Contemporary treatment of systemic lupus erythematosus: an update for clinicians

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Abstract: The prognosis for patients with systemic lupus erythematosus (SLE) has improved significantly, with 20-year survival now approximately 80% owing partly to effective treatment. SLE treatment has evolved from the use of conventional drugs such as hydroxychloroquine and corticosteroids, nonspecific immunosuppressants including mycophenolate mofetil, to targeting selective components of the immune cascade with a view to increased efficacy, tolerability and safety profile. These novel treatments include B-cell-depleting antibodies and fusion proteins that block the costimulatory pathways of B and T cells. A discussion of these pharmacological options and ongoing research forms the basis of this review.

Keywords: autoimmune, B-cell therapy, lupus, immunosuppressive, SLE, treatment

Introduction

The treatment of systemic lupus erythematosus (SLE) has evolved in the last few decades owing to improved understanding of the inflammatory and immunological processes underpinning the disease. Twenty to 30 years ago, patients had a 50% mortality rate at 5 years; however, survival rates have improved considerably, with a current 20-year survival rate of 80% due to earlier recognition of disease, introduction of corticosteroids and immunosuppressive therapy and the availability of effective treatment for comorbid conditions [Pons-Estel *et al.* 2010; Urowitz *et al.* 1976]. Although many drugs are available for the use in SLE, most are used off-label.

SLE is a complex, heterogeneous autoimmune disease, which involves inflammatory processes in multiple-organ systems resulting in a broad range of clinical phenotypes from mild to severe. It is a remitting and relapsing disease with substantial patient-to-patient variation in clinical and serological manifestations. The prevalence of SLE is approximately 28–60 per 100,000 people [Johnson *et al.* 1995; Jonsson *et al.* 1990] with a predilection for women of childbearing age and certain ethnic groups [Bertoli and Alarcón, 2007]. The hallmark of the disease is the formation of auto-antibodies

resulting in immune complex deposition, complement activation and end-organ failure. Some of the mechanisms behind this cascade include loss of immune tolerance, increased antigenic load, excess T-cell help, defective B-cell suppression and abnormal T-cell immune responses which lead to B-cell hyperactivity and subsequently to the production of pathogenic autoantibodies [Mok and Lau, 2003]. Flares can be induced by UV light and infections, so patients should be advised to wear sunblock effective against UVA and UVB (at least factor 25) and sun-protective clothing, and to obtain treatment for infections promptly.

SLE can be broadly categorized into mild, moderate and severe disease with autoimmune glomerulonephritis being the most common, life-threatening complication. Other major-organ involvement that can be associated with significant morbidity and mortality include neuropsychiatric, cardiopulmonary and haematological manifestations. Milder disease usually comprises mucocutaneous and musculoskeletal manifestations that can be treated with simpler, less-toxic treatment pathways. The treatment of moderate to severe disease comprises initially a period of intensive immunosuppressive treatment called induction therapy. The focus of induction

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therapy is to halt any ongoing systemic inflammation and to induce remission by controlling immunological activity. This is followed by less-aggressive maintenance therapy to consolidate remission and reduce the risk of flares [Mosca *et al.* 2008].

In some SLE patients, the disease course may be aggressive and unresponsive to established therapies such as corticosteroids, azathioprine and cyclophosphamide. Toxicity associated with prolonged use of these drugs can contribute to increased morbidity and mortality. As a result, there is a continuing need to develop new therapies that can be used in refractory cases and that are less toxic and more effective than standard treatment. This article reviews traditional therapeutic options for the management of SLE and emerging therapeutic agents. These new treatments have been developed to target various stages in the immune cascade involved in the pathogenesis of SLE, including monoclonal antibody therapy targeted against B- and T-cell molecules.

Established treatment for SLE

Nonsteroidal anti-inflammatory drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used for the symptomatic management of arthralgia, mild arthritis, myalgia, serositis and fever in patients with SLE. They do not have any immunosuppressive properties. Despite their widespread use in the lupus population there is little trial evidence for safety or efficacy. They should be used for short periods of time and with caution especially in patients with renal involvement, hypertension and established heart disease. They can cause fluid retention, renal impairment and interstitial nephritis. The more cyclo-oxygenase-2 (Cox-2)-selective NSAIDs in particular may increase the risk of heart attack and stroke, although they may cause less dyspepsia and peptic ulceration than traditional, less-selective NSAIDs. Active peptic ulceration and pre-existing renal disease are contraindications to their use [Lander *et al.* 2002; Østensen and Villiger, 2001].

Hydroxychloroquine

Antimalarial drugs have been used in rheumatology for the treatment of SLE for many years. These include chloroquine, mepacrine (quinacrine/atabrine) and hydroxychloroquine. Chloroquine sulphate and phosphate are

associated with the greatest risk of ocular toxicity and are now rarely prescribed. Mepacrine may be useful for lupus-induced skin rashes but it has little effect on other manifestations. Hydroxychloroquine has emerged as the drug of choice and some experts advocate its use in all patients provided that there are no contraindications. Owing to its anti-inflammatory and immunomodulatory properties, it has a significant impact on the long-term outcome by modifying the course of illness through reduction of low-grade flares and hence slows progression to severe disease requiring more intense treatment. Accrual of long-term damage assessed by the Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Damage Index was reduced in patients on hydroxychloroquine compared with those not given it in two prospective observational cohorts [Fessler *et al.* 2005; Gladman *et al.* 2000].

Hydroxychloroquine is most useful in the management of mucocutaneous, musculoskeletal and constitutional symptoms such as fatigue and fever. Recently, hydroxychloroquine has been shown to have cardioprotective properties in several studies, by reducing total cholesterol, low-density lipoprotein (LDL) cholesterol and triglycerides (TG) and increasing high-density lipoprotein (HDL) cholesterol levels [Petri *et al.* 1994; Wallace *et al.* 1990]. Rahman and colleagues found that when used in combination with steroid therapy there was a 9–11% reduction in total cholesterol compared with patients taking steroid alone [Rahman *et al.* 1999].

Hydroxychloroquine has a good safety profile and toxicity is infrequent, mild and largely reversible. In pregnancy, it is safe with noticeable reduction in SLE activity and no adverse effects on the child [Buchanan *et al.* 1996; Parke and West, 1996; Levy *et al.* 1991]. Retinal toxicity and macular damage are rare with hydroxychloroquine. Analysis of data from four studies looking at the occurrence of retinal toxicity in 647 patients treated with chloroquine for a mean of >10 years found 16 (2.5%) patients were diagnosed as having definite retinal toxicity in comparison with only 2 (0.1%) of 2043 patients observed in 6 studies taking hydroxychloroquine for a similar period ($p < 0.001$) [Ruiz-Irastorza *et al.* 2010]. Owing to the remote risk of hydroxychloroquine-related maculopathy, guidance from the Royal College of Ophthalmology, UK, states

that doses should not exceed 6.5 mg/kg/day and patients should have yearly visual acuity monitoring. Age-related macular degeneration may preclude monitoring for ocular toxicity [Royal College of Ophthalmologists, The British Society of Rheumatology and British Association of Dermatologists, 2009].

Mepacrine is used mainly to treat discoid lupus and subacute cutaneous lupus erythematosus. It can be combined with hydroxychloroquine due to the synergistic benefits of antimalarials. There are negligible effects on ocular toxicity; however, mepacrine can cause other side effects such as yellowing of the skin and bodily fluids, which resolves once the drug is discontinued [D'Cruz, 2001].

Corticosteroids

For many decades corticosteroids given in different preparations have been central to the treatment of SLE due to their anti-inflammatory properties in the short term and immunosuppressive actions in the long term. Prednisolone and prednisone are safe in pregnancy as they are inactivated by 11 β -hydroxysteroid dehydrogenase, so that less than 10% crosses the placenta [Østensen *et al.* 2006]. Topical steroids may be used for inflammatory skin rashes and, in severe cases of discoid lupus, intralesional preparations can be used. For localized soft tissue and joint involvement, intra-articular steroid injections with or without local anaesthetic agent may be a more direct and preferred treatment option.

In mild disease, prednisolone is given in doses starting at 0.1–0.3 mg/kg/day followed by a gradual tapering dose regimen according to clinical response. The dose rises to 0.4–0.6 mg/kg/day in moderate disease and as high as 0.7–1.5 mg/kg/day in very severe disease. At such high doses, pulse therapy with intravenous (IV) methylprednisolone (MP; 500–1000 mg on one to three occasions) is deemed by many physicians to be safer with fewer associated side effects. IV therapy is considered in patients that have not responded to oral therapy and/or have serious manifestations of SLE such as lupus nephritis, neuropsychiatric disease, severe refractory thrombocytopenia, haemolytic anaemia, severe vasculitis and cardiopulmonary disease.

Several studies have shown that a short course of moderate-dose corticosteroids can not only treat active disease but can also help prevent flares in

clinically stable but serologically active patients. Tseng and colleagues looked at 41 patients with serologically active disease (rise in quantitative dsDNA by 25% and fall in C3 by 50%) and randomized them to receive either 30 mg of prednisolone tapered rapidly over 1 month or placebo [Tseng *et al.* 2006]. Clinical deterioration (disease activity recorded by the SLE Disease Activity Index [SLEDAI]) was observed in 6 out of the 20 patients in the placebo arm and none in the prednisolone group ($n=21$, $p=0.007$) with an associated significant improvement in the serological markers in the active treatment arm. In practice, however, physicians usually stop steroid reduction in serologically active patients and await clinical manifestations before increasing doses due to the toxicity of steroids.

Corticosteroid treatment is not without complications. Patients are at risk of dose-related immediate problems such as fluid retention, hypertension, blurred vision and infection and more gradual effects such as weight gain, steroid-induced diabetes, osteoporosis and avascular necrosis. Corticosteroids contribute to premature atherosclerosis as they have pro-atherogenic properties through adverse effects on metabolic factors such as body fat distribution, blood pressure and glucose metabolism [Barnes *et al.* 2005; Roman *et al.* 2003; Esdaile *et al.* 2001]. They have been shown to cause a rise in the level of LDL cholesterol and TG and a fall in HDL cholesterol [Bruce *et al.* 1999; Leong *et al.* 1994]. The benefit/risk ratio of reducing chronic inflammation *versus* side effects and cardiovascular risk should be assessed on an individual basis, as there is increasing evidence that inflammation itself predisposes to atherosclerosis and steroids can reduce this risk [Roman *et al.* 2003].

Immunosuppressive therapies

In patients with moderate-to-severe disease who require 10 mg prednisolone/day or more to manage their disease, other immunosuppressive agents should be added to reduce the steroid requirements, reduce inflammation and ultimately organ damage.

Azathioprine

Azathioprine is commonly used for the induction of remission and as a steroid-sparing agent in mild-to-moderate disease. It works by affecting cell-mediated and humoral immune responses via the inhibition of lymphocyte proliferation,

reduction in antibody production and suppression of natural killer cell activity. In severe disease, it is used as maintenance therapy and data from lupus nephritis trials show significant improvement in disease activity following induction therapy with cyclophosphamide or mycophenolate mofetil (MMF) [Mok *et al.* 2004]. It may be associated with gastrointestinal side effects, such as nausea, vomiting and diarrhoea, occasionally severe enough to lead to drug withdrawal. Mild transaminitis may occur and reversible bone marrow suppression is not uncommon. Unique to azathioprine is the association with genetic polymorphisms that cause decreased thiopurine methyltransferase (TPMT) activity and thus impaired ability to degrade 6-mercaptopurine into the inactive metabolite. Testing for TPMT can help to predict drug-induced leucopenia in patients with low or absent TPMT activity [Boumpas and Papadimitraki, 2007]. It is safe in pregnancy, as the foetal liver cannot metabolise azathioprine to the active metabolites [Østensen *et al.* 2006].

Cyclophosphamide

Cyclophosphamide is an alkylating agent, which causes cell death at any stage of the cell cycle. It also depletes both B and T cells, hence reducing the production of pathogenic auto-antibodies [Boumpas and Papadimitraki, 2007]. It may be given orally or intravenously, however, research suggests that intermittent IV pulse therapy has a better efficacy-to-toxicity ratio and hence has largely replaced oral dosage.

Trials conducted by the National Institutes of Health (NIH) have shown more benefit from IV cyclophosphamide than high-dose oral corticosteroids for the treatment of lupus nephritis [Austin *et al.* 1986]. In a subsequent study, patients were randomized to receive either IV MP monthly for 6 months, short-course IV cyclophosphamide (monthly pulses for 6 months) or long-course IV cyclophosphamide (monthly pulses for 6 months followed by pulses every 3 months for 24 months) in addition to oral prednisolone. Sustained rise in creatinine and significantly higher probability of exacerbations were observed more often in the groups that received MP and the short-course cyclophosphamide compared with the group receiving long-course cyclophosphamide [Boumpas *et al.* 1992]. These findings were supported by longer duration studies that demonstrated that the combination of pulse cyclophosphamide and MP was

more effective than the individual treatments without conferring additional risk for adverse events [Illei *et al.* 2001]. IV cyclophosphamide became the standard of care, although unlicensed, for induction of remission in severe renal manifestations of lupus owing to the ability to slow the progression to end-stage renal failure [Flanc *et al.* 2004; Gourley *et al.* 1996].

Cyclophosphamide has been shown to be also effective for the treatment of nonrenal manifestations in patients with lupus nephritis [Ginzler *et al.* 2010]. In a study comparing the treatment of neurological syndromes (seizure, peripheral neuropathy, optic neuritis, transverse myelitis, brainstem disease, coma and internuclear ophthalmoplegia) using IV cyclophosphamide and IV MP, clinical response defined as $\geq 20\%$ improvement from basal conditions in clinical, laboratory or specific neurological testing was observed in 18 out of 19 patients who received cyclophosphamide compared with 7 out of 13 who received MP [Barile-Fabris *et al.* 2005].

The use of low-dose cyclophosphamide was investigated in the Euro-Lupus Nephritis Trial with a follow-up period of 10 years. Ninety patients were randomized to receive NIH-like high-dose regimen (six monthly pulses followed by two quarterly pulses) or Euro-Lupus low-dose regimen (six pulses of cyclophosphamide every 2 weeks at a fixed dose of 500 mg). The cumulative risk of end-stage renal disease or death was not significantly higher in the latter group [Houssiau *et al.* 2010]. Increasing evidence suggests that patients (mainly Caucasian in trials to date) may achieve disease control with lower cumulative doses of cyclophosphamide. Overall, established evidence for disease control and improved outcomes in lupus supports its use as a recognized standard of care.

Side effects of cyclophosphamide include nausea, reversible hair loss, ovarian failure which is both age and dose related and can affect up to 38–52% of women receiving treatment [Blumenfeld *et al.* 2000; Boumpas *et al.* 1993], myelotoxicity, and severe infections such as bacterial and opportunistic infections, reactivation of latent Herpes zoster, Mycobacterium tuberculosis and human papilloma virus. The risk of malignancy is reported to be higher with alkylating agents because of direct chromosomal damage and increased immune surveillance. Longer duration of use (greater than 2–3 years) or high

cumulative dose (greater than 20 g) increases the risk further [Stillwell *et al.* 1988]. Cancers that have been linked with cyclophosphamide use are haematological malignancies, namely myelodysplastic syndromes, acute leukaemia and myeloma, and skin and bladder cancer amongst others [Radis *et al.* 1995]. It is teratogenic and so must be avoided during pregnancy and for at least 3 months before a planned pregnancy [Østensen *et al.* 2006].

Newer agents

Mycophenolate mofetil

MMF is an ester prodrug for mycophenolic acid, which inhibits inosine-5-monophosphate dehydrogenase, an enzyme involved in the *de novo* synthesis pathway of purine. *In vitro*, it exerts its immunosuppressive effect by inhibiting B- and T-cell proliferation effects, causing suppression of antibody production and reduction of adhesion molecules that are necessary for the migration of lymphocytes to sites of inflammation [Allison, 2005]. It has been used to prevent transplant rejection for over 10 years and currently is recognized as an alternative immunosuppressive agent to cyclophosphamide or azathioprine for the treatment of lupus nephritis. Earlier studies showed that mycophenolate is as effective as IV cyclophosphamide for the induction of remission [Chan *et al.* 2005, 2000; Ginzler *et al.* 2005] and maintenance therapy [Contreras *et al.* 2004] in patients with lupus nephritis.

Following these results, a randomized, multicentre, prospective, open-label parallel group clinical trial, the Aspreva Lupus Management (ALMS) study, was set up to investigate the effects of mycophenolate and IV cyclophosphamide on the disease including the induction and maintenance of remission, prevention of flare in lupus nephritis (class III, IV or V) and assessed nonrenal manifestations as a secondary endpoint [Ginzler *et al.* 2010; Appel *et al.* 2009]. The treatment arms were oral mycophenolate (dose titrated to reach maximum dose of 3 g/day) *versus* IV pulses of cyclophosphamide (0.5–1.0 g/m²). Results from the ALMS trial did not support superior efficacy with MMF. Response rates at week 24 (end of remission–induction phase) were 56.2% in the MMF and 53% in the IV cyclophosphamide group, respectively, showing that MMF with corticosteroid demonstrated comparable efficacy to IV cyclophosphamide with corticosteroid for

induction therapy in lupus nephritis [Appel *et al.* 2009].

Efficacy of MMF for nonrenal manifestations was initially shown in case series and open-labelled studies [Mok, 2007] and showed good response to treatment with recurrence or worsening of symptoms when the dose was tapered in the majority of patients who had haematological or dermatological disease. More recent findings by [Ginzler *et al.* 2010] from the ALMS trial support previous observational data that MMF and IV cyclophosphamide are both able to reduce nonrenal (notably mucocutaneous, cardiovascular, respiratory, musculoskeletal and vasculitis) as well as renal lupus manifestations and can reduce the incidence of disease relapse. It was noted that Black and Hispanic patients responded better to MMF than to IV cyclophosphamide.

The data is not as robust and convincing for the use of MMF in neuropsychiatric disease, with poor response noted in patients with transverse myelitis experiencing relapse despite ongoing maintenance therapy with MMF and low-dose corticosteroids. As a result, pulse therapy with cyclophosphamide remains the mainstay of treatment in severe central nervous system (CNS) disease and MMF should only be considered in patients who are refractory to, intolerant of, or reluctant to use cyclophosphamide.

Adverse events associated with MMF include gastrointestinal side effects such as diarrhoea, nausea and vomiting which can be minimized by reducing or splitting the dose. Some studies reported infection (cellulitis, herpes zoster) as a complication of its use, however this is a recognized complication of all cytotoxic agents. MMF is more acceptable than cyclophosphamide in women of childbearing age as it does not cause gonadal toxicity. Patients, however, must be strongly advised against pregnancy during MMF treatment due to teratogenicity [Anderka *et al.* 2009; Østensen *et al.* 2008].

In conclusion, MMF, although unlicensed in SLE, is increasingly being used for the induction and maintenance of remission of proliferative lupus nephritis and other severe manifestations of SLE. Further studies are required to confirm efficacy and more robust conclusions can only be drawn once long-term data following exposure to the drug become available.

Other treatment strategies for lupus patients

So far, this review has focused on first-choice drugs for the treatment of SLE, but others include methotrexate [Fortin *et al.* 2008; Wong and Esdaile, 2005] and leflunomide [Tam *et al.* 2004; Remer *et al.* 2001] for controlling mild-to-moderate arthritis and cutaneous manifestations. The calcineurin inhibitor, cyclosporin, has demonstrated good efficacy in the treatment of moderate proliferative nephritis and may be used as an alternative maintenance drug to azathioprine or as a steroid-sparing agent in SLE [Griffiths *et al.* 2010]. Owing to the risk of hypertension, blood pressure should be monitored closely [Griffiths and Emery, 2001]. Tacrolimus has also been shown to be effective in the management of severe cutaneous disease and discoid lesions [Bohm *et al.* 2003]. Some lupus cohorts have reported success using IV immunoglobulin in patients with acute disease flares including cytopenias, neurological involvement and secondary antiphospholipid syndrome, with concomitant sepsis, but this has not been confirmed in trials.

As total care for SLE patients gets better and survival rates improve, the risk of developing comorbid conditions, either due to the disease and or its treatment rises. A bimodal pattern of mortality in SLE has been observed with an early peak, less than 5 years from diagnosis, due to active disease, lupus nephritis and/or sepsis and a later peak, more than 5 years after diagnosis increasingly due to cardiovascular complications [Urowitz *et al.* 1976]. Lupus patients develop cardiovascular disease earlier than the general population and overall women have a five- to six-fold increased risk of myocardial infarctions, stroke and congestive heart failure [Chung *et al.* 2006; Bessant *et al.* 2004; Esdaile *et al.* 2001; Manzi *et al.* 1997]. Strict surveillance of these patients must occur to address associated issues such as premature atherosclerosis, hypertension, dyslipidaemias, diabetes and osteoporosis with optimization of risk factors using targeted treatment to improve outcomes.

Novel therapies

In the past few years, based on improving knowledge of immunological abnormalities, intensive research has gone into the development of more targeted approaches, particularly involving T and B cells that are currently under evaluation for treating patients with lupus. Monoclonal antibodies targeting several surface molecules

on B cells have been developed to reduce the formation of auto-antibodies. Drugs include rituximab (anti-CD20), ocrelizumab (humanized anti-CD20), belimumab (anti-BAFF/BLyS), atacicept (anti-BLyS/APRIL) and epratuzumab (humanized anti-CD22). In addition, other key cell-surface markers have been developed to interfere with costimulatory molecules such as cytotoxic T lymphocyte antigen 4 (abatacept).

B-cell depleting therapies

Rituximab. Rituximab is a chimeric mouse-human monoclonal antibody with high specificity and affinity for CD20 antigen expressed on B lymphocytes from the pre-B stage to the mature B stage, but absent in haematopoietic precursor stem cells and plasma cells. It causes cell lysis via antibody-dependent cell-mediated cytotoxicity and induction of apoptosis causing depletion of B cells in peripheral blood, tissues, bone marrow and lymph nodes [Reff *et al.* 1994]. Treatment causes a rapid decline in peripheral B cells and this has been reported in open-labelled studies to occur in 1–4 weeks and last about 4–9 months (average approximately 6 months). It may be prolonged in some patients for up to 2 years [Leandro *et al.* 2005; Sfikakis *et al.* 2005]. Almost all patients achieve complete peripheral depletion which is recorded as <5 CD19⁺ B cells/ μ l and studies have shown that where there is failure to achieve this, patients do not experience significant reduction in SLE disease activity [Looney *et al.* 2004]. Relapse of disease occurs after the return of circulating B cells and some predictors of a flare have been identified to be the presence of anti-ENA antibodies (Ro, La, Sm) at the time of B-cell depletion and low levels of C3 complement [Cambridge *et al.* 2007; Ng *et al.* 2007].

Results from uncontrolled single-arm open-labelled trials have suggested that rituximab is efficacious in the treatment of severe, refractory SLE including renal lupus, CNS disorders and haematological disease [Lu *et al.* 2009; Gunnarsson *et al.* 2007; Tokunaga *et al.* 2007; Leandro *et al.* 2005; Sfikakis *et al.* 2005]. A systematic review of the literature from 2002–2007 identified 188 patients treated with rituximab for severe, refractory disease who matched the search criteria. Of these patients, 171 (91%) showed a significant improvement in at least one lupus manifestation, with 91% of patients with lupus nephritis showing therapeutic response

[Ramos-Casals *et al.* 2009]. These findings supporting the use of rituximab in the treatment of severe SLE were observed in other uncontrolled studies; however, data from the prospective multicentre, randomized, double-blind placebo-controlled studies of rituximab in patients with lupus nephritis (LUNAR) and nonrenal disease (EXPLORER) failed to show significant benefit.

In the phase III LUNAR study ($n=144$), patients with class III/IV lupus nephritis were randomized to receive rituximab or placebo on a background of MMF and corticosteroids. The primary endpoints of the study were to compare complete and partial responses in the two groups at week 52. Although there were more patients achieving complete and partial remission in the rituximab group, there was no significant difference in these endpoints (57% *versus* 46% in the rituximab *versus* placebo group respectively, $p=0.55$). Rituximab, however, had a greater effect on levels of anti-dsDNA and complement [American College of Rheumatology, 2009]. Whether or not a study of longer duration, as was performed at the NIH for IV cyclophosphamide, would have shown a difference remains unknown.

The EXPLORER study [Merrill *et al.* 2010] tested the safety and efficacy of rituximab *versus* placebo in patients with moderate-to-severe active extra-renal SLE. Patients were randomized to receive rituximab or placebo with a tapering oral prednisolone regime depending on BILAG scores at entry, in addition to baseline immunosuppressive therapy with MMF, methotrexate or azathioprine. The primary and secondary endpoints were not met with an overall response rate of 28.4% in the placebo group *versus* 29.6% in the rituximab group ($p=0.9750$). Further analysis suggested that rituximab may be more effective than placebo in patients with methotrexate as background therapy and in African Americans and Hispanics. Patients in the rituximab group demonstrated some biological response to treatment with improvement in immunological parameters as was seen in LUNAR, and there was a trend towards a reduction in the rate of severe (A) flares and a trend to increased time between flares but these were not predefined primary or secondary endpoints [Merrill *et al.* 2010; Tew *et al.* 2010]. However, these results suggest that it may be worth undertaking further trials with different endpoints and possibly different entry criteria.

Rituximab may still have a role for controlling severe disease in some refractory patients. Reasons for trial failure remain the subject of debate. Problems with study design and methodology, including failure to recruit the same type of patients as those treated in open-label studies, overuse of concomitant steroids and continued treatment with other immunosuppressive drugs and insufficient duration of follow up are some of the potential reasons. In addition, very stringent criteria were used to define response. For example, the development of mild sun-induced rash and transient episodes of arthritis constituted treatment failure despite milder disease compared with baseline.

Most studies suggest that rituximab is safe and well tolerated. The lack of CD20 expression on plasma cells means that there is preservation of pre-existing humoral memory and immunoglobulin levels are not significantly affected in patients treated with the drug. However, there is concern that B-cell depletion therapy may predispose to serious infections following repeated cycles of treatment or when used with concomitant immunosuppressive agents. Overall, most studies do not report significant change in total serum IgG levels, which may be a reason why infection rates remain low with rituximab [Cambridge *et al.* 2003]. This is in keeping with long-term safety data emerging from lymphoma patients receiving a cycle of rituximab every 6 months for a total of four courses. Median follow up in this group was 55 months. No late toxicities were observed and the overall infection rate was calculated to be 3% [Hainsworth, 2004]. Bacterial and viral infections have been reported and these respond fully to targeted antimicrobial or antiviral treatment. Progressive multifocal leucoencephalopathy (PML) is a fatal viral infection of the central nervous system caused by the John Cunningham (JC) virus (an opportunistic virus which remains latent indefinitely in about 80% of the arthritis receiving rituximab worldwide) [Allison, 2010] and two with SLE (see <http://www.fda.gov>). Safety warnings have been issued, patients should be counselled about it and there must be high awareness of this possibility, although the concerns are with immunosuppression in general in autoimmune diseases and not solely with rituximab in SLE.

Human antichimeric antibodies (HACAs) have been reported as a complication of treatment with rituximab and have been noted in

lymphoma and rheumatoid arthritis patients [Edwards *et al.* 2004]. They are more immunogenic in active SLE, hence may cause increased infusion reactions and have been associated with increased risk of serum sickness [Smith *et al.* 2006; Herishanu, 2002]. In addition they may lead to more rapid drug clearance and subsequently reduced clinical efficacy. One observational study showed that HACA levels >100 ng/ml have been associated with more rapid rituximab pharmacokinetics and less-effective B-cell depletion [Looney *et al.* 2004].

Epratuzumab. Another therapeutic target is CD22, which is first expressed in the cytoplasm of precursor B cells and then on the surface of B cells as they mature with expression ceasing with B-cell differentiation into plasma cells. Epratuzumab is a fully humanized monoclonal antibody hence greatly reducing the risk for immunogenicity. Unlike rituximab, a cytotoxic therapeutic antibody, epratuzumab works differently by acting as an immunomodulator. It does not completely deplete but reduces the population of hyperactive B cells by 30–45% without any apparent changes to T cells or immunoglobulin levels hence presenting as an attractive molecular target for treatment of SLE.

Preliminary data from an open-labelled study of 14 patients with moderately active SLE treated with epratuzumab was promising with sustained reduction in total BILAG scores by 50% in all 14 patients over the total duration of the evaluation period (32 weeks) [Dörner *et al.* 2006]. Subsequent phase II placebo-controlled trials, which were terminated prematurely due to lack of drug supply, have demonstrated improvement in BILAG index scores, reduction in corticosteroid requirements and improvement in general health status in patients treated with epratuzumab [Petri *et al.* 2008; Strand *et al.* 2008]. Results of a phase IIb dose and regimen-ranging trial in patients with nonrenal lupus has shown treatment advantage over placebo and full results will be presented at international meetings in 2010 [Reuters, 2009]. These results are encouraging but certainly longer-term, randomized, multicentre controlled studies need to be conducted for firmer conclusions on efficacy, safety and tolerability to be drawn.

Inhibition of B-lymphocyte stimulator. Serum B-cell activating factor belonging to the tumour necrosis factor (TNF) family (BAFF) also known

as B-lymphocyte stimulator (BLyS) regulates the development of marginal-zone and follicular B-cell populations and appears to be important for the development of peripheral B cells promoting SLE [Ding and Jones, 2006; Kalled, 2005]. Studies have shown that levels of BLyS are elevated in SLE. In a phase II study [Wallace *et al.* 2009], 449 patients with active SLE were given escalating doses of belimumab, a human monoclonal antibody that specifically recognizes and inhibits the activity of BLyS or placebo. Belimumab reduced circulating B cells by 50% and anti-dsDNA antibodies by 30%, but failed to reduce disease activity measured by SLEDAI or increase the time to flare. Failure to reach primary efficacy endpoints has raised concerns about study design as not all patients had autoantibodies at recruitment. This may have contributed to apparent lack of drug efficacy. The results of two phase III studies have been announced: BLISS-52 [D'Cruz *et al.* 2010] and BLISS-76 [GlaxoSmithKline, 2009]. The primary endpoint was met in both studies and belimumab treatment was associated with a reduction in prednisolone dosage and improvement in the physical component score of the SF-36 health survey in BLISS-52. These results are most encouraging and it is anticipated that belimumab may receive a license for use in SLE in 2011.

An alternative drug, atacicept, is a recombinant TACI-Ig fusion protein that also inhibits B-cell stimulation hence reducing the production of autoantibodies, by binding to BLyS and a proliferation-inducing ligand (APRIL) [Gatto, 2008]. Preliminary results from two phase Ib clinical trials in patients with SLE treated with atacicept were positive with reduction in circulating B-cell levels [Dall'Era *et al.* 2007], however a phase II study started in lupus nephritis had to be stopped due to adverse events in patients on background MMF. A phase II study in nonrenal lupus is ongoing.

Modulation of costimulatory pathways

Other mechanisms of disrupting the immune cascade in addition to B-cell inhibitory therapies involve targeting the interactions between B and T cells, which are necessary to induce T-cell-dependent autoantibody production. One such mechanism utilizes the CD40–CD40 ligand pathway. T-cell activation is required for the activation of other cells such as macrophages and B cells that are important in the inflammatory

cascade resulting in the release of TNF and other cytokines. Development of a recombinant fusion protein that causes direct inhibition of B- and T-cell collaboration through the inhibition of CD40 (on B cells) and CD40L (on T cells) has been demonstrated to be effective in murine models of lupus but the anti-CD154 (CD40 ligand) antibody, IDEC-131, did not show efficacy in humans [Kalunian *et al.* 2002]. Trials in humans with another anti-CD40 ligand antibody (BG9588;5c8) were terminated prematurely because, although one study showed encouraging results with reduction in anti-dsDNA antibody production and rise in C3 levels, there were reports of increased life-threatening prothrombotic activity [Boumpas *et al.* 2003].

Abatacept

Abatacept is a human CTLA4-Ig fusion protein that acts as a selective costimulation modulator as it has a higher affinity for CD80/86 on antigen-presenting cells than does CD28 on T cells. This prevents the interaction of CD28-CD80/86 and hence effectively suppresses T-cell activation [Cunnane *et al.* 2004; Liossis and Sfrikakis, 2004]. It is licensed for use in rheumatoid arthritis [Kremer *et al.* 2003]. The phase II trial in nonrenal SLE did not meet its primary endpoint of flare prevention but there was some evidence that it may be helpful in lupus arthritis and is worthy of further study [Merrill *et al.* 2010, 2008].

Conclusion

In summary, treatment of SLE should be planned on an individual basis with consideration for using the best-suited therapy to target the affected organ systems. The heterogeneity of the disease, lack of a specific biological marker and absence of a single outcome measurement for improvement makes this process difficult. Despite some research evidence supporting the use of several drugs in SLE, only hydroxychloroquine, corticosteroids and azathioprine are widely approved or licensed for use in lupus. IV pulses of cyclophosphamide and MP have emerged internationally as the gold standard for the induction of remission in severe lupus. Newer agents, such as MMF, have demonstrated comparable efficacy and less toxicity than cyclophosphamide. For maintenance therapy, less-toxic agents such as azathioprine, MMF or cyclosporin are equally effective and are used in the current management of lupus. The advent of new biological drugs brings hope for management of lupus

in the future as no new drugs have been licensed for over 50 years.

In addition to drug therapy, SLE patients should be educated about their disease to ensure concordance with treatment, as lack of compliance contributes to treatment failure with disease flares, accumulation of damage including renal failure and increased risk of death.

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Conflict of interest statement

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