Recent developments in biologic therapies for the treatment of patients with systemic lupus erythematosus

Pedro Lavado Carreira¹, David A. Isenberg²

¹ Autoimmune Diseases Unit, Internal Medicine 7.2 Department, Hospital Curry Cabral, Centro Hospitalar Lisboa Central, Lisbon, Portugal
² Department of Rheumatology, University College London, UK

Email correspondence to:
Professor Isenberg - d.isenberg@ucl.ac.uk

Abstract

Systemic lupus erythematosus (SLE) has a complex pathogenesis, and multiple therapeutic targets have been discovered in the last years. In spite of Belimumab being approved by the US Food and Drug Administration and the widespread of Rituximab, there have been many failed attempts to treat SLE successfully using biologic agents. In this review, we consider newer biologic approaches that might offer the hope of improving the outcome of SLE patients. These include the fully humanized anti-CD20 mAbs, PEGylated anti-CD40L, IFNα inhibitors, rigerimod and immune complexes blockade.

Keywords: lupus, biologic, anti-CD20, anti-CD40L, dapirolizumab, ofatumumab, obinutuzumab, rigerimod, interferon, FCyR

Key messages
There is still considerable morbidity with conventional immunosuppression in SLE patients.

Successful biologic use in SLE is a decade behind that for rheumatoid and psoriatic arthritis.

A number of new promising biologic therapies are in clinical trials.

Introduction

The use of biologic therapies in the treatment of patients with systemic lupus erythematosus (SLE) is, arguably, at least a decade behind their use in rheumatoid arthritis (RA), psoriatic arthritis (PSA) and ankylosing spondylitis. The need for more successful biologic/other new therapies remains important as it is clear we have reached the limit of what can be achieved with conventional immunosuppression (1). SLE patients have an approximated 90% survival rate at 10 years (2) with considerable morbidity, which remains very unsatisfactory for a disease that often develops before 30. Some encouragement is taken from the approval of Belimumab by the US Food and Drug Administration (and more recently the National Institute for Health and Clinical Excellence) and the widespread use of Rituximab (in spite of 2 trials that did not meet their endpoints). Neither drug alone will be a panacea for SLE, although interestingly attempts to combine those drugs are now being pursued. In this mini-review we will focus on several new/modified approaches which we believe, offer the best hope of improving the outcome of SLE patients. Our choice of new approaches is subjective, based on our reading of the recent literature.

Pathogenesis

The pathogenesis of SLE involves genetic and epigenetic factors, environmental triggers and immunological abnormalities. These abnormalities include defective apoptosis and loss of tolerance; inadequate development of dendritic cells; defective function of
regulatory T-cells and B-cells; defective B and T-cells apoptosis and defective signalling pathways. Figure 1 shows the link between these factors and the sites of action of relevant therapeutic agents.

CD 20 blockade

B-cells play an essential role in the development of SLE. Blocking B-cells with rituximab, a chimeric mAb against antigen CD20, is well established in SLE. Because it is a chimeric antibody causing allergic responses in approximately 10% of SLE patients. Fully humanized mAbs anti-CD20 have been developed including ofatumumab and obinutuzumab.

Ofatumumab is a mAb IgG1 anti-CD20 approved for chronic lymphocytic leukaemia. Experience of its use in SLE is restricted to a small number of cases. For example, an SLE patient whose previous flares had responded to rituximab, but became allergic to it, received 3 infusions of ofatumumab and achieved an SLEDAI decrease from 15 to 2, a reduction of anti-dsDNA antibodies levels >90% and C3 normalization (3). An SLE patient with autoimmune haemolytic anaemia (AIHA) refractory to rituximab, achieved B-cell depletion after ofatumumab, with remission of AIHA and a Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) of 0 (4). Four patients with lupus nephritis (LN) achieved proteinuria and anti-dsDNA reduction after ofatumumab (5). Formal clinical trials in SLE are awaited.

Obinutuzumab, a glycol-engineered mAb anti-CD20, is being used in the treatment of non-Hodgkin’s lymphoma. An in vitro study comparing rituximab to obinutuzumab in SLE demonstrated the latter to be a more efficient B-cell depletor (6). A 52-week, phase II trial studying safety and efficacy in LN is currently recruiting (NCT02550652). Its primary outcome is complete renal response.

B cell intracellular signalling blockade - Bruton’s Tyrosine Kinase (BTK)
BTK is a component of B-cell receptor signalling, involved in regulating cell proliferation and survival. Its blockade results in B-cell apoptosis. B-cells overexpressing BTK in mice led to anti-dsDNA antibody production and SLE-resembling organ involvement. Many inhibitors of BTK are in development, including Ibrutinib and GDC-0853. Ibrutinib is a tyrosine kinase selective and irreversible inhibitor. It binds to BTK causing B-cell apoptosis. Pre-clinical trials showed Ibrutinib reduced levels of autoantibodies (anti-nucleosome, anti-histone and anti-ssDNA but not anti-dsDNA) and renal disease(7). However no current clinical trial is ongoing in SLE. GDC-0853 is another BTK inhibitor(8). A phase II trial in SLE is ongoing (NCT02908100), to evaluate the safety and efficacy in patients with moderate-to-severely active SLE.

T-cell co-stimulation blockade

B-cell immune stimulation follows interaction with T-cells and antigen-presenting cells (APC) via co-stimulatory signals notably CD40/40L, CD28, cytotoxic T-lymphocyte antigen 4 and CD80/CD86.

Rigerimod is a 21-mer linear peptide derived from the small nuclear ribonucleoprotein U1-70K, whose mechanism of action seems to be due to chaperone-mediated autophagy(9). By reducing the stability of MHC molecules that present antigens to T cells, it blocks antigen presentation to autoreactive T-cells, which in turn blocks B-cells maturation.

A phase II trial involved 20 patients with moderately active SLE who received 3 subcutaneous injections (SC). Significant improvement in the SLEDAI score was reported with the 200µg/dose(10). A phase IIb trial showed a significant reduction of disease activity(11). 149 patients were randomised to receive Rigerimod or placebo every 2 or 4 weeks. Patients with SLEDAI-2K ≥ 6 who received Rigerimod 200µg every 4 weeks achieved a statistically higher SRI-4 response at week 12 (67.6 vs 41.5%, p<0.025) and week 24 (84.2 vs 45.8%, p<0.025). A phase III trial is underway, whose primary outcome is SLEDAI-2K reduction ≥4(NCT02504645).
CD40 Ligand (CD40L) is a protein expressed on activated T-cells and a member of the tumor necrosis factor (TNF) family. Its binding to CD40 on APC and B-cells induces co-stimulation and promotes B-cell maturation. Anti-CD40L mAbs block co-stimulation in experimental models. A phase II trial in 28 patients with proliferative LN showed significant reduction in circulating levels of anti-dsDNA antibodies and increased C3 levels, but was associated with thromboembolic events (TE)(12). Another phase II trial of a different anti-CD40L monoclonal antibody had no major adverse events (AE), however, efficacy was not proven(13). The TE were evidently caused by the functional Fc region of anti-CD40L which triggers platelet aggregation by interacting with platelet FcγRIIA receptor. In Dapirolizumab (DZP) the Fc portion has been changed to a high molecular polyethylene glycol without loss of efficacy(14). A 32-week, phase IB trial showed safety and tolerability of intravenous DZP in SLE patients. Clinical response was evident by both Systemic Lupus Erythematosus Responder Index (SRI) and British Isles Lupus Assessment Group (BILAG)-based Combined Lupus Assessment (BICLA) assessments(15). A 24 week phase II trial, followed by observational period to evaluate efficacy and safety on moderately to severely active SLE is recruiting (NCT02804763). The primary outcome is the BICLA response rate at 24-weeks.

Interferon (IFN) blockade

Interferons are a family of glycoproteins that consist of type I IFN (IFN-I) (including 12 isoforms of IFNα and 1 of IFNβ) and type II IFN (includes only IFNγ). IFN-I binds to the type I IFN receptor (IFNR), IFNγ binds to another receptor. IFN activates multiple signalling pathways, especially Janus kinase. IFN dysregulated activity and signalling is associated with autoimmune disease development. Rarely when IFNα has been used, for example, in hepatitis C and cryoglobulinemic vasculitis, autoimmune conditions, including SLE, have been reported to develop(16, 17). IFN-I levels are higher in SLE and recent studies have shown a link between IFNα levels and disease activity. In Ifnar1 gene knockout mice reduced disease activity is seen.
Rontalizumab is a humanised IgG1 mAb against IFNα. A phase I trial proved safe but showed no clinical benefit in those with a high IFN signature(18). A phase II trial evaluated efficacy and safety of rontalizumab in 159 patients with moderate to severe SLE. Patients were randomised to receive rontalizumab 750mg or placebo every 4 weeks plus standard of care (SOC) (Part 1) and subsequently, 300mg rontalizumab or placebo every 2 weeks (Part 2). The results did not confirm rontalizumab’s general superiority, however, paradoxically, in the low IFN signature group SRI response rates were superior in 31% (p=0.0285) and the SELENA-SLEDAI flare index rate was reduced(19). However, no further trial is ongoing.

Sifalimumab is fully human IgG1κ mAb that binds to most subtypes of IFNα and neutralizes it. Two phase I trials showed safety and IFN signature reduction in a dose-dependent manner. A 52-week phase IIb trial followed by a 22-week safety follow-up, enrolled 431 patients randomised to receive placebo or sifalimumab (200, 600 or 1200mg) every 28 days in addition to SOC. In all sifalimumab groups, the response rates were significantly higher than in the placebo group, however, only the group with the high IFN signature patients achieved significant improvement in SRI-4. Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) and joint counts also showed significant improvement. No differences in lowering anti-dsDNA antibodies or normalizing C3/C4 levels were observed. Herpes zoster was the principal AE as expected by IFN suppression(20). Currently no phase III trial is ongoing.

Unlike the other IFN blockers, directed against IFN, anifrolumab is a fully human IgG1κ mAb that blocks subunit 1 of the IFNR and consequently both IFNα and IFNβ. A phase I trial showed safety and sustained IFN signature reduction in systemic sclerosis patients. In a 52-week phase IIb lupus trial, 305 patients were randomised to receive placebo, anifrolumab 300mg or 1,000mg every 4 weeks until week 48 as well as SOC(21). Active LN or neuropsychiatric SLE were excluded. The primary efficacy end point was a combination of the SR-4 at week 24 and 52 with a sustained reduction in oral corticosteroids from week 12 to week 24. At both week 24 and 52, the response was
achieved in a significantly higher number of patients receiving both dosages of anifrolumab (300mg, p=0.014 and 1000mg, p=0.063). When evaluating the sub-groups by IFN signature levels, those with high levels of IFN achieved significantly better results compared to placebo at both 24 and 52-weeks. Significant improvement was also achieved using BICLA, BILAG 2004; CLASI; joint counts and other variables. Influenza and herpes zoster infections were the most frequent AE. Further studies are ongoing in active SLE patients, including in LN (NCT02547922).

Interferon-α-kinoid (IFN-K) is another option in blocking IFNα. IFN-K is a vaccine composed of IFNα2b coupled to a carrier protein. It acts by inducing antibody production against all IFNα subtypes. A phase I/II trial of 28 patients with mild-to-moderate SLE showed a dose-related anti-IFNα response and improvement of C3 levels(22). A phase II trial is ongoing to elicit IFN signature reduction and efficacy in SLE (NCT02665364).

Blocking Immune complexes (IC)

Fcγ Receptors (FcγR) are transmembrane proteins that recognize the Fc region of IgG. The binding of IC and FcγR initiates intracellular signalling which results in an autoimmune response. Most of the FcγR molecules act as activating receptors and only FcγRIIB is an inhibitory receptor. Both type of receptors are expressed on the same cells. Negative signalling by FcγRIIB is mainly important for the regulation of activated B-cells. SLE patients have a lower expression of FcγRIIB.

SM101 is an extracellular version of the human FcγRIIB. It binds to IC in SLE and blocks the Fcy-mediated signal. FcγRIIB was chosen as a therapeutic target because of its limited human polymorphism and lack of immunogenicity. In a 24-week phase IIa trial, 51 SLE patients were randomised to receive SM101 or placebo weekly for 4 weeks. The primary outcome was safety and the secondary outcomes included SLEDAI, BILAG, PGA, global response and renal parameters. No serious AE were reported. The SRI-4
response was twice as high in the SM101 group and in LN results were even better (23).
The results seem promising but phase III trials are needed.
Rather than binding to IC, binding to the receptor itself can produce an inhibitory
response. SM201 is an anti-FcγRIIB mAb, it binds to FcγRIIB but allows the binding
between IC and the FcγRIIB. A pre-clinical study showed that SM201 had a synergic
action with IC resulting in a better inhibition of B-cells (24). It also seems to be restricted
to activated B-cells allowing a functional memory response. Clinical trials are needed to
understand if it’s a valid therapeutic.

A resume of ongoing trials relevant to the approaches discussed in this review are
shown in Table 1.

CONCLUSIONS
Biologic treatment of Lupus has seen many “false dawns”. The relative successes of
Belimumab, Rituximab and Atacicept (not discussed here) have been counter balanced
by the failures of many others including, Abatacept, Tabalumab, Blisibimod and
Epratuzumab. But a number of new approaches, including fully humanized anti-CD20,
PEGylated anti-CD40L, IFNα inhibitors and Rigerimod, offer new hope that before too
long we will have a range of biologic options to offer our SLE patients that matches the
choices we have for our RA and PSA patients.
Other approaches, not discussed here, such as blocking the JAK/STAT-pathway, IL-6
and NfkB might also prove of value.

1. Croca SC, Rodrigues T, Isenberg DA. Assessment of a lupus nephritis cohort over a 30-
2. Mak A, Cheung MW, Chiew HJ, Liu Y, Ho RC. Global trend of survival and damage of
systemic lupus erythematosus: meta-analysis and meta-regression of observational studies
Successful treatment of life-threatening autoimmune haemolytic anaemia with ofatumumab in
Defective apoptosis results in production of uncleared nuclear material leading to dendritic cells (DC) activation and B-cell receptor (BCR) stimulation. DC will produce a number of cytokines which will result in B-cell activation (BAFF and APRIL) but also differentiation of monocytes to macrophages (IFNα) that will present self-antigens to T and B cells but also produce cytokines. The activation of B-cells needs co-stimulatory signal between T-cell receptor (TCR) and major histocompatibility complex (MHC) in antigen presenting cells (APC) but also CD40:CD40L binding with macrophage and dendritic cells. B-cells activation, differentiation and proliferation leads to autoantibody production. Immune complex formation and tissue deposition results in organ damage. pDC - plasmacytoid dendritic cells; mDC - myeloid dendritic cells; IDC - follicular dendritic cells; BTK - Bruton’s Tyrosine Kinase.
<table>
<thead>
<tr>
<th>Biologic</th>
<th>Immunologic action</th>
<th>Evidence to date in SLE</th>
<th>Number of patients</th>
<th>Inclusion Criteria</th>
<th>Primary outcome</th>
<th>Therapeutic regime</th>
<th>Results</th>
<th>Future trials in SLE</th>
<th>Inclusion Criteria</th>
<th>Primary outcome</th>
<th>Therapeutic regime</th>
<th>Prospects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obinutuzumab</td>
<td>B-cell depletion</td>
<td>Case reports(3-5)</td>
<td>1, 1 and 4 series of 4 patients</td>
<td>-</td>
<td>-</td>
<td>Variable</td>
<td>Reduction on disease activity Anti-dsDNA reduction and C3 normalization</td>
<td>No trials ongoing</td>
<td>-</td>
<td>-</td>
<td>Promising, needs clinical studies</td>
<td></td>
</tr>
<tr>
<td>Rontalizumab</td>
<td>B-cell depletion</td>
<td>Pre-clinical(6)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>B-cell depletion 2-fold the rituximab effect</td>
<td>Phase II ongoing on LN Class III or IV LN</td>
<td>Complete Renal Response at week 52</td>
<td>1000mg on Days 1, 15, 168, and 182 plus MMF</td>
<td>Promising, awaiting clinical results</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ofatumumab</td>
<td>B-cell depletion</td>
<td>Pre-clinical(7)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>BTK inhibition on mature B-cell and APC</td>
<td>No trials ongoing</td>
<td>-</td>
<td>-</td>
<td>Promising, needs clinical studies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GDC-0853</td>
<td>BTK inhibition</td>
<td>Pre-clinical and phase Ib(8)</td>
<td>111</td>
<td>-</td>
<td>-</td>
<td>BTK inhibition on mature B-cells</td>
<td>Phase II ongoing</td>
<td>Moderate to severe SLE SRI-4 response</td>
<td>Low and high dose daily vs placebo</td>
<td>Promising, awaits results</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rigerimod</td>
<td>T-cell blockade</td>
<td>Phase IIb(10, 11)</td>
<td>149</td>
<td>IFT SLEDAI20       No BILAG A</td>
<td>SRI-4</td>
<td>200 μg every 2 or 4 weeks</td>
<td>Improvement in subpopulation SLEDAI≥20 Best results 200 μg every 4 weeks</td>
<td>Phase III ongoing</td>
<td>SLEDAI-2K ≥6 points</td>
<td>SRI-4 response</td>
<td>250 mgq every 4 weeks</td>
<td>Very promising, awaits results</td>
</tr>
<tr>
<td>Dapirolizumab</td>
<td>T-cell co-</td>
<td>Phase IIb(15)</td>
<td>24</td>
<td>SLEDAI-2SLEDAI≥24</td>
<td>SRI-4 and BICLA</td>
<td>1st dose 30mg/kg then 5 doses of 15mg/kg every 2 weeks</td>
<td>SRI-4 and BICLA response across several endpoints</td>
<td>Phase II ongoing</td>
<td>Moderate to severe disease activity BICLA response rate at week 24</td>
<td>3 different doses vs placebo</td>
<td>Promising, awaits results</td>
<td></td>
</tr>
<tr>
<td>Rontalizumab</td>
<td>IFNα blocker</td>
<td>Phase II(18, 19)</td>
<td>159</td>
<td>Moderate to severe disease activity BILAG</td>
<td>-</td>
<td>-</td>
<td>No general superiority; in low IFN signature it had significant superiority</td>
<td>No trials ongoing</td>
<td>-</td>
<td>-</td>
<td>Dubious results</td>
<td></td>
</tr>
<tr>
<td>Siltalumab</td>
<td>IFNα blocker</td>
<td>Phase IIb(20)</td>
<td>431</td>
<td>SLEDAI-2K≥6</td>
<td>SRI-4</td>
<td>200, 600 or 1200mg every 28days</td>
<td>Better SRI-4 response in high IFN signature group</td>
<td>No trials ongoing</td>
<td>-</td>
<td>-</td>
<td>Promising but not pursued</td>
<td></td>
</tr>
<tr>
<td>Arritumab</td>
<td>IFNα blocker</td>
<td>Phase IIb(21)</td>
<td>305</td>
<td>SLEDAI-2K≥6</td>
<td>Composite of SRI-4 and corticosteroids reduction</td>
<td>300 or 1000mg every 4 weeks</td>
<td>Better SRI-4 response in high IFN signature group</td>
<td>Several phase III including LN and skin lesions</td>
<td>-</td>
<td>-</td>
<td>Very promising, awaits results</td>
<td></td>
</tr>
<tr>
<td>IFNα-kinoid</td>
<td>Induction of anti-IFNα antibodies</td>
<td>I/II(22)</td>
<td>28</td>
<td>Mild-to-moderate</td>
<td>-</td>
<td>30, 60, 120 or 240μmg</td>
<td>Dose-related response anti-IFNs Higher C3 level</td>
<td>Phase II trial ongoing</td>
<td>SLEDAI-2K ≥6</td>
<td>BICLA response at week 36</td>
<td>-</td>
<td>Promising, awaits results</td>
</tr>
<tr>
<td>SM101</td>
<td>Autoimmune complexes blockade</td>
<td>Phase IIa(23)</td>
<td>51</td>
<td>SLEDAI-2L was included</td>
<td>Safety, SRI-4 and BILAG</td>
<td>6 and 12mg/kg every week</td>
<td>Better SRI-4 response</td>
<td>No trials ongoing</td>
<td>-</td>
<td>-</td>
<td>Promising, needs clinical studies</td>
<td></td>
</tr>
<tr>
<td>SM201</td>
<td>Autoimmune complexes blockade</td>
<td>Pre-clinical(24)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>B-cell inhibition</td>
<td>No trials ongoing</td>
<td>-</td>
<td>-</td>
<td>Very early to know</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>