreement via use of an online platform (SurveyMonkey). The responses were given arbitrary scores of 10·0 for "strongly agree", 7·5 for "agree", 5·0 for "neutral", 2·5 for "disagree", and 0·0 for "strongly disagree". Delphi members were also invited to give feedback on the statements, indicate any reasons for disagreement, and suggest modifications. Agreement ("strongly agree" or "agree") by at least 80% of the members was regarded as representing consensus.

Results of the voting and blinded qualitative feedback from members during each Delphi round were summarised and presented by the facilitator (Roy Lau, the medical writer) for evaluation by the core group. Voting results, group opinions, and modified statements were distributed to the Delphi members for the subsequent rounds of voting until consensus was reached for all statements (figure 1).

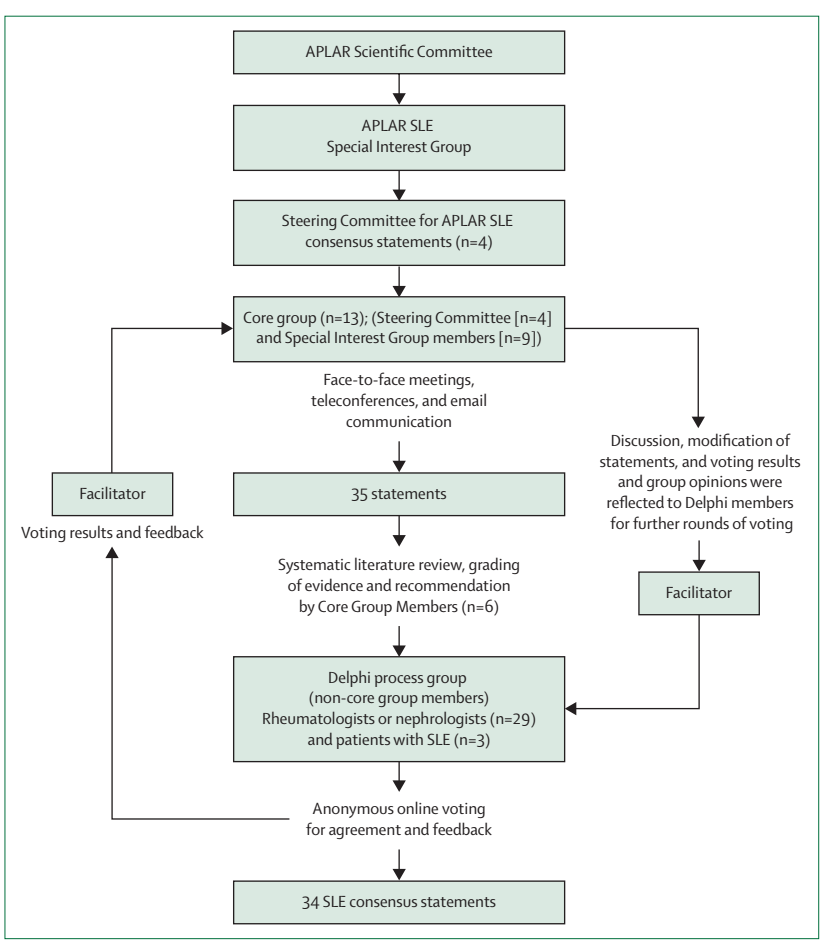


***Figure 1:*** **Flowchart of Delphi process**
APLAR=Asia-Pacific League of Associations for Rheumatology. SLE=systemic lupus erythematosus.

## Findings

Between June 29 and July 13, 2020, 29 independent specialists (25 rheumatologists, four nephrologists) and three patients with SLE participated in the Delphi process. In the first Delphi round, 30 of 35 proposed statements reached a consensus. The anonymous feedback on the five disagreed statements was evaluated by the core group members. One statement was removed for the low possibility of agreement on the basis of a re-evaluation of the evidence; the other four statements were modified and returned to the Delphi members for the second round of voting, after which a consensus

was obtained. The results of each round of voting and the major discussions during the Delphi rounds are shown in the appendix (pp 2–5). Table 1 shows the 34 consensus statements, and figure 2 summarises the resulting management algorithm for patients with SLE. Table 2 highlights the management strategies for Asian patients with SLE compared with the European recommendations.[14,15]

See Online for appendix

| | Strength of recommendations | Quality of evidence | Agreement (%) |
|---|---|---|---|
| **Overarching principles** | | | |
| (1) SLE should be managed by a multi-disciplinary team of lupus specialists, nurses and other health care professionals. A shared decision between physician and patient should be obtained for a management plan. | NA | NA | 100% |
| (2) Treatment of SLE should be individualised based on clinical manifestation, disease severity, comorbidities and capability to adhere to therapeutic plan. | NA | NA | 100% |
| (3) Early diagnosis of SLE and timely referral to a lupus specialist significantly improves outcomes. | NA | NA | 100% |
| (4) The overall goals of SLE treatment are to reduce organ damage, ensure long-term survival and improve health-related quality of life. | NA | NA | 100% |
| **General treatment strategy for SLE: assessment and therapeutic strategies** | | | |
| (5) SLE should be classified by validated criteria. Disease activity should be assessed by validated disease activity indices especially for research and administrative purposes. | A | B | 94% |
| (6) Treatment of SLE should aim at disease remission. When remission cannot be achieved, the lowest possible disease activity state should be targeted. | A | B | 100% |
| (7) Routine use of hydroxychloroquine in all SLE patients is recommended unless contraindicated. The maintenance dose of hydroxychloroquine should not exceed 5 mg/kg per day of actual bodyweight. | A | B | 88% |
| (8) Cardiovascular* and bone health† should be periodically assessed and optimised by pharmacological or non-pharmacological means. | A | B | 91% |
| (9) Given the adverse effects of therapies, immunosuppressive treatment should not be given or modified for serological activity alone. | A | C | 88% |
| **General treatment strategy for SLE: prevention of infective complications** | | | |
| (10) Screening and treatment for active hepatitis B and C virus infection (HBsAg, anti-hepatitis C virus) recommended before immunosuppressive therapies. Occult hepatitis B screening (IgG antibody to hepatitis B core antigen and hepatitis B virus-DNA), and pre-emptive treatment should be considered for patients undergoing B cell depleting therapy or intensive immunosuppression. | A | C | 88% |
| (11) Active tuberculosis should be excluded before immunosuppression. Screening and treatment of latent tuberculosis is not routinely recommended. | A | C | 81% |
| (12) Prophylaxis against pneumocystis pneumonia during immunosuppression may be considered in high-risk patients. | B | C | 88% |
| (13) Compliance with preventive and control measures (eg, physical distancing, personal hygiene, and protective facemask) according to national guidelines is recommended during viral epidemics, including COVID-19. Immunosuppressive medications should not be discontinued unless in an active infection where an individualised decision will be made after discussion with the infectious disease specialists. | A | D | 100% |
| (14) Vaccination for seasonal influenza, pneumococcus, human papilloma virus, and herpes zoster is recommended during disease quiescence with minimal immunosuppression. | B | B | 88% |
| **Management of major organ manifestations of SLE: lupus nephritis** | | | |
| (15) A renal biopsy should be obtained, unless contraindicated, before immunosuppressive therapy for active lupus nephritis. | A | B | 84% |
| (16) Mycophenolate mofetil or intravenous pulse cyclophosphamide (standard dose), in combination with moderate-dose glucocorticoids, are recommended as induction regimens for active lupus nephritis (International Society of Neurology and the Renal Pathology Society Classification 3, 4, and 5). | A | A | 91% |
| (17) Lower dose intravenous cyclophosphamide or tacrolimus, in combination with moderate-dose glucocorticoids, are second-line induction regimens. | B | C | 90% |
| (18) The dose of mycophenolate mofetil should be adjusted for bodyweight. An initial dose of 2 g per day is usually targeted in Asian patients. | B | C | 84% |
| (19) Mycophenolate mofetil/tacrolimus combination or rituximab may be considered for active lupus nephritis with suboptimal response to standard regimens. | B | B | 97% |
| (20) Mycophenolate mofetil or azathioprine may be considered as a maintenance immunosuppressive agent. Mycophenolate mofetil is preferred if it has been used for induction therapy. Low-dose calcineuin inhibitors are alternatives when mycophenolate mofetil and azathioprine are contraindicated or not tolerated. | A | B | 91% |
| (21) Maintenance therapies for lupus nephritis should continue for at least 5 years, with the aim to prevent renal flares. | B | C | 81% |

(Table 1 continues on next page)

| | Strength of recommendations | Quality of evidence | Agreement (%) |
|---|---|---|---|
| (Continued from previous page) | | | |
| **Management of major organ manifestations of SLE: neuropsychiatric SLE and antiphospholipid syndrome** | | | |
| (22) A combination of moderate or high-dose glucocortocoids (including pulse methylprednisolone) and cyclophosphamide is the first-line treatment for serious neuropsychiatric SLE manifestations that are inflammatory in origin; including, but not exhaustively, psychosis, an acute confusional state, myelitis, cranial and peripheral neuropathies, and aseptic meningitis. | A | B | 97% |
| (23) Rituximab may be considered in refractory neuropsychiatric SLE manifestations that are inflammatory in origin. | B | D | 88% |
| (24) Symptomatic therapies and reversal of aggravating factors are important for certain neuropsychiatric manifestations (eg, seizure, depression, and cognitive dysfunction). | A | D | 100% |
| (25) For neuropsychiatric SLE that is thromboembolic with antiphospholipid antibodies, anti-coagulation is required. | A | B | 97% |
| (26) Vitamin K antagonist is preferred to direct-acting oral anticoagulants in patients with thromboembolic antiphospholipid syndrome with a high-risk antiphospholipid antibody profile.‡ | A | B | 91% |
| (27) Low-dose aspirin (75–100 mg per day) for primary prophylaxis of thromboembolic events in patients with a high-risk antiphospholipid antibody profile‡ with or without the presence of other atherosclerotic risk factors may be considered. | B | C | 84% |
| **Management of major organ manifestations of SLE: other organ manifestations of SLE** | | | |
| (28) A combination of moderate-to-high-dose glucocorticoids (including intravenous pulse methylprednisolone) and cyclophosphamide should be considered for serious and life-threatening SLE manifestations (eg, haematological, cardiopulmonary, gastrointestinal). | A | C | 97% |
| (29) Plasma exchange may be considered for thrombotic thrombocytopenic purpura, pulmonary haemorrhage and some haematological manifestations, such as hemophagocytosis. | B | C | 91% |
| (30) Intravenous immunoglobulin G may be considered for refractory SLE, particularly haematological manifestations or when other immunosuppressive regimens are contraindicated. | B | D | 100% |
| (31) Methotrexate may be considered for persistent skin or articular manifestations. | B | C | 91% |
| (32) Belimumab may be considered for active SLE manifestations that are refractory to standard therapies. | B | A | 91% |
| (33) Options for maintenance therapies include azathioprine, mycophenolate mofetil, and the calcineurin inhibitors. | A | C | 94% |
| (34) Biosimilar and generic compounds (eg, rituximab, mycophenolate mofetil, or tacrolimus) are acceptable alternatives in the treatment of SLE. | B | D | 84% |

Strength of recommendation: A=strong, B=weak or conditional. Quality of evidence: A=high, B=moderate, C=low, and D=very low. SLE=systemic lupus erythematosus. *The regular assessment and modification of cardiovascular risk factors is recommended. †The measurement of bone mineral density is recommended for patients within 6 months of commencement of glucocorticoids, with bone mineral density monitoring repeated in 1–3 years depending on fracture risk. Oral or intravenous bisphosphonates, denosumab, or teriparatide are recommended for patients with a moderate to high fracture risk calculated by the Fracture Risk Assessment Tool formula with adjustment for glucocorticoid dose. ‡High-risk antiphospholipid antibody profile refers to the presence of lupus anticoagulant, double or triple positive antiphospholipid antibodies on two occasions 12 weeks apart, or persistently high antiphospholipid antibody titres.

*Table 1:* **Asia-Pacific League of Associations for Rheumatology recommendations for the management of SLE**

## Overarching principles

Four overarching principles were agreed on by all participants (table 1; appendix p 2). The treatment of patients with SLE should be managed by an inter-disciplinary team comprising SLE specialists, nurses, and primary care physicians, with an emphasis on shared decision making between the physician and patient (statement 1), to enhance the communication between the management team and the patients, to help allay concerns about treatment toxicities, and improve adherence. Treatment should be personalised on the basis of each patient's disease manifestations and severity, comorbidities, and ability to adhere to a therapeutic plan (statement 2). Early referral to specialist care is important to improve patient outcomes (statement 3); and, finally, the overall goals of treatment are to reduce organ damage, ensure long-term survival, and improve health-related quality of life (statement 4). Because concerns were raised around treatment adherence in Asian patients because of cultural beliefs and access to medications and specialist care in some Asia-Pacific regions, the panel concluded that improving patient empowerment and increasing training on rheumatic diseases in medical school and among primary care physicians would help to enable the early recognition of SLE and referral for specialist assessment in low-resource settings.[16] In addition, a shared care model between specialists and family physicians might be considered for those with mild and stable disease.[17,18]

The use of intravenous medications, such as cyclophosphamide, might help to improve treatment compliance in some patients. The access to costly medications might be improved by biosimilars and generic compounds, which were agreed to be acceptable alternatives in the treatment of SLE (statement 34).

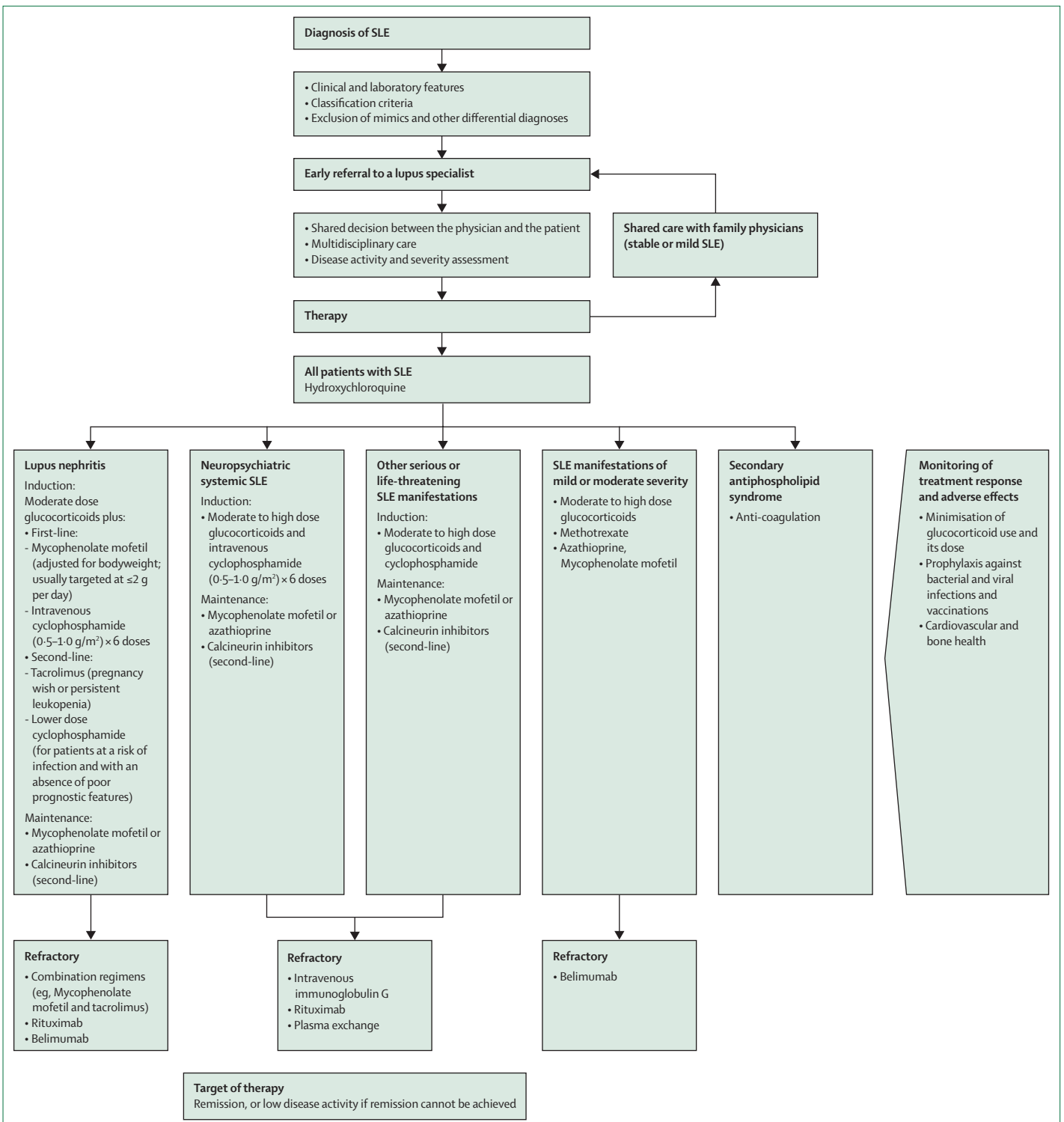


*Figure 2:* **Management algorithm of SLE**
SLE=systemic lupus erythematosus.

## General treatment strategy: assessment and therapeutics

10 statements on the general treatment strategies for patients with SLE reached consensus (table 1). SLE should be classified by validated criteria, and the assessment of disease activity should be on the basis of validated indices (statement 5). Newer SLE classification

| | Asia Pacific League of Associations for Rheumatology consensus statements | Updated EULAR and EULAR and European Renal Association-European Dialysis and Transplant Association recommendations 2019[14,15] |
|---|---|---|
| **Induction therapies of lupus nephritis** | | |
| Mycophenolate mofetil | First-line; adjusted for bodyweight in Asian patients; usually targeted at ≤2 g per day | First-line; standard dose: 2–3 g per day |
| Intravenous cyclophosphamide (standard dose; 0·5–1·0 g/m² once per month × six pulses) | First-line | Second-line; for patients at a high risk with poor prognostic factors |
| Lower dose intravenous cyclophosphamide (Euro-lupus regimen; 500 mg once every 2 weeks × six doses) | Second-line; for patients at risk of infection but without poor prognostic factors | First-line |
| Tacrolimus | Second-line; for those who wish to be pregnant or with persistent leukopenia | First-line for class 5 nephritis only |
| Mycophenolate mofetil–tacrolimus combination | Second-line; for rescue therapy | First-line for those with severe nephrotic syndrome |
| **Reduction of infection risk** | | |
| Screening and treatment for latent tuberculosis | Not recommended | .. |
| Screening for hepatitis B and C before immunosuppression and occult hepatitis B before B cell targeted therapies | Recommended | .. |
| *Pneumocystis jirovecii* pneumonia prophylaxis | In patients at a high risk | .. |
| COVID-19 and viral epidemic | Statement included | .. |
| Use of generic compounds and biosimilars | Acceptable | .. |

EULAR=European League Against Rheumatism.

*Table 2:* **Management strategies of SLE in Asian patients**

criteria, such as the Systemic Lupus Collaborating Clinics[19] and the European League Against Rheumatism and American College of Rheumatology[20] criteria, have high sensitivity and specificity and have been validated in Asian patients.[21,22]

The goal of the treatment of patients with SLE should be disease remission; if remission cannot be achieved, the lowest possible state of disease activity should be targeted (statement 6). The Definition of Remission in SLE (DORIS) remission criteria classify patients as being in clinical remission (clinical systemic lupus erythematosus disease activity index [SLEDAI]-2K=0, physicians' global assessment <0·5), or complete remission (clinical and serological), with or without therapy (prednisone <5 mg per day with or without other immunosuppressive agents).[23] Validation studies in Asian patients showed that remission by the DORIS definition was associated with less organ damage and better health-related quality of life,[24] which has also been shown in other patient populations. The Asia-Pacific Lupus Collaboration developed a low disease activity state, defined as a SLEDAI-2K score of 4 or less, a physicians' global assessment score of 1 or less, 7·5 mg or less per day of prednisone, no activity in major systems or new activity, and good medication tolerance.[25] In patients with SLE from the Asia-Pacific region, those who were in a low disease activity state for longer periods of time had significantly reduced organ damage accrual[25] and a better health-related quality of life.[26]

All patients with SLE should receive hydroxychloroquine, unless contraindicated (statement 7), although data from RCTs are scarce. In addition to its immunomodulating properties, hydroxychloroquine has antithrombotic, lipid, and glucose lowering effects.[27] Cohort and registry studies have shown that the use of hydroxychloroquine in patients with SLE was associated with fewer flares, a better response to treatment for lupus nephritis, the slowing of renal function decline, fewer vascular complications, less organ damage, and reduced mortality.[28–32] The low cost of hydroxychloroquine (and availability of generic compounds) makes it cost-effective, which is particularly important in low-resource settings. The use of hydroxychloroquine also offsets the burden of illness because of disease flares or admission to hospital. To reduce retinal toxicity, the daily dose of hydroxychloroquine should not exceed 5 mg/kg of actual bodyweight and should be adjusted for renal function.[33] Baseline and regular assessments for retinopathy by ophthalmologists is necessary, particularly in patients at high risk, such as those with renal insufficiency, those receiving higher daily doses of hydroxychloroquine, or those who have taken the drug for 10 years or more.[34–36] Although serum concentrations of hydroxychloroquine could reflect drug compliance, routine monitoring for drug toxicity is not recommended because evidence for its use is insufficient[34] and assays are not readily available.

Patients with SLE have a 2–3-times increased risk of stroke and myocardial infarction[37] and a 2-times higher risk of osteoporotic fractures[38] relative to the general population, which is attributed to disease activity, glucocorticoid treatment, and many traditional and non-traditional risk factors. This increased risk underscores the importance of periodic assessment and optimising understanding of cardiovascular and osteoporotic risk factors (statement 8).

Glucocorticoids are the mainstay of therapy of SLE. A cohort study showed that prednisone exceeding 6 mg per day was associated with an increased risk of organ damage by 50% in patients with SLE.[39] In Asian patients with SLE, the time-adjusted mean prednisolone dose was independently associated with damage accrual, including in those with an inactive disease.[40] Thus, the minimal effective dose of glucocorticoids should be used. Although several small studies have shown that preemptive prednisone treatment of serologically-active, but clinically quiescent, SLE reduced clinical flares without an increase in the cumulative doses,[41–43] whether organ damage would be ultimately reduced is uncertain.[44] Given the adverse effects of glucocortocoids and a potentially large number needed to treat to prevent one flare in patients with serologically-active but clinically-quiescent disease, preemptive treatment based on serological activity alone is not recommended unless future RCTs show a favourable benefit-to-toxicity ratio (statement 9).

### General treatment strategy: prevention of infective complications

Prevention of infective complications is an important consideration in the treatment of patients with SLE, particularly in the Asia-Pacific region; as such, patients with SLE should be screened for active infections, including hepatitis B and C (statement 10) and tuberculosis (statement 11).

Hepatitis B virus (HBV) infection is prevalent in Asia, with studies from Japan and Taiwan reporting chronic HBV infection in 0·8–4·2% of patients with SLE, and evidence of past (ie, resolved) HBV infection in 16·5–17·0% of patients.[45,46] Upon commencing immunosuppressive treatment for SLE, the reactivation of HBV occurred in 39·5% of patients who were HBV carriers and 1·9% of those with a past infection.[46] Thus, screening for HBsAg is mandatory before immunosuppression in patients with SLE. In those receiving B cell depleting therapies or intensive immunosuppression (eg, cyclophosphamide-based combination regimens), screening and preemptive treatment of occult HBV infection (HbsAg-/IgG anti-HBc+/HBV-DNA+) is recommended (statement 10).

The prevalence of hepatitis C virus (HCV) infection in patients with SLE was reported to be 1·1–16·5%, which was significantly higher than in population controls.[47,48] Because risk factors for HCV infection might not be apparent from medical history, routine screening for anti-HCV antibodies is recommended before starting immunosuppressive therapy (statement 10). In patients with an active HCV infection, the co-administration of immunosuppression and antiviral therapy might be considered.

Tuberculosis is endemic in Asia, and the prevalence of an active tuberculosis infection in patients with SLE in hospital has been reported to be significantly higher than in patients without SLE.[49] In addition, in a prospective study of patients with rheumatic diseases treated with glucocorticoids, 5·2% of patients with latent tuberculosis at baseline developed an active infection after 2 years.[50] Among these, the highest rate of tuberculosis reactivation was seen in patients with SLE, particularly those on a daily prednisone equivalent of more than 15 mg for more than 4 weeks. As such, for patients living in tuberculosis-prevalent areas, those with an active tuberculosis infection should be excluded by symptom evaluation and imaging studies before immunosuppressive therapies are commenced (statement 11). However, there is insufficient evidence to show a favourable benefit-to-toxicity ratio to support routine screening and the treatment of latent tuberculosis before commencing immunosuppression.

*Pneumocystis jirovecii* pneumonia is uncommon in Asian patients with SLE (estimated prevalence, 0·45% in hospital admissions), but is associated with high mortality.[51,52] Risk factors for *P jirovecii* pneumonia in patients with SLE include a more active disease, renal impairment, low lymphocyte count, higher glucocorticoid doses, and concomitant treatment with cyclophosphamide or biologic drugs.[53,54] A study of 1092 Korean patients given high-dose glucocorticoids over long periods of time showed that co-trimoxazole prophylaxis reduced the incidence of *P jirovecii* pneumonia in 1 year.[52] Given the low prevalence of *P jirovecii* pneumonia and potential toxic effects associated with co-trimoxazole treatment in patients with SLE, it was agreed that *P jirovecii* pneumonia prophylaxis should be considered only in patients at high risk (statement 12).

In view of the ongoing COVID-19 pandemic, recommendations around therapy for patients with SLE in the context of viral epidemics or pandemics were discussed. Patients are recommended to comply with preventive and control measures (eg, physical distancing, personal hygiene, and protective masks), according to national guidelines during viral epidemics (statement 13). Notably, obesity and renal insufficiency are risk factors for more severe COVID-19 pneumonia in patients with SLE.[55] However, patients with rheumatic diseases, including SLE, do not appear to be more susceptible to viral infection during epidemics, including COVID-19,[56,57] nor have treatments for SLE (including hydroxychloroquine)[58] been associated with a more severe disease in those who develop COVID-19.[58] As such, it is not recommended that patients discontinue immunosuppressive medications, except those with serious COVID-19 infections for whom individualised decisions are required.

In patients with SLE whose disease is well-controlled with minimal immunosuppression, vaccination against seasonal influenza, pneumococcus, human papillomavirus, and herpes zoster is recommended (statement 14). Influenza and pneumococcal vaccines are generally safe and offer protection despite lower immunogenicity in patients with SLE.[59,60] The quadrivalent human papillomavirus vaccine was reported to be immunogenic and well-tolerated in patients with SLE with stable disease activity,

with no resulting increase in lupus flares.[61,62] Although live vaccines carry an infection risk in patients who are immunocompromised, one RCT showed that a live-attenuated herpes zoster vaccine was safe and immunogenic in patients with SLE and stable disease,[63] with no patients experiencing virus reactivation in the 6 weeks post-vaccination and no increase in the incidence of SLE flares. A new recombinant herpes zoster subunit vaccine (Shingrix) is available in some Asian countries and might provide an alternative for patients in whom the live herpes zoster vaccine is contraindicated. Because the availability of the above vaccines is variable in the Asia-Pacific region, members agreed to a conditional recommendation of vaccine administration in patients with SLE confined to periods of disease quiescence.

### Management of major organ manifestations

Several consensus statements refer to management of major organ manifestations of SLE, including lupus nephritis (statements 15–21), neuropsychiatric SLE (statements 22–25), and antiphospholipid syndrome (statements 26 and 27).

Asian patients with SLE have a higher incidence of renal disease compared with White patients.[2] The routine screening for renal involvement by urinary protein and sediments and estimated glomerular filtration rate is essential during clinic visits. Unless contraindicated, all patients with active lupus nephritis should have a renal biopsy (statement 15), because clinical symptoms and proteinuria might not necessarily be associated with histological severity. Because of the absence of validated and specific biomarkers for the diagnosis and monitoring of lupus nephritis, renal biopsy is the gold standard to differentiate non-SLE-related causes from SLE-related causes of renal disease; biopsy also provides information on the histology and severity of active and chronic lesions, which is important for guiding therapy.[64] Moreover, thrombotic microangiopathy, podocytopathy, and tubulointerstitial lesions can only be unveiled by histological examination.[65]

Higher doses of glucocorticoids are often used for the treatment of lupus nephritis. RCTs of lupus nephritis adopted a lower initial dose of oral prednisolone (eg, 0·6 mg/kg per day for 6 weeks, with tapering to <10 mg per day by 6–8 weeks; or 20–25 mg per day with a rapid taper to 2·5 mg per day within 16 weeks after two 500 mg intravenous pulses of methylprednisolone).[66,67] Despite the fact that glucocorticoid induction regimens are highly variable in real life practice, Delphi members agreed with the use of moderate-dose glucocorticoids (~0·6 mg/kg per day of prednisolone) for the therapy of lupus nephritis in combination with other non-glucocorticoid immunosuppressive agents (statement 16 and 17). Intravenous pulse cyclophosphamide and mycophenolate mofetil are recommended as first-line treatment options for induction therapy in patients with lupus nephritis (statement 16), as currently used for patients with International Society of Nephrology and Renal Pathology Society histological lupus nephritis class 3, 4, and 5 (with significant proteinuria). Data from RCTs have shown that mycophenolate mofetil is non-inferior to standard dose intravenous cyclophosphamide pulses (0·5–1·0 g/m² once per month for six doses) as induction therapy for lupus nephritis,[8,68] including in the subgroup of Asian patients in the ALMS study.[69] Although meta-analyses did not show a difference in the relative risk of infection and gastrointestinal intolerance between mycophenolate mofetil and cyclophosphamide, the former was associated with less alopecia and leukopenia and no ovarian toxicity.[70] In fact, mycophenolate mofetil has been increasingly used as an induction therapy for patients with lupus nephritis, especially in younger women.

Because Asian patients with SLE generally have a lower bodyweight, they are less tolerant to higher doses of mycophenolate mofetil and are at a greater risk of infective complications.[8–10] Thus, the dose of mycophenolate mofetil should be adjusted for bodyweight, with 2 g per day recommended as the target dose in an average Asian patient (statement 18). The up-titration of mycophenolate mofetil dose should be done cautiously, and therapeutic drug monitoring by assessing trough concentrations of mycophenolic acid might be helpful.[71–74] However, there was some concern that the mycophenolic acid test is not routinely available, and the evidence is incomplete. Thus, routine mycophenolic acid monitoring was not recommended.

Low-dose intravenous cyclophosphamide or the calcineurin inhibitor tacrolimus are recommended as second-line induction regimens for patients with lupus nephritis (statement 17). A RCT of mainly European White patients showed that a lower dose of intravenous cyclophosphamide (500 mg every 2 weeks for six doses), and subsequently azathioprine (known as the Euro-Lupus regimen) was non-inferior to eight pulses of high-dose intravenous cyclophosphamide as an induction therapy for lupus nephritis, with a similar efficacy of the two regimens but fewer infections with the lower dose regimen after 10 years of follow-up.[75] Based on these data, low-dose cyclophosphamide might be a safer regimen in patients at risk of infective complications, although the RCT was not powered to address this. Although there are few published studies on the Euro-Lupus regimen in Asian patients, one short-term RCT revealed a similar efficacy between the Euro-Lupus regimen and mycophenolate mofetil as induction therapies in Indian patients with lupus nephritis.[76]

Tacrolimus and other calcineurin inhibitors (eg, cyclosporin A) reduce proteinuria through the stabilisation of the actin cytoskeleton and inhibition of podocyte apoptosis.[77] A meta-analysis of five small controlled trials from Asia showed that tacrolimus was superior to intravenous pulse cyclophosphamide for the induction therapy of lupus nephritis,[78] and another RCT showed

that tacrolimus was non-inferior to mycophenolate mofetil in inducing a complete renal response at 24 weeks,[66] although alopecia, hyperglycaemia, tremor, and transient increases in serum creatinine were more frequent. Tacrolimus was associated with the better amelioration of proteinuria in the subgroup of patients with pure membranous lupus nephritis. After 10 years of follow-up, there was no difference in renal function deterioration, chronic kidney disease development, and mortality between the treatment groups.[79] A meta-analysis[10] of tacrolimus trials in patients with lupus nephritis suggested a lower infection rate with tacrolimus than mycophenolate mofetil as induction therapy (risk ratio 0·50 [95% CI 0·33–0·76]). Moreover, tacrolimus is not associated with ovarian toxicity and is generally safe during pregnancy. Despite evidence for the benefit of tacrolimus, it was not recommended as first-line induction therapy because of the concerns about nephrotoxicity and the absence of long-term effectiveness data for tacrolimus as induction and maintenance therapy for lupus nephritis. Cyclosporin A was not recommended as the first-line calcineurin inhibitor in patients with SLE because of the visible side effects, such as gum hypertrophy and hirsutism, and lower amount of evidence. With the narrow therapeutic index of the calcineurin inhibitors, the monitoring of pre-dose trough concentrations is recommended to ensure an adequate dose and adherence, and to reduce toxic effects. Extra caution should be taken in patients with histological thrombotic microangiopathy and renal impairment. Close monitoring for blood pressure changes and neurotoxicity is warranted. Data regarding the newer generation of calcineuin inhibitors, such as voclosporin, in patients with lupus nephritis are awaited.[67]

For patients with lupus nephritis who are refractory to induction treatment regimens, a combination of tacrolimus and mycophenolate mofetil or rituximab is recommended (statement 19). A large RCT of Chinese patients with lupus nephritis showed that a combination of low-dose mycophenolate mofetil (1 g per day) and tacrolimus (4 mg per day) was superior to intravenous pulse cyclophosphamide (0·5–1·0 g/m²) in the induction of a complete renal response at 6 months,[80] although serious infections such as herpes zoster and pneumonia were numerically more frequent in the combination group. Responders were treated for a further 18 months with either azathioprine (after cyclophosphamide) or lower doses of mycophenolate mofetil plus tacrolimus as maintenance therapy,[81] with no significant difference in the renal relapse rates between the two groups observed. The combination of mycophenolate mofetil and tacrolimus has also been shown to be effective in patients with refractory lupus nephritis.[82,83] In view of the increased risk of infections and the absence of long-term safety and effectiveness data, the combination of mycophenolate mofetil and tacrolimus was recommended only for patients with refractory lupus nephritis.

Despite the negative results of a pivotal RCT of rituximab in patients with lupus nephritis,[84] a pooled analysis of registry studies showed that rituximab, commonly used in combination with glucocorticoids and other immunosuppressive agents, was effective in more than 70% of patients with refractory lupus nephritis.[85,86] As such, rituximab might be considered for patients with lupus nephritis and an inadequate response to standard of care.

The optimal duration of maintenance therapy in lupus nephritis is uncertain, but renal flares are common when immunosuppression is stopped.[66,87,88] Mycophenolate mofetil or azathioprine are recommended as maintenance immunosuppressive agents, and low-dose calcineurin inhibitors are second-line alternatives (statement 20). An observational study revealed that maintenance therapy for less than 3 years in patients with lupus nephritis was independently associated with a poorer long-term outcome.[89] A long-term cohort study of Chinese patients with lupus nephritis given either mycophenolate mofetil or tacrolimus induction and azathioprine maintenance showed that maintenance therapy for less than 62·5 months best predicted a renal flare by receiver operating characteristic analysis.[79] Thus, it is recommended that maintenance therapy for lupus nephritis should continue for at least 5 years to reduce renal flares (statement 21).

In a RCT, patients were randomly assigned to mycophenolate mofetil or azathioprine maintenance, regardless of their response to induction therapy with the use of the Euro-Lupus cyclophosphamide regimen for 12 weeks.[90] At 10 years, the incidence of renal flares was not significantly different between the groups. The ALMS study randomly assigned patients who responded to either mycophenolate mofetil or cyclophosphamide induction to receive either mycophenolate mofetil or azathioprine for maintenance.[91] After 3 years, mycophenolate mofetil was superior to azathioprine in terms of the rate of treatment failure (renal flares, renal function deterioration, the need for rescue therapy, or mortality).[91] The rate of treatment failure was the highest with mycophenolate mofetil induction and azathioprine maintenance. A meta-analysis revealed a non-significant trend of better efficacy with mycophenolate mofetil than azathioprine as the maintenance therapy of lupus nephritis;[92] mycophenolate mofetil was also associated with a lower incidence of cytopenia. On the basis of these data, Delphi members agreed that both mycophenolate mofetil and azathioprine might be considered as maintenance therapy for lupus nephritis, but mycophenolate mofetil is preferred if it has been used for induction therapy. Azathioprine is preferred in female patients considering pregnancy. Low-dose calcineurin inhibitors should be reserved for patients who are intolerant to or have contraindications for mycophenolate mofetil or azathioprine.[93]

Neuropsychiatric manifestations occur in 11·5% of patients within 5·3 months of SLE diagnosis,[3] with

inflammatory manifestations including, but not restricted to, psychosis, an acute confusional state, myelitis, cranial and peripheral neuropathies, and aseptic meningitis. Therapies for neuropsychiatric SLE include immunosuppression, anticoagulation, and symptomatic control. A combination of moderate to high doses of glucocorticoids (0·6–1·0 mg/kg per day of prednisolone or equivalent) and cyclophosphamide is recommended as a first-line treatment for serious neuropsychiatric SLE (statement 22). As discussed, higher doses of glucocorticoids, including additional pulses of intravenous methylprednisolone, might be needed for the neuropsychiatric compared with the renal manifestations of SLE, although moderate-dose glucocorticoids can be used for patients with less severe neuropsychiatric disease.

A combination of glucocorticoids with intravenous or oral cylophosphamide has been used in severe cases of neuropsychiatric SLE.[94,95] In a small RCT, monthly intravenous cyclophosphamide was superior to intravenous pulse methylprednisolone alone in patients with severe neuropsychiatric SLE, with no increase in the number of new infections.[96] The evidence for the use of rituximab in neuropsychiatric SLE comes only from case series,[97] and this medication might be considered for patients with refractory disease with an inflammatory mechanism (statement 23). For patients with specific neuropsychiatric manifestations, such as seizure, depression, and cognitive dysfunction, symptomatic therapies and the reversal of aggravating factors are important (statement 24). For patients with neuropsychiatric SLE and thromboembolic manifestations with antiphospholipid antibodies, anticoagulation is required (statement 25).

In patients with thromboembolic antiphospholipid syndrome and a high-risk antiphospholipid antibody profile, vitamin K antagonists are recommended over direct-acting oral anticoagulants (statement 26). Previous studies have shown the superiority of the vitamin K antagonist warfarin over aspirin in preventing the recurrence of venous thrombosis in patients with antiphospholipid syndrome.[98,99] By contrast, in patients with ischaemic stroke and who are positive for antiphospholipid antibodies in a single test (lupus anticoagulant or anticardiolipin antibodies), results from one RCT showed no difference between warfarin and aspirin in the reduction of subsequent arterial events over 2 years.[100] In patients with antiphospholipid syndrome and previous arterial thrombosis, two RCTs and two cohort studies revealed no difference in the recurrence rate between high intensity (international normalised ratio 3·0–4·0) and standard intensity warfarin (2·0–3·0).[101]

Direct oral anticoagulants have been tested in patients with antiphospholipid syndrome. One RCT compared the effect of rivaroxaban and standard intensity warfarin on the potential of endogenous thrombin ex vivo in patients with antiphospholipid syndrome and a history of venous thrombosis, showing a higher endogenous thrombin potential in the rivaroxaban group; however, this did not meet the non-inferiority threshold compared with warfarin.[102] A phase 3 RCT comparing the efficacy of warfarin to rivaroxaban in patients with antiphospholipid syndrome and triple positive antiphospholipid antibodies was prematurely terminated because of an excess of thrombotic and bleeding events in the patients given rivaroxaban after a mean of 569 days.[103] On the basis of these data, Delphi members agreed that patients with thromboembolic antiphospholipid syndrome in SLE should be given anticoagulants, with warfarin recommended and with an international normalised ratio maintained between 2·0 and 3·0 in Asian patients. In the absence of new data—eg, data showing that higher doses of the direct-acting anticoagulants are non-inferior to warfarin—direct-acting anticoagulants are not recommended in patients with thromboembolic SLE with a high-risk antiphospholipid antibody profile.

The benefit of low-dose aspirin as the primary prevention of thrombotic events in patients with SLE and a persistently positive, moderate-to-high titre of antiphospholipid antibodies has been shown in cohort studies.[104] A meta-analysis reported a protective effect of low-dose aspirin against thrombosis in the subgroup of patients with SLE who were asymptomatic carriers of antiphospholipid antibodies.[105] Delphi members agreed that low-dose aspirin prophylaxis might be considered in patients with SLE who have a high-risk antiphospholipid antibody profile, especially when concomitant atherosclerotic risk factors are present (statement 27).

Finally, in patients who develop serious and life-threatening SLE manifestations, including diffuse alveolar haemorrhage, thrombotic thrombocytopenic purpura, myocarditis, shrinking lung syndrome, and haemophagocytosis, cyclophosphamide combined with moderate-to-high dose glucocorticoids is recommended (statement 28).[106,107] Plasmapheresis can be considered for patients with thrombotic thrombocytopenic purpura, diffuse alveolar haemorrhage, or haemophagocytosis (statement 29). Plasmapheresis, often in combination with high doses of glucocorticoids and cyclophosphamide, has reported efficacy in these manifestations, although it is controversial whether survival can be improved.[108–110] Although the immunomodulating mechanisms of intravenous immunoglobulin are not understood, this approach can be considered for patients with refractory SLE manifestations, particularly haematological manifestations, or when other immunosuppressive regimens are contraindicated (statement 30).[111,112] Azathioprine, mycophenolate mofetil, and the calcineurin inhibitors are options for the maintenance therapy of these manifestations (statement 33) and methotrexate might be considered for persistent lupus skin and articular disease (statement 31).

Belimumab—a fully humanised monoclonal antibody targeting the B-lymphocyte stimulator—can be considered as add-on therapy in patients with active SLE mani-

festations that do not respond to standard therapies (statement 32), except for patients with severe or life-threatening manifestations that were excluded from the belimumab trials. Several pivotal RCTs have shown the efficacy of intravenous and subcutaneous belimumab in patients with SLE who did not respond to standard-of-care treatments.[113–115] Extension studies showed that in patients who respond to belimumab, continuous treatment for 8 years was associated with no increase in organ damage.[116] One multi-national RCT in China, Japan, and Korea substantiated the efficacy of intravenous belimumab in Asian patients with SLE who did not respond the standard-of-care treatment.[117] Belimumab was associated with a glucocorticoid-sparing effect without new safety signals. Although the results of a new belimumab RCT in patients with lupus nephritis are affirmative,[118] these data were not available at the time of the Delphi process; however, it was agreed that belimumab might be considered as add-on therapy in these patients.

## Discussion

This Review is a consensus on the management of SLE in the Asia-Pacific region developed through a Delphi process by SLE experts. The ultimate goals of SLE therapy are to reduce mortality and enhance quality of life through better disease control and reduced organ damage. Because the prognosis of SLE is unsatisfactory in some Asia-Pacific locations because of delayed diagnosis, little access and low adherence to medications, and infective complications, early referral to specialists, patient empowerment, shared care models with primary care physicians, and the use of biosimilars and generic compounds are recommended. Assessment of disease activity during regular follow-up is essential to gauge the response to therapies, assess whether treatment target has been reached (remission or low disease activity state), detect flares, and decide on the switching of therapeutic regimens. In view of the heavy patient load, little consultation time, and paucity of personnel in many Asia-Pacific regions, we did not formally recommend the routine use of validated instruments to document disease activity in real-life practice, but this is encouraged.

This report describes the methods of a formal consensus process and its outcomes. The authors and contributors note, however, that many complexities underly SLE management decisions, and not all can be captured in such a process. The below discussion focusses on these complexities, to add context to the main recommendations.

The minimisation of glucocorticoid use is of paramount importance in the management of SLE, especially in Asian patients in whom infective complications are a major concern. Early combination with other immunosuppressive or biological agents might allow for lower glucocorticoid doses to be used, as shown in protocols adopted in RCTs in patients with lupus nephritis.[66,67,119] Belimumab has been shown to have a glucocorticoid-sparing effect in patients with SLE.[113–115,117] However, the available evidence did not persuade the Delphi participants to recommend use of belimumab as a first-line agent in SLE. This resistance was partly because of the issue of cost-effectiveness, which is particularly important in the Asia-Pacific region. One RCT of belimumab in patients with lupus nephritis (the BLISS-LN trial) showed the efficacy of the drug in enhancing the renal response rates at 2 years when added to the standard of care.[118] Although the data from this trial were unavailable during the Delphi rounds, the process yielded high agreement that this biologic could be used as an add-on therapy for patients with SLE, including those with renal disease who did not respond adequately to first-line treatment.

Rituximab is effective for some cases of refractory SLE, including in patients with a wide range of manifestations, from arthritis to life-threatening disease. Although a prospective study has shown the efficacy of combined mycophenolate mofetil and rituximab (without oral glucocorticoids) in White patients with lupus nephritis,[120] the response rate and time to response of this regimen has not been tested against conventional regimens with higher doses of oral glucocorticoids. Because the efficacy of lupus nephritis protocols cannot be extrapolated across ethnicities, the absence of data on Asian patients means that further evaluation is needed before rituximab can be recommended as first-line treatment for lupus nephritis in the Asia-Pacific region.

Non-immunological and target-organ protective strategies are also important in the treatment of SLE. Angiotensin converting enzyme inhibitors or angiotensin receptor blockers should be used early for patients with lupus nephritis. The periodic screening for pulmonary arterial hypertension should be considered, and treatment with phosphodiesterase 5 inhibitors, endothelin receptor antagonists, prostanoids, and prostacyclin receptor agonists should be instituted as appropriate. Antifibrotic agents are now available for interstitial lung disease. Thrombopoietin receptor agonists can be considered for refractory immune thrombocytopenia without undue immunosuppression.

Our process did not yield a recommendation to use direct-acting anticoagulants for patients with thromboembolic SLE manifestations and a high-risk antiphospholipid antibody profile. In White patients with antiphospholipid syndrome and non-recurrent venous thrombosis alone, a single RCT did not show new thrombotic events or major bleeding episodes in patients given standard intensity warfarin or rivaroxaban for 6 months.[102] Because this RCT was not designed to compare the clinical efficacy of the two anticoagulation regimens, and the study duration was too short for safety analysis, further evidence focusing on patients with SLE and antiphospholipid syndrome is needed before the use of direct-acting anticoagulants is recommended for Asian patients in this scenario, particularly in view of the lower incidence of venous thromboembolism[121] and the absence

### Search strategy and selection criteria

References for the consensus statements were identified through searches of PubMed with the search terms "lupus", "disease activity", "remission", "nephritis", "neuropsychiatric", "infection", "vaccination", "antiphospholipid", "glucocorticoid", "hydroxychloroquine", "biologics", and other relevant key words in the statements, covering the period from January, 1990 to April, 2020, by six core group members (CCM, LH, NK, DYC, SC, and KO). Articles were also identified through searches of the authors' own files. Only clinical trials, cohort studies, and case series published in English were included. The strength of recommendations and the quality of evidence of each statement were evaluated on the basis of the Grades of Recommendations Assessment, Development and Evaluation system (appendix p 1).[122] The overarching principles of systemic lupus erythematosus management were not graded.

of data on direct-acting anticoagulants in Asian patients with SLE.

There are some limitations to this work. Although this consensus was not obtained from all physicians involved in SLE care, we considered a group of 29 SLE experts along with 13 rheumatologists in the core group to be largely representative of expert opinion in the Asia-Pacific region. We acknowledge that the number of patients with SLE involved in the process was small and that more direct (ie, non-electronic) communication on the medical information would have been given if not for the COVID-19 pandemic. Not all aspects of SLE management have been formally trialled in patients from the Asia-Pacific region, and thus some recommendations are necessarily extrapolated from other populations. Finally, cutaneous lupus, pregnancy, assisted reproduction, non-immunological therapies for pulmonary arterial hypertension and interstitial lung disease, anticoagulation therapy for obstetric antiphospholipid syndrome, and other issues will be addressed formally in future works.

The APLAR SLE special interest group has developed this first set of recommendations on the management of SLE based on a formal consensus method and involving experts from the Asia-Pacific region, as well as, where possible, data from studies in patients from the Asia-Pacific region. Regular updates of these recommendations will be done upon the emergence of new evidence.

#### Contributors

All authors contributed to drafting, discussing, modifying, and finalising the consensus statements. CCM, SN, EM, and YT drafted the manuscript. CCM, LH, NK, DYC, SC, and KO did the systemic literature search. All authors designed the study, and edited and approved the final manuscript.

#### Declaration of interests

KY reports honoraria from Abbvie, Actelion, Asahi-Kasei, Astellas, Boehringer Ingelheim Japan, Bristol-Myers Squibb, Chugai, Daiichi-Sankyo, Eisai, Eli Lilly Japan, Gilead GK, Janssen, Japan Tobacco, Mitsubishi-Tanabe, Nippon Shinyaku, Ono, Otsuka, Pfizer, Takeda Industrial, and Teijin; and personal fees from GlaxoSmithKline, outside the submitted work. SN reports personal fees from Astellas, outside the submitted work. EM reports grants from Astra Zeneca, Bristol-Myers Squibb, Eli Lilly, EMD Merck Serono, GlaxoSmithKline, Janssen, and UCB; and personal fees from AbbVie, Astra Zeneca, Biogen, Bristol-Myers Squibb, Eli Lilly, EMD Merck Serono, GlaxoSmithKline, Janssen, Neovacs, Novartis, Sanofi, UCB, and Wolf, outside the submitted work. YT reports personal fees from Abbvie, Asahi-Kasei, Astellas, Bristol-Myers Squibb, Chugai, Daiichi-Sankyo, Eisai, Eli Lilly, Gilead, GlaxoSmithKline, Janssen, Mitsubishi-Tanabe, Novartis, Sanofi, Pfizer, and YL Biologics; and grants from AbbVie, Chugai, Daiichi-Sankyo, Eisai, Mitsubishi-Tanabe, Takeda, and UCB, and outside the submitted work. All other authors declare no competing interests. This Review was funded by the APLAR secretariat to support a medical writer who assisted with the online voting platform and the initial manuscript draft. There are no commercial conflicts of interest to be declared.

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