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REVIEW

Current and emerging treatment options in the management of lupus

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Abstract: Systemic lupus erythematosus (SLE) is a complex autoimmune disease with variable clinical manifestations. While the clearest guidelines for the treatment of SLE exist in the context of lupus nephritis, patients with other lupus manifestations such as neuropsychiatric, hematologic, musculoskeletal, and severe cutaneous lupus frequently require immunosuppression and/or biologic therapy. Conventional immunosuppressive agents such as mycophenolate mofetil, azathioprine, and cyclophosphamide are widely used in the management of SLE with current more rationalized treatment regimens optimizing the use of these agents while minimizing potential toxicity. The advent of biologic therapies has advanced the treatment of SLE particularly in patients with refractory disease. The CD20 monoclonal antibody rituximab and the anti-BLyS agent belimumab are now widely in use in clinical practice. Several other biologic agents are in ongoing clinical trials. While immunosuppressive and biologic agents are the foundation of inflammatory disease control in SLE, the importance of managing comorbidities such as cardiovascular risk factors, bone health, and minimizing susceptibility to infection should not be neglected.

Keywords: hydroxychloroquine, mycophenolate mofetil, azathioprine, cyclophosphamide, rituximab, belimumab

Introduction

Systemic lupus erythematosus (SLE) is a complex autoimmune disease, with variable clinical manifestations, that follows an unpredictable relapsing remitting course. In the past, the main causes of death in SLE patients were uncontrolled inflammatory disease activity and infection due to immunosuppression.[1] While patients may still succumb to these complications, early atherosclerotic disease has become a major cause of morbidity and mortality in patients with SLE.[2]

It is now well recognized that cumulative organ damage, in particular renal damage, is an important predictor of mortality in SLE.[3] Recurrent flares of disease activity such as lupus nephritis are associated with poor long-term outcomes.[4,5] There remains an unmet clinical need in SLE, particularly in patients with disease refractory to conventional immunosuppressive therapies. Another key issue in the therapeutic management of SLE is the longstanding overreliance on corticosteroid therapy which contributes substantially to damage accrual and patient mortality. In this review, we focus on therapeutic advances in the management of SLE with a discussion of recent optimizations in the use of established immunosuppressive therapies and an overview of new biologic agents.

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Conventional immunosuppressive agents in the management of SLE

Induction and maintenance therapies in lupus nephritis

Immunosuppressive treatment of lupus nephritis is divided into induction and maintenance phases. There are a number of existing guidelines for the treatment of lupus nephritis including the American College of Rheumatology and European League Against Rheumatism guidelines, which are in agreement on some areas of lupus nephritis management, but differ in others.[6,7]

The aims of induction therapy in lupus nephritis are to initiate immunosuppressive therapy without delay and achieve remission of renal disease in terms of proteinuria and renal function as promptly as possible. Definitions of partial and complete renal response vary somewhat in different treatment guidelines and as endpoints in clinical trials.

The aims of maintenance therapy in lupus nephritis are consolidation of renal response achieved during induction therapy, prevention of disease flares, and prompt identification of disease relapse, ultimately leading to long-term preservation of renal function. There are no data to guide the appropriate duration of maintenance therapy beyond 3 years and hence treatment should be tailored to the individual patient. Ideally, corticosteroid should be tapered and when possible withdrawn before immunosuppression is tapered. In both the induction and maintenance phases of lupus nephritis management, avoidance of treatment-related toxicity is essential for improved quality of life and patient survival.

The main therapeutic options for induction therapy of lupus nephritis are mycophenolate mofetil (MMF) and cyclophosphamide (CYC), which are generally given with concurrent corticosteroid therapy. MMF and CYC are considered equivalent in terms of efficacy and frequency of adverse events based on clinical trials.[8–10] Unlike CYC, MMF does not adversely affect fertility, although both agents are absolutely contraindicated in pregnancy due to teratogenicity. Patients of different ancestral backgrounds may respond differently to therapy with evidence that African and Hispanic lupus nephritis patients respond less well to intravenous CYC than Caucasian or Asian patients, thus MMF may be a more preferable choice for induction therapy in these groups.[8,11,12]

It should be noted that the response to treatment with MMF versus CYC seems to be very dependent upon the treatment center. Some centers have consistently good results with MMF but poor results with CYC, while the opposite holds true in other centers. Some physicians adjust the CYC dose according to the trough white cell count 10–14 days after the infusion to ensure that the therapeutic benefit of the drug is achieved.

There are two widely used regimens of intravenous CYC as induction therapy for lupus nephritis; the low-dose Eurolupus regimen (500 mg once fortnightly for 3 months), and the high-dose NIH regimen (500–1,000 mg/m^2 intravenously monthly for 6 months).[13–15] The long-term results of these CYC regimens are comparable in terms of safety and efficacy.[16–18] The Eurolupus regimen may be preferable in patients of European ancestry.

The main choices for maintenance therapy in lupus nephritis are azathioprine (AZA) or MMF, which have been shown to have similar efficacy and frequency of adverse events in clinical trials, although one large study showed superiority of MMF over AZA.[13,16,19] As part of the decision-making process as to which maintenance therapy to use, the patients' future desire to become pregnant must be considered as MMF is known to be teratogenic whereas AZA is widely used in pregnancy.[20] The optimal duration of maintenance therapy in lupus nephritis before tapering or withdrawal is as yet unknown and is currently at the treating physician's discretion.

Calcineurin inhibitors may provide a useful adjunctive therapy in lupus nephritis. A recent Chinese study comparing MMF in combination with tacrolimus was proven to be superior to intravenous CYC in terms of achieving complete renal remission.[21] In a previous study, tacrolimus was found to be noninferior to MMF when combined with prednisolone for induction therapy of active lupus nephritis.[22] When followed by AZA maintenance for 5 years, a trend toward higher incidence of renal flares and decline in renal function was observed in those who received tacrolimus induction therapy.[23] Tacrolimus may be particularly useful as adjunctive therapy in patients with persistent proteinuria despite other therapies, and in the management of lupus nephritis in pregnancy.[24]

Immunosuppression in nonrenal lupus

Neuropsychiatric lupus

The approach to the management of neuropsychiatric lupus depends on the underlying etiology which may be inflammatory, thromboembolic, or neurotoxic in origin. Clinical manifestations such as cerebral vasculitis, aseptic meningitis, optic neuritis, transverse myelitis, refractory seizures, acute confusional state, and psychosis are frequently driven by inflammation and may be managed with immunosuppression. Unlike lupus nephritis, there is a

paucity of randomized controlled trials in neuropsychiatric lupus given the heterogeneity of clinical manifestations and lack of standardization of outcome measures. In 2010, the European League Against Rheumatism published recommendations for the management of neuropsychiatric manifestations in SLE.[25] On the basis of published case series, one nonrandomized clinical trial, and numerous case reports, intravenous CYC is the treatment of choice for severe neuropsychiatric lupus manifestations.[26–33] Similar to lupus nephritis, AZA and MMF are frequently used as maintenance therapies for neuropsychiatric lupus.[34,35]

Inflammatory arthritis and myositis related to lupus

Hydroxychloroquine and corticosteroids remain first-line therapies for musculoskeletal manifestations of SLE; however, patients with severe inflammatory arthritis and myositis may require further management with immunosuppressive or biologic agents for inflammatory disease control.

Methotrexate (MTX), which is the disease-modifying therapy of choice in rheumatoid arthritis, has been shown to be effective in controlling inflammatory arthritis related to lupus in clinical trials, case series, and several case reports.[36–39] In patients unable to tolerate MTX, leflunomide may be considered for treatment of inflammatory arthritis related to lupus.[40,41] MMF and to a lesser degree AZA have shown efficacy in the treatment of inflammatory myositis in SLE patients and have demonstrated a steroid sparing effect.[42–44] In severe lupus-related inflammatory myositis refractory to corticosteroids and other immunosuppression, intravenous CYC has been used with some success.[42,45]

Severe cutaneous lupus

Severe cutaneous lupus may present as acute, subacute lupus erythematosus, discoid lupus erythematosus, lupus panniculitis, and lupus cutaneous vasculitis. Topical corticosteroids and immunomodulators such as topical tacrolimus and pimecrolimus, antimalarials such as hydroxychloroquine or mepacrine, and corticosteroids remain first-line therapies.

A number of randomized controlled trials and case series have shown the effectiveness of MTX in managing severe cutaneous lupus at doses ranging from MTX 10 to 25 mg per week.[46–49] Both AZA and MMF have been used to good effect in cases of recalcitrant cutaneous lupus.[50–54]

Dapsone, an immunomodulatory agent, has been shown to be effective in a number of cutaneous lupus forms including bullous lupus erythematosus, lupus panniculitis, subacute lupus erythematosus, and discoid lupus erythematosus.[55] Dapsone can cause dose-related hemolysis and patients should be screened for glucose-6-phosphate dehydrogenase deficiency prior to commencing this medication.

Thalidomide has also been used with some success in the treatment of cutaneous lupus.[56] Thalidomide is known to be teratogenic and hence female patients of childbearing age need to be taking an effective form of contraception while on this medication.

Biologic therapies, particularly rituximab and belimumab, have shown good promise in treating cutaneous lupus unresponsive to conventional immunosuppression and will be discussed in detail further on in this review.

Severe hematologic manifestations of SLE

Immune-mediated cytopenias such as thrombocytopenia, leucopenia, and hemolytic anemia frequently occur in lupus patients. Corticosteroids and immunosuppressive agents may be prescribed to manage these hematological manifestations of SLE. AZA and MMF have both been used to good effect in severe refractory lupus-related thrombocytopenia, leucopenia, and hemolytic anemia, with a steroid-sparing effect.[57,58] Intravenous CYC has been used with success in the treatment of autoimmune thrombocytopenia unresponsive to standard treatment.[59,60] Intravenous immunoglobulin has been shown to have a good therapeutic response in SLE patients with hematologic manifestations such as autoimmune thrombocytopenia and hemolytic anemia.[61,62] Biologic agents particularly rituximab have been used in refractory cases of hematologic lupus. The BLISS-52 and BLISS-76 Phase III trials of belimumab in SLE have shown efficacy in treating hematologic manifestations of SLE and will be discussed in detail later in this review.

The advent of biologic therapies in the management of SLE

In recent years, an increased understanding of the etiopathogenesis of SLE has led to the introduction of a number of biologic agents that specifically target disease pathways underlying the development and progression of lupus. These biologic agents can be broadly categorized into those directed at B-cells and non-B-cell targets. Some of these therapies such as rituximab and belimumab have entered the realm of clinical practice while others are in ongoing clinical trials.

B-cell depletion with rituximab

Rituximab is a chimeric monoclonal antibody which selectively targets B-cells with the surface marker CD20. Rituximab is widely used for the treatment of SLE in clinical

practice but remains unlicensed. It has been found to be particularly useful in SLE patients with recalcitrant disease including renal, hematologic, and cutaneous manifestations. A number of published case series and open label trials of rituximab in SLE patients have demonstrated beneficial results in these areas.[63–67] However, it is unclear whether rituximab is exclusively working via B-cell depletion, as it may have additional effects via binding of Fc gamma receptor IIB on B-cells and macrophages, thus inhibiting their activation.

A significant setback to the more widespread acceptance of rituximab in the treatment of SLE was the failure of two pivotal randomized controlled trials. Both the EXPLORER study of rituximab in nonrenal SLE and the LUNAR study in lupus nephritis failed to achieve their primary endpoints.[68,69] On a more positive note, a recent prospective observational study of rituximab as part of a corticosteroid sparing regimen in lupus nephritis has shown encouraging results.[70]

Clinical experience to date has found rituximab to be generally safe and well tolerated. However, infusion reactions, allergic or anaphylactic reactions, severe or recurrent infections, and progressive multifocal leuco-encephalopathy have been reported in rituximab-treated SLE patients (Table 1).[71,72]

Targeting B-cell survival with belimumab

B lymphocyte stimulator (BLyS), also known as B-cell activating factor (BAFF), and a proliferation-inducing ligand (APRIL) are members of the tumor necrosis factor (TNF) ligand superfamily and play key roles in the regulation of B-cell proliferation, differentiation, and immunoglobulin secretion.[77,78] BLyS exists in both membrane bound and soluble forms and is expressed by cells of the innate immune

Table 1 B-cell targeted biologic therapies in SLE

Mechanism of action and scientific rationale	Pivotal clinical trials	Ongoing trials[#]
Rituximab Chimeric anti-CD20 monoclonal antibody	Failed to meet primary endpoints in LUNAR (nephritis) and EXPLORER (nonnephritis) Phase III studies[68,69] Encouraging results from a prospective study of RITUX as part of a corticosteroid sparing regimen in lupus nephritis[70]	RITUXILUP trial (Phase III) RITUX as induction therapy followed by maintenance MMF (NCT01773616) RING study (Phase III) Persistent proteinuria in lupus nephritis despite 6 months of standard immunosuppression (NCT01673295)
Epratuzumab Humanized anti-CD22 monoclonal antibody[73]	Safe and well tolerated in early phase studies[74–76]	Two Phase III trial results of epratuzumab in moderate-to-severe SLE pending (NCT01262365, NCT01261793)
Belimumab Humanized anti-BLyS monoclonal antibody	BLISS-52 and BLISS-76 showed efficacy in general, musculoskeletal, and hematologic disease domains[84,85]	The BLISS-LN study of BEL plus standard of care versus placebo, plus standard of care in lupus nephritis (NCT01639339) Comparison of the combination of RITUX and CYC (at weeks 0 and 2) and a combination of RITUX and CYC followed by BEL (at weeks 4, 6, 8, and every 4 weeks until week 48) (NCT02260934) EMBRACE study of BEL in SLE patients of black race; recruitment ongoing (NCT01632241)
Atacicept TACI-Ig fusion protein[95]	Phase I trial showed dose-dependent reductions in Ig levels and mature and total B-cells[96] The APRIL-LN Phase II/III study in active lupus nephritis was prematurely terminated due to unexpected but significant reductions in Ig levels and serious infections[97] APRIL-SLE study was terminated early due to two unexpected deaths in the atacicept 150 mg arm[98]	ADDRESS II study examining the efficacy and safety of atacicept in SLE (NCT01972568)
Blisibimod Humanized anti-BLyS monoclonal antibody	Safe and well tolerated in early phase trials (NCT01162681)	CHABLIS-SC1 and CHABLIS-SC2 Efficacy and safety of subcutaneous blisibimod in addition to standard therapy in SLE with and without nephritis (NCT01395745, NCT02074020)
Tabalumab Humanized anti-BAFF monoclonal antibody	ILLUMINATE 1: failed to meet study endpoint[152] ILLUMINATE 2: effective at higher study dose[153]	Not for further development currently

Note: [#]Information regarding ongoing clinical trials in SLE obtained from ClinicalTrials.gov.

Abbreviations: BEL, belimumab; CYC, cyclophosphamide; Ig, immunoglobulin; MMF, mycophenolate mofetil; RITUX, rituximab; SLE, systemic lupus erythematosus; APRIL, a proliferation-inducing ligand; BLyS, B lymphocyte stimulator; TACI, TNF transmembrane activator and calcium modulator and cyclophilin ligand interactor; TNF, tumor necrosis factor; BAFF, B-cell activating factor.

system such as monocytes, macrophages, and dendritic cells. BLyS can bind to three receptors, all of which are expressed by B-cells, including TNF transmembrane activator and calcium modulator and cyclophilin ligand interactor (TACI), B lymphocyte maturation antigen (BCMA), and BAFF/BLyS receptor 3 (BR3).[79,80] Plasma and peripheral blood leukocyte mRNA BLyS levels have been shown to correlate with disease activity and autoantibody levels in SLE patients.[81,83]

Belimumab is a monoclonal antibody targeting BLyS that has been shown to be safe and efficacious in two large randomized controlled trials in SLE, the Belimumab International SLE Studies, BLISS-52, and BLISS-76.[84,85] Both of these studies excluded SLE patients with active lupus nephritis or neuropsychiatric disease.

A post hoc analysis of the organ domain scores combining both BLISS studies showed that clinical improvement with belimumab treatment was most evident in musculoskeletal and mucocutaneous domains. Less worsening of disease activity with belimumab therapy was seen in hematologic, immunological, and renal domains.[86] Another pooled post hoc analysis was performed of the BLISS studies to determine the effect of belimumab on patients with renal involvement and showed that those receiving MMF, or those with serologic activity at baseline, had a greater improvement in renal disease with belimumab than with placebo.[87] In a further post hoc analysis of the BLISS trials, greater clinical efficacy with belimumab was seen in SLE patients who were serologically more active and had higher clinical disease activity as defined as SELENA-SLEDAI (Safety of Estrogens in Lupus Erythematosus National Assessment) (Systemic Lupus Erythematosus Disease Activity Index) >10.[88]

On the basis of the BLISS clinical trial results, the US Food and Drug Administration and the European Medicines Agency approved belimumab (10 mg/kg) for use in addition to standard of care in autoantibody positive SLE patients with moderate-to-severe disease activity, with the exception of those with active lupus nephritis or neuropsychiatric lupus.

Safety and tolerability data following 7 years of belimumab patient exposure have been published showing that the most common adverse events reported were mild-to-moderate infections particularly upper respiratory tract infections.[89] One case of progressive multifocal leuco-encephalopathy has been reported to date in a belimumab-treated SLE patient.[90]

Therapies targeting T-B lymphocyte interactions with abatacept

Immunological tolerance may be induced by the blockade of costimulatory interactions between T- and B-cells. CD28 is a T-cell costimulatory ligand that interacts with the receptors B7-1 (CD80) and B7-2 (CD86). CTLA4 on activated T-cells interacts with B7 with greater affinity than CD28 resulting in a negative feedback loop that inhibits T-cell activation.[95–97] Abatacept is a fusion protein comprised of CTLA-4 (cytotoxic T-lymphocyte antigen) combined with the Fc portion of human IgG1 (CTLA-4-Ig). CTLA-4-Ig has been shown to slow progression of lupus nephritis in murine models of disease.[98–100] Clinical trials of abatacept in SLE are summarized in Table 2.

Table 2 Non-B-cell targeted biologic therapies in SLE

Mechanism of action and scientific rationale	Pivotal clinical trials	Ongoing trials
Abatacept CTL4-Ig fusion protein	Failed Phase II trial in nonrenal lupus[101] Phase II/III trial in lupus nephritis failed,[102] however, a very strict end definition of complete renal response was used A reanalysis of the same study data using alternate definitions of complete renal response and showed a positive outcome in favor of abatacept[103]	Trial of abatacept plus CYCLO versus CYCLO alone in the lupus nephritis (NCT00774852)
Sifalimumab Humanized anti-IFNα monoclonal antibody	Safety demonstrated in Phase I and II trials. Inhibition of type I interferon mRNA signature seen in moderately active SLE patient.[109–111]	No current trials
Rontalizumab Humanized anti-IFNα monoclonal antibody	Safe and well tolerated in a Phase I, dose-escalation study in mildly active SLE patients[112] Failed Phase II study (NCT00962832)	Not for further development currently
Anifrolumab Humanized anti-IFNα receptor 1 monoclonal antibody[113]	Anifrolumab was shown to have a more significant and sustained impact on the interferon gene signature as compared to sifalimumab and a Phase III study of this agent is planned[114]	Phase III study planned
Tocilizumab Humanized anti-IL-6 monoclonal antibody[115–120]	Well tolerated in a Phase I trial with reduction in active urinary sediment and autoantibody titres[121] A further study of tocilizumab in 15 SLE patients with mild-to-moderate disease activity showed reduced activated T- and B-cells[122]	No current trials

Note: Information regarding ongoing clinical trials in SLE obtained from ClinicalTrials.gov.
Abbreviations: CYCLO, cyclophosphamide; IFN, interferon; Ig, immunoglobulin; IL, interleukin; mRNA, messenger RNA; SLE, systemic lupus erythematosus.

Targeting type I interferon in SLE

The type I interferon family plays a key role in innate immunity and host viral defense. It is well established that SLE patients have high serum levels of interferon-α which correlate with disease activity.[104–106] In addition, SLE patients have an interferon gene expression signature in peripheral blood mononuclear cells, particularly in the early stages of their disease course.[107,108] A number of anti-interferon-α therapies have been investigated in SLE patients with promising results and these clinical studies are outlined in Table 2. It should be noted that to date the main finding in SLE patients treated with anti-interferon-α therapies has been a decrease in the interferon gene expression signature and clinical response to these agents has yet to be fully determined. Phase III studies are now planned to investigate this further.

Adjunctive therapies in SLE

While immunosuppressive and biologic agents are the cornerstone of inflammatory disease management in SLE, the importance of managing comorbidities such as cardiovascular risk factors, bone health, and minimizing susceptibility to infection should not be neglected.

The role of antimalarials in SLE

Hydroxychloroquine, while most ostensibly used in the symptomatic treatment of musculoskeletal and cutaneous features of SLE, has a plethora of unseen beneficial effects. Low serum levels of hydroxychloroquine, suggesting poor medication adherence, have been found to be predictive of disease flares in SLE patients.[123] Furthermore, SLE patients with quiescent disease who are taking hydroxychloroquine are less likely to have a clinical flare if they are maintained on the drug.[124] Hydroxychloroquine usage is associated with a reduced risk of damage accrual in SLE patients and has a protective effect on renal damage.[125,126] In addition, hydroxychloroquine has been shown to have a beneficial effect on patient survival.[127]

Hydroxychloroquine has been shown to have a positive effect on lipid profiles in SLE patients with significant reductions in total cholesterol, low density lipoprotein, and triglycerides and significant increases in high density lipoprotein levels.[128–130] Hydroxychloroquine may also play a role in reducing cardiovascular and thrombotic risk in SLE patients.[131–133] Both current and past use of hydroxychloroquine have been associated with a beneficial effect on bone mineral density, with higher mean bone mineral density of the spine and the hip.[134,135]

Patients receiving hydroxychloroquine are at risk of developing retinopathy. While this complication is rare, it is recommended that patients have a baseline eye visual field examination. Thereafter, in low risk patients, no further testing is required for the next 5 years. After the first 5 years of therapy, an annual eye examination is recommended. In high risk patients, those with macular degeneration, retinal dystrophy, or greater than 5 year's duration of hydroxychloroquine therapy, yearly eye examinations are recommended.[136] Patients with severe renal or hepatic impairment are at greater risk of toxicity related to hydroxychloroquine due to reduced clearance of the drug and dose adjustment should be considered in such individuals.

Managing cardiovascular risk in SLE

Atherosclerosis has become a leading cause of morbidity and mortality in SLE patients. The risk of cerebrovascular and coronary heart disease-related events is 5–10 times higher in those with SLE as compared to the normal population.[137–140] SLE patients are known to have an increased prevalence of cardiovascular risk factors such as hypertension and dyslipidemia, and often tend to have a sedentary lifestyle.[137–142] Furthermore, SLE patients frequently receive corticosteroid therapy which may exacerbate their cardiovascular risk factors. In addition to an excess of traditional risk factors, it has been established that SLE patients have an inherent increased risk of cardiovascular disease and premature atherosclerosis.[143–145]

Cardiovascular risk factors in SLE patients should ideally be assessed at baseline and during follow-up on an annual basis and should include a smoking assessment, review of vascular events (cerebral/cardiovascular), and levels of physical activity, and family history of cardiovascular disease. Lipid profile, glucose, and blood pressure should be monitored and treated accordingly. All patients with SLE should have antiphospholipid antibody markers measured at diagnosis and confirmatory testing at least 12 weeks later performed if the baseline tests are positive. Those on long-term corticosteroids may require more frequent monitoring.[146]

Minimizing infection risk in SLE

Patients with SLE are at high risk of infections both as a consequence of their disease and the infection therapies used in their clinical management. The administration of inactivated vaccines, particularly the inactivated influenza vaccine and the 23-valent polysaccharide pneumococcal vaccine, is strongly encouraged in SLE patients on immunosuppression. Vaccines should ideally be given before commencing B-cell depleting therapy such as rituximab, or at least 6 months after the start of therapy but 4 weeks before the next course.

Live attenuated vaccines should be avoided in immunosuppressed patients.[147]

Bone health in SLE

The prevalence of osteoporosis in SLE varies from 4% to 24% and vertebral fracture prevalence ranges between 7.6% and 37%.[148,149] Several factors may contribute to reduced bone mineral density in a patient with SLE including persistently active disease and chronic inflammation, reduced physical activity, vitamin D deficiency, ovarian failure, and renal failure.[150] With this in mind, all patients with SLE should be assessed for adequate calcium and vitamin D intake and supplemented if necessary. Existing guidelines for the treatment and prevention of osteoporosis should be followed for postmenopausal women and those on corticosteroids.

Conclusion

The management of SLE has progressed enormously in the last 10 years and we are now in the era of biologic therapies for this complex disease. While there are currently two such agents available in some developed countries (belimumab and rituximab), intensive efforts are underway to develop further biologic therapies to address a major unmet need in patients refractory to conventional therapies. Funding for these therapies remains a major limitation to availability for patients. For example, while belimumab is widely used in North America, its use has been limited on the grounds of cost-effectiveness in many European countries.

The indications for the use of B-cell depletion therapies remain uncertain and they are currently used in patients with very active disease who have failed one or more immunosuppressive therapies. However, as in rheumatoid arthritis, there may be a case for introducing biologic therapies very early in the disease course to prevent disease progression and damage accumulation. Selecting appropriate patients for biologic therapies is very challenging and, unless done accurately, risks over treating patients who could have responded well to conventional approaches.

Designing and delivering clinical trials in SLE remains exceptionally challenging given the complexity of the disease, the variability of clinical features between patients, and the high usage of concomitant corticosteroids and effective immunosuppressive therapies. Other challenges include defining outcome measures for clinical trials – the choice of outcome can make or break a clinical trial as demonstrated in lupus nephritis.[102,103] There have been ~20 industry led trials of 16 molecules in patients with SLE, with only two successful studies (BLISS-52 and BLISS-76). Nevertheless, several ongoing studies have been outlined in this review with some grounds for cautious optimism.

Biosimilar monoclonal antibodies are becoming available. The US patent for rituximab expires in 2016 and the European patent expired in 2013. There are at least 20 pharmaceutical companies investigating rituximab biosimilars in rheumatoid arthritis and lymphoma and many of these studies are direct comparisons with MabThera/Rituxan branded rituximab. To our knowledge, there are no studies of biosimilar rituximab molecules in SLE.

Overreliance on corticosteroid therapy remains an important issue in the management of SLE and contributes significantly to cardiovascular risk, long-term damage accrual, and mortality.[151] A recent prospective observational study of rituximab as part of a corticosteroid sparing regimen in lupus nephritis patients has shown encouraging results.[70] The RITUXILUP multicenter randomized controlled trial of rituximab and MMF with limited corticosteroid for the treatment of lupus nephritis is ongoing.

Hydroxychloroquine use remains the first-line agent in the treatment of SLE and evidence continues to accumulate attesting to its benefits in improving morbidity and mortality. Equally important is the fundamental need for each patient to participate in a chronic disease management program to minimize comorbidities such as infection, cardiovascular risks, bone health, and the detection and early management of disease flares to limit damage accumulation.

Disclosure

D D'Cruz reports participation in advisory boards and consultancies for Human Genome Sciences and Roche and has received consulting fees and/or has participated in clinical trials for GlaxoSmithKline, Bristol Myers Squibb, TEVA, Merck Serono, and Eli-Lilly. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the paper apart from those disclosed.

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