

Key issues in the management of patients with systemic lupus erythematosus: latest developments and clinical implications

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Abstract: Systemic lupus erythematosus (SLE) is a chronic multisystem disease with significant associated morbidity and mortality. A deeper understanding of the pathogenesis of SLE has led to the development of biologic agents, primarily targeting B cells and others inhibiting costimulatory molecules, type I interferons and cytokines such as interleukin-6. Several of these agents have been studied in clinical trials; some have shown promise while others have yielded disappointing results. Economic and regulatory issues continue to hamper the availability of such therapies for SLE patients. With increasing recognition that recurrent flares of disease activity lead to long-term damage accrual, one of the most important recent developments in patient management has been the concept of treat-to-target in SLE while minimizing patient exposure to excessive corticosteroid and other immunosuppressive therapy. This article reviews these key issues in SLE management, outlining recent developments and clinical implications for patients.

Keywords: biologic therapies, long-term damage accrual, treat-to target

Introduction

Systemic lupus erythematosus (SLE) is a complex heterogeneous disease which follows an unpredictable relapsing remitting course. With the advent of earlier detection, rationalization of immunosuppressive regimens and advances in renal supportive therapy such as dialysis and renal transplantation, the prognosis and survival of patients with SLE has significantly improved over recent decades. In the past the major cause of death in SLE was uncontrolled disease activity [Merrell and Shulman, 1955]. Currently, atherosclerotic complications, malignancy, infection and to a lesser degree active disease are the chief causes of mortality in SLE [Bernatsky *et al.* 2006].

There remains an unmet clinical need in SLE, particularly in lupus nephritis and neuropsychiatric disease resistant to conventional immunosuppressive therapies. Recurrent flares of lupus nephritis activity are associated with poor long-term renal outcomes [Moroni *et al.* 1996; Mosca *et al.* 2002]. Renal damage is known to be the

overall most important predictor of mortality in SLE patients [Danila *et al.* 2009]. Overreliance on corticosteroids remains an issue in the management of SLE and contributes to long-term damage accrual and mortality [Bruce *et al.* 2014].

The advent of biologic agents in the management of SLE

Over the past decade, advances in our understanding of SLE pathogenesis have led to the introduction of biologic therapies specifically designed to target areas of the immune system that are integral to disease development and progression. These therapies can be broadly divided into those directed at B cells and non B-cell targets. There is a clear logic of targeting B cells in SLE given their key role in autoantibody formation resulting in immune complex deposition in tissues such as the kidneys and skin. Other targets of biologic therapies in SLE include B-cell and T-cell interactions and cytokines with pivotal roles in SLE pathogenesis such as type I interferons.

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B-cell depletion therapies

Rituximab

The predominant B-cell depleting therapy currently used in the clinical management of SLE is rituximab, a chimeric monoclonal antibody which selectively targets B cells with the surface marker CD20. Rituximab, while widely used, particularly in SLE patients with resistant disease, remains unlicensed. Rituximab has been approved for the management of other rheumatic diseases such as rheumatoid arthritis and antineutrophil cytoplasmic antibody (ANCA) associated vasculitis on the basis of positive data from randomized controlled trials [Cohen *et al.* 2006; Stone *et al.* 2010; Jones *et al.* 2010]. Several case series and open label trials of rituximab in SLE have yielded encouraging results [Lu *et al.* 2009; Terrier *et al.* 2010; Catapano *et al.* 2010; Diaz-Lagares *et al.* 2012; Pepper *et al.* 2009]. However, two randomized controlled trials of rituximab in nonrenal SLE (EXPLORER) and in lupus nephritis (LUNAR) failed to achieve their primary endpoints [Merrill *et al.* 2010b; Rovin *et al.* 2012]. It should be noted that patients in both the LUNAR and EXPLORER studies were taking significant amounts of background immunosuppression, including corticosteroid, which may in part account for the poor study outcomes highlighting the importance of study design in clinical trials of SLE.

A recent prospective observational study of rituximab as part of a corticosteroid sparing regimen in lupus nephritis patients has shown promising results [Condon *et al.* 2013]. This has led to a multicentre randomized controlled trial (RITUXILUP) with rituximab as induction therapy followed by maintenance mycophenolate mofetil. This study is ongoing, the results of which are keenly anticipated [ClinicalTrials.gov identifier: NCT01773616].

Another ongoing trial of rituximab in SLE is the RING study (Rituximab for Lupus Nephritis With Remission as a Goal), which is an open-label, multicentre trial aiming to determine the efficacy of rituximab in achieving complete renal remission in lupus nephritis patients with persistent proteinuria despite a minimum of 6 months of standard immunosuppression [ClinicalTrials.gov identifier: NCT01673295].

From a safety point of view while rituximab is generally safe and well tolerated, infusion reactions, allergic or anaphylactic reactions, severe or

recurrent infections and progressive multifocal leucoencephalopathy (PML) have been reported in rituximab treated SLE patients [Diaz-Lagares *et al.* 2011; Calabrese and Molloy, 2008]. The US Food and Drug Administration (FDA) recently issued a warning regarding the possibility of hepatitis B reactivation in patients who have received rituximab [Burton *et al.* 2015].

Epratuzumab

Epratuzumab is a monoclonal antibody targeting anti-CD22, a cell surface marker on transitional B cells and naïve mature B cells causing moderate B-cell depletion *via* antibody-dependent cellular cytotoxicity (ADCC). Epratuzumab has been shown to inhibit the proliferation of B cells from SLE patients but not normal B cells under all culture conditions [Jacobi *et al.* 2008]. The therapeutic activity of epratuzumab may not result completely from B-cell depletion. In addition, epratuzumab mediates the Fc (fragment, crystallizable) /Fc receptor (FcR) dependent membrane transfer from B lymphocytes to effector cells *via* trogocytosis, resulting in reduction of multiple B-cell receptor modulators including CD22, CD19, CD21 and CD79b, as well as important adhesion molecules [Rossi *et al.* 2013, 2014].

The first open-label study of epratuzumab treated 14 SLE patients with moderately active disease and showed that total British Isles Lupus Assessment Group (BILAG) scores decreased by $\geq 50\%$ in all participants at some point during the course of the study. The drug was well tolerated with no evidence of immunogenicity or significant changes in T cells, immunoglobulins or autoantibody levels [Dorner *et al.* 2006].

The ALLEVIATE studies of epratuzumab in moderate-to-severe active SLE were discontinued prematurely because of an interruption in drug supply. Exploratory pooled analyses of the trials showed improved BILAG scores at week 12 in 44.1% and 20.0% of epratuzumab 360 and 720 mg/m², respectively, compared with 30.0% for placebo. Adverse events were similar between groups [Wallace *et al.* 2013].

The phase IIb EMBLEM study of epratuzumab in 227 patients with moderate-to-severe active SLE used a novel composite endpoint, the BILAG-based Combined Lupus Assessment (BICLA) at 12 weeks. The proportion of responders was higher in epratuzumab treated groups

than with placebo. Adverse events were not significantly higher in those who received epratuzumab and no significant reductions in immunoglobulin levels were seen [Wallace *et al.* 2014a].

Phase III trials examining the efficacy and safety of epratuzumab in moderate to severe SLE are ongoing [ClinicalTrials.gov identifier: NCT01262365, NCT01261793].

Inhibitors of the BLyS/APRIL pathway

B lymphocyte stimulator (BLyS) and APRIL (a proliferation-inducing ligand) are part of the tumour necrosis factor (TNF) ligand superfamily and play important roles in modulating the innate immune system in the regulation of B-cell activation. A complex interplay exists between BLyS/APRIL and their receptors. BLyS is also known as B-cell activating factor (BAFF) and its functions include induction of B-cell proliferation, differentiation and immunoglobulin secretion [Moore *et al.* 1999; Schneider *et al.* 1999]. BLyS exists in both membrane bound and soluble forms and is expressed by monocytes, macrophages and dendritic cells. BLyS can bind to three receptors, all of which are expressed by B cells, including TACI (TNF transmembrane activator and calcium modulator and cyclophilin ligand interactor), BCMA (B lymphocyte maturation antigen) and BR3 (BAFF/BLyS receptor 3) [Gross *et al.* 2000; Thompson *et al.* 2001]. A further TNF superfamily member, APRIL, can also bind TACI and BCMA with biologic functions similar to BLyS. APRIL binds with higher affinity to TACI than BLyS. BLyS and APRIL may circulate as heterodimer complexes with various combinations of the two cytokines; however, the exact role of these heterodimers in the context of SLE is as yet unknown [Stohl, 2010]. Plasma and peripheral blood leukocyte mRNA BLyS levels correlate with disease activity and autoantibody titres in SLE patients [Cheema *et al.* 2001; Petri *et al.* 2008; Collins *et al.* 2006]. BLyS levels are also elevated in other autoimmune diseases such as rheumatoid arthritis and Sjögren's syndrome [Mariette *et al.* 2003].

Belimumab

Belimumab is a monoclonal antibody targeting BLyS and has been studied in two large randomized controlled trials in SLE. The Belimumab International SLE Study (BLISS-52) phase III trial enrolled 865 SLE patients from central and

eastern Europe, Latin America and Asia Pacific [Navarra *et al.* 2011]. The Belimumab International SLE Study (BLISS-76) enrolled 819 SLE patients from North America, western and central Europe [Furie *et al.* 2011]. Both of these studies excluded SLE patients with active lupus nephritis or neuropsychiatric disease.

The primary clinical endpoint in these studies was improvement in the SLE responder index (SRI). SRI clinical response is defined as: ≥ 4 points reduction in the Safety of Estrogen in Lupus Erythematosus National Assessment (SELENA) – Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score; no new BILAG A organ domain score and no new >1 new B organ domain score; and <0.3 increase in the Physicians Global Assessment (PGA) or no worsening of PGA compared with baseline.

The SRI clinical response rate at week 52 in the BLISS-52 study was 58% in belimumab 10 mg/kg with standard therapy treated patients and 51% in belimumab 1 mg/kg with standard therapy treated patients compared with 44% in those who received placebo and standard therapy ($p = 0.0006$, $p = 0.013$ respectively) [Navarra *et al.* 2011].

The SRI clinical response rate at week 52 in the BLISS-76 study was 43% in belimumab 10 mg/kg with standard therapy treated patients and 41% in belimumab 1 mg/kg with standard therapy treated patients compared with 34% in placebo and standard therapy treated patients ($p = 0.021$ and $p = 0.1$, respectively) [Furie *et al.* 2011]. There was no significant difference in SRI clinical response rates between the placebo and belimumab treated patients at week 76 of the BLISS-76 study.

Combining data from the BLISS trials, greater clinical efficacy was seen in SLE patients who were serologically more active, that is those who were anti double stand DNA antibody positive, and were hypocomplementemic. In addition, patients with higher clinical disease activity as defined as a SELENA–SLEDAI score >10 had a more efficacious response to belimumab [van Vollenhoven *et al.* 2012].

Following the BLISS-52 and BLISS-76 trials, the FDA and the European Medicines Agency (EMA) approved belimumab (10 mg/kg) for use in autoantibody positive SLE with moderate-to-severe disease activity, with the exception of patients with

active lupus nephritis or central nervous system (CNS) disease. Thus belimumab became the first drug in over 50 years to be licensed for the treatment of SLE.

The potential role of belimumab in lupus nephritis, neuropsychiatric disease and in combination with other biologic agents and cyclophosphamide has yet to be established and clinical trials addressing these issues are ongoing. The BLISS-LN phase III study has been devised to evaluate the efficacy and safety of belimumab plus standard of care *versus* placebo plus standard of care in active lupus nephritis, and is actively recruiting patients [ClinicalTrials.gov identifier: NCT01639339]. BlyS levels are known to increase post rituximab therapy in SLE patients and an interesting approach may be to give both therapies sequentially [Cambridge *et al.* 2008]. A trial examining sequential rituximab and belimumab in lupus nephritis has been proposed but is not yet open for recruitment. The study will compare the combination of rituximab and cyclophosphamide (at weeks 0 and 2) and a combination of rituximab and cyclophosphamide followed by belimumab (at weeks 4, 6 and 8, and every 4 weeks to week 48) [ClinicalTrials.gov identifier: NCT02260934]. An exploratory analysis of the BLISS studies showed lower clinical efficacy of belimumab in SLE patients of African ancestry. The EMBRACE study, a phase III/IV randomized, controlled trial of belimumab in SLE patients of African descent is actively recruiting and addresses this important issue [ClinicalTrials.gov identifier: NCT01632241]. A phase III trial of subcutaneously administered belimumab (BLISS-SC) in SLE patients is also ongoing [ClinicalTrials.gov identifier: NCT01484496].

Overall, belimumab has been found to be safe and well tolerated, although an increased susceptibility to common infections such as bronchitis, pharyngitis, cystitis and viral gastroenteritis has been reported. No specific opportunistic infections or patterns of infection have been associated with belimumab treatment to date. Two cases of PML have been reported in the medical literature in belimumab treated patients [Fredericks *et al.* 2014].

Tabalumab

Tabalumab is a humanized monoclonal antibody targeting membrane bound and soluble BlyS. Recently, tabalumab failed to meet its primary

endpoint of significant improvement in SRI in one of two large phase III trials (ILLUNINATE 1 and 2) and development of the drug has been discontinued [Eli Lilly and Company, 2014].

Atacicept

Atacicept is a fully humanized, recombinant TACI receptor fusion protein that targets the BlyS/APRIL axis [Dillon *et al.* 2010]. A phase I trial of atacicept in SLE patients showed dose-dependent reductions in immunoglobulin levels and in mature and total B cells [Dall'era *et al.* 2007]. The APRIL-LN phase II/III study of atacicept in active lupus nephritis was prematurely terminated after recruitment of only six patients due to unexpected but significant reductions in immunoglobulin levels and development of serious infections including haemophilus influenza pneumonia, legionella pneumonia and bacillus bacteraemia [Ginzler *et al.* 2012]. However, it should be noted that the reduction in the immunoglobulin levels took place when the study patients were given mycophenolate mofetil, prior to the introduction of atacicept. A further double-blind placebo controlled study of atacicept in moderate-to-severe nonrenal lupus (APRIL-SLE) was terminated early due to two unexpected deaths. One of these patients died from acute respiratory failure secondary to alveolar haemorrhage. This patient was known to have an overlap syndrome with features of scleroderma. The second patient died from pneumococcal pneumonia and alveolar haemorrhage secondary to lupus [Isenberg *et al.* 2014]. A further phase II trial examining the efficacy and safety of atacicept in SLE (ADDRESS II) is ongoing [ClinicalTrials.gov identifier: NCT01972568].

Therapies targeting T-B lymphocyte interactions

Abatacept

Abatacept is a fusion protein comprised of cytotoxic T-lymphocyte antigen (CTLA4) combined with the Fc portion of human IgG1 (CTLA4-Ig). Blockade of costimulatory interactions between T and B cells may result in the induction of immunological tolerance. 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 [Scheipers and Reiser, 1998; Reiser and Staderker, 1996; Brunet *et al.*

1987]. In murine models of lupus nephritis, the combination of CTLA-4-Ig and cyclophosphamide has been shown to significantly reduce proteinuria, autoantibody levels and increase longevity [Daikh and Wofsy, 2001; Cunnane *et al.* 2004; Finck *et al.* 1994].

A phase II trial of abatacept in nonrenal SLE patients failed to meet its primary endpoint of reduction in new BILAG A/B flares [Merrill *et al.* 2010a], but did show improvements in fatigue and quality of life measures. A phase II/III trial of abatacept in proliferative lupus nephritis (classes III and IV) failed to meet its study endpoint of complete renal response. However, a very strict end definition of complete renal response was used in the study and was defined as achieving a glomerular filtration rate within 10% of the pre flare/baseline value, urinary protein creatinine ratio <0.26 mg/mg and an inactive urinary sediment [Furie *et al.* 2014]. A re-analysis of the same study data was undertaken using outcome measures from the LUNAR and ALMS trials and showed a positive outcome in favour of abatacept therapy [Wofsy *et al.* 2013]. Overall, this emphasizes the importance of study design and standardization of outcome measures in SLE clinical trials. A further phase II multicentre trial of abatacept plus cyclophosphamide *versus* cyclophosphamide alone in the lupus nephritis is ongoing [ClinicalTrials.gov identifier: NCT00774852].

Targeting type I interferon

Type I interferon family members play a major role in innate immunity and host viral defence. Several lines of evidence link type I interferon to the pathogenesis of SLE. It is well established that patients with SLE have high serum levels of interferon- α [Hooks *et al.* 1979; Ytterberg and Schnitzer, 1982]. It has also been noted that viral hepatitis and oncology patients receiving interferon- α therapy develop autoimmune side effects [Ronnblom *et al.* 1990, 1991; Kalkner *et al.* 1998].

Serum interferon- α levels have been shown to correlate with disease activity and severity in SLE patients [Bengtsson *et al.* 2000]. While not all SLE patients have raised serum interferon- α , the majority have an interferon gene expression signature in peripheral blood mononuclear cells (PBMCs), particularly in the early stages of their disease [Bennet *et al.* 2003; Baechler *et al.* 2003]. Gene expression microarray profiles demonstrate

upregulation of interferon-inducible genes, particularly in those with severe SLE manifestations such as lupus nephritis and neuropsychiatric disease.

Additional evidence of the contribution of type I interferon to lupus pathogenesis is provided by the regularity with which variants in genes involved in interferon signalling pathways are identified in SLE genome wide association studies (GWAS) including *IRF5*, *IRF7*, *IRF8*, *STAT4*, *TYK2* and *IFIH1*. Furthermore, there is a strong link between monogenic causes of SLE and interferonopathies such as Aicardi-Goutieres syndrome [Lee-Kirsch *et al.* 2007; Rice *et al.* 2013, 2014].

Sifalimumab

Sifalimumab, a fully human anti-interferon α monoclonal antibody, was shown in a phase I study to induce a dose-dependent inhibition of type I interferon-induced mRNAs in whole blood of moderately active SLE patients. No significant increase in viral infections was seen and disease activity generally improved [Merrill *et al.* 2011]. A further phase I dose-escalation study of sifalimumab in adult patients with moderate-to-severely active SLE showed good safety and tolerability and inhibition of the type I interferon gene signature particularly in those with a high baseline signature [Petri *et al.* 2013].

A phase IIb trial evaluating the efficacy and safety of sifalimumab in SLE achieved its primary endpoints using the SRI(4) and the more stringent SRI(6-8). Organ specific endpoints were also significantly improved with sifalimumab including the Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI), 28 joint count and FACIT-Fatigue score. There was a minor increase in viral infections, particularly herpes zoster, in the sifalimumab treated group [Khamashta *et al.* 2014].

Rontalizumab

Rontalizumab, a recombinant humanized monoclonal antibody to interferon- α , was shown to be safe and well tolerated in a phase I, dose-escalation study in mildly active SLE patients [McBride *et al.* 2012]. However, a further study did not meet its primary end point of significant improvement in SRI and rontalizumab has been withdrawn from further development.

Anifrolumab

A third agent targeting type I interferon is anifrolumab, an anti-interferon- α receptor 1 antibody [Peng *et al.* 2015]. Two phase II randomized, open label studies of sifalimumab ($n = 30$) and anifrolumab ($n = 17$) have been undertaken in Japanese patients with SLE [Morehouse *et al.* 2014]. Anifrolumab had a more significant and more sustained impact on the interferon gene signature as compared to sifalimumab [Morehouse *et al.* 2014]. Anifrolumab is now being brought forward to phase III studies.

Targeting interleukin-6

Tocilizumab

The pleiotropic cytokine interleukin-6 (IL-6) has both pro-inflammatory and anti-inflammatory effects. In murine models of lupus nephritis, exogenous IL-6 increases autoantibody titres and accelerates progression of renal disease [Ryffel *et al.* 1994; Yang *et al.* 1998]. Giving an IL-6 monoclonal antibody was shown to reduce anti-dsDNA titres, proteinuria and mortality in these models [Liang *et al.* 2006; Mihara *et al.* 1998]. IL-6 levels correlate with clinical activity and anti-dsDNA antibody titres in SLE patients [Chun *et al.* 2007; Linker-Israeli *et al.* 2001]. Urinary excretion of IL-6 is increased during active proliferative lupus nephritis and levels subsequently decline following immunosuppression with cyclophosphamide [Peterson *et al.* 1996; Tsai *et al.* 2000].

Tocilizumab is a fully humanized monoclonal antibody against the IL-6 receptor and prevents binding of IL-6 to both its membrane bound and soluble forms. A phase I trial of tocilizumab in SLE showed good tolerance to the drug with reduction in active urinary sediment and autoantibody titres [Ilei *et al.* 2010]. A further study of tocilizumab in 15 SLE patients with mild-to-moderate disease activity showed reduced activated T and B cells [Shirota *et al.* 2013]. A number of cases reports are to be found in the literature suggesting efficacy of tocilizumab in severe refractory lupus including resistant haematologic manifestations and serositis [Kamata and Minota, 2012; Garcia-Hernandez *et al.* 2012; Makol *et al.* 2012; Adler *et al.* 2013]. Further studies are needed to define the role of tocilizumab in the treatment of SLE.

A further monoclonal antibody (PF-04236921) has been studied in 183 patients with active SLE

and has been shown to reduce severe flares. The drug was given subcutaneously at 10, 50 and 200 mg doses. The safety profile with 10 and 50 mg doses appeared acceptable, but dosing with 200 mg was terminated due to safety concerns given that there were 3 deaths including cardiorespiratory arrest, urosepsis with pulmonary embolism and disseminated tuberculosis [Wallace *et al.* 2014b].

Other biologic agents in development

Further to the biologic agents discussed in this review, a number of other therapeutic targets have been identified on the basis of our increased knowledge of the aetiopathogenesis of SLE and are in early stages of development. Potential targets include toll-like receptor pathways, TWEAK (TNF-related weak inducer of apoptosis), a mediator of nuclear factor- κ B (NF- κ B) pathway activation and the tyrosine kinase SYK.

A novel strategy in the treatment of SLE is the concept of resetting the autoreactivity of the immune system by using tolerogenic peptides. One such agent is Lupuzor, which has been studied in a phase II trial of 149 SLE patients, shown to be efficacious in terms of SRI and was well tolerated [Zimmer *et al.* 2013].

Bortezomib, a proteasome inhibitor approved for use in multiple myeloma, has been reported to be effective in murine models of lupus nephritis and in refractory cases of human SLE [Hainz *et al.* 2012; Wang *et al.* 2015; Alexander *et al.* 2015; Quartuccio *et al.* 2014]. The proteasome regulates protein expression and function by degradation of ubiquitinated proteins and inhibition of this process may result in programmed cell death in plasma cells. Studies to date in SLE have had a relatively short duration of clinical follow up and long-term safety data of bortezomib in autoimmune diseases have yet to be seen.

Table 1 shows pivotal trials of biologic therapies in SLE.

Treat-to-target in SLE

The concept of treating-to-target (T2T) has been successfully applied to many diseases including diabetes mellitus, hypertension and hypercholesterolaemia, and more recently to rheumatoid arthritis. In 2014, a task force of specialists involved in the care of SLE patients including those in rheumatology, nephrology, dermatology

Table 1. Pivotal trials of biologic therapies in systemic lupus erythematosus (SLE).

Therapeutic target	Drug under investigation	Pivotal clinical trials	Current status
Chimeric anti-CD20 monoclonal antibody	Rituximab	Failed to meet primary endpoints in LUNAR (nephritis) and EXPLORER (non-nephritis) phase III studies.	Phase III trial of rituximab and mycophenolate mofetil with corticosteroid minimizing regimen ongoing
Humanized anti-CD22 monoclonal antibody (nondepleting)	Epratuzumab	Safe and well tolerated ALLEVIATE study EMBLEM studies	Phase III study ongoing
Humanized anti-CD20 monoclonal antibody	Ocrelizumab	BELONG study terminated due to a high incidence of opportunistic infections	No studies ongoing
TACI-Ig fusion protein	Atacicept	Phase II study terminated due to risk of serious infections	Phase II trial (ADDRESS II) ongoing
Humanized anti-BLyS monoclonal antibody	Belimumab	BLISS-52 and BLISS-76 showed efficacy excluding severe renal and neuropsychiatric disease	Phase III trial in lupus nephritis ongoing trial of belimumab following rituximab induction therapy planned
Humanized anti-BAFF monoclonal antibody	Blisibimod	Safe and well tolerated in early phase trials	Phase III study ongoing
Humanized anti-BAFF monoclonal antibody	Tabalumab	ILLUMINATE 1: failed to meet primary endpoint ILLUMINATE 2: effective at higher study dose	To be determined
CTL4-Ig fusion protein	Abatacept	Failed phase II trial in nonrenal lupus. Phase III trial in lupus nephritis failed. Subgroup analysis using different outcome measures showed positive results however.	Further phase III trial pending
Humanized anti-IL6 monoclonal antibody	Tocilizumab	Well tolerated in phase I trial	To be determined
Humanized anti-IL6 monoclonal antibody	Sirukumab	Not efficacious in reducing proteinuria, increased risk of infection	No studies ongoing
Humanized anti-IFN α monoclonal antibody	Rontalizumab	Failed phase II study	No studies ongoing
Humanized anti-IFN α monoclonal antibody	Sifalimumab	Well tolerated and efficacious in phase 2b trial	To be determined
Humanized anti-IFN α receptor 1 monoclonal antibody	Anifrolumab	Significant impact on interferon gene signature	Phase III trial planned

BAFF, B-cell activating factor; BLyS, B lymphocyte stimulator; CTL4-Ig, cytotoxic T lymphocyte antigen-4 immunoglobulin; IFN α , interferon α ; IL6, interleukin 6; TACI-Ig, transmembrane activator and calcium modulator and cyclophilin ligand interactor immunoglobulin.

and immunology developed key recommendations for T2T in SLE (T2T/SLE) [van Vollenhoven *et al.* 2014]. Prominent features of the T2T/SLE recommendations include early identification of lupus nephritis, targeting remission, minimizing exposure to corticosteroids, optimal management of co-existent antiphospholipid syndrome, prevention of long-term damage accrual and improving quality of life in SLE patients. It is hoped that the T2T/SLE recommendations will lead to improved care for SLE patients and provide useful guidance

for those involved in their clinical management. However, targeting some SLE manifestations may be more easily quantified than others such as lupus nephritis compared with CNS manifestations which may make T2T/SLE challenging. Table 2 summarizes T2T in SLE.

Conclusion and future perspectives

Overall, physicians involved in the management of SLE should be enthusiastic given the array of

Table 2. Treat-to-target recommendations in systemic lupus erythematosus (SLE).

Aim for remission of systemic symptoms and organ manifestations. Where remission cannot be achieved, aim for the lowest possible disease activity. Use validated lupus activity indices and/or organ-specific markers.

Prevention of flares

Avoidance of escalation of therapy in clinically asymptomatic patients based solely on stable or persistent serological activity

Prevention of damage accrual

Address factors that negatively influence health-related quality of life (fatigue/pain/depression).

Early recognition and treatment of renal involvement

At least 3 years of immunosuppressive maintenance treatment is recommended in lupus nephritis.

Aim for the lowest glucocorticoid dosage required for disease control. Withdraw glucocorticoids completely when possible.

Prevention and treatment of antiphospholipid syndrome-related morbidity

Importance of the role of anti-malarials

Relevant adjunctive therapies should be considered to control comorbidity in SLE.

Adapted from van Vollenhoven *et al.* (2014).

promising new therapies becoming available for lupus disease control and further therapies yet to emerge. The clinical implications of biologic therapies in the management of SLE are, on the whole, positive. The advent of more targeted therapies should, in theory, increase our ability to control disease activity in SLE patients and minimize unnecessary toxicity.

However, a number of questions remain unanswered as to the optimal use of biologics in a complex and heterogeneous disease such as SLE. It is highly unlikely that one biologic agent will successfully treat all disease manifestations of lupus in all patients. Diagnostic and prognostic strategies will need to be developed to determine which biologic therapy is likely to be efficacious in which SLE patient and at what time point in their disease course.

Currently, biologic therapies are primarily used in clinical scenarios where SLE patients remain resistant to conventional immunosuppressive agents. Perhaps the ideal use of biologics in SLE is early in the disease course akin to anti-TNF therapy in rheumatoid arthritis. Ongoing clinical trials of rituximab and belimumab may help clarify this issue.

Belimumab is now licensed for use in the treatment of SLE and, on the basis of currently available evidence from the BLISS-52 and BLISS-76 studies, physicians are most likely to use belimumab in

addition to standard therapy in patients with musculoskeletal and mucocutaneous manifestations of SLE. Further studies are needed to clarify the role of belimumab in patients with severe lupus nephritis and severe CNS disease.

Clinical trial design and standardization of study outcomes are of utmost importance as exemplified by the LUNAR and EXPLORER trials of rituximab where high background levels of corticosteroids and immunosuppression may have hampered interpretation of results, and in the case of abatacept in lupus nephritis with varying study outcomes depending on which definition of complete renal response was used.

The long-term toxicity of biologic agents in SLE patients is also unknown. Rituximab has the most accumulated data of long-term patient exposure given its use in the treatment of lymphoma, but for many of these other agents there is limited long-term safety data. Biologics registries both on a nation and international basis will be crucial in accumulating and collating these important data.

Issues with regulation and the cost of new drugs remain significant stumbling blocks preventing patients from gaining access to these medications and further challenges lie ahead. The future advent of biosimilars may reduce cost and increase availability of such agents; however, caution must be exercised that these agents are as efficacious and safe as the original compounds.

The common goal of all of these agents is control of inflammatory disease activity, prevention of flares and hence minimization of long-term damage accrual in SLE patients. It is vital that important adjunctive therapies such as hydroxychloroquine and optimization of cardiovascular risk factors should not be forgotten in SLE management. T2T/SLE recommendations will be pivotal in achieving treatment goals, minimizing toxicity and improving quality of life in SLE patients.

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