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Biologicals for the treatment of systemic lupus erythematosus: current status and emerging therapies

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Abstract

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease resulting from the dysregulation of various immunological pathways. There has been major progress in recent years in the understanding of the pathogenesis of SLE, which has led to an emergence of a new class of drugs designed to target specific components of the disease process.

Evidence from a number of open-label, uncontrolled studies has supported the use of Rituximab (an anti-CD20 monoclonal antibody) in SLE for more than one decade. However, these promising results are in clear contrast with the poor results of the completed Efficacy and Safety of Rituximab in Patients with Severe SLE (EXPLORER) and Efficacy and Safety of Rituximab in Subjects with ISN/RPS Class III or IV Lupus Nephritis (LUNAR) randomized controlled trials (RCTs). In contrast to EXPLORER and LUNAR results, controlled trials for Belimumab (a fully humanised monoclonal antibody against B lymphocyte stimulator) showed positive results and subsequently, Belimumab was the first drug approved for the treatment of SLE patients. This has paved the way for the development of further biological agents, potentially revolutionising the treatment of SLE.

In this article, the potential benefits of novel biological agents are explored, obstacles to the development of a treatment target in SLE are identified, and possible strategies to achieve this goal are discussed.

Introduction

Systemic lupus erythematosus (SLE, lupus) is a chronic autoimmune inflammatory disease, mainly affecting young women. It is often considered paradigmatic of systemic autoimmune diseases. SLE has a wide range of systemic effects with multi-organ involvement. Although the exact cause of SLE is unknown, its pathogenesis is based on the production of autoantibodies and pro-inflammatory cytokines that results in multisystem inflammation and presents in a highly variable relapsing and remitting disease course. The clinical spectrum of SLE varies, ranging from general malaise, arthralgia and fever to more severe manifestations including renal and CNS disease (1).

The current treatment of SLE includes hydroxychloroquine, an anti-malarial agent, corticosteroids, and cytotoxic immunosuppressive agents (2). Corticosteroids, given orally or intravenously, are effective for almost all SLE related manifestations. However, the short and long-term adverse effects including those related to the metabolic (such as hyperglycemia and hyperlipemia), musculoskeletal, endocrine, cardiovascular, and the central nervous system, limit their usage (3). Among others, Thamer et al. demonstrated that a dose of as low as 6 mg prednisone per day greatly increases the risk of corticosteroid-induced organ damage (4). More recently, Ruiz-Arruza et al showed that prednisone doses >7.5 mg/day are associated with damage accrual (5) and thus, a steroid sparing therapeutic approach is mandatory.

Other immunosuppressive agents such as cyclophosphamide, azathioprine, methotrexate and mycophenolate mofetil were shown to be effective in the treatment of SLE but these agents also have significant short and long-term adverse effects (6). Moreover, although the above treatment modalities are quite effective they are not specific for SLE and the control of disease activity with those agents remains suboptimal. Thus, in spite of treatment, SLE patients have active lupus related flares in substantial fractions of their life (6). Therefore, there is an unmet need for alternative nontoxic, effective and more lupus-specific therapeutic approaches.

Pathogenesis

Although the precise aetiology of SLE remains unclear, it is well understood that deregulation of both the innate and the adaptive immune system results in ineffective clearance of apoptotic nuclear fragments. These fragments are then processed and presented by antigen presenting cells, such as B cells, to auto-reactive T cells, which in turn triggers auto-B cells into self-antibody production. Cytokines released at the same time are thought to enhance this effect and further induce auto T cell activation (7).

The role of the B cell in SLE pathogenesis has been repeatedly demonstrated by murine studies, most notably by one study using a knockout gene mutation to prevent lupus mice developing B cells. This resulted in no evidence of autoantibody formation or clinical manifestation of lupus and thus validates the key role of B cell auto-reactivity in the disease course (8). Furthermore, these mice had a significantly reduced number of activated T cells, which indicates the crucial interaction between B and T cells in SLE pathogenesis (9).

With the plethora of evidence that places B cells at the heart of the disease process underlying SLE, it is by no means surprising that in recent years a great deal of research has been focused on the development of novel B cell specific biologics for the treatment of SLE. In this article we will review the current biologic agents available and up to date research on newer drugs that have all been specifically designed to target the most intricate pathways that are central to SLE pathogenesis (figure 1).

B cell targeted therapies

B cells can be selectively targeted for depletion either via direct killing by monoclonal antibodies against B cell surface molecules CD19, CD20 (Rituximab, Ocrelizumab) and CD22 (Epratuzumab) or by attrition due to inhibition of B cell survival factors BLyS (Belimumab) and APRIL (Atacicept) (10). Here we discuss the key cell surface markers implicated in the pathogenesis of SLE that are the targets of these novel biologic drugs.

Anti-CD20

Rituximab

Rituximab is perhaps the most well known biologic agent and is widely used in the treatment of rheumatoid arthritis and ANCA-associated vasculitis. Rituximab is an anti-CD20 human-murine monoclonal chimeric antibody that causes selective short-term depletion of matured B cells (7). Two recent randomised controlled trials (RCTs) have evaluated the use of rituximab in patients with SLE.

The controlled EXPLORER (The Exploratory Phase II/III SLE Evaluation of Rituximab) trial included 257 patients with moderate-severe SLE and extra-renal manifestations over a 1-year period (11). Patients were randomised to the addition of rituximab or placebo to the standard therapy of immunosuppressive agents and corticosteroids. Anti-CD20 therapy significantly improved serological markers including reduced autoantibodies ($p < 0.06$), improved complement levels ($p = 0.0045$, $p = 0.0029$) and B cell depletion. However, there was in fact no statistically significant reduction in clinical activity between placebo (28.4%) and treatment (29.6%) arms in achieving a clinical response ($p = 0.975$).
Although the results of this study suggest the use of monoclonal antibodies such as Rituximab may not be effective therapies for moderate-severe SLE, it is important to note that the follow-up period was short and as the SLE activity score assessment was thoroughly scrutinised, any mild disease flare was seen as a failure of treatment. Furthermore, the Rituximab arm showed minimal disease activity and no further flares in 14.5% more patients compared to the placebo arm ($p = 0.027$), which suggests that rituximab may provide benefit to those with severe lupus (12).

The second RCT was the Lupus Nephritis Assessment With Rituximab (LUNAR) trial, which evaluated the efficacy of rituximab compared to placebo in combination with Standard of Care therapy in 144 patients with proliferative lupus nephritis (13). Treatment with Rituximab was associated with the successful depletion of B cells in 99% of patients and ameliorating serological markers of active lupus. Despite this improvement, again there was no significant difference in overall renal response rates or clinical efficacy at 1 year between placebo (45.8%) and treatment arms (56.9%) of the trial ($p = 0.18$).

However, before concluding that Rituximab is not a good therapy for SLE, a careful evaluation of the design of the EXPLORER and LUNAR trials is mandatory. With regard to disease severity, a high percentage of patients included are likely to have had mild to moderate SLE (especially in the EXPLORER trial) with no history of poor response to standard therapies. This

observation, in itself, may explain why Rituximab was not superior to the other drugs in these predominantly non-complicated patients. Considering concomitant therapies, the high doses of corticosteroids permitted in both arms of these trials could lead to significant differences not being apparent in a short-term evaluation. In addition, the possible synergistic effect of Rituximab in combination with immunosuppressive agents (cyclophosphamide or mycophenolate), suggested by some authors to have significant advantages in complicated, refractory SLE cases (14), was not evaluated in these RCTs. Regarding ethnic factors, the two RCTs included a different sub set of patients (mainly american patients, predominantly from the US and Canada, but also from Mexico, Brazil, and Argentina) when compared to the majority of patients from uncontrolled studies were (European). This consideration about ethnicity is important because some studies have suggested a variable therapeutic response to the main immunosuppressive agents in different ethnic groups (15).

Finally, the demonstration of the superiority of Rituximab over current first-line therapies in SLE (corticosteroids, cyclophosphamide, and mycophenolate) does not correlate with the use of Rituximab in clinical practice, i.e. its overwhelming use in patients with SLE refractory to these therapies. Furthermore, the fact that Rituximab was not shown to be superior to other therapies does not necessarily signify that it is inferior.

Ocrelizumab

A further anti-CD20 monoclonal antibody, Ocrelizumab, was studied in two doses (400mg and 1g) in The Study to Evaluate Ocrelizumab in Patients With Nephritis Due to SLE (BELONG) trial that included 381 patients with severe lupus nephritis. However the trial was suspended early due to the detection of a severe infection-related safety signal in the treatment arm. Nonetheless the report from the BELONG trial did show a trend to a better response in the ocrelizumab 400mg (62%) and 1g (64%) treatment arm compared with placebo (51%); thus suggesting there is potential for the use of this drug in SLE. Despite the results, ocrelizumab has not been studied further (16).

Anti-CD22

Epratuzumab

Epratuzumab is a humanised monoclonal antibody to the CD22 surface receptor present on mature B cells. Like CD20, CD22 play a key role in controlling B cell responses to antigens. Epratuzumab reduces the number of auto-B cells via antibody dependent cellular cytotoxic mechanisms (17).

Two studies reported clinical improvement, compared to placebo, in 14 (ALLIVIATE 1) and 90 (ALLIVIATE 2) patients with active lupus disease following epratuzumab treatment (12). Epratuzumab was well tolerated without severe adverse events. The 12-week phase IIb, multicentre, randomised controlled study was conducted with 227 patients and the primary endpoint was the week 12 responder rate measured using a novel composite endpoint, the British Isles Lupus Assessment Group (BILAG)-based Combined Lupus Assessment (BICLA). There was a significantly greater reduction in BILAG scores 48 weeks post treatment with increasing doses of treatment. The treatment also enabled steroid sparing, suggesting a significant clinical benefit. Overall treatment with epratuzumab 2400 mg was well tolerated in patients with moderately to severely active SLE, and associated with improvements in disease activity (18).

These encouraging results have lead to the development of two phase III studies (EMBODY 1 and 2), that aim to confirm the clinical efficacy of Epratuzumab in the treatment of patients with moderate to severe SLE, in addition to continuing standard of care treatments (19).

B Lymphocyte Stimulator (BLyS) and A Proliferation Inducing Ligand (APRIL) targeted therapy

BLyS and APRIL are two key B cell stimulatory cytokines. BLyS is a 285 amino acid transmembrane protein belonging to the tumour necrosis factor ligand superfamily and is present on the surface of macrophages, monocytes, dendritic cells and activated T cells (20). BLyS is a growth factor required for B-cell

maturation, activation and survival and acts by binding to thee receptors (BCMR – B cell maturation antigen, TACI – transmembrane activator and calcium modulator and cyclosporin interactor and BR3 and BR3 – BLyS/BAFF receptor 3). APRIL has been shown to bind to BCMA and TACI on B cells. Studies have shown that the concentration of these cytokines correlates with disease severity and serological markers, such as anti-dsDNA antibody levels, suggesting they play a key role in the pathogenesis of SLE (21). This is supported by evidence from murine studies whereby lupus-prone mice engineered to overexpress BLyS go on to develop severe SLE (7). Similarly, knockout-BLyS mice have reduced mortality and approximately 80% reduced disease severity at 1 year (22).

Belimumab

Belimumab is an IgG1 monoclonal antibody that antagonises BLyS and inhibiting its activity (20). The efficacy and safety of this new drug have been tested in two pioneering multicentre, double blind randomized controlled trials, BLISS-52 (23) and BLISS-76 (24), which included 1684 lupus patients with mild to moderate disease activity (without lupus nephritis/CNS). These studies demonstrated a significant improvement in disease outcome with 10mg/kg of Belimumab as compared to placebo. The beneficial effects of Belimumab were measured using the SLE responder index (SRI), which combines the SLE disease activity index (SLEDAI), the British Island lupus assessment group (BILAG) and the physicians' global assessment (PGA) (24,25).

The BLISS-52 group showed SRI rates 1-year post treatment as 58% (p=0.0006), 51% (p=0.00129), and 44% in the Belimumab 10mg/Kg, 2mg/Kg and placebo groups respectively. This demonstrates a significant clinical benefit with increased dose of Belimumab. In addition, Belimumab treatment also reduced SLE-related flares, normalised C3 levels and reduced steroid usage (23). This is particularly useful for the patient in terms of reduced steroid associated side effects.

The BLISS-76 trial further supported the significant clinical benefits of Belimumab shown by the BLISS-52 trial, with the results demonstrating reduced

active disease, relapse rates, time to onset of relapse and steroid requirement compared to placebo, in a dose-dependent manner (24). Furthermore, they showed that Belimumab significantly reduced the risk of severe relapses over the trial period compared to placebo, with 26.5% of the placebo arm reporting a severe flare compared to only 18.5% in the low dose treatment arm ($p=0.023$). Overall the results from these studies provide robust evidence for the use of Belimumab in the treatment of SLE. It was based on the results of the BLISS trials that in 2011 Belimumab was approved by the FDA and EMA and has become the first drug approved for SLE for over 50 years (25).

Since the approval there has been an on going seven-year follow up of lupus patients assessing the tolerability and efficacy of Belimumab in addition to standard of care therapies. The results remain positive with a maintained reduction in corticosteroid use and low rates of adverse effects (26). The authors also described a 70% decline from baseline in autoantibodies to dsDNA at 7 years after treatment.

Overall these results suggest that targeting BLyS with the novel biologic Belimumab can provide significant clinical benefit to SLE patients and is well tolerated long-term (27). However, it is important to note that Belimumab displays only marginal effectiveness in mild to moderate manifestations of the disease, a considerable proportion of patients did not respond to the treatment (65% response rate over 7 years) and Belimumab was less effective among African-American patients (28). However some of these failings could be explained by the fact that only half of lupus patients show permanent BLyS elevation (29).

Blisibimod and Tabalumab

Owing the success of Belimumab and its recent FDA approval, there has since been two further anti-BLyS drugs introduced, Blisibimod and Tabalumab, which are currently being assessed in a phase III RCT to evaluate their benefit in the treatment of SLE (30,31).

Blisibimod is a fusion between the Fc portion of IgG and a peptide that selectively binds to BLyS. Results of the phase II trial (PEARL-SC) were positive, with high dose Blisibimod (200mg once weekly) producing significantly higher responder rates compared to placebo in patients with ≥7 (25%) or ≥8 (25%) point reduction in SLEDAI ($p = 0.003$, $p = 0.001$ respectively). Furthermore, patients with baseline severe SLE (SLEDAI ≥ 10 and under corticosteroid treatment) showed an even greater improvement with 41.7% responder rate achieving either ≥7 or ≥8 SLEDAI point decrease in the high dose Blisibimod group compared to placebo ($p = 0.002$, $p < 0.001$ respectively). These results were associated with a significant decrease in anti-ds DNA ($p < 0.001$) and increase in C3 ($p < 0.01$) and C4 ($p < 0.001$) in the Blisibimod arm compared to placebo (32). Due to positive early results of this trial, the efficacy and tolerability of Blisibimod is currently being assessed in patients with highly active and refractory SLE, the results of which are eagerly anticipated.

Tabalumab is a monoclonal antibody directed against soluble and membrane bound BLyS. The efficacy and safety of Tabalumab in SLE patients was recently assessed in two phase III RCTs (33,34). However, the Eli Lilly and Company announced that further development of Tabalumab would be discontinued due to insufficient efficacy (34). It has been reported that the decision was not based on safety concerns. In the ILLUMINATE 1 study, Tabalumab did not achieve the primary endpoint, at either dose studied, of statistically significant improvement on SRI-5 (SLE Responder Index-5, a measurement of lupus disease activity and response), compared to standard of care therapy. In ILLUMINATE 2, the higher dose of Tabalumab met this endpoint, the first time a lupus study has achieved this efficacy measure as a primary endpoint in a Phase 3 trial. Collectively, the data from these studies did not meet the company's expectations for efficacy in the context of existing treatments. The overall safety profile showed a similar frequency of adverse events in patients treated with either Tabalumab or normal standard of care.

Atacicept

Atacicept is a recombinant fusion protein containing the Fc portion of IgG and the TACI receptor that binds both BLyS and APRIL, thus inhibiting both these B cell stimulating factor (35). In a phase I RCT, which included 49 patients with mild to moderate lupus, Atacicept was shown to have beneficial therapeutic effects, inducing a 45-60% attenuation in mature B cells and dose dependent decreases in autoantibody levels, compared to placebo (36). However, despite these early positive results, the phase I/II RCT of Atacicept in patients with lupus nephritis was terminated prematurely due to safety concerns (37).

T cell targeted therapies

T cells are activated by two independent signals, one from the engagement of the MHC complex with the T cell receptor and the other via the interaction of co-stimulatory molecules, such as CD28 and CTLA-4 (expressed on T cells) and CD80/86, expressed on antigen presenting cells (38). It is thought that inhibiting T cell activation could be effective in the treatment of SLE.

Abatacept

Abatacept is a fusion protein of cytotoxic T lymphocyte antigen 4 (CTLA-4) and the Fc portion of human IgG1. CTLA-4 binds efficiently to CD80/86, thus preventing T cell co-stimulation via the CD28 pathway. Abatacept was proven to be effective in the treatment of murine lupus (39) and in patients with rheumatoid arthritis (40). However, the results from clinical trials of patients with SLE were disappointing and Abatacept treatment was deemed to be not effective compared to placebo. The primary endpoint was the proportion of patients who flared following tapering of their glucocorticoids and, after 1 year, around 80% of patients had flared in both groups. However Abatacept did show evidence of biologic activity and was well tolerated in patients with active class III or IV lupus nephritis (41). Interestingly Wofsy et al. (42) looked at the choice of parameters for abatacept trials and deemed that if alternative parameters were chosen then the trial is likely to have been a success. They suggest there is strong rationale to conduct further studies of abatacept in the treatment of lupus nephritis.

Six patients suffering from overlapping rheumatoid arthritis and SLE (Rhupus syndrome) with active arthritis refractory to methotrexate treatment were shown to benefit significantly from Abatacept treatment according to Clinical Disease Activity Index (CDAI), Health Assessment Questionnaire-Disability Index (HAQ-DI) and EULAR scores (43). Median CDAI scores attenuated by 16.55 ($p = 0.028$) 3 months post treatment suggesting significant clinical benefit of Abatacept in these patients. SLEDAI scores were also shown to significantly decrease up to 6 months post treatment with improvements seen in both articular and non-articular manifestations, which included rash and fever. In correlation with this, anti-DNA antibody decreased by median 10.7 ($p = 0.043$) 6 months post treatment suggesting Abatacept may have its benefits by affecting autoantibody production in SLE. Currently Abatacept is not approved for lupus treatment, although some clinicians use it as an off label agent.

Cytokine blockade targeted therapies

Tocilizumab (anti-IL-6 receptor mAb)

IL-6 is a pro-inflammatory cytokine with high levels were found in the sera of patients with active lupus (44). Tocilizumab is a humanised monoclonal antibody against the IL-6 receptor, thus preventing IL-6 activation. The drug is yet to be assessed by controlled trials but a small phase I trial that included 16 patients suggested that Tocilizumab is safe and beneficial in SLE (17). Further trials are required to fully assess the therapeutic role of Tocilizumab in the treatment of lupus.

Sirukumab (anti-IL-6 mAb)

Like Tocilizumab, sirukumab is also a humanised, anti-IL-6 monoclonal antibody that binds to IL-6 and inhibits its biological activity (45). A recent phase II trial using Sirukumab on lupus nephritis patients showed that patients with active lupus nephritis did not result in a median improvement in proteinuria and almost half of those who treated with Sirukumab developed a serious adverse

event (46). Thus owing to these negative results, the trials for Sirukumab in lupus nephritis have been discontinued.

Anakinra (human recombinant IL-1 receptor antagonist (IL-1 Ra))
IL-1 is another pro-inflammatory cytokine implicated in the pathogenesis of SLE. Anakinra is a recombinant IL-1 Ra that blocks IL-1 activity and thus has potential in the treatment of SLE (47). It is currently used in the treatment of severe rheumatoid arthritis. Although recent uncontrolled trials have demonstrated beneficial effects of Anakinra (48), further controlled trials are required to assess its efficacy and safety in the treatment of SLE.

Sifalimumab (anti-interferon alpha (IFN-α))
One of the most exciting advances in the field of cytokine-targeted therapy in SLE is the development of Sifalimumab, a human IgG1 monoclonal antibody that targets IFN-α, an inflammatory cytokine thought to play a key role in the development of SLE (17). The results from a recent phase IIb trial showed that the study met its primary endpoint of percentage of subjects that responded by the SLE Responder Index (SRI-4) at Day 365, and clinical benefits in organ-specific outcomes measures (joints, skin) was also observed (49).

The study evaluated three doses of Sifalimumab (200mg, 600mg, 1200mg) against placebo when added to standard of care therapy in patients with moderate to severe lupus despite standard of care therapy. As well as the meeting its primary endpoint, the study also achieved improvements in skin rashes as measured by CLASI (Cutaneous Lupus Erythematosus Disease Area and Severity Index) and improvement in fatigue.

Although still in their early stages, the results from these studies assessing the efficacy of cytokine-targeted therapies are promising and could be a key breakthrough in the treatment of SLE.

Expert commentary

There has been major progress in the understanding of the intricate pathogenesis underlying SLE, most notably the critical role of auto B cells in autoantibody formation, antigen presentation and T cell activation. There are disadvantages with the current standard of care therapy and this has led to a pursuit for biologics that target specific SLE disease pathways.

The approval of Belimumab by the FDA in 2011 was a significant milestone for the treatment of SLE. Furthermore murine models and early phase studies of epratuzumab and sifalimumab have shown promising results and multicentre randomised controlled trials with long-term follow-ups are ongoing.
However, response to B cell target therapy is still heterogeneous among the studies. Understanding the B cell signalling pathways along with their lupus-relevant molecular aberrations identified may allow for more targeted and rational interventions. More critically, this will explain the different rate of response showed when targeting different compounds of B cell populations.
Taking into account the successful implementation of small molecule-mediated inhibition in haematologic malignancies, the idea of providing a specific, tailored to the patient's 'molecular identity' and possibly less toxic therapeutic agent in patients with SLE appears fascinating. In order to avoid unnecessary effects on other cells, and not creating another unspecific immunosuppressant, it would be ideal to target molecules that are B cell specific. In light of this, Lyn and Btk modulation appears to be more rational (50). The study of small molecules that inhibit specific B cell signalling enzymes and mediators in lupus-prone animal models offers an important insight and also provides the background to attempt similar trials in humans.

The actual body of evidence on safety issues of biologic therapies in SLE is limited for most drugs. The only exception is the use of B cell blockade with Rituximab (off-label) and anti-BLyS with Belimumab (approved).

While the use of B cell depletion therapies as first-line treatment or in patients with a predominantly mild form of the disease is not recommended, their off-

label use in severe, refractory SLE cases appears to be sufficiently positive to warrant their continued use in these patients.

Although the results of these trials suggest that the use of Rituximab in SLE may be controversial, it is still used extensively 'off label'. Further trials will need to prove more successful in order to establish Rituximab has an effective novel therapy for SLE; however this may prove to be difficult with the increasing emergence of biosimilars to the market (51).

5-year view

Agents that target B cells are not appropriate for all patients with SLE. Patients may have slightly different underlying pathophysiology rendering interventions ineffective in some patients but effective in others. Comparing the efficacy of various biologics in different patient subpopulations as well as in different SLE manifestations would help determine which biologics are most suited for certain types of patients and clinical manifestations. This would result in both clinically and cost effective novel biologics for SLE.

The principle of treating-to-target has been successfully applied to many diseases outside rheumatology and more recently to rheumatoid arthritis. Identifying appropriate therapeutic targets and pursuing them systematically has led to improved care for patients with these diseases and useful guidance for healthcare practitioners and administrators. More recently, an initiative to evaluate possible therapeutic targets and develop treat-to-target guidance in the management of SLE was established. The therapeutic armamentarium for SLE consist of a relatively small number of agents in the therapeutic classes of glucocorticoids, anti-malarials, immunosuppressives and biologics. In the latter category, only one agent (Belimumab) is approved for use in SLE, and one (Rituximab) is used not infrequently 'off-label' in refractory cases. Fortunately, several new agents of considerable interest are in the development for the

treatment of SLE, raising expectations that will soon be possible to aim for therapeutic targets with greater confidence that they can be achieved (2).

Key issues

- Belimumab is the first drug licensed for use in SLE in more than fifty years.
- Open label and uncontrolled studies supported the use of B cell depleting agents in refractory/life-threatening SLE, despite the poor outcome of two RTCs.
- Careful evaluation of the risk/benefit profiles of biologic agents in SLE is essential.
- Understanding the B cell signalling pathways along with their lupus-relevant molecular aberrations identified may allow for more targeted and rational interventions

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Figure legend

Novel biologics and their respective targets in the pathogenesis of SLE. IL-1: Interleukin 1; IL-1 R: Interleukin 1 Receptor; IL-6: Interleukin 6; IL-6 R: Interleukin 6 Receptor; INFα: Interferon alpha; INFα R: Interferon alpha Receptor; CTLA4: Cytotoxic T Lymphocyte-associated antigen 4; BLyS: B Lymphocyte stimulator; APRIL: A Proliferation Inducing Ligand; BAFF-R: BLyS receptor; TACI: Transmembrane Activator and Calcium-modulator and Cyclophilin Ligand Interactor; BCMA: B Cell maturation antigen.