Lupus Nephritis in Asia: Clinical Features and Management

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Key Words

Asians · Azathioprine · Cyclophosphamide · Lupus nephritis · Mycophenolate

Abstract

Background: Lupus nephritis (LN) is a common and severe organ involvement manifesting itself in systemic lupus erythematosus (SLE). There is a considerable difference in prevalence, severity, treatment response and outcomes between Asian LN patients and LN patients from other racial backgrounds. **Summary:** Asian SLE patients have a higher prevalence of LN than Caucasian SLE patients and often present with a more severe disease. Increasing data from genetic studies, accompanied by progress in high-throughput genotyping, have advanced our knowledge about genetic predispositions that might partly contribute to the clinical variations observed. Corticosteroids combined with either cyclophosphamide (CYC) or mycophenolic acid (MPA) is the current standard-of-care induction regimen for severe LN irrespective of race or ethnicity. However, the preference for MPA or CYC, and possibly the optimum dose for MPA, is influenced by the patient's origin. Also, there is an insufficient evidence base for reduced-dose intravenous CYC in Asian patients. Health economics and access to prompt diagnosis and treatment are still challenging issues in some Asian regions. The former represents a significant obstacle limiting the access of patients to MPA despite the proven efficacy of the drug as an induction agent and its superiority over aza-

thioprine (AZA) in preventing disease flares when used for long-term maintenance immunosuppression. Calcineurin inhibitors such as tacrolimus deserve further investigation in view of their additional effect on podocytes by reducing proteinuria and the promising data from Asian patients. Despite considerable advances in the clinical management of LN over the past few decades with resultant improvements in patients' outcomes, there are still knowledge gaps and unmet clinical needs. Asia has made substantial contributions to the evidence base that guides clinical management and continues to offer invaluable opportunities for research pursuits. **Key Messages:** Treatment responses and clinical outcomes in Asian patients with LN compare favorably with patients from other parts of the world. The prevention and treatment of infective complications remain significant challenges in managing LN in Asia. **Facts from East and West:** (1) The prevalence of SLE is lower among Caucasians than other ethnicities. A higher prevalence is observed among Asians and African Americans, while the highest prevalence is found in Caribbean people. The prevalence of LN in Asian SLE patients is much higher than in Caucasians as well. However, the 10-year renal outcome and renal survival rate appear to be better in Asians. (2) Polymorphisms of genes involved in the immune response, such as Fcγ receptor, integrin αM, TNF superfamily 4, myotubularin-related protein

For lupus nephritis in Europe, see Tesar and Hruskova Kidney Dis 2015;1:110–118.

3 and many others, might be partly responsible for the differences in prevalence between the different ethnic groups. European ancestry was shown to be associated with a decrease in the risk of LN even after adjustment for genes most associated with renal disease. (3) Access to health care is a key determinant of disease progression, treatment outcome and the management of complications such as infections, particularly in South Asia, and might also explain disparities between clinical outcomes. (4) The efficacy of low-dose CYC combined with corticosteroids for induction treatment of LN was proved in European Caucasian patients. This treatment is also used in Asia, although no formal evaluation of efficacy and safety in comparison with other treatment regimens exists in this population. The efficacy of mycophenolate mofetil (MMF) is similar to that of CYC, and similar between Asians and Caucasians. MMF may be more effective than CYC in inducing response in high-risk populations such as African American or Hispanic patients. MMF might cause less infection-related events in Asians, but its high cost prevents broader usage at present. (5) For maintenance therapy, corticosteroid combined with AZA or MMF is used worldwide, with a broadly similar efficacy of both treatments, although there are data suggesting that in high-risk populations (e.g. African Americans) MMF may be more effective in preventing renal flares. AZA is often preferred in Asia due to economic constraints and because of its safety in pregnancy. (6) Alternative therapies under investigation include rituximab, which might be more efficient in Caucasians, as well as belimumab. Recent Japanese and Chinese studies have indicated a potential benefit of tacrolimus as a substitute for or in addition to CYC or MMF (dual or triple immunosuppression). Mizoribine is used in Japan exclusively.

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Introduction

Systemic lupus erythematosus (SLE) is a severe autoimmune disease characterized by involvement of multiple organs. Lupus nephritis (LN) denotes a common and severe manifestation of SLE and is a major factor exerting a negative impact on long-term renal and patient survival. There is a considerable difference in prevalence, disease severity, treatment response and clinical outcomes between LN patients from different racial and ethnic backgrounds. In this context, LN is an important concern among Asian SLE patients due to the high incidence of kidney involvement and more severe renal disease compared with patients of other races and its association with unfavorable long-term outcomes [1–4]. These attributes

have also fueled extensive studies on the treatment of LN in Asians, which have contributed to the evidence base for the management of LN. This review will discuss the epidemiology, clinical features and outcomes as well as the current and emerging immunosuppressive treatments in Asian LN patients.

Epidemiology, Clinical Features and Genetics of LN: An Asian Perspective

Epidemiology, Clinical Features and Outcomes of LN in Asia

Asian SLE patients exhibit higher rates of renal involvement when compared with Caucasians (50–60 vs. 30–38%) and also often herald a more severe renal disease [1–3]. Even among Asians populations, there is a notable disparity in the prevalence of LN. While around 50–60% of Asian SLE patients have renal involvement, much higher rates of LN (70–100%) have been observed in certain Asian countries such as Thailand or Sri Lanka [3, 5]. As for clinical severity, nephrotic-range proteinuria and decreased creatinine clearance (<50 ml/min) were reported in 43.6 and 58% of SLE patients, respectively, in a Thai series [6], and diffuse proliferative glomerulonephritis was ranked the commonest renal histopathological finding in different Asian cohorts [4–7].

Previous studies have reported a higher incidence of death in SLE patients of Asian descent, which was attributed to the high rates of renal involvement among the SLE patients in these cohorts [8, 9]. LN constitutes an important cause of renal failure in Asia, and renal involvement may also portend inferior long-term patient survival [4]. Recent survival analyses in Asian LN patients have reported 10-year patient survival rates of 92–98% in the current era of effective immunosuppressive therapies [4, 10, 11]. These long-term patient survival rates in Asian LN patients compare favorably with the survival rates in patients of other races (a 10-year patient survival rate of 81–97% in Caucasians and around 60% in Afro-Americans) [12–14]. Furthermore, 10-year renal survival rates of 81–98% have been reported in Asian LN patients, compared with 68–95% in Caucasians and 38–70% in Afro-Americans [4, 12, 15–17]. It is probable that the high response rates to immunosuppressive treatment observed in Asian LN patients contribute to the relatively favorable long-term outcomes in Asian patients [18–21]. Chronic renal insufficiency in Asian LN patients is often associated with repeated nephritic flares, each resulting in cumulative attrition of the nephron mass and renal reserve.

Data from Genetic Studies in Asian LN Patients

The underlying reasons for the high incidence of SLE in Asia and the high prevalence of renal involvement in Asian SLE patients remain to be elucidated. Accumulating data from genome-wide association studies and the International HapMap Project, in parallel with recent technological progress in high-throughput genotyping, have increased the knowledge of the genetic factors which might account for these clinical observations. In this regard, Fcγ receptor (FcγR) polymorphism has been investigated for its role in a genetic predisposition for LN in Asians. FcγR is a cell surface molecule expressed on immunoreactive cells which can bind to IgG immune complexes and mediate phagocytosis and antibody-dependent cytotoxicity. A meta-analysis of FcγRIIIA-V/F158 polymorphism showed that the F158 allele was associated with an elevated risk of LN in Asian SLE patients (OR 1.15, 95% CI 1.04–1.28) [22]. The FF homozygosity also conferred an increased risk of LN in Asians (OR 1.30, 95% CI 1.04–1.64) [22]. The FcγRIIb and IIb polymorphisms, however, were found to have no association with LN among Asians in another meta-analysis [23].

Integrin alpha M (ITGAM) is expressed on different immunoreactive cells and exerts pleiotropic actions such as cell adhesion and migration, phagocytosis, chemotaxis and cell-mediated cytotoxicity. Associations between ITGAM and SLE have been reported in patients from different ethnic backgrounds including Caucasians, Hispanics, Afro-Americans and Asians [24]. One genome-wide association study on ITGAM which genotyped 910 Hong Kong Chinese and 278 Thai SLE patients revealed that single nucleotide polymorphisms (SNPs) of ITGAM in rs1143679 (OR 3.61, 95% CI 1.6–7.98; $p = 0.00073$), rs1143683 (OR 2.42, 95% CI 1.51–3.89; $p = 0.0017$) and rs1143678 (OR 1.95, 95% CI 1.10–3.47; $p = 0.02$) were tightly associated with LN in Chinese and Thai [25]. However, one limitation of this study is the low allele frequency of these variants in the Chinese population, which diminishes the power of the study.

The TNF superfamily 4 (TNFSF4) gene encodes for OX40 ligand (OX40L) protein expressed on T and B lymphocytes and dendritic cells. A defect in the TNFSF4 gene would result in a compromised interaction between OX40 and OX40L and, therefore, impaired Th2 polarization and enhanced Th17 differentiation. SNP polymorphisms in TNFSF4 rs2205960 (T) and rs10489265 (G) were both strongly linked with renal disease in Chinese SLE patients ($p = 0.014$ and $p = 0.005$, respectively) and have a negative correlation with C3 levels and TNFSF4 renal expression [26]. Myotubularin-related protein 3

(MTMR3) is an autophagy-related gene which is involved in autophagy initiation and, hence, a susceptibility gene for SLE. SNP polymorphisms in rs9983A showed a positive association with kidney involvement in Han Chinese SLE patients (OR 1.61, 95% CI 1.19–2.19; $p = 0.002$), and lower transcription levels of MTMR3 were detected in the blood and renal biopsy samples of the corresponding Chinese LN patients [27]. The mechanistic contribution of TNFSF4 and MTMR3 to pathogenesis remains to be further elucidated. Apart from its impact on immunoreactivity, there could be genetically determined variations in the progression of chronic kidney disease. The renin-angiotensin system has been investigated as a candidate mediator for the progression of chronic kidney disease in patients with LN. One study which genotyped 642 SLE patients for angiotensin-converting enzyme gene polymorphisms [Alu insertion/deletion (I/D) and (CT)_{2/3}] showed that ACE D (OR 5.9, 95% CI 2.1–16.4; $p = 0.001$) and (CT)₂ (OR 6.2, 95% CI 2.2–17.6; $p = 0.001$) polymorphisms were associated with renal progression in Asian LN patients [28].

Current Immunosuppressive Treatments for LN: An Asian Perspective

In general, treatment of LN is guided by renal histopathological findings and clinical parameters. Immunosuppressive treatment of active severe LN begins with an induction phase in which potent immunosuppressive medications are administered to abrogate renal inflammation. This phase lasts for approximately 4–6 months and is followed by a prolonged maintenance phase in which low-dose immunosuppression is conducted to prevent relapses [29]. The distinction between the induction phase and the maintenance phase is clear in sequential immunosuppressive regimens such as cyclophosphamide (CYC) followed by either mycophenolic acid (MPA) or azathioprine (AZA), but it becomes a gradual evolution with continuous regimens, for example when MPA is used for both induction and maintenance purposes. In parts of Asia where renal biopsy may not be readily available due to limitations to expertise or economic reasons, serological activity combined with an active urinary sediment and proteinuria and/or renal functional impairment of varying severity is taken to indicate active severe LN. The following discussion gives an overview of current treatments for Asian patients with proliferative (class III or IV) and/or pure membranous (class V) LN (table 1).

Table 1. Standard-of-care immunosuppressive agents in Asian patients with LN

Immunosuppressive medication	Advantages	Disadvantages
<i>Induction phase^a</i>		
CYC (NIH regimen) Intravenous CYC 0.5–1 mg/m ² monthly titrated according to WBC count, for approximately 6 months	<ul style="list-style-type: none"> – Proven efficacy in Asian LN patients – Ensures drug delivery 	<ul style="list-style-type: none"> – Higher treatment cost than oral CYC – Requires intravenous facilities and administration by medical personnel – Short-term and long-term toxicities including infections, leukopenia, gonadal failure, hemorrhagic cystitis and malignancies
CYC (Euro-Lupus regimen) Intravenous CYC 500 mg every 2 weeks for 3 months	<ul style="list-style-type: none"> – Reduced exposure to CYC and, hence, its toxicities compared with standard-dose intravenous or oral CYC 	<ul style="list-style-type: none"> – Not extensively studied in Asians
CYC (oral) 2–2.5 mg/kg/day (max. 150 mg/day) for up to 6 months	<ul style="list-style-type: none"> – Proven efficacy in Asians – Relatively less costly – Ease of administration compared with intravenous CYC 	<ul style="list-style-type: none"> – Long-term toxicities similar to intravenous CYC
MMF 1.5–2 g/day for 6 months or longer	<ul style="list-style-type: none"> – Established efficacy in Asians – Favorable tolerability profile 	<ul style="list-style-type: none"> – Expensive – Cannot be used in pregnancy – Not well studied in aggressive LN (e.g. with rapidly progressive renal failure)
<i>Maintenance phase^b</i>		
AZA 2–2.5 mg/kg/day	<ul style="list-style-type: none"> – Proven efficacy in Asian LN patients – Cheap – Well tolerated – Safe during pregnancy 	<ul style="list-style-type: none"> – May be less effective than MMF in preventing disease flares
MMF 1.5–2 g/day	<ul style="list-style-type: none"> – Favorable long-term efficacy and tolerability – Long-term safety and tolerability data for Asian LN patients – Appears more effective than AZA in preventing flares 	<ul style="list-style-type: none"> – Teratogenic – Expensive

WBC = White blood cell.

^a All regimens include corticosteroids (starting dose 0.8–1 mg/kg/day tapered to reach 5–7.5 mg/day after 4–6 months) with or without initial IV pulse methylprednisolone (commonly used in patients with more severe nephritis).

^b All regimens include low-dose corticosteroids up to 7.5 mg/day.

Proliferative (Class III or IV) LN

Induction Treatment

Focal (class III) or diffuse proliferative (class IV) LN is characterized by severe renal inflammation and a natural history of rapid progression to renal failure if left untreated. The current standard-of-care immunosuppressive treatment for class III/V LN, i.e. high-dose corticosteroids combined with either CYC or MPA, also applies to Asian patients, as its efficacy and tolerability have been substantiated in various clinical trials, including the Aspreva Lupus Management Study (ALMS), which has the biggest sample size to date [30–32]. The intravenous CYC regimen, as used in the US National Institutes of Health (NIH) clinical trials, is still widely adopted as standard treatment for active proliferative LN. Additional merits

of intravenous CYC include its intermittent administration to patients living in relatively remote areas and ensuring compliance. Reduced-dose CYC, as used in the Euro-Lupus clinical trials, has been shown to be as effective as the standard-dose CYC regimen when used in Caucasians, and it was even associated with fewer side effects [33]. However, there is relatively little data on the efficacy of the Euro-Lupus regimen in Asians. Despite the lack of an evidence base, this regimen is not uncommonly used, especially when infection is of particular concern. Corticosteroids combined with oral CYC are also used in some Asian centers, because of its ease of administration without the need for intravenous facilities and its low cost. There is a considerable amount of data on the use of oral CYC, for defined durations up to 6 months, in Asian

LN patients. Induction treatment with prednisolone and oral CYC could achieve complete or partial remission rates of 55–77% and 22–28%, respectively, within the first year, and a cumulative complete response rate of over 80% after 91.7 ± 36.7 months [19, 34, 35]. Although hemorrhagic cystitis can be prevented to a large extent by limiting the treatment duration and cumulative exposure to CYC, other adverse effects of CYC remain significant concerns, such as gonadal toxicity and late-onset neoplasms.

The use of MPA signifies a major advance in the immunosuppressive therapy for severe LN. The first randomized prospective study on mycophenolate mofetil (MMF) was conducted in Chinese patients with diffuse proliferative LN. In this study, corticosteroids combined with MMF achieved a high renal remission rate (>80%) that was comparable to a sequential regimen which started with 6 months of oral CYC induction followed by AZA maintenance; however, treatment with MMF was associated with fewer adverse events including infections as compared with CYC [18]. Subsequent reports from Malaysia, Korea and Taiwan provided confirmatory evidence on the efficacy and tolerability of MMF-based induction therapy [20, 36, 37]. Results from the subsequent ALMS concluded that Asian LN patients had similar renal response rates to MMF or intravenous CYC induction therapy [31, 32]. The currently recommended dose of MMF during induction treatment for Asians is 1.5–2 g/day [38, 39]. In this context, MMF at 2 g/day has been associated with favorable efficacy and tolerability profiles in Chinese patients [18, 36, 40, 41]. A lower MMF dose (980 ± 100 mg/day) showed inferiority to intravenous CYC (850 ± 30 mg/month) with regard to renal functional preservation in Korean patients, while a higher dose up to 3 g/day was associated with increased infection-related mortality in Asians [31, 37]. Enteric-coated MPA was reported to show an efficacy similar to that of MMF in Asians, but with slightly fewer gastrointestinal side effects [42–44]. The long-term outcomes of Asian LN patients who received corticosteroids and MMF induction were relatively favorable, with 10-year patient and renal survival rates of 91 and 86%, respectively; these rates were comparable to the survival rates observed in patients treated with CYC induction followed by AZA maintenance [16, 19, 35, 41]. A growing body of evidence shows that, from a clinical point of view, MMF-based treatment is effective in the majority of Asian patients with severe proliferative LN and its tolerability profile is more advantageous compared with CYC. However, the use of MMF is often hampered by its cost.

Maintenance Treatment

Low-dose corticosteroids combined with AZA or MMF are the two commonly used maintenance immunosuppressive regimens in Asia. Sequential immunosuppression with CYC followed by AZA was shown to be effective in preserving renal function and preventing relapse in Asian patients with proliferative LN, with a cumulative renal flare rate of around 40% over 8 years [19, 45]. Compared with MMF, AZA has the advantage of low cost and safety in pregnancy. The potential liver complication with AZA makes it a less preferred option in patients with chronic hepatitis B virus infection, which is endemic in some Asian countries. MMF has been continuously used as both induction and maintenance immunosuppressive treatment, and a report on Chinese patients showed renal outcomes and flare rates comparable to those in patients treated with a sequential CYC-then-AZA regimen [40]. The data also suggest that in patients who received corticosteroids and MMF as induction treatment, continuation with MMF maintenance for a total treatment duration of 2 years or longer was associated with a lower relapse risk compared with patients who had their MMF substituted with AZA within the first 2 years (relapse-free survival rates at 5 and 10 years 76 vs. 56% and 69 vs. 32%, respectively; $p = 0.019$) [41]. Despite the fact that the MMF-based treatment can bring about savings from reduced hospitalization and treatment complications, the cost of MMF remains an important factor hindering access to this drug, especially when used as maintenance therapy [46].

Membranous (Class V) LN

Immunosuppressive treatment of class V LN is guided by the severity of proteinuria, as the risk of renal damage is lower compared with class III/IV LN. It should be noted that the data on the management of class V LN, in the absence of concomitant class III/IV features, is mostly based on trials of relatively small sample size and/or short-term follow-up, or on post hoc subgroup or pooled analysis. Notwithstanding these limitations, it is generally agreed that patients with low levels of proteinuria, stable kidney function, low serological activity, no evidence or risk of concomitant severe proliferative features based on clinical judgment and an adequate renal biopsy should be managed with blood pressure control and renin-angiotensin pathway blockade, while patients with nephrotic and/or increasing proteinuria despite conservative management warrant an escalation of immunosuppressive therapy to aim for induction of proteinuria response [38, 47]. The latter should be a combination of

Table 2. Alternative (nonbiologic) immunosuppressive treatments for Asian patients with LN

Immunosuppressive medication	Clinical indications and potential merits	Disadvantages
TAC	<ul style="list-style-type: none"> – Efficacious when used in dual immunosuppressive or triple immunosuppressive treatment regimens in Chinese patients with class III/IV/V LN – Reduces proteinuria in patients who have not responded adequately to other treatments – Emerging long-term safety data promising 	<ul style="list-style-type: none"> – Relatively expensive – Acute and chronic nephrotoxicity – Necessitates drug level monitoring – Adverse effects such as hand tremor, hypertension, diabetes mellitus and dyslipidemia
Leflunomide	<ul style="list-style-type: none"> – Preliminary data showed an efficacy comparable to that of intravenous CYC induction in Chinese patients with class III/IV LN 	<ul style="list-style-type: none"> – Potential hepatotoxicity and bone marrow toxicity – Insufficient data
Mizoribine	<ul style="list-style-type: none"> – Preliminary data on its use as induction or maintenance treatment in Japanese LN patients – Has been used in triple induction immunosuppressive regimen together with corticosteroids and TAC in Japan 	<ul style="list-style-type: none"> – Unsatisfactory data quality – Data limited to Japanese LN patients – Potential bone marrow-suppressive effect
Proliferation signal (mTOR) inhibitors	<ul style="list-style-type: none"> – Pilot results in Chinese patients suggested their efficacy and tolerability – Theoretical beneficial effect on the incidence of malignancies 	<ul style="list-style-type: none"> – Side effects include oral aphthous ulcers, dyslipidemia and bone marrow suppression

corticosteroids and any one of the following, CYC, AZA, MPA or a calcineurin inhibitor, and the efficacy of these treatment regimens has been observed in Asian patients [34, 48–50].

Emerging Treatments in Asia and Concluding Remarks

Despite the fact that the majority of Asian patients respond quite well to current standard-of-care therapies, the search for novel therapies and alternative immunosuppressants continues so that treatment can be tailored to suit the varying needs of different patients, and some of the novel treatments have been studied in Asia (table 2).

Calcineurin Inhibitors in the Treatment of LN

Calcineurin inhibitors have antiproteinuric effects independent of their immunosuppressive properties. These drugs have a relatively narrow therapeutic window and are associated with acute and chronic nephrotoxicity when susceptible kidneys are exposed to excessive circulating drug levels. In the Cyclofa-Lune Study, Zavada et al. [51] reported that cyclosporine A (CYA) as continuous induction-maintenance therapy was as efficacious as CYC, both in combination with corticosteroids, in the

treatment of LN. Data from a Japanese series suggested that treatment with corticosteroids and CYA resulted in an improvement in SLE disease activity index and proteinuria within 1 month in active class IV LN [52]. In Chinese patients with class IV LN, corticosteroids and CYA led to a significant proteinuria reduction after treatment for 1 month and histological improvement at 1 year, and there was no significant deterioration in serum creatinine level or creatinine clearance after a follow-up of 48 months [53]. The recent data on tacrolimus (TAC) in LN from studies conducted in Asian patients deserves discussion. TAC is preferred to CYA in the treatment of lupus – despite the higher diabetogenic potential of TAC when it is used together with high-dose corticosteroids – due to its more favorable tolerability profile, which includes minimal aesthetic adverse effects and less dyslipidemia as compared with CYA. Preliminary data from Japan suggested the efficacy of TAC in proliferative LN [54, 55]. Subsequent studies in China showed that triple immunosuppression comprising corticosteroids, TAC and reduced-dose MMF might be more effective than corticosteroids combined with CYC in the treatment of patients with concomitant class IV and V LN, while dual immunosuppression with corticosteroids and TAC achieved a response rate similar to that with corticosteroids plus either CYC or MMF in the treatment of class III/IV LN [21, 56, 57]. A recent report by Liu et al. [58] showed that the

'multitarget induction therapy' of triple immunosuppression with corticosteroids, TAC and reduced-dose MMF resulted in a higher complete remission rate (45.9 vs. 25.6%; $p < 0.001$) and also overall response rate (83.5 vs. 63.0%; $p < 0.001$) at 6 months in patients with class III/IV with or without concomitant class V LN when compared with corticosteroids and intravenous CYC, while the incidence rates of adverse events were similar between the two regimens. About 80% of the patients in this study had an estimated glomerular filtration rate at or above 60 ml/min, and only patients who showed low chronicity indices on their renal biopsies were included. Therefore, the safety of TAC, especially when given as long-term treatment, in patients with pre-established chronic kidney damage remains to be investigated. We have reported our data on the efficacy of TAC when used as add-on therapy, guided by therapeutic drug level monitoring, in patients with LN who showed persistent significant proteinuria despite treatment with other immunosuppressive agents, and in patients given long-term TAC therapy the renal survival rate at 3, 5 and 8 years was 93, 83 and 83%, respectively [50]. Mok et al. [59] reported the outcomes of patients with class III/IV/V LN given corticosteroids and TAC as induction therapy followed by low-dose corticosteroids and AZA maintenance, and the complete remission rate at 6 months was comparable to that for patients treated with corticosteroids and MMF for induction followed by AZA during maintenance (59 vs. 62%; $p = 0.71$). The two groups showed similar rates of major infection (9.2 vs. 5.4%; $p = 0.53$) and cumulative incidence of renal failure at 5 years (21 vs. 22%; $p = 0.35$) [59]. The numerically higher rate of renal flares in the TAC induction group did not reach statistical significance, and there was no definite conclusion on the impact of TAC on the long-term evolution of renal function. It should be noted that in this study TAC was given at a standard dose according to body weight, and the dose was reduced when there was a rise in serum creatinine level, without conventional therapeutic drug level monitoring. Although our data showed stable renal function after 46.9 ± 37.9 months of follow-up when the TAC trough blood level was maintained within the range of 4–6 ng/l, the issue of chronic nephrotoxicity of TAC and other calcineurin inhibitors remains a concern with long-term treatment especially in patients with chronic renal impairment due to prior renal scarring [50].

Mizoribine has been used in Japan for many years to treat patients with SLE [60, 61]. Mizoribine is an imidazole nucleoside that inhibits inosine monophosphate synthetase and guanosine monophosphate synthetase. Its ac-

tions are thus similar to those of MMF. While the drug appears to be effective and well tolerated and thus is extensively used in Japan in combination with corticosteroids for induction or maintenance [60, 61], or as part of triple immunosuppression together with corticosteroids and TAC for induction [62], there is relatively little published data in the English literature on this topic, and there are recent reports suggesting that the optimum dose of mizoribine in LN treatment remains to be determined [63].

Leflunomide, which is used in the treatment of rheumatoid arthritis, has been investigated in a clinical trial in China that compared its efficacy with intravenous CYC in patients with active proliferative LN, and the results showed comparable rates of complete remission (21 vs. 18%) and partial remission (52 vs. 55%) [64]. Infective complications and bone marrow suppression were recognized complications. A pilot study reported favorable results with proliferation signal inhibitors (also known as mTOR inhibitors) in Chinese LN patients who could not tolerate MMF or who had a history of malignancies [65]. The recent clinical trials of biological therapies for LN have included a significant number of patients from Asia [66–70]. The overall results showed that these biologics were well tolerated, but their role in the overall management paradigm of LN requires further investigation, since the clinical trials to date have failed to substantiate the advantage of using a biological agent such as anti-CD20 or CTLA4-Ig as add-on therapy to conventional immunosuppressive regimens [66, 67]. Two randomized placebo-controlled phase III trials demonstrated that belimumab (a B-lymphocyte stimulator antagonist), when added to standard treatment, could improve response rates in SLE patients without severe nephritis [68, 69]. Post hoc analysis of patients with renal involvement from these trials suggested an efficacy signal of belimumab in LN, and thus further studies are underway [70].

Conclusions

The clinical management of LN has progressed considerably over the past few decades. There is reduced reliance on corticosteroids alone, with a concomitant reduction of its associated adverse effects, following a series of studies demonstrating the efficacy and optimal ways of using immunosuppressive medications such as CYC, MPA, AZA and calcineurin inhibitors. Progress in immunosuppressive therapies and the prevention and management of disease- or treatment-related complications has brought

about improvements in the clinical outcome of patients with LN globally. In a recent survival analysis of 230 Chinese LN patients, the 20-year patient and renal survival rates were 90.5 and 89.7%, respectively [4]. By comparison, 5-year and 10-year patient survival rates of Asian SLE patients in the 1970s to 1980s were 70 and 60%, respectively [71]. This shows that despite presenting with severe renal involvement, many of the patients may respond favorably to currently available treatments. The advent of effective immunosuppressive therapies has also transformed the pattern of mortality in Asian LN patients. The leading causes of death in Asian LN patients, as in patients from other parts of the world, have changed from early complications such as acute renal failure or uncontrolled lupus disease to late complications such as infections and cardiovascular disease (occurring in patients with chronic renal failure) and malignancies [4]. Despite these clinical improvements, there are still many knowledge gaps that are highly relevant to managing LN patients in Asia. For example, much of the data on Asian patients to date has come from Chinese and, to a lesser extent, Japanese and Korean patients, with little data from South Asia, where LN is a leading cause of renal failure. In this regard, a study from India reported a remission rate of 44% at 6 months (complete remission in 21% and partial remission

in 23%) when patients with severe LN were treated with current standard-of-care therapies, but the relatively poor baseline renal function and the high prevalence of chronic changes in renal biopsies suggested that some of the patients presented rather late [72]. The results also highlighted the importance of socioeconomic issues in health care access and delivery in Asian countries. Also, studies in Thai patients have shown that there was a marked interindividual difference in MPA metabolism and that drug exposure was related to therapeutic response [73, 74]. In this regard, there are ongoing studies on the pharmacokinetics and pharmacogenomics of MPA in different Asian populations. The role of biological therapies remains to be established, as does the optimal management of patients with crescentic LN or thrombotic microangiopathy. Infective complications present a leading cause of morbidity and mortality in LN patients in many parts of Asia, and their prevention as well as treatment may vary according to local circumstances; thus, management strategies should be based on local data.

Disclosure Statement

The authors have no conflict of interest to declare.

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