Biologics in systemic lupus erythematosus: current options and future perspectives

Data from clinical trials highlighted the potential and pitfalls of the use of biologics to treat systemic lupus erythematosus. With improved understanding of immunopathogenesis and lessons learned from controlled trials, there is a growing optimism for personalized treatment from an increasing range of targeted therapies.

Systemic lupus erythematosus is a complex inflammatory disorder involving dysregulation of the immune system, leading to production of autoantibodies affecting the skin, joints and internal organs such as brain, lungs, heart and kidneys. The management of systemic lupus erythematosus is challenging as a result of heterogeneity in clinical presentation, disease severity and response to therapy. Use of conventional immunosuppressants such as hydroxychloroquine, azathioprine, cyclophosphamide and mycophenolate mofetil have helped to improve 10-year survival rates from 50% in the 1950s to greater than 90% now (Cervera et al, 2003).

Nevertheless, a proportion of patients will continue to have either active uncontrolled disease despite using these agents or may have unacceptable toxicities from such drugs. Furthermore, the mechanism of action of these agents and the selection of potentially responsive patients is not fully understood. Thus, the development of targeted therapies using newer biological agents is an important addition to the armamentarium of therapies for systemic lupus erythematosus. However, translating targeted therapy from bench to bedside has been more problematic than in other autoimmune diseases, with many theoretically well-founded agents appearing to have failed in clinical trials as a result of inefficacy, problems with trial design and/or safety issues (*Table 1*). This review summarizes advances in the use of biological therapies to treat

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Table 1. Biologics currently available and in late development for the treatment of systemic lupus erythematosus

Drug	Molecular target	Phase	Comments	References
Belimumab	BAFF blockade	III	Both phase III trials met their primary end points. First biologic approved by the Food and Drug Administration for use in systemic lupus erythematosus	Furie et al (2011); Navarra et al (2011)
Rituximab	CD20 depletion	III	Both phase III trials failed to meet primary and secondary end points. Post-hoc analysis showed primary end point was achieved in Hispanics and African–Americans	Merrill et al (2010b); Rovin et al (2012)
Abatacept	Selective T-cell co-stimulation modulator	II/III	Phase II study in extra-renal disease failed to achieve primary end point. May be beneficial in arthritis manifestation. Phase III trial in renal lupus was negative	Merrill et al (2010a); Furie et al (2014a)
Epratuzumab	CD22 depletion and inhibition	III	Phase II trial was positive at a cumulative dose of 2400 mg/month. Completed recruitment for two phase III trials	Wallace et al (2014)
Atacicept	BAFF and APRIL blockade	II/III	Phase II/III trial in renal systemic lupus erythematosus was suspended as a result of severe infection. Phase II/III trial in non-renal systemic lupus erythematosus is ongoing	Isenberg et al (2014)
Blisibimod	BAFF blockade	II	Primary end point was not met in the pooled blisibimod groups compared with placebo but was attained in the highest dose of blisibimod (200 mg once-weekly)	Furie et al (2014b)
Tabalumab	BAFF blockade	III	Phase III trial in systemic lupus erythematosus is ongoing	Md Yusof et al (2013)
Rontalizumab	Type 1 interferon-alpha blockade	II	Primary end point was not met. Higher SRI rates and reduced number of flares (rontalizumab *vs* placebo) were observed in the interferon signature-negative patients	Kalunian et al (2012)
Sifalizumab	Type 1 interferon-alpha blockade	II	Primary end point was met with clinically important improvement in skin and joint manifestations	AstraZeneca (2014)
Sirukumab	Interleukin-6 receptor blockade	II	Primary end point was not met. About 15–20% of the sirukumab-treated group achieved meaningful reduction in proteinuria *vs* placebo 0%	van Vollenhoven et al (2014a)

APRIL = a proliferation-inducing ligand, BAFF = B-cells activating factor of the tumour necrosis factor family; SRI = Systemic lupus erythematosus Responder Index

systemic lupus erythematosus, challenges in clinical trials and future approach to treatment.

Targeted therapies based on immunopathogenesis

The hallmark of systemic lupus erythematosus pathogenesis is the loss of self-tolerance leading to production of auto-antibodies against numerous self-antigens. B cells have traditionally been seen as central to this through production of autoreactive antibodies, antigen presentation to T cells and secreting cytokines. Thus various strategies for B cell blockade have been investigated including B cell depletion, inhibition of the survival factors, inhibition of B cell receptor signalling, development of B cell tolerogens and targeting plasma cells with varying degree of success in clinical trials (Md Yusof et al, 2013).

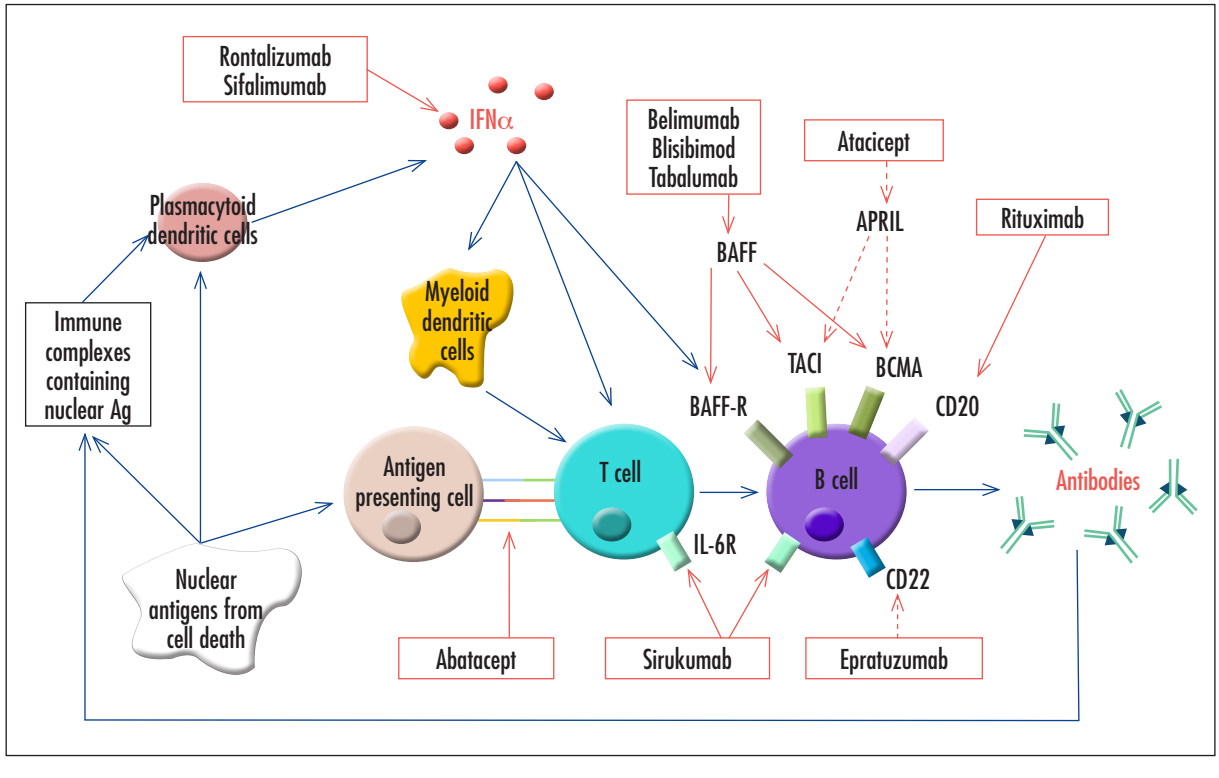
T cells may be involved in pathogenesis via T cell–antigen-presenting cell interaction and B cell help, defects in various intracellular signal transductions in T cell pathways and inadequate suppression of auto-reactive cells by the regulatory T cells (La Cava, 2009). Advances in lupus pathogenesis have focussed on abnormalities in clearance of apoptotic and secondary necrotic cells and increased innate sensing of nuclear antigen, demonstrated by overactive type 1 and 3 interferon production and Toll-like receptor signalling in patients with systemic lupus erythematosus. These models have led to the development of anti-interferon targeted biological therapies. *Figure 1* illustrates the range of target molecules and corresponding therapeutic agents currently available or under investigation.

Biologics currently available

Belimumab and the BAFF-APRIL system

Belimumab is a fully humanized monoclonal antibody that specifically binds to and neutralizes the soluble cytokine, B cell activating factor of the tumour necrosis family (BAFF, also known as B lymphocyte stimulator; BlyS), preventing it from binding to its receptors on the surface of B cells. B cell survival, maturation and differentiation are mediated by BAFF and its homologue, a pro-

Figure 1. Range of target molecules (based on immunopathogenesis of systemic lupus erythematosus) and the corresponding therapeutic agents. Nuclear antigen could be immunostimulatory even without being part of an immune-mediated complex. Deficiency in clearance of apoptotic debris leads to an abundance of nucleic acid remnants. These activate Toll-like receptors (TLR7 and 9) expressed by plasmacytoid dendritic cells which then stimulate excessive production of IFN-α. IFN-α activates a variety of components of the immune system including myeloid dendritic cells, T cells and B cells, leading to cell proliferation, maturation, differentiation and survival, and excess autoantibody and cytokine production. T cell receptors interact with the major histocompatibility complex on antigen-presenting cells and trigger the T cell response. However, T cells need a second co-stimulatory signal. Co-stimulatory molecules such as CD28:B7 and CD40:CD40 ligands help activate B cells. When these immune elements remain dysregulated, this leads to further tissue damage and cell death, perpetuating the cycle of inflammation. APRIL = a proliferation-inducing ligand; BAFF = B cell-activating factor of the tumour necrosis factor family receptor; BAFF-R = BAFF-receptor; BCMA = B cell maturation antigen; IFN-α = interferon-alpha; IL-6R = interleukin-6 receptor; TACI = tumour necrosis factor receptor superfamily member 13b.



liferation-inducing ligand (APRIL). Human BAFF and APRIL bind to three tumour necrosis factor superfamily receptors and activate their own set of signalling pathways:

1. BAFF receptor (BAFF-R) binds BAFF strongly
2. B cell maturation antigen binds APRIL
3. Tumour necrosis factor receptor superfamily member 13b (TACI) binds both BAFF and APRIL.

Belimumab is the first therapy in over 50 years that has gained approval from the United States Food and Drug Administration and European Medicines Agency for the treatment of active, autoantibody-positive systemic lupus erythematosus following the success of two randomized controlled trials (BLISS-52 and BLISS-76). Both trials used a new composite index as the primary end point: improvement in the SLE Responder Index (SRI) at week 52 (reduction ≥4 points in Safety of Estrogens in Lupus Erythematosus National Assessment–SLE Disease Activity Index (SELENA-SLEDAI) score, no new British Isles Lupus Assessment Group (BILAG) A organ domain score and no more than 1 new B organ domain score, and no worsening (<0.3 increase) in Physician's Global Assessment score). Significantly higher SRI rates were achieved with belimumab 1 mg/kg (51%, P=0.0129) and 10 mg/kg (58%, P=0.0006) than placebo (44%) at week 52 in BLISS-52 (Navarra et al, 2011) while significantly greater SRI response at week 52 was only achieved in the belimumab 10 mg/kg dose compared with placebo (43.2% *vs* 33.5%; P = 0.017) in BLISS-76 (Furie et al, 2011). Thus the higher dose was approved as a result of its efficacy in both trials. Long-term data from antibody- positive systemic lupus erythematosus patients (from the phase II extension studies) showed SRI response and safety profile were maintained in patients taking belimumab plus standard therapy for up to 7 years (Ginzler et al, 2014).

The success of these trials is a prime example of how to conduct a positive clinical trial based on lessons learned from earlier trials. The phase II trial of belimumab was negative. This was attributed to recruitment of around 30% of patients who had negative anti-nuclear antibody (ANA) (Wallace et al, 2009), with post-hoc analysis showing ANA-positive patients maintained responses better in extension studies (Furie et al, 2010). Thus, ANA positivity was set as the inclusion criteria. Importantly, the phase II investigators also reviewed the various components of clinical response criteria used in the phase II study and derived a new composite response index – the SLE Responder Index (SRI) – as the primary end point. The SRI combines elements of the SLEDAI and the BILAG to ensure that both clinical improvement and no simultaneous clinical worsening (e.g. in another organ system) are required. Such combined end points are now standard for efficacy trials before submissions for Food and Drug Administration approval (the BILAG-based Combined Lupus Assessment (BICLA) is the other commonly used example, discussed further below). Lastly, a larger number of patients were recruited (>800 patients in each trial).

Despite meeting its primary end point, the effect size of belimumab in ANA-positive active systemic lupus erythematosus appears small, prompting a search for subgroups with higher levels of response. In practice, rheumatologists resort to biological agents in severe cases, i.e. end-organ involvement and refractory to conventional immunosuppressants, whereas both BLISS trials recruited patients mainly with mucocutaneous and musculoskeletal manifestations (about two thirds of cases). Patients with severe lupus nephritis and neuropsychiatric manifestations were excluded although 15% of patients with lupus nephritis had improvement in proteinuria in post-hoc analysis (Manzi et al, 2012). These factors have made estimation of the cost-effectiveness problematic. In the UK, the National Institute for Health and Care Excellence has not recommended the use of belimumab for these reasons. Although a pooled analysis showed that greater therapeutic benefit in the belimumab group over standard of care may be achieved in patients with higher disease activity as well as greater serological activity (i.e. anti-dsDNA positivity and hypocomplementaemia) (van Vollenhoven et al, 2012), a more accurate means of identifying patients likely to respond well to belimumab is needed. Several further studies are already in the pipeline including a phase III trial in lupus nephritis.

Rituximab

Rituximab was the first licensed anti-CD20 monoclonal antibody, initially approved in 1997 for the treatment of B cell non-Hodgkin's lymphoma. It has since been licensed for use in follicular and diffuse large B cell lymphomas, chronic lymphocytic leukaemia, refractory rheumatoid arthritis and anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis. Rituximab kills B cells through a combination of:

1. Activation of complement resulting in complement-dependent cytotoxicity
2. Inducing antibody-dependent cell-mediated cytotoxicity in the presence of effector cells
3. Cross-linking of multiple CD20 molecules, resulting in cell death via induction of non-classical apoptosis (Boross and Leusen, 2012).

The use of CD20 as a B cell target is attractive as it spares progenitor cells (permitting B cell regeneration) as well as long-lived plasma cells (preventing excessive reduction of normal immunoglobulin levels, at least with initial therapy).

A high degree of efficacy in a wide spectrum of systemic lupus erythematosus manifestations (Ramos-Casals et al, 2009), including a pooled efficacy analysis of lupus nephritis (Díaz-Lagares et al, 2012), was reported in the initial open label case series of rituximab, generally in cases of highly resistant systemic lupus erythematosus. Despite the success of these series, two phase III randomized placebo-controlled trials in non-renal lupus (EXPLORER) and renal lupus (LUNAR) failed to meet their primary end points (Merrill et al, 2010b; Rovin et al,

2012). Studies explaining the potential mechanism of resistance to rituximab in human systemic lupus erythematosus are limited. However, B cell killing in patients with systemic lupus erythematosus appears less efficient than when the same agent is used in patients with rheumatoid arthritis. Experience in B cell malignancies suggested that this might be the result of internalization through interaction with FcγRIIb resulting in reduced effector activity and its clearance from serum as well as circulating immunoglobulin (IgG) and immune complexes, which might limit phagocytosis (Lim et al, 2011).

It is worth noting that failure of controlled trials of rituximab has been largely attributed to poor trial design including inappropriate end points, the use of an active comparator, inadequate inclusion criteria for a heterogeneous disease and non-powered sample size (Md Yusof et al, 2013). For this reason, rituximab is the only biologic commissioned by the NHS England for use in patients with refractory systemic lupus erythematosus although further evidence pertaining to its efficacy is demanded. Better-designed trials of rituximab in renal and extra-renal lupus are currently being planned.

Abatacept

Abatacept, a fusion protein of the extracellular domain of cytotoxic T-lymphocyte antigen 4 (CTLA4) and the constant region of IgG, has been developed to block the co-stimulatory interactions between B and T cells. CTLA4-Ig acts as a competitive inhibitor of CD28 on the T-cell surface by binding with either CD80 (ligand B7-1) or CD86 (ligand B7-2), thus preventing T-cell activation (Vital and Emery, 2006). Consequently, this reduces both T cell-dependent inflammatory pathways and T cell-dependent B cell responses.

Despite promising results in animal models, controlled trials in extra-renal lupus and renal lupus failed to meet their primary end points. However, in the former, abatacept was associated with fewer major BILAG A flares and a subset of patients with polyarthritis did show significant response in secondary analysis (Merrill et al, 2010a). In the latter, problems with choosing an appropriate primary end point again resurfaced. In this renal lupus trial, the stringent end points in defining renal response might have led to negative results, with only 8–11% achieving the complete renal response in treatment and placebo arms at 52 weeks (Furie et al, 2014a). Based on this consideration, a reanalysis was performed by applying the definition of renal response used in the LUNAR trial. This showed renal response rates of more than 22% in the abatacept groups *vs* only 6% in placebo (Wofsy et al, 2012). For this reason along with other findings from post-hoc analysis (i.e. significant reduction in proteinuria in patients with nephrotic-range proteinuria and improvement in anti-dsDNA levels), abatacept may still have a role in systemic lupus erythematosus. A trial combining abatacept and cyclophosphamide in lupus nephritis is still ongoing.

Biologics currently in late phase II or early phase III trials

B cell-targeted therapies

Another means of achieving B cell depletion and inhibition is by targeting the CD22 molecule, which is responsible for regulation of B cell function, functioning as a lectin-like adhesion receptor and as a component of the B cell activation complex. Epratuzumab, an anti-CD22 humanized monoclonal antibody, has recently completed recruitment for two phase III trials. The phase IIb trial, EMBLEM, was positive using the new composite index BICLA in patients receiving a cumulative dose of 2400 mg epratuzumab per month *vs* placebo (Wallace et al, 2014). BICLA consists of BILAG improvement without worsening, no worsening in SLEDAI or Physician's Global Assessment and no treatment failure. The BILAG response used in this index has been shown to correlate with clinical and laboratory parameters in the open label extension study (Furie et al, 2014c). Clinical improvement was also sustained at week 96 in the epratuzumab-treated group. There were no major safety signals across all arms as well as no reduction in immunoglobulin at week 12 in any of the epratuzumab regimens.

Atacicept is a TACI-Fc decoy receptor, capable of binding both circulating BAFF and APRIL. The first phase II/III trial, APRIL-LN, evaluated patients with severe lupus nephritis, treated with high-dose glucocorticoids and mycophenolate mofetil at screening (for 14 days). These patients were subsequently randomized on day 1 to either atacicept 150 mg or placebo. This trial was terminated prematurely as a result of development of significant hypogammaglobulinaemia, leading to two cases of severe pneumonia in the treatment group. The decrease in serum IgG had already started before study treatment was initiated, and it was possible that this was an expression of severe nephrotic syndrome rather than a complication of atacicept (Ginzler et al, 2012). The second phase II/III trial of atacicept in combination with standard of care other than mycophenolate mofetil in lupus nephritis, APRIL-SLE, was terminated as a precautionary measure as a result of two deaths from pneumonias complicated by pulmonary haemorrhage in the 150 mg subcutaneous injection twice-weekly dose arm (Isenberg et al, 2014). These infections were not associated with hypogammaglobulinaemia. A post-hoc analysis showed the primary end point – flare rates based on BILAG – was not met in the atacicept 75 mg arm compared with placebo. However, treatment with atacicept 150 mg might suggest beneficial effect *vs* placebo in flare rates (odds ratio = 0.48, P=0.002). The phase III results in extra-renal manifestations are still unpublished.

Blisibimod is a biological therapeutic agent composed of four high-affinity BAFF binding domains fused to the Fc domain of human IgG1. Blisibimod selectively inhibits soluble and membrane-bound BAFF. The results of the phase II trial (PEARL-SC) showed the primary end

point, SRI-5 response rates (a more stringent adaptation of the SRI discussed above that requires a 5-point SLEDAI reduction rather than the standard four), were not significantly improved in the pooled blisibimod groups compared with placebo (Furie et al, 2014b). However, higher response rates were attained in subjects randomized to the highest dose of blisibimod (200 mg once weekly) compared with pooled placebo at week 20 (P=0.02). Importantly, this study identified subgroups of patients who would benefit from the therapy – those with 'severe' systemic lupus erythematosus with SELENA-SLEDAI ≥10 and receiving corticosteroid at baseline although patients with severe lupus nephritis, neuropsychiatric systemic lupus erythematosus and vasculitis were excluded.

Tabalumab, another anti-BAFF monoclonal antibody that may have superior blockade of soluble trimers and membrane-bound BAFF, is currently recruiting patients in two phase III systemic lupus erythematosus trials. The phase III trial of this drug in rheumatoid arthritis was terminated as a result of lack of efficacy (Md Yusof et al, 2013).

Interferon-blocking therapy

Type I (alpha and beta) interferons are key mediators that link the sensing of classic lupus-associated nuclear antigens with an adaptive immune response. Their importance is indicated by numerous genetic associations as well as the high spontaneous expression of type I interferon-induced genes in circulating mononuclear cells and peripheral tissues in systemic lupus erythematosus patients. High levels of these genes are associated with high disease activity (Dall'era et al, 2005). Type I interferon is therefore a logical therapeutic target that may have certain advantages over B and T cell targets.

Rontalizumab is an anti-interferon alpha monoclonal antibody. Although it did not demonstrate efficacy in a phase II clinical trial (Kalunian et al, 2012), there was evidence that baseline interferon activity might help to identify responsive patients. In a phase II study, patients were screened at baseline to characterize interferon signature-positive *vs* -negative patients using gene expression in a 3:1 ratio. As predicted, patients with a positive signature had higher biological indices of disease activity compared with signature-negative patients, although clinical indices of disease activity were similar in both groups. Surprisingly, higher SRI response rates as well as reduced number of flares were observed in the rontalizumab group in the interferon signature-negative patients (compared to placebo). None of these differences were demonstrated in patients with a positive interferon signature at baseline. This intriguing evidence may suggest that either the dose of rontalizumab is too low to neutralize the interferon in patients with high interferon scores or a problem with variability in detection of type 1 interferon-inducible genes with the simple 3 gene whole blood signature that was used.

Sifalimumab, another anti-interferon-α monoclonal antibody, was evaluated in a phase IIb trial of moderately to severe systemic lupus erythematosus (excluding severe lupus nephritis and neuropsychiatric systemic lupus erythematosus). The primary end point, SRI-4 at day 365, was met with clinically important improvement in skin and joint manifestations (AstraZeneca, 2014). The secondary end points, skin improvement measured using Cutaneous Lupus Erythematosus Disease Area and Severity Index and improvement in fatigue, were also achieved, albeit that these were dose-dependent. There was no major safety signal apart from numerical increase in herpes zoster reactivation (consistent with the physiological role of interferon in viral immunity).

IL-6 blocking therapy

Interleukin-6 (IL-6) is a highly pleiotropic cytokine that is overexpressed in lupus nephritis. Sirukumab, an anti-IL-6 monoclonal antibody, was evaluated in patients with either class III or IV lupus nephritis, refractory to azathioprine or mycophenolate mofetil. The primary end point, median reduction in proteinuria at week 24, was not met in the sirukumab-treated group (van Vollenhoven et al, 2014a). However, about 15–20% of the sirukumab-treated group achieved meaningful reduction in proteinuria – >50% from the baseline – *vs* 0% in the placebo group. Nearly half of the sirukumab-treated group had one or more serious adverse events.

Future direction in biological therapies

Most of the early challenges of development of biologics to treat systemic lupus erythematosus have been related to trial design including the use of active comparator and choice of an appropriate end point. Assessment of disease activity can also be difficult owing to concurrent infection and multiple comorbidities often present in patients with systemic lupus erythematosus. Current disease activity indices such as the BILAG require adequate training and may be complex for inexperienced clinicians to use while the SLEDAI may fail to capture partial response to therapy. Thus, the development of composite indices such as SRI and BICLA, which aim to more accurately identify true response, is welcomed with interest. However, these need validation and the definition of clinically meaningful, cost-effective responses needs further characterization.

The next phase of research will see the development of numerous molecules and immunomodulators such as peptide-based agents that are currently in pre-clinical and early phase trials. These will be evaluated based on lessons learned from previous trials of rituximab, belimumab and abatacept. Nevertheless, results from randomized trials consistently show variable response rates ranging from 30–60% (Md Yusof et al, 2013). Given the heterogeneity in clinical phenotype and immunopathogenesis, it may be that there is no one-size-fits-all therapy for systemic lupus erythematosus. Mechanistic studies concerning

stratification and personalization of therapy to individual patients and disease manifestations are needed but currently limited. Alternatively, combination therapy may be effective as evidenced from treatment in B cell malignancies. However, vigilance is needed in terms of safety from prolonged B cell depletion.

With regards to safety, it is worth noting that several promising agents (in pre-clinical phase) have failed in the trials as a result of safety issues. These include ocrelizumab, a humanized anti-CD20 monoclonal antibody. A trial in lupus nephritis was terminated as a result of increased risk of opportunistic infection, which might have been related to the high dose used (Mysler et al, 2013). Thus, long-term safety data from open label extension studies of the newer biologics are paramount. Studies should also aim to monitor the risk of major cardiovascular events and infection – the two commonest causes of mortality in systemic lupus erythematosus.

The patents of older biologics including rituximab will soon expire and will lose exclusivity in the USA by 2018. Thus, the development and licensing of 'biosimilars' that seek to imitate originator biologics as closely as possible in the next few years may greatly influence the cost-effectiveness of therapies. This could become a major factor in choice of biologic. Despite failure of several first-wave biosimilars in meeting the standard issued by the European Medicines Agency (Vital et al, 2013), two biosimilar versions of a monoclonal antibody that inhibits tumour necrosis factor-alpha were approved in September 2013 thus reinstating optimism among other manufacturers. There are important questions to be addressed regarding the extrapolation of efficacy data between indications, such as rheumatoid arthritis and malignancy.

KEY POINTS

- The development of biologics through B cells, T cells, interferon and cytokines blockade represent a major advance in treatment of systemic lupus erythematosus.
- Translating bench to bedside has been problematic with many of these agents have failed in clinical trials as a result of inefficacy, problem with trial design and/or safety issues.
- Belimumab is the only biologic licensed for auto-antibody positive systemic lupus erythematosus but choosing the right patient for the therapy remains problematic. Better indication for use including clinical phenotype that will response to therapy will be identified from several studies currently planned.
- Although trials in rituximab were negative, their methodology has been disputed and NHS England has agreed to commission rituximab based on strong open label evidence.
- Choosing the best possible and clinically meaningful end point in clinical trial is critical to the success of trials in systemic lupus erythematosus. Stringent definition of complete renal response might have hampered the clinical trial of abatacept.
- The future research agenda will focus on better trial design including the use of composite disease activity index as end points, combination therapies, biomarkers and the development and licensing of biosimilars.

Finally, the introduction of the treat-to-target concept in systemic lupus erythematosus provides a new personalized approach for managing patients. The target of achieving low disease active or remission with reduction in oral corticosteroid is attainable (van Vollenhoven et al, 2014b). Consequently, there is a need to define the subset of patients who continue to have active disease and will require treatment with biologics. Biomarkers that may allow prediction of active disease, prognosis and/or response to therapy are lacking but are likely to emerge with new the application of new technologies. **BJHM**

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