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Biologic therapies for systemic lupus erythematosus – Where Are We Now?

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ABSTRACT:

Conventional approaches using hydroxychloroquine, corticosteroids and immunosuppressives have considerably improved the prognosis for patients with systemic lupus erythematosus(SLE) . Unfortunately they have reached the limits of what they can achieve and we still see patients dying much too early of their disease and/or find their quality of life greatly impaired. For 20 years we have hoped that the great successes of the biologic therapies in rheumatoid arthritis and psoriatic arthritis would be replicated in SLE, but we have been generally disappointed. However, the clear success of B-cell depletion using Rituximab in many open clinical studies, the approval of Belimumab (which blocks the B-cell activating factor BAFF) and the recognition that clinical trial design can be improved has given some cause for hope. In this review, we will review the problems of assessing activity in SLE, the challenges of setting up optimal clinical trials and some more recent biologic approaches. These include the use of fully humanized anti-CD20 and CD19 monoclonals, blocking interferons, inhibiting Bruton's tyrosine kinase [BTK], blocking the CD40 ligand (CD40L), utilising a peptide approach to interfere with antigen presentation to autoreactive T-cells, utilising an analogue of the FcγRIIB and, utilising an IL12-23 blocker and recently targeting the JAK-STAT pathway.

INTRODUCTION:

The introduction of corticosteroids and the now standard immunosuppressive drugs such as azathioprine, methotrexate, cyclophosphamide and mycophenolate has driven the improved outlook for patients with systemic lupus erythematosus (SLE) in the past 70 years. Thus the 4-year prognosis of approximately 50% survival in 1950, has risen to approximately 85% 15-year survival currently (1). However, even these drugs, aided by a variety of others to mitigate against other consequences of lupus (eg anti-hypertensives and statins), or the side effects of steroids (eg vitamin D reducing osteoporosis) and immunosuppression (long term antibiotics to reduce infection risk in some patients) are unlikely to bring about any further significant improvement. In renal lupus in particular, the outcome has hardly changed in the past 30 years (2). We need to effect the kind of transformative approach that the biologic drugs have brought about for the treatment of rheumatoid arthritis (RA) and psoriatic arthritis (PsA) (3). Unlike these diseases, biologic therapy for the treatment of SLE has, in the main, been much less successful.

SLE is characterised by a breakdown in both B and T cell tolerance. Abnormal B cell functioning in particular, seems to be at the heart of the pathogenic process leading to the disease. The development of numerous autoantibodies targeting self antigens such as DNA and extractable nuclear antigens is characteristic of SLE. These cells are also involved in antigen presentation and cytokine production. However the precise contribution of B cells to disease initiation and perpetuation is complicated in SLE. Figure 1 shows the likely interplay of cells involved in lupus pathogenesis and the places at which biologic drugs have been targeted.

Disappointingly, many biologic agents including rituximab (which blocks the CD20 molecule), epratuzumab (which blocks the CD22 molecule), abatacept which blocks the link between the antigen-presenting cell and the T-cell) and blisibimod which blocks the B cell activating factor (BAFF) have not met their primary and/or secondary endpoints in large-scale phase III clinical trials (4).

Many lupus trials target B cell pathways. The approaches vary from targeting selective markers on B cells notably CD20 (rituximab) and CD 22 (epratuzumab), to inhibition of B cell survival (anti-BAFF, anti- IL-6,-IL17 and IL-21) to interfering with B cell antigen receptor signalling (eg inhibition of CD40/CD40 ligand and inducible costimulator ICOS/ICOS ligands (5).

In this chapter we will review the variety of biologic approaches that have been attempted in the treatment of SLE, discussing why many seem to have failed, but also emphasizing our belief that some at least will, ultimately, prove successful.

FIRST PRINCIPLES

For any drug, biologic or not, three key elements have to be in place to guarantee its success. Obviously the approach must be shown to be clinically beneficial, but this must be accompanied by a relative lack of side effects. It must also come at a price that is affordable.

Determining clinical success in SLE has proved challenging. In rheumatoid arthritis where a single system ie the musculoskeletal system is involved, the use of relatively simple tender/painful/swollen joint counts and physician assessments eg the American College of Rheumatology's 20/50/70 criteria (6) is relatively easy to adopt universally. In contrast, SLE provides a much bigger challenge. Its capacity to affect virtually every organ/ system in the body requires both detailed assessment of some important systems eg the kidney, but also a broad-based approach to capture the wide variety of possible clinical features. As discussed in detail elsewhere (7,8) it is important to distinguish clinical features in SLE due to disease activity (ie those features which have the possibility of improving such as arthritis and serositis) from those (damage) aspects which are permanent (eg avascular necrosis, renal failure).The most widely used activity indices are the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), which is a global score index and the British Isles Disease Activity Group (BILAG) index which captures disease in 9 organs/systems and distinguishes those features that are worse or partially, but not fully, improved.

These indices have been combined (together with the addition of a physician's global assessment) into the SLE–Responder Index (SRI) and BICLA composite indices (see Table1) (9). They differ in that BICLA requires only partial improvement, but in all organs, whereas the SRI requires full improvement in some manifestations but not all organs. Whilst now widely used in clinical trials, they do require considerable attention to detail and experience in managing SLE patients for optimal use. A more recently introduced index, the Lupus low disease activity state may also prove to be a useful tool (10)

BLOCKING B CELL ACTIVATING FACTORS

Belimumab was approved for use in systemic lupus erythematosus in 2011 by the Federal Drug Administration (FDA) in the United States and (in 2016) by the National Institute of Clinical Excellence in the United Kingdom following the successful clinical trials which focussed on SLE patients skin and/or joint disease(11,12). It was the first drug for over 50 years to be approved by the FDA for the treatment of lupus. However, its use in the United Kingdom is currently limited to those patients with active skin and joint disease.

Support for its use came from a trial (13) of intravenous Belimumab, involving 677 patients in China, Japan and South Korea [patients with renal or central nervous system disease were excluded]. In this trial, a response rate [using the SRI-4 end point] of 53.8% in the Belimumab treatment arm was observed compared with 40.1% in those patients given placebo (in addition to standard of care) Odds Ratio (OR): 1.99 (95% CI: 1:40, 282 p = 0.001).

The headline results of a trial looking at belimumab in renal disease (Trial number NCT01639339) appear promising. This Phase 3 study which compared IV belimumab in conjunction with standard of care (mycophenolate or cyclophosphamide induction followed by mycophenolate or azathioprine maintenance respectively) (14) included 448 patients with active lupus nephritis. Its primary endpoint of primary efficacy Renal Response (PERR- eGFR of >60 or no decrease in eGFR from a pre-flare level of >20% in addition to urine protein:creatinine ratio of <0.7 in patients who were not deemed to be treatment failures) was reached by 43% of patients in the intervention arm compared with 32% in the placebo group OR 1.04, 2.32), p=0.03). With publication pending this appears to offer promise of an additional treatment option for patients with lupus nephritis. Notable gaps in our knowledge in relation to belimumab still exist. Thus a more detailed knowledge of its effectiveness for a host of other lupus manifestations including pleuropericarditis, gastrointestinal disease and central nervous systemic disease is awaited.

Despite the cost of belimumab, the time taken for patients to show improvement (often several months) and regulatory limitations ,'real life' experience with belimumab is emerging. In the United States an observational cohort study of 501 patients (15) who received belimumab plus standard of care for up to 2 years reported improvements in disease severity and laboratory markers (eg the numbers of anti ds DNA antibody positive patients fell from 69.1% at baseline to 48.6% after 2 years). A reduction in steroid use was also noted. Similarly a study from Italy [16] of 188 patients followed up for a mean of 17.5, $\pm$ 10.6 months confirmed both efficacy [though polyarthritis and skin rashes were the commonest manifestations] and safety. In addition, the efficacy and safety of a subcutaneous form of belimumab has also been reported [17] in a study of 839 SLE patients, [556 of whom were given the monoclonal and 280 a placebo]. Among those given belimumab 61.4% met the primary end points, achieving an SRI-4, compared to 48.4% who received placebo [OR, 1.68 confidence interval (95% (1) 1.25-2.25, p = 0.0006].

Frustratingly, two substantial trials (both involving > 1100 patients) of another anti-BAFF monoclonal, tabalumab, apparently came to different conclusions. In the first trial, ILLUMINATE 1 (18), the primary end point (SRI-5) was not met. However, in the second trial ILLUMINATE 2 (19) the identical primary end point was met . The critical difference between the trials was that in the first, any alteration in steroid dose resulted in the patient being withdrawn from the trial. This stipulation did not apply in the second trial. On reflection, this withdrawal clause meant that patients whose disease had improved due to tabalumab and who had reduced their steroids were deemed to have failed the trial and this clearly was illogical.

Blisibimod which also blocks BAFF, showed promise in a phase II clinical trial (20) using the SRI-4 end point, but the phase III trial failed to meet its primary end point (21) . Neither this monoclonal nor tabalumab are being pursued in further studies

Atacicept which blocks two B-cell activating factors (BAFF and APRIL) was first utilised in the APRIL-SLE phase II/III flare prevention study (22) . In this trial patients with active lupus (defined by the presence of a new BILAG A or B) were brought under control by a sharply reducing dose of corticosteroids. They were then put onto a higher (150mg) or lower (75mg) dose of atacicept or placebo – the aims being to look for the time to first flare and the numbers of flares in the one-year follow-up period. The safety committee, concerned about two deaths in the higher-dose arm, suspended this arm of the trial. However, two deaths (out of around 500 patients) in a lupus trial is, regrettably, not exceptional (discussed in 5) and reassuringly in a trial of 300 patients with active disease, there were no deaths among those given atacicept that could be ascribed to the drug. The serious infection rate was found to be 7% in the placebo arm, 8% in the 75mg arm and just 1% in the high dose (150mg arm) (23). A post hoc analysis of the APRIL-SLE study (24) showed a dose

relationship between atacicept concentrations, reduced immunoglobulin levels and reduced flare rates. These data suggested that baseline biomarkers such as elevated levels of BAFF and APRIL might identify patients most likely to benefit from atacicept treatment. This observation has echoes of an earlier study (25) reporting that a rise in serum BAFF levels are linked to rise in ds DNA antibody levels and disease flare following B cell depletion therapy (25)

B CELL DEPLETION

Edwards and Cambridge from University College London, were the first to demonstrate that B cell depletion achieved by combining rituximab, steroids and cyclophosphamide was an effective approach in the treatment of an autoimmune rheumatic disease, rheumatoid arthritis (26). One of us (DAI) together with other colleagues, extended their work to patients with lupus (27). Subsequently many open-label studies (reviewed in 28) and data from national registries (29, 30) reported encouraging results with Rituximab. Our experience in the Lupus Clinic at University College Hospital, London has been that since 2000 we have treated approximately 175 patients out of 700 with rituximab , principally because classic immunosuppression with steroids and drugs like azathioprine, mycophenolate and cyclophosphamide was either not effective or causing major side-effects. Our most recently published data indicate that 86% of patients treated with B cell depletion reduced their BILAG scores with renal disease being particular susceptible to this approach (31). These data support a study from the British Isles Lupus Assessment Group (BILAG) group which reported that over 6 months in 261 rituximab treated SLE patients a fall in the mean baseline BILAG score from 15 (range 10-23) to 4 (0-7) $p<0.001$), was recorded with a notable reduction in concomitant steroids (32).

In contrast, two large double blind clinical trials , one in non-renal lupus (33)and one in renal disease (34) did not meet their primary end points. The likely reasons for the failure of these trials are discussed in detail elsewhere (28). On balance both the American College of Rheumatology (35) and the European League Against Rheumatism (36) felt able to recommend rituximab for lupus nephritis and NHS England also sanctions its use in hard-to-treat patients. It should however be noted that rituximab may cause hypogammaglobulinaemia (37), which clearly carries an increased risk of infection, and we have recorded an allergic response in 16% ranging from mild cutaneous rash with flushing and pruritus to symptomatic bronchospasm with dysphonia, hypoxia and wheeze (38).

Rituximab is not fully humanized and fully humanized, anti-CD20 monoclonals are becoming available to help reduce the risk of allergic responses. Ocrelizumab was previously studied in 2 phase II trials of patients with SLE (reviewed in 39). The first, BEGIN, a phase III study of non-renal SLE was terminated early when the sponsor decided not to pursue this indication. The second, BELONG, a Phase II study in lupus nephritis patients was terminated early due to a higher serious infection rate in patients also receiving MMF. A 32 week assessment revealed renal response rates of 63% and 51% in the ocrelizumab and placebo groups respectively with an apparent benefit in those receiving background cyclophosphamide.

Ofatumumab an IgG 1 which binds CD20 with greater affinity than rituximab has been approved for the treatment of chronic lymphocytic leukaemia. Small numbers of patients with autoimmune haemolytic anaemia and immune medicated thrombocytopenia (40) and lupus nephritis (41,42) have also shown benefit though no large scale study has been undertaken with this agent in SLE

Obinutuzumab has been shown to induce better B-cell cytotoxicity than rituximab in rheumatoid arthritis and SLE (43). A phase II trial that is ongoing and due to last for one year is studying the

efficacy and safety of this drug in lupus nephritis (NCT02550652). Its primary outcome is complete renal response.

Combinations of biologics are also being considered. In particular the notion of linking B cell depletion therapy with rituximab and inhibition of B cell survival with belimumab. This idea is based on the premise that, after B cell depletion, the consequent BAFF production encourages the maturation of autoreactive B cells. Several groups have recently reported preliminary data based on such strategies. The largest of these (the CALIBRATE trial) compared the impact of rituximab with one pulse of cyclophosphamide followed by monthly IV belimumab (n=21) from 4 weeks with rituximab and cyclophosphamide (n=22) alone in patients with active lupus nephritis (44). Unfortunately 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 hypogammaglobulinaemia. The SynBiose study was an open label proof of concept study using a similar infusion protocol without the additional cyclophosphamide (45). While clinical improvement was noted with an improvement in SLEDAI scores out to week 24 (renal response noted in 11/16 patients) in a cohort of refractory patients, the Phase 3 studies are awaited. In the SynBioSe study clinical improvement was also mirrored by a reduction of autoantibodies including anti- dsDNA and a reduction in neutrophil extracellular trap (NET) formation, a process implicated in lupus pathogenesis.

An ongoing trial, BEAT-Lupus, based in the UK is fully recruited (ISRCTN47873003) with the results expected in late 2020. It is a multi-centre, double blind placebo-controlled Phase III trial investigating the safety and efficacy of belimumab commencing 4-8 weeks after Rituximab. Patients with the full diversity of lupus features have been enrolled.

Anti-CD19:

A phase II study of 104 SLE patients using a humanized anti-CD19 antibody Fc engineered and with increased affinity to FcγRIIb, designated Xm Ab 5871, has been reported (46). Low disease activity was first achieved by using intramuscular steroid injections. Background immunosuppression was stopped and those with the required disease activity improvement were randomized 1:1 to XmAb5871 or placebo. Patients were followed to Day 225 and improvement was maintained with no "loss of improvement" (defined as an increase in SLEDAI >4 or new BILAG A or B score) in 42% of XmAb5871 treated compared to 23% of placebo treated patients (p= 0.06)

OTHER APPROACHES:

It has been a notable feature in the history of biologic therapies used in SLE, that success in a phase II trials does not guarantee success in a phase III study. Part of the problem, alluded to above, is the challenge of capturing disease activity accurately and the need to ensure that physicians involved in clinical trials are trained and ideally tested, to ensure their competence in using the activity assessment systems. It is also likely that the high placebo rates noted (often in the region of 40%), together with the complexity and heterogeneity of the underlying immune dysregulation present in SLE have contributed to this problem. A variety of other approaches beyond blocking B cell activating factors and B cell depletion have been / are being attempted. We will now review a broad selection of them

B-cell intracellular signalling blocking (Bruton's tyrosine kinase - BTK):

Many immune cells including macrophages, monocytes and B-cells express BTK. It regulates signalling 'downstream' of the B-cell receptor and Fc receptors. It may be involved in toll-like receptor signalling (47). The loss of BTK activity ameliorates murine lupus (48). Several BTK inhibitors have been developed including ibrutinib and GDCO853. The former is a tyrosine kinase selective and irreversible inhibitor which binds to BTK leading to increased B-cell apoptosis. Early trials (49) showed it could reduce autoantibodies including anti-nucleosome and anti-histone but not anti-dsDNA antibodies. Renal disease also appeared to improve. GDC-0853 is another BTK inhibitor which is currently in an ongoing phase II trial in non-renal lupus (NTC02908100). This study will review the efficacy and safety in patients with a SLEDAI global score in excess of 6 points. A study of fenebrutinib in non-renal SLE reported 51% achieved an SRI-4 response (the primary end point) in 87 patients give the 150 mg/day of the drug; compared to 52% given 200mg bd and 44% of 86 placebo treated patients – the differences are not significant (50) . The drug did however reduce CD19 + B cell numbers, increase C4 and lower ds DNA antibody levels statistically significantly.

BLOCKING INTERFERON

Many SLE patients have high levels of Type 1 interferon regulated genes in peripheral blood, known as the IFN gene signature. The products of these genes have diverse effects on the innate and adaptive arms of the immune system (51). Other links include the genetic association between SLE and Type 1 IFN-associated genes (52) and that the use of therapeutic IFN α, has led to the development of a form of 'drug-induced' lupus (53). These observations have led to the development of biologics targeting interferon alpha to ascertain any clinical benefit.

Most studies have, so far, focussed on inhibition of IFNα, the Type I interferon family which comprises 13 subtypes of IFNα in addition to IFN-β, -ε and –ω . These subtypes mediate their biological effect after binding to a common receptor, the Type IFN-α, -β and –ω receptor (IFNAR).

Frustratingly, there have been conflicting results from studies to date in relation to inhibition of the IFN pathway. Rontalizumab and sifalimumab are monoclonal antibodies which both directly inhibit IFNα. In Phase 2 studies the former did not meet either primary or secondary endpoints, though paradoxically suggested a benefit for patients with a low baseline IFN gene signature in peripheral blood cells (54). Sifalimumab, also in Phase 2 studies, did meet its primary end point with the anticipated benefit for patients with a high interferon signature. However, the clinical benefits were modest compared with placebo, with 56% and 58% of patients in the two sifalimumab groups achieving an SRI-4 response compared with the high 45% responder rate in the placebo group (55) .

Anifrolumab is a fully human IgG1κ antibody which blocks the type 1 interferon receptor . It down-regulates the effect of all Type I IFNs. A Phase IIb study of anifrolumab showed superiority to placebo in patients with moderate to severe SLE treated over a 48 week period with the intravenous formulation, in addition to background therapy (56) . The primary endpoint was the percentage of patients achieving an SRI (4) response at 24 weeks plus a sustained reduction of oral corticosteroids from weeks 12-24. This was achieved in 34% of patients receiving the lower of the 2 trial dosages of 300mg/ month compared with 17.6% receiving placebo ($p<0.05$). In the higher dose arm this was less pronounced (28.8%), suggesting a possible plateau effect. A greater effect was noted in those patients with a high baseline IFN gene signature. In the anifrolumab study 75% of patients treated had a high baseline IFN signature and it was this subpopulation whose response led to the discrepancy between active and inactive arms of the study, suggesting that selecting this cohort of patients for treatment with additional IFN inhibition to standard of care may yield the most benefit.

Similar to the previous studies targeting Type 1 IFNs, an increase in viral infections, in particular herpes zoster infections, were noted in the active treatment arms, consistent with the mechanism of action of these agents. In spite of the optimism generated by the phase II trial, a Phase 3 study involving 463 patients with mucocutaneous and/or musculoskeletal disease (NCT02446899) [TULIP 1]did not meet its endpoint of reducing disease activity as measured by SRI (4) (57). A second study TULIP 2 did meet its primary end point using BICLA as its end point (58). This multinational study (16 countries) enrolled 365 patients with moderate-severe SLE and compared 300mg of IV anifrolumab with placebo. A BICLA response of 47.8% was observed in the anifrolumab arm compared with 31.5% in the placebo arm, p=0.001. When taking into account baseline IFN gene signature only those with a high baseline signature demonstrated significant benefit over placebo. It should be noted however that the majority of patients in the study, 83%, were in the high IFN signature group. Key secondary endpoints achieved were a sustained reduction in corticosteroid use to <7.5mg/day in those using >10mg at baseline in 51.5% of anifrolumab treated patients compared with 36.2% in the placebo group, p=0.01. In addition patients with high cutaneous activity at baseline (CLASI>10) had a significant improvement, defined by a CLASI reduction of 50%, compared to those in the placebo arm. No significant difference between groups was noted for improvements in swollen joint counts or annualized lupus flare rates. A further study specifically addressing the efficacy in active proliferative lupus nephritis (NCT02547922) is ongoing

Indirectly inhibiting the Type 1 IFN pathway by means of an IFNα kinoid (IFN-K) vaccine has also been studied in SLE. This vaccine comprises IFNα2b coupled with a carrier protein which together induce native polyclonal neutralizing anti-IFNα antibodies. In SLE this vaccine, in Phase 1 studies, has been shown to significantly reduce the IFN gene signature (59) . A larger Phase 2b study is ongoing to address the efficacy, safety and immunogenicity of this agent in SLE (NCT02665364).

CD40/CD40 LIGAND INHIBITION

CD40 ligand, a member of the tumour necrosis superfamily, engages with its receptor, CD40 (expressed on B cells) leading to B cell differentiation, isotype switching and formation of germinal centres. It is central to the induction of a robust immune response and has been suggested as a potential mechanism for the development of autoimmunity. It is conjectured that in SLE both CD4+ and CD8+ T cells over-express CD40L in active disease. CD40L is also expressed aberrantly by monocytes and B cells in these patients (60) . Transgenic mice which express CD40L on B cells develop a lupus-like disease (61). Pre-clinical studies suggested that inhibition of the CD40-CD40L pathway might ameliorate disease. Thus, lupus-prone mouse strains (NZB X NZW) F1 and (SWR X NZB)F1, given an anti-CD40L monoclonal antibody prior to the onset of symptoms had delayed onset or prevention of proteinuria, and improvements in renal parameters and survival (62).

To date clinical studies have not, unfortunately been very successful. Ruplizumab a humanized anti-CD40L antibody gave a partial therapeutic response in SLE patients, but was linked to an increased incidence in thrombosis leading to the early termination of this study (63). Toralizumab also did not significantly improve the clinical aspects of SLE (64). Development of this agent was also stopped following a further thrombosis signal noted in trials of Crohn's disease (65) .

These thromboembolic effects of the previous antibodies were mediated through the Fc portion. Immune complexes consisting of anti-CD40L antibodies and soluble CD40L formed leading to platelet aggregation and activation (66) .

Dapirolizumab, a polyethelene glycol conjugated anti-CD40L Fab fragment has been designed to overcome this problem and preclinical studies were re-assuring (67) . This agent has been evaluated in a Phase 1 study in SLE(68). This 32 week study did also show potential improvement in disease activity in those with high baseline disease activity (although it was not powered to address this question). In the active treatment arm an SRI-4 response of 41.7% was noted in dapirolizumab treated patients compared with 14.3% in the placebo arm. There was no increase in serious infection and thromboembolism was not noted. The results of a Phase II study (NCT02804763) have shown (69) that the primary endpoint [to establish a dose response with a $p \leq 0.055$ at week 24) was not met, (p = 0.06). However, evidence of improved serological activity and improvement in the majority of clinical endpoints to those given dapirolizumab, were observed. In retrospect the placebo response rate in the phase II study was surprisingly low.

INHIBITION OF ICOS LIGAND:

Functionally similar to CD28, the inducible costimulator (ICOS) is a T cell specific molecule. T cell activation leads to its surface expression. It then interacts with ICOS-ligand, a constitutively expressed molecule present on antigen presenting cells including B Cells (70) . It is a costimulatory molecule leading to T cell activation and contributes to B cell differentiation. In SLE, increased numbers of ICOS-expressing T cells are noted in the context of reduced expression of ICOS-L on SLE B cells. This may be indicative of recent T Cell- B cell interaction. An early phase II trial of inhibition of ICOS-L in SLE to determine its safety profile and tolerability was reported in 2016 (71) in patients with mild stable SLE. It demonstrated an acceptable safety profile with the anticipated pharmacokinetic profile. Further trials to determine its clinical efficacy are awaited.

BLOCKING IMUNE COMPLEXES

Fcɣ receptors [FcɣR] (also known as CD32B) are transmembrane proteins expressed on B-cells and morbid dendritic cells which bind the Fc region of IgG and can be triggered by binding immune complexes (72). This triggering of intracellular signalling can lead to an autoimmune response. Unlike most of the other FcɣR molecules which tend to activate receptors, FcɣRIIB is an inhibitory receptor (73)). It is important as a regulator of activated B-cells. Patients with lupus have a lower expression of FCɣRIIB (74).

A molecule (known initially as SM101) was developed (as an extracellular version of the human FcɣRIIB) which blocks the Fcɣ-mediated signal that binds to immune complexes. FcɣRIIB has a limited degree of human polymorphism and is not immunogenic. In a 24-week phase IIa trial, 51 patients were randomised to receive SM101 or placebo doses weekly for 4 weeks (75) . The SLEDAI, BILAG and physicians global assessment together with global response and measurement of renal parameters were recorded, even though this was primarily a safety study. The SRI 4 response was twice that in the SM101 treated patients compared to the controls, with particularly encouraging results in those patients with lupus nephritis. No major unexpected side-effects were noted. The results of a phase III trial of SM101 in lupus nephritis [ISRCT 84672048] are awaited.

RIGERIMOD:

Rigerimod or lupuzor, is a 21mer linear peptide derived from the small nuclear ribonucleoprotein U1-70K (with phosphorylation of the Ser 140) (76). It causes the elimination of autoreactive T cells via apoptosis, but does not affect the ability of both T and B cells to respond to antigens, implying it is immuno-modulatory rather than immunosuppressive. In the MRL/lpr lupus mouse strain lupuzor reduced lupus activity, (particularly vasculitis, protein excretion and skin disease) and reduced anti dsDNA antibody production (77) . Early phase II clinical studies were encouraging. In 2012, a Phase 2 study of 149 patients with active SLE (SLEDAI > 6, but excluding patients at screening with an A score in any BILAG domain) were randomized to placebo or subcutaneous lupuzor (2 or 4 weekly) in addition to background therapy (78). 53% of patients receiving monthly lupuzor attained an SRI-4 response at week 12 compared with 36% in the placebo arm ($p < 0.05$). A post hoc analysis of a subpopulation with a clinical SLEDAI >6 at baseline demonstrated a better response comparing the monthly active treatment arm and placebo. A further analysis at 24 weeks following a further 12 week treatment-free period showed less evidence of benefit. Unfortunately the phase III study (NCT02504645) of 153 patients who completed the trial reported that although Lupuzor demonstrated a good safety profile ,and superior response rates compared to placebo of 68.8% v 59% (the difference being greatest among those patients positive for anti-ds DNA antibodies), the difference was not statistically significant (79).

INHIBITION OF THE JAK-STAT PATHWAY

Polymorphisms in Janus-kinase (JAK)-Signal transducer and activator of transcription(STAT) genes have been shown to increase susceptibility to SLE (80) This pathway is the primary signalling mechanism downstream from Type 1 and type 2 cytokine receptor engagement. Inhibiting the JAK/STAT pathway is therapeutic in several musculoskeletal conditions notably rheumatoid and psoriatic arthritis.

Tofacitinib (which inhibits JAK 1and 3) ameliorates murine lupus nephritis and reduces the level of pathogenic autoantibodies (81). A phase II trial of baricitinib (inhibitor of JAK1/2) in SLE assessed the effects of the 2mg and 4mg once daily doses (82). This study recruited patients with active musculoskeletal and/or cutaneous lupus. 67% of patients on the higher dosing regimen achieved a SLEDAI-2K response, significantly greater than the placebo arm (p=0.04). Treatment with 4mg Baricitinib significantly reduced the proportion of patients with 'Worst Joint Pain' compared to placebo (p=0.016). Other general measures of disease activity notably the Physician Global Assessment and Low Disease Activity Score also improved. The lower dose did not offer any benefit over placebo. The BRAVE I and II studies assessing the effect of baricitinib in SLE are currently recruiting and awaited with interest (NCT 03616964 and NCT 03616912).

INTERLEUKIN 12/23 INHIBITION:

Blocking the IL 12/23 pathway has been successful in the treatment of psoriasis and psoriatic arthritis (83). Some data suggest this pathway might be involved in some aspects of lupus pathogenesis and that blocking this pathway could be of clinical benefit. A phase II placebo controlled trial using ustekinumab (anti- IL12/23) in serologically active SLE patients has been undertaken(84). Patients were recruited if they had a SLEDAI score of 6 or more, and/or 2 BILAG B scores. They were all were on standard of care to which either intravenous (one infusion), followed

by subcutaneous, ustekinumab or placebo was added. Achieving an SRI4 at 6 months was the primary end point. 62% of the ustekinumab treated patients achieved an SRI 4 compared to 33% of the group given the placebo p= 0.006) which was very encouraging. The risk of a new BILAG flare (one BILAG A or 2 new B scores) was also significantly lower in the ustekinumab group ($p<0.01$). In addition, individual assessment of the effect on the SLEDAI-2K and PGA showed numerical improvement in ustekinumab treated patients though lacked statistical significance . The safety profile was satisfactory. A larger trial is currently recruiting to assess the role for ustekinumab in SLE therapeutics (NCT03517722).

CAN WE IMPROVE ON CLINICAL TRIAL DESIGN?

Invariably SLE clinical trials fall into two categories, those focussing on patients with lupus nephritis and those treating patients with non renal disease, mostly skin and joint involvement. The former are easier to design as they involve 'hard' endpoints, such as renal histology, serum creatinine and protein creatinine ratios. These parameters are widely available and do not require physician assessment, interpretation or training. In contrast, trials of non renal lupus have proved more challenging given the potentially highly diverse nature of lupus involvement.

As indicated above the composite indices BICLA and SRI have been increasingly utilised (see Table 2) over the past 10 years. However, the BILAG and to a lesser extent the SLEDAI indices, on which they are based, require training. Ideally, this would be followed by formal testing or assessment of individuals seeking to participate. Increasingly the use of organ specific 'tools' such as the CLASI (Cutaneous Lupus Erythematosus Disease Area and Severity Index) for dermatological disease are being used (56,57) and the use of ultra sound may better distinguish genuinely inflammatory joint disease from degenerative disease or concomitant disorders such as fibromyalgia. It seems likely that the 'over indulgence' of corticosteroids, as concomitant medications in clinical trials, has frustrated the ability to distinguish genuine drug effects from placebo, so minimising steroids would be helpful. An independent peer review panel (or even an electronic version of this in real time) can be used to help ensure the quality of data coming from individual sites and particular participants. Finally, does every clinical trial need to be a comparison of the ability of placebo and two/three test doses of the trial to achieve an agreed end point of reduction in disease activity? Other more inventive clinicial trials eg time to first flare in patients brought to remission by a short dose of steroids (22) can be designed and the ability to cut steroid use be made more prominent. These ideas are set out in Table 3.

CONCLUSION:

It is a truth universally acknowledged that the biologic treatment of SLE has lagged far behind the successes seen in patients with RA and PsA. It has been particularly galling that several successful phase II trials have not been followed by successful phase III studies. The reasons for this are likely to be multi factorial including the complex and diverse nature of lupus pathogenesis; problems with patient and investigator recruitment, the 'over-indulgence' of concomitant ' standard of care ' (especially with regard to high doses of steroids) and challenges in agreeing optimal endpoints. However, rituximab, although failing to meet primary/ secondary end points in major clinical trials has been sufficiently convincing in real life, that it is now recommended by authoritative bodies. Other drugs such as benlysta and anifolumab have met their endpoints in clinical trials and the former has been approved by the FDA. In addition, there are, as documented in this review a variety of other drugs targeting other molecules/pathways in which encouraging early data are now being

pursued in large phase III clinical trials. The road is hard and long, but we remain confident that the next decade will see several approaches receiving official approval for use in SLE. We need to revisit the trial design for SLE in order to determine the most objective indicator of response for this complex condition and enable a clear distinction between active treatment and placebo when both are receiving standard of care. We have highlighted a number of novel pathways in this review, but SLE clinical trials should minimise background [especially corticosteroid] therapy; utilize individual organ/system outcome measures (ie not rely solely on composite measures) and be stringent when it comes to selecting trial sites. These measures would at least maximise the chances of these new approaches being successful. While trying to remain optimistic the challenges of bringing successful new biological therapies into everyday clinical practice in SLE remains daunting, but not 'mission impossible'!

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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.

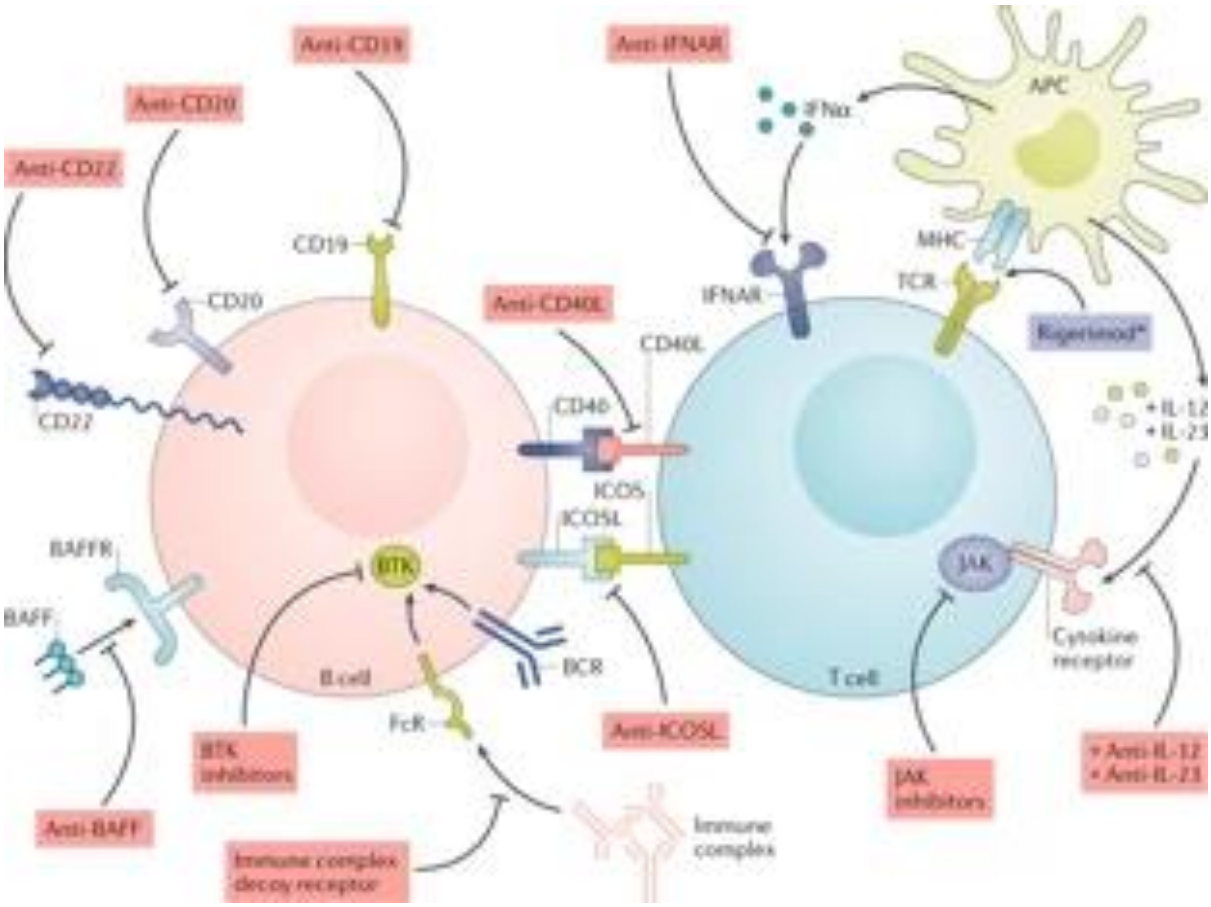

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FIGURE LEGEND- Various immune cells and molecules interact during the pathogenesis of systemic lupus erythematosus and are the target of monoclonal antibodies and other treatments that have the potential to offer therapeutic advantage.* The mechanism of rigerimod is not fully elucidated. APC=antigen presenting cell; BAFF= B call-activating factor; BAFFR= BAFF receptor; BCR= B cell receptor; BTK= Bruton tyrosine protein kinas; CD40L= CD 40 ligand; FcR= Fc receptor; ICOS= inducible T cell co-stimulator; ICOSL= ICOS ligand; IFNAR= type 1 interferon receptor; JAK= Janus kinase; TCR= T cell receptor

TABLE 1 - Derivation of the SRI and BICLA Composite Indices

SRI [SLE Responder Index]	BILAG-based Combined Lupus Assessment [BICLA] response at Week 12
Improvement of 4 points or more using SELENA-SLEDAI	**BILAG improvement:** ● **All BILAG A scores at study entry improved to B/C/D, and** ● **All BILAG B scores at study entry improved to C/D, and** ● **No BILAG worsening in other body systems = no new BILAG A or ≥2 new BILAG B scores**
No new BILAG A; only 1 new BILAG	**SLE Disease Activity Index (SLEDAI):** ● **No worsening in SLEDAI total score compared with study entry**
No increase in Physicians Global Assessment of > 0.3cm	**Physician's global disease activity assessment:** ● **No worsening (defined as <10% worsening) compared to study entry on 100 mm visual analogue scale (VAS)**
	Treatment failure: **Defined as added or increased immunosuppressants or anti-malarials, or corticosteroid increase above baseline or tapering level at any point following randomization**
	All criteria must be achieved to meet 'responder' classification

TABLE 2 – Review of a selection of clinical trials and their endpoints of new therapies for systemic lupus erythematosus.

Therapy	Target(s)	Trial phase	Size	Primary outcome	Reference
Rituximab	CD20	II/III	257 participants	Achieving and maintaing a major/ partial clinical response at wk 52 in non renal patients using 'classic' BILAG	34
Rituximab	CD20	III	72 participants	Achieving complete and partial renal response using pre-defined parameters	33
Belimumab (IV)	BAFF	III	867 participants	SRI4 response at week 48	12
Belimumab (S/C)	BAFF	III	839 participants	SRI4 response at week 52	13
Dapirolizumab	CD40L	II	182 participants	Proportion of patients with a BICLA response at 24 weeks	69
Anifrolumab	IFNAR	III	Target of 362 participants	Comparison of patients achieving a BICLA response, anifrolumab vs placebo	57

Baricitinib (BRAVE I)	JAK1 and JAK2	III	Target of 750 participants	Percentage of patients achieving an SRI-4 response at 52 weeks	82
Ustekinumab	IL-12 and IL-23	III	Target of 500 participants	Percentage of patients achieving and SRI-4 response at 52 weeks	84

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 – Considerations for improving the chances of lupus clinical trials being successful

• Minimise the use of concomitant steroids (less than 20mg per day if possible) and immunosuppressives.
• Mandate steroid tapering to 5mg per day or less ideally within 12 weeks.
• Utilise individual centres with experience of doing the lupus clinical trials.
• Utilise investigators used to doing lupus clinical trials.
• Ensure adequate training and, ideally, testing of the individual investigators in the use of the activity assessment systems to be used in the clinical trial.
• Make use of an independent assessment panel to review, regularly, (ideally in real time) data entry used in defining activity.
• Remember that for a drug to be successful it needs to be effective, with few side-effects and at a cost individual societies can afford!

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