

New therapies for systemic lupus erythematosus — past imperfect, future tense

Grainne Murphy¹ & David A. Isenberg^{2*}

¹Department of Rheumatology, Cork University Hospital, Cork, Ireland

²Centre for Rheumatology, University College London, London, UK

*e-mail: d.isenberg@ucl.ac.uk

Abstract

The failure of many new, mostly biologic, drugs to meet their primary endpoints in double-blind clinical trials in patients with systemic lupus erythematosus (SLE) has caused a profound sense of disappointment among both physicians and patients. Arguably, the success of B cell depletion with rituximab in open-label clinical trials, the approval of belimumab (which blocks the B cell activating factor (BAFF)) for use in patients with lupus nephritis in the USA and in difficult-to-treat patients with SLE in the UK, and the recognition that clinical trial design can be improved has given some cause for hope. However, changes to therapies in current use and the development of new approaches are urgently needed. The results of the latest studies investigating the use of several new approaches to treat SLE are discussed in this Review, including: fully humanized anti-CD20 and anti-CD19 monoclonal antibodies; inhibition of protein tyrosine kinase BTK; CD40 ligand blockade; interfering with the presentation of antigen to autoreactive T cells using a peptide approach; a receptor decoy approach using an analogue of Fcγ receptor IIB; dual blockade of IL-12 and IL-23; and inhibition of Janus kinases.

[H1] Introduction

The outlook for patients with systemic lupus erythematosus (SLE) improved from a 4-year survival rate of ~50% in 1950 to a 15-year survival rate of ~85% by 2013¹. However, patients continue to die prematurely, and morbidity in SLE, such as osteoporosis², an increased risk of infection³ and atherosclerosis⁴, is often substantial. An analysis of patients with lupus nephritis (potentially the most harmful disease manifestation) indicated that there had not been a major improvement in outcome in the 30 years to 2011⁵, suggesting that conventional drugs are unlikely to produce any further clinically important beneficial effects in these patients. Hopes had been high that, as with patients with other autoimmune rheumatic diseases, patients with SLE would benefit from biologic

therapies. However, biologic therapy for the treatment of SLE has been relatively unsuccessful and several biologic agents have failed to meet their primary endpoints in large-scale clinical trials^{6,7}. Thus, physicians treating patients with SLE currently cannot choose between several highly successful approved biologic drugs when conventional therapies fail, as is the case for those treating patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA) or ankylosing spondylitis⁸. Hence, particularly in aspects of disease, such as lupus nephritis, where is a limited number of proven therapies, there is a clear un-met need for targeted biologic therapies.

In this Review, we consider the current use of biologic therapies to treat patients with SLE and provide some discussion about why previous trials have failed. We also outline several potential new therapies, indicating the pathways that each approach seeks to block. Many therapeutic targets are currently under investigation, and several ongoing clinical trials for SLE have been discussed elsewhere⁷, so in this Review, we focus only on those approaches that we consider to be particularly encouraging.

[H1] Current use of biologic therapy

In SLE, evidence exists of a general breakdown in both B cell and T cell tolerance, and a number of aspects of B cell biology have been implicated in its pathogenesis⁹.

Perhaps the most obvious pathogenic function of B cells in SLE is the production of autoantibodies that target self-antigens such as DNA and extractable nuclear antigens. The contribution of B cells to disease initiation and perpetuation in SLE is complex, but it is probable that they help to prime autoreactive T cells, function as antigen-presenting cells (APCs) and are a rich source of the cytokines involved in immune dysregulation in SLE. Not surprisingly, many of the therapeutic agents that have been trialled in SLE target B cell pathways¹⁰. The approaches of these therapeutic agents vary, from targeting B cell-selective cell surface molecules (such as CD22 or CD20), to inhibiting B cell survival by targeting cytokines and signalling molecules (such as B cell activating factor (BAFF), IL-6, IL-17 and IL-21), to interfering with B cell antigen presentation by targeting co-stimulatory molecules (such as CD40–CD40 ligand (CD40L) interactions and inducible T cell costimulator (ICOS)–ICOS ligand (ICOSL) interactions). Many of these therapies, including rituximab (an anti-CD20 monoclonal antibody (mAb))¹¹, epratuzumab (an anti-CD22 mAb), abatacept (which stops APCs from interacting with T cells via CD80 and CD86) and tabalumab (an anti-BAFF mAb), have not shown a statistically significant benefit in clinical trials for SLE, reviewed recently¹². (CCarreira P, Isenberg D. Recent developments in biologic therapies for the treatment of patients with systemic lupus erythematosus. *Rheumatology* 2011; 50: 382-87. However, despite the disappointing results of these (mostly) biologic

therapies in clinical trials, not all of the approaches attempted in the past few years have been a complete failure.

Rituximab and belimumab (an anti-BAFF mAb), are the biologic drugs most commonly used to treat SLE in clinical practice. The results of a large number of open-label studies of rituximab¹¹ and the encouraging data from national registries^{12,13} were sufficient for both the ACR¹⁴ and EULAR¹⁵ to recommend rituximab as a treatment for lupus nephritis, and for the National Health Service (NHS) England to sanction its use in difficult-to-treat patients¹⁶. For example, in the Lupus Clinic at University College Hospital, London, ~140 patients have been treated with rituximab since 2000 owing to inefficacy of treatment or adverse events following immunosuppression with steroids, azathioprine, mycophenolate mofetil (MMF) or cyclophosphamide (D.A.I. unpublished observations). Importantly, although rituximab is regarded as being generally effective, its use is associated with hypogammaglobulinaemia¹⁷ (which causes an increased risk of infection), and allergy-like responses (ranging from a mild cutaneous rash with flushing and pruritus to symptomatic bronchospasm with dysphonia, hypoxia and wheeze) were reported at one centre in 16% of patients treated with rituximab^{18, 19}.

Following successful clinical trials^{20, 21}, belimumab was approved by the FDA in 2012 for use in the USA in patients with SLE and by the National Institute of Clinical Excellence in 2016 for use in the UK in patients with SLE who have active skin and joint disease. Belimumab thus became the first drug to be approved by the FDA for the treatment of SLE in more than 50 years. Encouragingly a 2018 trial²⁷ of intravenous belimumab that included 677 patients from China, Japan and South Korea reported a response rate (using the SLE Responder Index (SRI)-4 end point) of 53.8% in the belimumab-treated group versus 40.1% in those given placebo in addition to standard of care treatment. However, this trial²² excluded patients who had renal disease or central nervous system disease. The efficacy and safety of a subcutaneous form of belimumab has also been reported²³. In a study of 839 patients with SLE, 556 of whom were given belimumab and 280 of whom were given placebo, 61.4% of those taking belimumab met the primary end point of achieving an SRI-4 response.

Although limited by regulatory bodies and cost, 'real life' data on belimumab use is also emerging. For example, the results of a study from Italy²⁴ of 188 patients with SLE treated with belimumab who were followed up for a mean of 17.5 months has been reassuring in terms of both efficacy and safety. In this population, the most common disease manifestations that required belimumab to be started were polyarthritis and skin rashes. The results of a trial of belimumab in patients with renal

disease²⁵ are still awaited, and a more detailed knowledge of the effectiveness of belimumab in SLE manifestations such as pleuropericarditis, gastrointestinal disease and central nervous systemic disease is also desired.

Thus, there remains a 'gap in the market' for successful and relatively adverse-effect-free biologic therapies to treat SLE.

[H1] Challenges for SLE clinical trials

[H2] Assessment of disease activity Assessing disease activity in SLE can be challenging, not least because it is essential to distinguish clinical features resulting from disease activity from those resulting from concomitant diseases or damage. Several disease activity assessment systems have been developed and validated²⁵. The best known disease activity measures are probably the SLE Disease Activity Index 2000 (SLEDAI-2K) and the British Isles Lupus Assessment Group (BILAG)-2004 disease activity index. The SLEDAI-2K provides a simple comprehensive score that is easy to calculate but that does not distinguish features of clinical activity that are only partly improved from those that have not changed²⁵. This index also misses out some important clinical features of SLE including gastrointestinal disease, ophthalmic disease and haemolytic anaemia. By contrast, the BILAG-2004 disease activity index is more comprehensive and is able to distinguish between different disease states, but takes longer to complete when the disease is active²⁵. A BILAG A or B score refers to new severe (A) or moderate (B) disease activity within a particular domain, which typically leads to a change in therapy.

Several composite endpoints have also been developed, such as the SRI and the BILAG-based Composite Lupus Assessment (BICLA), both of which include components of the BILAG 2004 and the SLEDAI-2K. Both the SRI and the BICLA aim to capture clinical features in patients with SLE that are caused by active SLE and not by concomitant disease (~30% of patients with SLE have one or more additional autoimmune rheumatic diseases), damage (for example, a painful hip might be caused by active synovitis or by avascular necrosis, and the treatment will differ accordingly) or the adverse effects of other drugs (such as steroids, which can cause proximal muscle weakness).

SLE is a complicated disease, and the majority of pharmaceutical companies perform two kinds of trials renal and non-renal. Those that focus on lupus nephritis have the advantage of hard endpoints, such as the measurement of protein-creatinine ratios, serum creatinine concentrations and glomerulo-filtration rates, which are not dependent upon subjective interpretation, as is the case

with non-renal SLE. As discussed elsewhere²⁶, the use of composite endpoints such as the SRI and the BICLA in addition to the Physicians Global Assessment (PGA) is demanding for clinicians, and whether or not such assessments are better performed without consideration of medication changes is an ongoing debate. DAI is currently writing this!! Ideally, clinicians who participate in international clinical trials should receive formal training in the use of these disease activity measures and be assessed to ensure that they understand the important principles behind these measures. The addition of an independent review panel (separate from the assessors at individual centres and central monitors) to review the data from different centres on a regular basis throughout the trial should also be encouraged. Such an addition makes it easier to highlight individual centres and clinicians whose disease activity assessment results differ substantially from those of other centres and individuals, and to therefore correct any problems during the trial.

[H2] Adverse outcomes

Given the failures of many trials, it is encouraging that pharmaceutical companies are still willing to 'engage' with SLE.

As with many new forms of therapy the biologic drugs that have been given to SLE patients are monitored very closely for side-effects. These include infection, allergic responses and malignancies. The risk of infection has been a particular concern. For example, atacicept (which blocks BAFF and a proliferation-inducing ligand (APRIL)) was first used in a flare prevention study²⁷. In this study, patients with active SLE (defined by the presence of one or more BILAG A or B scores) were initially treated with glucocorticoids that were sharply tapered once the active disease had been brought under control, and were then treated with either a high (150mg) or low (75mg) dose of atacicept or placebo. The aims of this study were to look for the time to first flare and the numbers of flares in the one-year follow-up period²⁷. However, the safety committee became concerned after two deaths due to infection in the high-dose group, which was subsequently suspended. Despite this setback, atacicept continued to be developed for SLE, and reassuringly, a trial of 300 patients with active SLE reported no deaths due to atacicept and a serious infection rate of 7% in the placebo group, 8% in the 75mg atacicept group and 1% in the 150mg atacicept group²⁸. Additionally, a trial of ocrelizumab²⁹ (an anti-CD20 mAb) was terminated early owing to an increase in the infection rate when combined with MMF hence, toxicity in patients on background immunosuppressive therapy is an important concern. In future trial design due consideration should be given to the potential for background immunosuppressive therapies to increase risk, particularly infective risk in combination with study drug- and thought should be given to minimization of background therapy where possible

[H2] Glucocorticoid use

The use of glucocorticoids and other immunosuppressive drugs in therapeutic trials in the past ten years seems to have been liberal. In effect, the consequence has been to raise the bar so high, that it has become almost impossible for the test drug to really show its merits. For example, two trials of tabalumab, each involving ~1,100 patients, came to different conclusions as to the efficacy of the drug because in one trial³⁰ the primary endpoint was not met, whereas it was in the second study³¹. The critical difference between the trials was that in the first trial³⁰, a stipulation was included that any alteration in the steroid dose implied a failure of the drug. On reflection, this stipulation meant that in patients whose disease had improved while taking tabalumab and whose dose of steroids was subsequently reduced, tabalumab was deemed to have failed. Despite setbacks such as these, detailed post-hoc analyses of some trials have revealed encouraging results even when the primary outcomes were not achieved. Clearly this needs to be taken into account in the design of trials to come with clear reporting of concomitant glucocorticoid use and consideration of necessary deviations from pre-defined dosing strategies in the final statistical analysis.

[H1] Promising new therapeutic approaches

The history of SLE therapeutics is littered with agents that seemed promising in pre-clinical or early-phase clinical studies, but then failed in late-phase trials. Although some of the challenges surrounding trial design will have contributed to these failures, the issues involved are complex, and pre-clinical success does not guarantee success in clinical practice. Likewise, success in a phase II trial does not guarantee success in a phase III trial. The complexity and heterogeneity of the underlying immune dysregulation in SLE probably also contributes to the failure of trials; targeting particular cytokines or cell-specific pathways within defined patient subgroups will be beneficial in the future.

Figure 1 shows the targets of interventions aimed at immune cells thought to be involved in the pathogenesis of SLE. Accurately predicting which (if any) of these approaches might ultimately prove to be successful is extremely difficult, and for several therapies, trial results are still awaited (Table 2). Given the complex nature of the aetiopathogenesis of SLE, more than one approach will probably be required. Nonetheless, it is hoped that one or more of the agents discussed below will prove successful for patients with SLE.

[H2] Targeting B cells

[H3] Anti-CD20 antibodies. The high rate of allergy-like responses¹⁹ to rituximab in patients with SLE seems to be related, at least in part, to the fact that rituximab is not fully humanized. A number of alternative, fully humanized, anti-CD20 mAbs are becoming available. Two types of anti-CD20 mAbs (known as type I and type II) have been identified according to various functional properties³² (Table 3).

Ocrelizumab has been studied in two clinical trials in patients with SLE. BEGIN, a phase III study³³ in patients with non-renal SLE, was terminated early when the sponsor decided not to pursue this indication BELONG, a phase III study in patients with lupus nephritis who were treated with ocrelizumab and either cyclophosphamide or MMF was terminated early owing to a high serious infection rate in patients receiving ocrelizumab and MMF³⁴. An assessment of the 32 week data from this trial revealed renal response rates of 63% and 51% in the ocrelizumab and placebo groups, respectively, and an apparent benefit for those patients receiving additional cyclophosphamide³⁴. Another fully humanized anti-CD20 mAb, obinutuzumab induced better B cell cytotoxicity than rituximab in patients with RA or SLE³⁵. An ongoing phase II trial that is due to last for one year aims to investigate the efficacy and safety of this drug in lupus nephritis with complete renal response as the primary outcome³⁶. Although it is unlikely that all of the new anti-CD20 agents will reach the market, ofatumumab (an IgG1)³⁵ has been approved for the treatment of chronic lymphocytic leukaemia, and has also been used to treat autoimmune haemolytic anaemia and immune-mediated thrombocytopenia³⁷, and lupus nephritis in a small number of patients³⁸. These agents may particularly have a role for patients in whom rituximab has shown efficacy but allergic-like responses have led to their discontinuation.

[H3] Combination rituximab and belimumab therapy. The combination of B cell depletion with rituximab and inhibition of B cell survival with belimumab is based on the premise that the production of BAFF following B cell depletion may facilitate the maturation of autoreactive B cells³⁹. Several groups have reported preliminary data from small studies that outline the efficacy of such a strategy. The largest of these studies, the CALIBRATE trial, assessed the effect of rituximab with one pulse of cyclophosphamide followed by monthly intravenous belimumab infusions beginning at 4 weeks (n=21) compared with rituximab and cyclophosphamide alone (n=22) in patients with active lupus nephritis⁴⁰. No significant difference in renal response was noted between the groups, although the addition of belimumab did lead to a delay in B cell repopulation without an increase in hypogammaglobulinaemia⁴⁰. The results of the SYNBIOSE study, an open label proof of concept study using a similar infusion protocol without the additional cyclophosphamide, have also been

reported⁴¹. Clinical improvement was noted in a cohort of previously refractory patients, who had improved SLEDAI scores at week 24 (renal responses were noted in 11 out of 16 patients), and the results of phase III studies are awaited. In this study⁴¹, clinical improvement was also mirrored by a reduction in autoantibodies, including anti-dsDNA antibodies, as well as a reduction in neutrophil extracellular trap formation, a process implicated in SLE pathogenesis. A multi-centre, double blind placebo-controlled phase III trial, BEAT-Lupus, investigating the safety and efficacy of starting belimumab 4-8 weeks after rituximab has completed enrolling patients⁴².

[H3] Anti-CD19 antibodies. A novel humanized anti-CD19 antibody called obexelimab (XmAb5871) that has been engineered to have an increased affinity for FcγRIIb has been used to treat SLE in a phase II study of 104 patients with moderate to severe disease⁴³. Low disease activity was first achieved by a short course of disease-suppressing intramuscular steroids, after which background immunosuppression was stopped, and those with the required disease activity improvement were randomly allocated 1:1 to XmAb5871 or placebo. Patients were followed up until day 225, and the preliminary results showed that disease activity levels were maintained with no 'loss of improvement' (defined as an increase in SLEDAI of >4 or a new BILAG A or B score referring to a significant increase in disease activity) in 42% of patients treated with XmAb5871 compared with 23% of patients treated with placebo⁴³. Given the clinical success of other B Cell targeting strategies Phase III studies of this agent are awaited with interest.

[H3] Targeting BTK. Bruton's Tyrosine-protein kinase BTK is expressed by many immune cells, including macrophages, monocytes and B cells, and regulates signalling downstream of the B cell receptor, Fc receptors and, possibly, Toll-like receptors. The loss of BTK activity ameliorated lupus-like disease in mice⁴⁵, whereas overexpression of BTK in cells from mice with lupus-like disease caused an increase in anti-DNA antibody production⁴⁶. Kil LP, de Bruijn MJ, van Nimwegen M, et al. Btk levels set the threshold for B-cell activation and negative selection of autoreactive B cells in mice. *Blood*. 2012;119(16):3744–3756 A number of BTK inhibitors have been developed, including ibrutinib and GDC-0853. Ibrutinib is an irreversible tyrosine kinase-selective inhibitor that binds BTK and causes increased B cell apoptosis. A pre-clinical trial in a mouse model of lupus nephritis⁴⁷ showed that ibrutinib treatment reduced the amount of some autoantibodies, including anti-nucleosome antibodies and anti-histone antibodies, but not anti-dsDNA antibodies, and improved renal disease. GDC-0853³⁸ is currently being used in an ongoing phase II trial of SLE that aims to assess the efficacy and safety of this therapy in patients with a SLEDAI score of >6⁴⁹ Like many agents we await confirmation that strong pre-clinical evidence can translate into clinical success.

[H3] Targeting CD40–CD40L interactions. Interest in CD40–CD40L interactions in the pathogenesis of SLE and the potential to therapeutically target this interaction has been re-ignited in the past few years. CD40L is a member of the TNF superfamily that engages with its receptor CD40 on B cells, leading to B cell differentiation, isotype switching and the formation of germinal centres⁵⁰. Owing to their centrality in the induction of a robust immune response, CD40–CD40L interactions are thought to be an important mechanism in the development of autoimmunity. In SLE, both CD4⁺ T cells and CD8⁺ T cells overexpress CD40L during active disease, and CD40L is also aberrantly expressed by monocytes and B cells from patients with SLE⁵¹. Moreover, transgenic mice that ectopically express CD40L on B cells develop lupus-like disease⁵². The results of pre-clinical studies suggest that inhibition of the CD40–CD40L pathway might help to ameliorate lupus-like disease. Specifically, lupus-prone NZB/W mice had delayed onset or prevention of proteinuria, improved survival and less severe renal disease when treated with an anti-CD40L mAb before the onset of symptoms⁵³.

Unfortunately, initial clinical studies of anti-CD40L mAbs were not promising. Rupilizumab, a humanized anti-CD40L antibody, produced a partial therapeutic response in patients with lupus nephritis in an early-phase open-label study⁵⁴; however, an increased incidence in thrombosis in patients receiving rupilizumab led to the early termination of this study. Another humanized anti-CD40L mAb, toralizumab, was also used in a phase II study in patients with SLE but showed no statistically significant improvements in disease⁵⁵. Similarly, further development of this agent was stopped owing to increased thrombosis in trials of toralizumab in patients with Crohn's disease⁵⁶.

The thromboembolic effects of rupilizumab and toralizumab transpired to be mediated by the Fc portions of these antibodies, resulting in the formation of immune complexes that caused platelet aggregation and activation⁵⁷. Langer F, Ingersoll SB, Amirkhosravi A, Meyer T, Siddiqui FA, Ahmad S, et al. The role of CD40 in CD40-L and antibody-mediated platelet activation. *Thromb Haemost.* 2005;93:1137–46 Dapirolizumab pegol, a polyethelene glycol-conjugated anti-CD40L Fab fragment has been designed to circumvent these issues and showed no evidence of prothrombotic effects in pre-clinical studies. This therapeutic agent was evaluated in a 32 week phase I study⁵⁸ of 24 patients with SLE that was primarily designed to explore the safety, tolerability and pharmacokinetics of the repeated intravenous dosing regimen. The results of this study revealed potential improvements in disease activity in patients who had high baseline disease activity scores, although the study was not powered to address this question. Treatment with dapirolizumab pegol resulted in an SRI-4 response in 41.7% of patients with SLE, compared with 14.3% of patients in the

placebo group⁵⁸. A higher incidence of non-serious infection was noted in the dapirolizumab pegol group than in the placebo group, but there was no increase in serious infection and notably, no evidence of thromboembolism. The initial results of a phase II study⁵⁹ have been announced in a press release⁵⁰. Few data have been provided, but the primary endpoint of establishing a dose response with a P value of ≤ 0.055 at week 24 was not met ($P = 0.06$), although “strong evidence of histological activity and improvement in the majority of clinical endpoints” was reported in patients given dapirolizumab⁶⁰. We await the full results of this study and a decision as to whether further trials of this agent will be pursued in lupus.

[H3] Targeting ICOS–ICOSL interactions. ICOS is a T cell-specific molecule that is expressed on the cell surface upon T cell activation and interacts with ICOSL, which is a constitutively expressed molecule on APCs, including B cells⁶¹. Functionally, ICOS is a co-stimulatory molecule similar to CD28 that causes T cell activation and contributes to B cell differentiation. Increased numbers of ICOS-expressing T cells and B cells with reduced expression of ICOSL are found in the blood of patients with SLE⁶², indicating that T cell–B cell interactions might have just taken place. The results of a phase II trial to assess the safety profile and tolerability of AMG 557, an anti-ICOSL mAb, in patients with mild SLE was reported in 2016⁶³. AMG 557 had an acceptable safety profile and the anticipated pharmacokinetic profile⁶³. Further trials are awaited to assess the clinical efficacy of anti-ICOSL antibody therapy in SLE.

[H3] Targeting immune complexes. The Fc region of IgG is recognised by Fcγ receptors (FcγRs), transmembrane proteins that are expressed on B cells and dendritic cells⁶⁴. The binding of immune complexes to FcγRs triggers intracellular signalling pathways that ultimately causes an immune response. FcγRIIB is an inhibitory receptor, unlike most other FcγR molecules, which tend to be activatory, and is an important regulator of activated B cells. Notably, patients with SLE have a reduced expression of FcγRIIB⁶⁵.

FcγRIIB has a limited degree of polymorphism in humans and is not immunogenic. An extracellular version of human FcγRIIB has been developed (known as SM101), which acts as a decoy receptor by binding to immune complexes and thereby preventing FcγR-mediated signalling. In an encouraging 24 week phase IIa trial, 51 patients with SLE were randomly allocated to receive weekly doses of SM101 or placebo for 4 weeks⁶⁶. SLEDAI, BILAG and PGA scores were recorded, as well as global response and renal parameter measurements, even though this was primarily a safety study. No serious unexpected adverse events occurred and the SRI-4 response was doubled in the SM101

group compared to the placebo group; results were particularly encouraging in patients with lupus nephritis⁶⁶. Given the encouraging results of the Phase II it will be interesting to see if this is a viable agent in Phase III studies, particularly in treating renal disease.

The results of a phase III trial of SM101 in patients with lupus nephritis are awaited.

[H3] Rigerimod. Rigerimod is a therapeutic agent that is theoretically appealing for the treatment of SLE. Rigerimod is a 21-mer linear peptide derived from the small nuclear ribonucleoprotein U1-70K that has the addition of phosphorylation at Ser140⁶⁷. Mechanistically, while not completely understood, rigerimod causes the depletion of autoreactive T cells via apoptosis without affecting the ability of T cells and B cells to respond to antigens, making it immuno-modulatory rather than immunosuppressive. In lupus-prone MRL/lpr mice, rigerimod treatment reduced disease activity (particularly vasculitis, protein excretion and skin disease) and anti-dsDNA antibody production⁶⁸. Phase II clinical studies of rigerimod have shown some promise. In a 2012 phase IIb study, 149 patients with active SLE (SLEDAI-2K score of ≥ 6 , patients with an A score in any BILAG domain excluded at screening) were randomly allocated to receive placebo or subcutaneous rigerimod every 2 or 4 weeks in addition to standard of care therapy⁶⁹. 53% of patients treated with monthly rigerimod attained an SRI-4 response at week 12 compared with 36% in those treated with placebo ($P = 0.048$). A post hoc analysis of a subpopulation of patients who had a clinical SLEDAI score of ≥ 6 at baseline revealed an even greater magnitude of response between the monthly rigerimod group and the placebo group ($P < 0.025$)⁶⁹. Similar to belimumab, it seems that the greatest clinical benefit occurs in patients with predominant articular and cutaneous disease. This study also included an analysis at 24 weeks, but the beneficial effects of rigerimod at the end of this additional 12 week treatment-free period were less evident. However, the initial results of a phase III study of rigerimod⁷⁰ (reported in a press release) showed that although rigerimod demonstrated a good safety profile and a superior response rate to placebo (68.8% versus 59%) in the 153 patients who completed the trial (the difference was greatest among anti-dsDNA antibody-positive patients), the difference was not statistically significant⁷¹. Given the equivocal and non-significant response noted in Phase 3 trials, the exact role of rigerimod in treating lupus is yet to be defined; interestingly an open label extension of the Phase III study was announced in 2018 and is yet to be reported.

[H2] Targeting the interferon pathway

Many patients with SLE have an increased expression of genes regulated by type I interferons in peripheral blood cells (known as the IFN gene signature), the products of which have diverse effects on the innate immune system and the adaptive immune system⁷². Evidence also exists to support a

genetic association between SLE and type I interferon-associated genes⁷³, and a high prevalence of 'drug-induced SLE' occurs in patients receiving therapeutic IFN α ⁷⁴. Together, these findings have promoted a strong interest in developing agents targeting type I interferons for use in SLE. Importantly, although most studies to date have focused on the inhibition of IFN α , the type I interferon family comprises 13 subtypes of IFN α , as well as IFN β , IFN ϵ , IFN κ and IFN ω , which mediate their biological effects by binding to the common type I interferon receptor (IFNAR)⁷⁵.

Contrary to expectations, there have been conflicting results from studies of type I interferon pathway inhibition. Rontalizumab and sifalimumab are mAbs that directly inhibit IFN α . In a phase II study of patients with SLE, rontalizumab did not meet the primary or secondary endpoints, although the results surprisingly suggested a benefit for patients with a low baseline IFN gene signature in their peripheral blood cells⁷⁶. By contrast, sifalimumab met its primary endpoint in a phase II study of patients with SLE and the results suggested a benefit for patients with a high IFN signature; however, the clinical benefits were modest compared with placebo (56% and 58% of patients in the two sifalimumab groups achieved an SRI-4 response compared with 45% of patients in the placebo group)⁷⁷.

The fully human IgG1 κ antibody anifrolumab antagonizes IFNAR, thereby down-regulating the effects of all type I interferons. In a 2017 phase IIb study⁷⁸, in addition to standard of care therapy, intravenous anifrolumab was superior to placebo in patients with moderate to severe SLE treated over a 48 week period. The primary endpoint of this study was the percentage of patients attaining an SRI-4 response at 24 weeks in addition to a sustained reduction of oral glucocorticoids from weeks 12-24, which was achieved in 34% of patients receiving 300mg/month anifrolumab compared with 17.6% receiving placebo⁵⁹. The advantage over placebo was less pronounced for patients receiving 1,000mg/month anifrolumab (28.8% of patients achieved an SRI-4 response), suggesting a possible plateau effect⁵⁹. Similar to sifalimumab, in this study⁷⁸, the greatest benefit was noted in patients with a high baseline IFN gene signature; 75% of patients had a high baseline IFN gene signature, and it was the response rate in this subpopulation that caused the difference between the treatment and placebo groups in the study, suggesting that selecting this cohort of patients for treatment with type I interferon inhibition could be beneficial. Similar to other studies of type I interferon inhibitors, an increase in viral infections (particularly herpes zoster infections) was noted in the anifrolumab groups, consistent with the mechanism of action of these agents. However, despite the optimism generated by the results of the phase II trial, a phase III study (TULIP1)⁷⁹ of 463 patients with SLE who have mucocutaneous and/or musculoskeletal disease did not meet its

endpoint of reducing disease activity (SRI-4 response)⁸⁰. A further phase II study specifically addressing the efficacy of anifrolumab in patients with active proliferative lupus nephritis is ongoing⁸¹.

Indirectly inhibiting the type 1 interferon pathway by means of an IFN α kinoid (IFN-K) vaccine has also been studied in patients with SLE. This vaccine comprises IFN α 2b coupled to a carrier protein, which together induce native, polyclonal neutralizing anti-IFN α antibodies⁸². Interferon α kinoid induces neutralizing anti-interferon α antibodies that decrease the expression of interferon-induced and B cell activation associated transcripts: analysis of extended follow-up data from the interferon α kinoid phase I/II study *Rheumatology*2016; 55(10):1901-5. This vaccine substantially reduced the IFN gene signature in patients with SLE in a phase I study⁸³. A larger phase IIb study is ongoing to address the efficacy, safety and immunogenicity of this agent in SLE⁸⁴.

[H2] Targeting the JAK–STAT pathway The Janus kinase (JAK)–signal transducer and activator of transcription (STAT) pathway is the primary signalling mechanism downstream of type 1 and type 2 cytokine receptors. Polymorphisms in genes encoding JAK and STAT proteins increase susceptibility to SLE⁸⁵ and inhibition of the JAK–STAT pathway is already used to treat many autoimmune diseases (including RA and PsA)⁸⁶.

In a pre-clinical study, tofacitinib (a JAK1 and JAK3 inhibitor) reduced both kidney disease and the concentration of pathogenic autoantibodies in lupus-prone mice⁸⁷. The results of a phase II trial of baricitinib⁸⁸ (an oral JAK1 and JAK2 inhibitor) in 314 patients with SLE who have active cutaneous disease or musculoskeletal activity were reported in 2018. 67% of patients receiving 4mg/day baricitinib achieved a SLEDAI-2K response at 24 weeks, which was significantly more than those receiving placebo (53%; $P=0.04$)⁸⁸. Treatment with 4mg/day baricitinib also reduced the proportion of patients with ‘worst joint pain’ compared with placebo and improved PGA and low disease activity scores; however, the 2mg/day dose of baricitinib did not show any benefit compared with placebo⁶⁴. The phase III BRAVE I⁸⁹ and BRAVE II⁹⁰ studies, which aim to assess the effects of baricitinib in patients with SLE, are currently recruiting and the results are awaited with interest. It is not clear whether this target may be more efficacious for non-organ threatening disease, particularly those with active joint or cutaneous disease and the results of these studies are keenly awaited.

[H2] Targeting IL-12 and IL-23

Blocking IL-12 and IL-23 is already used to successfully treat psoriasis and PsA⁹¹. Ustekinumab, an anti-IL-12/23 p40 monoclonal antibody, inhibits radiographic progression in patients with active psoriatic arthritis: results of an integrated analysis of radiographic data from the phase 3, multicentre, randomised, double-blind, placebo-controlled PSUMMIT-1 and PSUMMIT-2 trials. *Ann Rheum Dis* 2014; 73 (6): 10000-6

] and evidence suggests that these cytokine might be involved in some aspects of SLE pathogenesis⁹². The results of a phase II, placebo-controlled trial of ustekinumab⁹³ (an antibody against IL-12 and IL-23) in 102 seropositive patients with SLE were reported in 2018. All patients had a SLEDAI-2K score of ≥ 6 and/or two BILAG B scores and were receiving standard of care therapy to which was added either a single infusion of intravenous ustekinumab followed by subcutaneous ustekinumab every 8 weeks, or a single infusion of intravenous placebo followed by subcutaneous placebo every 8 weeks⁹³. 60% of patients treated with ustekinumab achieved the primary endpoint of an SRI-4 response at 6 months compared with 31% of the placebo treated group ($P = 0.0046$)⁶⁵, which was a very encouraging result. The risk of a new flare (one BILAG A score or two new BILAG B scores) was significantly lower in the ustekinumab-treated group than in the placebo-treated group ($P = 0.0078$). Particularly encouraging results were also observed for patients with active cutaneous disease and articular involvement at baseline, and the safety profile of ustekinumab in this study was similar to the safety profile in studies for other indications. Patients are currently being recruited for a phase III study to assess the efficacy of ustekinumab as a therapy for SLE⁹⁴.

[H1] Conclusions

The development and implementation of new therapies for SLE has lagged behind that of other rheumatic diseases, but many new molecular pathways and targets have been studied in the past two decades, some of which show promise for SLE. Given the problems encountered in previous clinical trials, most notably those of rituximab, it is clear that the design of trials for SLE needs to be revisited to decide the most objective indicator of response for this complex condition and to enable a clear distinction between the active treatment and, often quite substantial, background immunosuppression. In this Review, we have highlighted a number of promising targets and pathways but increasingly, success in phase II trials has not been followed by the achievement of primary endpoints in phase III trials. In general, clinical trials for SLE should aim to minimise background therapy (particularly glucocorticoids); use individual organ or system outcome measures rather than relying solely on composite measures; and have stringent requirements for the selection of trial sites. Such measures would help to maximise the chances of the therapies in development being successful. Although there is room for some optimism, the challenges of bringing successful new biological therapies into everyday clinical practice for SLE remains daunting.

- 1) Bernatsky, S. et al. Mortality in SLE. In: Dubois Lupus Erythematosus and Related Syndromes. 8th edition. Wallace, D.J., Hahn, B.H. etc Elsevier pp 666-75 (2013).
- 2) Caili, L. et al. Risk factors for osteoporosis and fragility fractures in patients with systemic lupus erythematosus. *Lupus Sci Med*. **3**:e000098 (2016).
- 3) Goldblatt, F., Chambers, S., Rahman, A. & Isenberg, D.A. Serious infections in British patients with systemic lupus erythematosus: hospitalizations and mortality. *Lupus* **18**, 682-689 (2009).
- 4) Petri, M. Atherosclerosis in systemic lupus erythematosus. *J Cardiovasc Pharmacol*. **62**, 255-62 (2013).
- 5) Croca, S. Rodrigues, T. & Isenberg, D.A. Assessment of a lupus nephritis cohort over a 30-year period. *Rheumatology*. **50**, 1424-1430 (2011).
- 6) Isenberg, D.A. & Rahman, A. Taking a closer look at biologic therapy for SLE. *Nat Rev Rheum*. **10**, 71-72 (2014).
- 7) Toumi, Z. & Gladman, D.D. Current and future therapies for SLE obstacles and recommendations for the development of novel treatments. *Lupus Sci Med* <http://dx.doi.org/10.1136/lupus-2017-000231>
- 8) Biologics in Rheumatology. New Developments, Clinical Uses and Health Implications. Eds Ciurtin E & Isenberg DA. Nova Biomedical, New York 2016.
- 9) Nashi, E., Wang, Y., & Diamond, B. The role of B Cells in Lupus Pathogenesis. *Int J Biochem Cell Biol* **42**, 543-550 (2010).
- 10) Tsang, H., Tam, R., Lu, L. & Lau, C. B Cell Targeted Therapies in Systemic Lupus Erythematosus. *Cell Mol Immunol* **10**, 133-142 (2013).
- 11) Ramos, L. & Isenberg, D.A. Rituximab: the lupus journey. *Curr Treat Opt In Rheum*. **11**, 1093-1107 (2015).
- 12) Carreira, P., L. & Isenberg, D.A. Recent developments in biologic therapies for the treatment of patients with systemic lupus erythematosus. *Rheumatology* **58**, 382-387 (2019).
- 13) McCarthy, E.M. et al. Short-term efficacy and safety of Rituximab therapy in refractory systemic lupus erythematosus: results from the British Isles Lupus Assessment Group Biologic Register. *Rheumatology* **57**, 410 – 479 (2018).
- 14) Hahn, B.H. et al. American College of Rheumatology guidelines for screening, treatment and management of lupus nephritis. *Arthritis Care Res* **64**, 797-808 (2012).
- 15) Bertias, G.H. et al. Joint European League Against Rheumatism and European Renal Association – European Dialysis and Transplant Association [EULAR-ERA-EDTA] recommendations for the management of adult and paediatric lupus nephritis. *Am Rheum Dis*. **71**, 1771-1782 (2012).

- 16) www.england.nhs.uk/wp-content/uploads/2018/07/Rituximab-for-the-treatment-of-systemic-lupus-erythematosus-in-adults.pdf
- 17) Reddy, V., Martinez, L., Isenberg, D.A., Leandro, M.J. & Cambridge, G. Pragmatic treatment of patients with systemic lupus erythematosus with rituximab: Long-term effects on serum immunoglobulins. *Arthritis Care Res.* **69**, 857-866 (2017).
- 18) Aguiar, R. et al. Use of rituximab in systemic lupus erythematosus: a single centre experience over 14 years. *Arthritis Care Res.* **69**, 257-262 (2017).
- 19) Hennessey, A., Lukawaska, J., Cambridge, G., Isenberg, D. and Leandro, M. Infusion reactions to Rituximab in systemic lupus erythematosus. *Ann Rheum Dis* 76; 1205. 1-1205.10.1136/annrheumdis-2017.eular.5876
- 20) A phase III randomized placebo-controlled study of Belimumab, a monoclonal antibody that inhibits B-lymphocyte stimulation, in patients with systemic lupus erythematosus. *Arthritis Rheum.* **63**, 3918-3930 (2011).
- 21) Navarra, S.V., et al. Efficacy and safety of Belimumab in patients with active systemic lupus erythematosus: a randomized placebo-controlled phase III trial. *Lancet* **377**, 721-731 (2011).
- 22) Furie, R. et al. Zhang, F., et al. A pivotal phase III randomised, placebo-controlled study of Belimumab in patients with systemic lupus erythematosus located in China, Japan and South Korea. *Am Rheum Dis* 2018; doi 10 1136/amrheumdis 2017 – 211631.
- 23) Stahl, W. et al. Efficacy and safety of subcutaneous Belimumab in systemic lupus erythematosus. *Arthritis Rheumatology* **69**, 1016-1027 (2017).
- 24) Iaccarino, L. et al. Clinical predictors of response and discontinuation of Belimumab in patients with systemic lupus erythematosus in real life setting. Results of a large, multicentric, nationwide study. *J Autoimmunity* 86, 1-8 (2018).
- 25) US National Library of Medicine. *ClinicalTrials.gov*
<http://www.clinicaltrials.gov/ct2/NCT01639339>
- 26) Feld, J., Isenberg D.A. Why and how should we measure disease activity and damage in lupus. *Quart Med Rev* 43, 151-156 (2014).
- 27) Isenberg, D.A. et al. Efficacy and safety of Ataccept for prevention of flares in patients with moderate-to-severe systemic lupus erythematosus [SLE]: 52 week data [APRIL-SLE randomized trial]. *Am Rheum Dis.* **74**, 2006-2015 (2015).
- 28) Merrill, J.T. et al. Safety profile in SLE patients treated with Ataccept in a phase IIb study [ADDRESS II] and its extension study. *Arthritis Rheum.* **69**, (suppl 10), (2017).
- 29) US National Library of Medicine. *ClinicalTrials.gov*
<http://www.clinicaltrials.gov/ct2/show/NCT00626197>

- 30) Isenberg, D.A. et al. Efficacy and safety of subcutaneous Tabalumab in patients with systemic lupus erythematosus: results from ILLUMINATE-1, a 52-week phase III, multi-centre randomized, double-blind controlled trial. *Ann Rheum Dis.* **75**, 323-331 (2016).
- 31) Merrill J et al. Efficacy and safety of sub-cutaneous Tabalumab, a monoclonal antibody to B-cell activating factor, in patients with systemic lupus erythematosus: results from ILLUMINATE-2, a 52-week, phase III, multi-centre, randomized, double-blind controlled study. *Ann Rheum Dis.* **75**, 332-340 (2016).
- 32) Du FH, Mills EA, Mao-Draayer. Next generation anti-CD20 monoclonal antibodies in autoimmune disease treatment. *Auto Immun Highlights* 2017; 8(1): 12
- 33) US National Library of Medicine. *ClinicalTrials.gov*
<http://www.clinicaltrials.gov/ct2/show/NCT00539838>
- 34) Mysler, E.F. et al. Efficacy and safety of Ocrelizumab in active proliferative lupus nephritis; results from a randomized, double blind Phase III study. *Arthritis Rheum* **65**, 2368-2379 (2013).
- 35) Reddy, V. et al. Obinutuzumab induces superior B-cell cytotoxicity to Rituximab in rheumatoid arthritis and systemic lupus erythematosus patient samples. *Rheumatol.* **56**, 1227-1237 (2017).
- 36) US National Library of Medicine. *ClinicalTrials.gov*
<http://www.clinicaltrials.gov/ct2/show/NCT02550652> (US National Library of Medicine).
- 37) Montillo, M. et al. Autoimmune haemolytic anaemia and immune mediated thrombocytopenia in the phase III RESONATE™ study of Ibrutinib Vs Ofatumumab in relapsed/refractory chronic lymphocytic leukaemia, including a case report. *Blood* **124**, 565 – (2014).
- 38) Haorhaus, M., Svenungsson, E., and I. Gunnarsson. Ofatumumab treatment in lupus nephritis patients. *Clin Kid J* **9**, 552-555 (2016).
- 39) Lavie, F., Miceli-Richard, C., Ittah, M. Increase of B Cell Activating Factor of the TNF family (BAFF) after Rituximab treatment: insights into a new regulating system of BAFF production. *Ann Rheum Dis* **66**, 700-703 (2007).
- 40) D'all Era M., et al. Phase 2 trial of induction therapy with anti-CD20 (Rituximab) followed by maintenance therapy with anti-BAFF (Belimumab) in patients with active lupus nephritis. Am College of Rheumatology College 2018. Abstract 1870.
- 41) Kraaij, T. et al. Synergistic B cell immune-modulation with Rituximab and belimumab combination treatment in severe, refractory lupus. EULAR 2018. Abstract PS7:129
- 42) BEAT Lupus. *BEAT Lupus* <https://beatlupus.uk/> (2017)
- 43) Merrill, J.T., et al. Top line results of a phase 2, double-blind randomised, placebo-controlled study of a reversible B-cell inhibitor Xm ab® 5871 in systemic lupus erythematosus. American College of Rheumatology Congress 2018. Late Breaking Abstract NL19.

- 44) Lopez-Herrera, A. et al. Bruton's tyrosine kinase – an integral protein of B-cell development that also has an essential role in the innate immune system. *J Leukol Biol* **95**, 243-250 (2014).
- 45) Runkin, A.L., et al. Selective inhibition of BTK prevents murine lupus and antibody mediated glomerulonephritis. *J Immunol* **95**, 243-250 (2014).
- 46) Kil, L.P. et al. Btk levels set the threshold for B-cell activation and negative selection of autoreactive B cells in mice. *Blood* **16**, 3744-3756 (2012).
- 47) Hutcheson, J., et al. Modulating proximal cell signalling by targeting BTK ameliorates humoral autoimmunity and end organ disease in murine lupus. *Arthritis Ther Res* **14**, R243 (2012).
- 48) Katsumato, T. W. H., et al. Safety, pharmacokinetics and biomarker profile from phase I clinical trials of healthy volunteers treated with BDC-0853, a highly selective reversible oral Burton's Tyrosine Kinase (BTK) inhibitor **510**, 68 (2016)
- 49) US National Library of Medicine. *ClinicalTrials.gov*
<http://www.clinicaltrials.gov/ct2/show/NCT02908100>
- 50) Elgueta, R. et al. Molecular mechanism and function of CD40/CD40L engagement in the immune system. *Immunol Rev* **1**, 10 (2009).
- 51) Koshy, M. Berger, D. & Crow M.K. Increased expression of CD40 ligand on systemic lupus erythematosus lymphocytes. *J Clin Invest* **98**, 826-37 (1996).
- 52) Higuchi, T., Aiba, Y., Nomura, T., Matsuda, J., Mochida, K., Suzuki, M., et al. cutting edge: Ectopic expression of CD40L on B cells induces lupus-like autoimmune disease. *J Immunol* **168**, 9-12 (2002).
- 53) Early, G., Zhao, W. & Burns, C. anti-CD40L antibody treatment prevents the development of lupus-like nephritis in a subset of NZB-NZW mice. *J Immunol* **157**, 3159-64 (1996).
- 54) Boumpas, D.T., Furie, R., Manzi, S., Illei, G.G., Wallace, D.J., Barlow, J.E., et al. a short course of BG9588 improves serological activity and decreases hematuria in patients with proliferative lupus GN. *Arth Rheum* **48**, 719-27 (2003).
- 55) Kalunian, K.C., Davis, J.C., Merrill, J.T., Totoritis, M.C., & Wofsy, D. Treatment of SLE by inhibition of T cell costimulation with anti-CD154.: A randomized, double-blind, placebo-controlled trial. *Arth Rheum* **46**, 3251-8 (2002).
- 56) Law, C.-L., Grewal, I.S. Therapeutic interventions targeting CF40L and CD40: The opportunities and challenges. In: Grewal IS, editor. Therapeutic Targets of the TNF Superfamily. *Landes Bioscience*, 8-36 (2009).
- 57) Langer, F., et al. The role of CD40 in CD40-L and antibody mediated platelet activation. *Thromb Haemost* **93**, 1137-1146 (2005).

- 58) Chamberlain, C., Colman, P.J., Ranger, A.M. et al. Repeated administration of dapirolizumab pegol in a randomised phase I study is well tolerated and accompanied by improvements in several composite measures of systemic lupus erythematosus disease activity and changes in whole blood transcriptomic profiles. *Ann Rheum Dis* **76**, 1837-1844 (2017).
- 59) US National Library of Medicine. *ClinicalTrials.gov*
<http://www.clinicaltrials.gov/ct2/show/NCT028047863>
- 60) <https://www.ucb.com/stories-media/Press-Releases/article/UCB-and-Biogen-Announce-Topline-Results-from-a-Phase-2b-Study-of-Dapirolizumab-Pegol-in-Systemic-Lupus-Erythematosus>
- 61) Hutloff, A., et al. ICOS is an inducible T-cell co-stimulator structurally and functionally related to CD28. *Nature* **397**, 263-266 (1999).
- 62) Yang, J.H. et al. Expression and function of inducible co-stimulator on peripheral blood T cells in patients with systemic lupus erythematosus. *Rheumatology* **44**, 1245-1254 (2005).
- 63) Sullivan BA, Tsuji W, Kivitz A et al. Inducible T cell co-stimulator ligand (ICOSL) blockade leads to selective inhibition of anti-KLH IgG responses in subjects with systemic lupus erythematosus. *Lupus Sci Med* 2016; 3(1):e000146
- 64) Daeron, M. Fc Receptor Biology. *Annu Rev Immunol* **15**, 203-34 (1997).
- 65) Niedere, H.A., Clatworthy, M.R., Willocks, L.C. and Smith, K.G. Fc-gamma-RIIB, Fc-gamma- R11B and systemic lupus erythematosus. *Am N Y Acad Sci* **83**, 69-86 (2010).
- 66) Tillmans, S., et al. SM101, a novel recombinant soluble human FcγIIB receptor in the treatment of systemic lupus erythematosus: results of a double blind placebo controlled multicentre study. *Arthritis Rheum* **67**, Abst No 2833 (2014)
- 67) Monneaux, F., Lozano, J.M., Patarroyo, M.E., Briand, J.P. & Muller, S. T cell recognition and therapeutic effect of a phosphorylated synthetic peptide of the 70K nRNP protein administered in MR/lpr mice. *Eur J Immunol* **33**, 287-96 (2003).
- 68) Page, N., Schall, N., Strub, J.M. et al. The spliceosomal phosphopeptide P140 controls the lupus disease by interacting with the HSC70 protein and via a mechanism mediated by gammadelta T cell. *PLoS One* **4**, e5273 (2009).
- 69) Zimmer, R., Scherbarth, H.R., Rillo, O.L., Gomez-Reino, J.J. & Muller, S. Lupuzor/P140 peptide in patients with systemic lupus erythematosus: a randomized, double-blind, placebo-controlled phase IIb clinical trial. *Ann Rheum Dis* **72**, 1830-5 (2013).
- 70) US National Library of Medicine. *ClinicalTrials.gov*
<http://www.clinicaltrials.gov/ct2/show/NCT02504645>
- 71) <https://lupusnewstoday.com> 2018/04/23/lupuzor-shows-promising-results-in-phase-3-study-in-lupus-patients

- 72) Bennett, L., Palucka, A.K., Arce, E. et al. Interferon and granulopoiesis signatures in systemic lupus erythematosus blood. *J Exp Med* **197**, 711-23 (2003).
- 73) Bronson, P.G., Chaivorapol, C., Ortmann, W., Behrens, T.W. & Graham, R.R. The genetics of type I interferon in systemic lupus erythematosus. *Curr Opin Immunol* **24**, 530-7 (2012).
- 74) Niewold, M.D. Interferon-alpha induced lupus: proof of principle. *J Clin Rheumatol* **14**, 131-132 (2008).
- 75) De Weerd, N.A., Samarajiwa, S.A. & Hertzog, P.J. Type 1 Interferon receptors. *J Biol Chem* **8**, 20053-20057 (2008).
- 76) Kalunian, K.C., Merrill, J.T. Werth, V.P. et al. Maciuga RA Phase II study of the efficacy and safety of Rontalizumab (rhuMAb interferon- α) in patients with systemic lupus erythematosus (ROSE). *Ann Rheum Dis* **75**, 196-202 (2016).
- 77) Khamashta, M. et al. Sifalimumab, an anti-interferon- α monoclonal antibody, in moderate to severe systemic lupus erythematosus: a randomized, double-blind placebo controlled study. *Ann Rheum Dis*. **75**, 1909-1916 (2016).
- 78) Furie, R., Khamashta, M., Merrill, J.T. et al. Anifrolumab, an Anti-Interferon- α Receptor Monoclonal Antibody, in Moderate-to-Severe Systemic Lupus Erythematosus. *Arthritis Rheumatol* **69**, 376-386 (2017).
- 79) US National Library of Medicine. *ClinicalTrials.gov*
<http://www.clinicaltrials.gov/ct2/show/NCT02446899>
- 80) <https://www.astrazeneca.com/media-centre/press-releases/2018/update-on-tulip-1-phase-III-for-anifrolumab-in-sytemic-lupus-erythematosus>
- 81) US National Library of Medicine. *ClinicalTrials.gov*
<http://www.clinicaltrials.gov/ct2/show/NCT02547922>
- 82) Ducreux, J., Houssiau, F.A. & Vandepapeliere, P. Interferon α kinoid induces neutralizing anti-interferon α antibodies that decrease the expression of interferon-induced and B cell activation associated transcripts: analysis of extended follow-up data from the interferon α kinoid phase I/II study. *Rheumatology* **55**, 1901-5 (2016).
- 83) Lauwerys, B.R., Hachulla, E., Spertini, F. et al. Down-regulation of interferon signature in systemic lupus erythematosus patients by active immunization with interferon α -kinoid. *Arthritis Rheum* **65**, 447-56 (2013).
- 84) US National Library of Medicine. *ClinicalTrials.gov*
<http://www.clinicaltrials.gov/ct2/show/NCT02665364>

- 85) Comprehensive assessment of the association between genes on JAK-STAT pathway (IFIH1, TYK2, IL-10) and systemic lupus erythematosus: a meta-analysis. Yin Q, Wu LC, Zheng et al. *Arch Dermatol Res*. 2018 Nov;310(9):711-728
- 86) Fragoulis, G.E., McInnes, I.B., & Siebert, S. JAK-inhibitors. New players in the field of Immune-mediated diseases, beyond Rheumatoid Arthritis. *Rheumatology* **58**, (suppl 1 i43-54) (2019).
- 87) Tofacitinib Ameliorates Murine Lupus and Its Associated Vascular Dysfunction. Furumoto Y, Smith CK, Blanco L et al. *Arthritis Rheumatol*. 2017 Jan;69(1):148-160.
- 88) Baricitinib for systemic lupus erythematosus: a double-blind, randomised, placebo-controlled, phase 2 trial. Wallace DJ, Furie RA, Tanaka Y et al. *Lancet*. 2018 Jul 21;392(10143):222-231
- 89) US National Library of Medicine. *ClinicalTrials.gov*
<http://www.clinicaltrials.gov/ct2/show/NCT03616864>
- 90) US National Library of Medicine. *ClinicalTrials.gov*
<http://www.clinicaltrials.gov/ct2/show/NCT03616912>
- 91) Kavanaugh, A. et al. Ustekinumab, an anti-IL-12/23 p40 monoclonal antibody, inhibits radiographic progression in patients with active psoriatic arthritis: results of an integrated analysis of radiographic data from the phase 3, multicentre, randomised, double-blind, placebo-controlled PSUMMIT-1 and PSUMMIT-2 trials. *Ann Rheum Dis* **73**, 1000 (2014).
- 92) Leng, R.X. et al. IL-23 a promising therapeutic target for systemic lupus erythematosus. *Arch Med Res* **41**, 221-225 (2010).
- 93) Van Vollenhoven. R., et al Efficacy and safety of Ustekinumab an Interleukin 12/23 inhibitor, in patients with active systemic lupus erythematosus: results of a phase 2, randomize placebo controlled study. *Lancet* 2018 <http://dx.doi.org/10.101G/50140-6736> (18) 32167-6.
- 94) US National Library of Medicine. *ClinicalTrials.gov*
<http://www.clinicaltrials.gov/ct2/show/NCT03517722>

Acknowledgements

D.A.I. acknowledges the support of the Biomedical Research Centre [Au: Correct expansion of BRC?] award to University College Hospital and University College London.

Author contributions

The authors contributed equally to all aspects of the article. [Au: Please confirm that this statement is correct]

Competing interests

D.A.I. declares that he has received honoraria from Anthera, Celgene, Eli Lilly, Merck Serono, UCB Pharma and XTLBio. G.M. declares no competing interests.

Publisher's note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Key points

- The approval of new therapies, especially biologic drugs, for systemic lupus erythematosus (SLE) has been scarce in comparison to rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis.
- Belimumab (FDA-approved) and rituximab (National Health Service England-approved) are available for use in some countries, although the cost (particularly of belimumab) mitigates their universal uptake.
- Clinical trial design for SLE is problematic and success in phase II trials is not often followed by success in phase III trials.
- Several new approaches are under investigation that target either B cells, cytokines or intracellular signalling pathways, providing hope that new therapies will be approved for SLE.

Figure 1 Diagram indicating the cells and molecules which interact in the immunopathogenesis of SLE and the monoclonal antibodies which bind to them offering the hope of therapeutic advantage.

Table 1. Deaths in clinical trials of biologic therapies in systemic lupus erythematosus.

Drug	Total number of patients in trial	Deaths in placebo group (n(%))	Deaths in low dose treatment group (n(%))	Deaths in medium dose treatment group (n(%))	Deaths in high dose treatment group (n(%))	Reference
Atacicept	455	0 (0.0)	0 (0.0)	NA	2 (1.4)	27
Tabalumab	1164	2 (0.5)	2 (0.5)	NA	3 (0.8)	30
Tabalumab	1124	3 (0.8)	2 (0.5)	NA	1 (0.3)	31
Belimumab	865	3 (1.0)	2 (0.7)	NA	4 (1.0)	21
Belimumab	819	0 (0.0)	2 (0.7)	NA	1 (0.4)	22
Sifalimumab	431	2 (1.9)	0 (0.0)	2 (1.9)	2 (1.9)	77

Table 2 – Ongoing clinical trials of new therapies for systemic lupus erythematosus.

Therapy	Target(s)	Trial phase	Status	Size	Primary outcome	Reference
Obintuzumab	CD20	II	Active, not recruiting	127 participants	Percentage of patients with complete renal response at 52 weeks	35
Combination therapy with rituximab and belimumab	CD20 and BAFF	II	Recruiting	Target of 30 participants [Au: OK?]	Reduction in disease-relevant auto-antibodies at 28 weeks	4
Combination therapy with rituximab and belimumab	CD20 and BAFF	III	Recruiting	Target of 200 participants [Au: OK?]	Proportion of patients with a SLEDAI-2K score of <2 without the use of additional immunosuppression	40
Combination therapy with rituximab and belimumab	CD20 and BAFF	II	Active, not recruiting	Target of 50 participants (fully recruited)	Reduction in anti-dsDNA antibodies at 52 weeks	42
GDC 0853	BTK	II	Active, not recruiting	240 participants	SRI-4 response at 48 weeks	48
Dapirolizumab	CD40L	II	Active, not recruiting	182 participants	Proportion of patients with a BICLA response at 24 weeks	58
Anifrolumab	IFNAR	II	Recruiting	Target of 150 participants [Au: OK?]	Relative change from baseline in urine protein-to-creatinine ratio	79
IFN α kinoid	B cells to stimulate the production of anti-IFN α antibodies	II	Active, not recruiting	178 participants	Change from baseline in expression of IFN-induced genes at 36 weeks Treatment response as assessed by BICLA at 36 weeks	82
Baricitinib (BRAVE I)	JAK1 and JAK2	III	Recruiting	Target of 750 participants [Au: OK?]	Percentage of patients achieving an	89

					SRI-4 response at 52 weeks	
Baricitinib (BRAVE II)	JAK1 and JAK2	III	Recruiting	Target of 750 participants	Percentage of patients achieving an SRI-4 response at 52 weeks	90
Tofacitinib	JAK1 and JAK3	I/II	Complete	34 participants	Safety of tofacitinib in patients with mild-moderate disease activity	82
Ustekinumab	IL-12 and IL-23	III	Recruiting	Target of 500 participants	Percentage of patients achieving and SRI-4 response at 52 weeks	93

BAFF, B cell activating factor; BICLA, BILAG-based Composite Lupus Assessment; BTK, protein tyrosine kinase BTK; CD40L, CD40 ligand; dsDNA, double stranded DNA; IFN, interferon; IFNAR, type I interferon receptor; JAK, Janus kinase; SLEDAI-2K, Systemic lupus erythematosus disease activity index 2000; SRI-4, SLE Responder Index 4.

Table 3. The characteristics of type I and type II anti-CD20 monoclonal antibodies.

Type of antibody	Examples	Redistributes CD20	Internalisation of anti-CD20 mAb complexes	Complement-dependent cellular cytotoxicity	Antibody-dependent cellular cytotoxicity	Antibody-dependent cell phagocytosis	Method of direct cell death
Type I	Rituximab, Ofatumumab, Ocrelizumab and Velutuzumab	Yes	Yes, but highly variable	Potent	Yes	Yes	Apoptosis
Type II	Obinutuzumab and Tositumomab	No	Yes, to a small extent	Weak	Yes	Yes	Non-apoptotic lysosome-mediated cell death

mAb, monoclonal antibody.