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Anticytokine therapies in systemic lupus erythematosus

Antonio La Cava

Division of Rheumatology, Department of Medicine, University of California Los Angeles, 1000 Veteran Avenue 32–59, Los Angeles, CA 90095-1670, USA Tel.: +1 310 267 4975 Fax: +1 310 206 8606 alacava@mednet.ucla.edu

Abstract

The dysfunctional immune response that characterizes systemic lupus erythematosus (SLE) associates with an unbalanced production of soluble mediators that are crucial in promoting and sustaining chronic inflammation. The successful use of biologics in several autoimmune diseases has led to studies in SLE aimed at contrasting the proinflammatory responses that contribute to tissue and organ damage in the disease. Several approaches have been developed and tested as potential therapeutic agents in SLE in preclinical studies and in clinical trials. This article provides an overview on antibody-based approaches in SLE that, although preliminary, have the potential to expand the current therapeutic possibilities in the disease.

Keywords

anticytokine therapy; clinical trial; cytokine; immunotherapy; systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is an autoimmune disease that affects multiple tissues and systems and is characterized by significant interindividual variability in clinical manifestations and organ involvement. Despite new and improved therapeutic options having positively impacted the prognosis of SLE, some SLE patients experience an aggressive disease course and/or unresponsiveness to therapy. Moreover, the risk of fatal outcomes and the damaging side effects of immunosuppressive therapies in SLE (increased risk of infection, infertility and liver toxicity, among others) call for an improvement in the current therapeutic management of SLE.

From a pathogenesis standpoint, unbalanced immune homeostasis and aberrant autoreactivity in SLE associate with inflammatory cells and the production of autoantibodies that play key roles in the development of tissue damage. Since cytokines promote and/or sustain the proinflammatory environment, anticytokine therapies have come under scrutiny as new modalities to dampen or reduce the deleterious inflammatory responses associated with hyperactivity of immune cells and autoantibody production. The envisioned benefits could significantly affect patients that cannot tolerate or are unresponsive to conventional therapies. They could also prove beneficial in reducing dosages of immunosuppressive drugs (and thus side effects) and improving clinical control (e.g., reduce risk of flare-ups) in patients that respond to therapy.

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Antibody-based therapies in systemic lupus erythematosus

Monoclonal antibodies (mAbs) and fusion (or chimeric) proteins that target proinflammatory cytokines have been used in the clinic for several rheumatic diseases, often with great success (a classical example is the use of TNF inhibitors in rheumatoid arthritis [RA]). The advantage in using mAbs is that they target a single molecule or its receptor(s) with great specificity and can be produced in large amounts by hybridomas. The mAbs that have been used in the clinic include murine, chimeric, humanized and fully human antibodies. In particular, chimerization consists of the replacement of the mouse constant domains with their human counterparts, and humanization is achieved by transplanting the complementary determining regions of murine antibodies (the parts that interact with the antigen) into a fully human antibody framework. While reducing immunogenicity, this procedure still leads to mAbs with murine components against which the host immune system can mount an immune response, leading to a reduced therapeutic efficacy over time. The order indicated above (murine, chimeric, humanized and fully human antibodies) somehow reflects a chronological approach in the development of these molecules as therapeutics, which have progressively become less antigenic/immunogenic (owing to reduced murine components), with resulting increased efficacy, prolonged half-life and availability for continuous use in patients.

This article focuses on anticytokine mAbs used as new therapeutic approaches in SLE. Other approaches (e.g., immune cell-based intervention and costimulatory blockade and inhibition of complement factors) have been reviewed elsewhere [1].

Cytokines as therapeutic targets in systemic lupus erythematosus

Inflammatory responses in SLE can be favored and/or sustained by the availability of cytokines that are overexpressed systemically and/or in local tissues. Proinflammatory cytokines such as TNF- α , IL-1, -6, -12, -15, -18 and IFN- α and - γ are upregulated in SLE and play important roles in the inflammatory processes that leads to tissue and organ damage. Thus, many of these cytokines have been considered potential targets for the reduction of chronic inflammation in SLE. Blockade of these cytokines has been studied in preclinical models, with the acknowledged caveat that murine lupus models and human SLE may not fully share pathogenic mechanisms. For some cytokines – which are reviewed below – specific biologics have been developed and tested in clinical trials.

■ TNF- α

The role of TNF- α in SLE is controversial. TNF- α promotes apoptosis and significantly affects the activity of B cells, T cells and dendritic cells (DCs). In different strains of lupus mice, the expression of TNF- α is often variable, and beneficial effects on the disease can be observed either after administration of TNF or upon TNF blockade [2–4]. In kidney inflammation, the renal expression of TNF is usually increased [5]. In lupus mice, skin disease may be TNF dependent, and anti-TNF treatment can deteriorate nephritis. In humans, some studies have found relatively low concentrations of serum TNF- α , while other studies have found elevated amounts or no significant differences between SLE patients and healthy controls. Similarly, high TNF- α has been described in both active and inactive SLE [6–8]. Furthermore, TNF- α levels might correlate with clinical disease because they are increased in lupus nephritis in relation to the activity of renal disease [9].

Infliximab & etanercept—The TNF blockers that have been successful in the management of RA, Crohn's disease and psoriasis are known to induce autoantibodies and lupus-like syndromes. Thus, their use in SLE is controversial [10–12]. Although with the cessation of the administration of TNF inhibitors, the lupus-like symptoms and most auto-antibodies disappear

(they are IgM and possibly are not pathogenic), it has been reported that a few RA patients who use TNF-blockers can develop nephritis [13,14].

In SLE, the use of anti-TNF antibodies has been associated with amelioration of poly-arthritis, cutaneous manifestations, disease activity, proteinuria and nephritis, but also severe infusion reaction [15,16]. An open-label study of infliximab in a small number of SLE patients with arthritis and/or lupus nephritis that were refractory to standard therapy has shown clinical improvement and an increased risk of infection [17]. However, it appears that anti-TNF treatment is not promising in SLE, after the termination of studies on TNF blockade in a Phase II/III multicenter trial where infliximab was combined with azathioprine in lupus membranous nephritis, and also in a randomized, double-blind, multicenter Phase II study that evaluated safety and tolerability of etanercept in patients with active lupus nephritis.

■ Interferons

Both type I (IFN- α) and type II (IFN- γ) interferons have been implicated in the pathogenesis of SLE, with IFN- α being a key player in inflammation and immune hyperactivity in the disease owing to its ability to directly affect T cells and B cells and induce the activation of peripheral DCs.

IFN- α —DNA-containing immune complexes in lupus serum stimulate plasmacytoid DCs to produce IFN- α [18,19]. IFN- α levels often correlate with anti-dsDNA antibody production, complement activation and IL-10 production [20]. This cytokine promotes activation, differentiation, survival and antibody production in B cells. In SLE, patients can have increased levels of IFN- α , which in turn promotes the expression of interferon-regulated inflammatory genes in the peripheral blood mononuclear cells of the SLE patients (a characteristic often referred to as the ‘interferon signature’).

Sifalimumab—This human antibody that blocks multiple IFN- α subtypes is currently being tested in Phase Ib and IIa clinical trials, to evaluate safety and tolerability of multiple intravenous and subcutaneous doses in SLE.

Rontalizumab—This humanized mAb against IFN- α (rhuMAb IFN- α) is in a Phase II, randomized, double-blind, placebo-controlled trial that evaluates the efficacy and safety in patients with moderately to severely active SLE.

IFN- γ —The role of IFN- γ in SLE is not fully elucidated. IFN- γ is elevated in (New Zealand Black [NZB] $\times$ New Zealand White [NZW])F₁ (NZB/W) lupus mice, where it correlates with disease. In addition, administration of IFN- γ accelerates murine lupus, while anti-IFN- γ antibody (or soluble IFN- γ receptor or IFN- γ receptor-immunoglobulin) delays the disease [21–23]. Finally, late treatment with IFN- γ in MRL/lpr mice accelerates SLE, while early treatment protects from disease [24].

In humans, elevated serum IFN- γ correlates with disease activity and kidney involvement in SLE patients [25]. However, some studies show an increase of IFN- γ in SLE patients and other studies find decreased titers of IFN- γ in lupus nephritis [26].

AMG 811—The safety, tolerability, pharmacokinetics and pharmacodynamics of multiple doses of this human mAb to IFN- γ are under investigation in a Phase Ib, randomized, multicenter study in SLE patients with and without glomerulonephritis.

■ IL-1

IL-1 includes the proinflammatory cytokines IL-1 α and IL-1 β . IL-1 binds to IL-1 receptor (IL-1R). The IL-1R antagonist (IL-1Ra) competes for receptor binding with IL-1 α and IL-1 β , thus blocking these cytokines.

IL-1 is overexpressed in inflamed kidneys of MRL/lpr and NZB/W lupus mice, and low-dose administration of IL-1 accelerates renal disease in the latter strain of mice [3]. IL-1R deficiency causes arthritis in mice, and MRL/lpr mice with nephritis do not respond to therapy with IL-1Ra [3,27,28].

In human SLE, IL-1 α and -1 β are increased in glomerulonephritis, and IL-1 β is increased in the serum and cerebrospinal fluid of patients with CNS lupus [29,30]. Although kidney involvement associates with low serum levels of IL-1Ra, some reports have shown an increase of IL-1Ra during active disease and a decrease during disease flares [30,31].

Anakinra—This nonglycosylated version of the human IL-1Ra (which neutralizes the biological activity of IL-1) has shown both safety and efficacy in improving arthritis in an open trial on four SLE patients, with only short-lasting therapeutic effects in two patients [32].

■ IL-6

IL-6 induces B-cell differentiation to plasma cells, hyperactivity and secretion of antibodies, and also promotes T-cell proliferation, cytotoxic T-cell differentiation and local inflammation. IL-6 can be induced by TNF- α and IL-1, and signals through the ligand-binding membrane-bound IL-6R and the nonligand-binding signal transducer gp130. A soluble form of IL-6R, which lacks transmembrane and cytoplasmic domains (and can form a complex with soluble IL-6) is elevated in SLE patients and in experimental lupus nephritis.

Blockade of IL-6R improves renal disease [33]. Similarly, treatment with IL-6 promotes disease, while anti-IL-6 therapy delays lupus nephritis in NZB/W mice [34].

In the serum of active SLE patients, IL-6 is elevated and correlates with disease activity [35]. IL-6 is found in lupus kidneys and in the urine of patients with lupus nephritis [29,36]. Finally, IL-6 is elevated during cardiopulmonary complications of SLE and in the cerebrospinal fluid of SLE patients with neuropsychiatric symptoms [37,38].

Tocilizumab—By binding both the membrane-bound IL-6R and the soluble form of IL-6R, this humanized mAb inhibits IL-6 signaling. An open-label Phase I dosage-escalation study with tocilizumab in SLE patients with mild-to-moderate disease demonstrated improved disease activity scores and amelioration of arthritis, in addition to a decrease in the frequency of circulating plasma cells and reduced IgG and anti-dsDNA antibody titers, but also induced neutropenia [39].

■ IL-10

IL-10 is generally considered an inhibitory cytokine for T cells and contrasts the activity of other proinflammatory cytokines such as IFN- γ , TNF- α and GM-CSF. In B cells, IL-10 promotes differentiation and antibody production.

New Zealand Black/White lupus mice treated with anti-IL-10 mAb have reduced anti-DNA antibody titers and a delay in the onset of proteinuria and glomerulonephritis. Conversely, their treatment with IL-10 associates with accelerated disease [40]. However, these effects appear to be strain dependent [41].

IL-10 levels are elevated in sera of SLE patients and correlate with clinical and sero-logical disease activities [42]. Treatment of cells from lupus patients with anti-human IL-10 antibody reduces antibody production [43]. Interestingly, the dysregulation of IL-10 in SLE patients is linked to certain genetic polymorphisms [44].

B-N10—In the absence of a human (or humanized) mAb to IL-10, the murine anti-IL-10 mAb B-N10 was used to neutralize IL-10 in a small uncontrolled, open-label study in patients with relatively mild disease [45]. Disease activity improved and inactivity was observed in SLE patients up to 6 months after treatment [45]. However, all patients developed antibodies against the murine mAb [45].

B-lymphocytic stimulator

B-lymphocyte stimulator (BLyS), a member of the TNF family, is also known as B-cell-activating factor (BAFF), TALL-1; THANK; and zTNF4. BLyS can be released in a soluble form or can be expressed as a transmembrane protein on monocytes, DCs, activated T cells and some malignant B cells. The production of BLyS is favored by IFN- γ , IFN- α , IL-10, G-CSF and CD40L [46,47]. Elevated levels of BLyS associate with lupus-like disease in mice, and SLE patients have elevated serum levels of BLyS [48–50].

B-lymphocyte stimulator interacts with transmembrane receptors that are not present in early B-cell precursors or in pre-B cells and are mainly present in mature B cells [51–53]. They are the TNF receptor superfamily member 13C (TNFRSF13C), also known as BAFF receptor (BAFF-R) or CD268; the TNFRSF13B, also known as transmembrane activator and calcium modulator and cyclophilin ligand interactor (TACI) or CD267; and the TNFRSF17, also known as B-cell maturation antigen (BCMA) or CD269. The stimulation of all three receptors promotes B-cell differentiation and proliferation by increasing the intracellular levels of NF- κ B, but the three receptors have differing binding affinities for BLyS. TACI has the worst affinity for BLyS and actually has higher affinity for a molecule similar to BLyS, termed a proliferation inducing ligand (APRIL). BCMA has an intermediate binding phenotype and can bind either BAFF or APRIL.

B-lymphocyte stimulator appears to play an important role in the differentiation of B cells into plasma cells. Signaling through BAFF-R and BCMA increases the levels of the antiapoptotic protein Bcl-2, thus promoting B-cell survival, while blockade of the BLyS–BAFF-R pathway (with anti-BLyS mAb or fusion proteins) leads to a reduced number of peripheral B cells [48].

■ Benlysta (belimumab)

Belimumab is a fully human IgG1 λ mAb that binds BLyS, thus inhibiting its activities on B cells. When Phase II studies failed to show an efficacy of belimumab in reducing SLE, it was found that an improvement in measures of SLE disease activity had occurred in serologically active patients. In addition, the drug required some time to work because better therapeutic effects were observed at 52 weeks [54]. Thus, after missing the end point in the Phase II lupus trial, belimumab entered two double-blind, placebo-controlled, multicenter Phase III trials evaluating the drug's efficacy, safety, tolerability and impact on quality of life in seropositive SLE patients at 52 weeks and at 76 weeks. These two Phase III trials, termed BLISS-52 and BLISS-76, recruited patients in different continents and used a newly designed individual responder index (IRI), similar to that used in RA, to measure an individual patient's improvement from baseline. The IRI took into account a reduction from baseline of SELENA SLEDAI and BILAG scores, and the physician global assessment (these parameters were analyzed on an *ad hoc*-adjusted intention-to-treat). At 52 weeks, both the BLISS-52 and the

BLISS-76 trials met their primary end points, and a statistically significant improvement versus the placebo group was observed in both studies [101].

B-lymphocyte stimulator has also been targeted by other biologics such as AMG 623 and BR3-Fc [55]. Preclinical studies have also tested anti-BR3 antibodies that block BLyS-dependent B-cell survival *in vitro* and *in vivo* [56]. Interestingly, anti-BR3 antibodies reduce the numbers of B cells more effectively than anti-BLyS mAb, BR3-Fc and TACI-Fc [57].

■ A-623 & BR3-Fc

A-623, formerly AMG 623, is a polypeptide fusion protein (peptibody) that inhibits B-cell survival and maturation by neutralizing BLyS. A-623 is currently in Phase II clinical trials. BR3-Fc (briobacept) is a homodimeric fusion glycoprotein of the extracellular ligand-binding portion of BAFF-R and the Fc portion of an IgG₁ that blocks BLyS from binding to BAFF-R, thus inhibiting activation and promoting a poptosis of B cells.

Both AMG 623 and BR3-Fc are in clinical trials and appear well tolerated. Their efficacy in SLE is unknown at present [58–59].

■ Atacicept

Atacicept is a recombinant fusion protein made of the extracellular ligand-binding portion of TACI (see previous section) fused to the Fc portion of a human IgG. It is a soluble receptor that binds BLyS and APRIL, thus blocking the activation of TACI. Although a Phase II/III lupus nephritis trial that evaluated dose–effectiveness in SLE patients gave disappointing results and the study was discontinued owing to the development of severe infections in some patients, a new Phase II/III trial of atacicept in generalized SLE is ongoing [60].

Conclusion

Biologics have dramatically improved the clinical management of several autoimmune diseases. In SLE, where multiple immune imbalances associate with a significant complexity and a diversity of clinical disease manifestations, the use of mAbs to cytokines has shown rapid advancement and potential promise. Concerns with the use of biologics remain the risk of immediate and delayed toxicities and the development of drug resistance. Although no biological response modifiers are currently approved for SLE, it is likely that belimumab will be approved this year, and new open-label trials will soon be added to the list reviewed here. While most data available derive from open-label trials, controlled trials are also underway to confirm the preliminary data in multicenter, randomized trials (Table 1). Importantly, mechanistic studies are paralleling some of those studies, so that an increased understanding of some cellular and molecular events associated with clinical and serologic responses can facilitate and possibly improve the use and targeted efficacy of selected biologics in SLE.

Future perspective

Driven by promising data with belimumab and tocilizumab in the recent clinical trials, the field of anticytokine immunotherapy in SLE is likely to expand to include the targeting of additional proinflammatory cytokines in the near future. Even if some trials in SLE have been disappointing (such as the ones involving TNF inhibitors), pitfalls may be somehow instrumental in the design of better trials and to optimize parameters that can ultimately increase effectiveness and reduce side effects in the testing of new drugs in SLE. After approximately half a century without approval of new drugs for SLE, the next decade is most likely to see the addition of biologics such as anticytokine antibodies to the physician's armamentarium in the treatment of SLE.

Executive summary

- Systemic lupus erythematosus (SLE) is an incurable disease in which new drugs are required to improve a patient's well-being, clinical disease management and prognosis.
- Since proinflammatory cytokines are key elements in the chronic inflammation and tissue damage in SLE, a reduction of their deleterious activity represents a possible therapeutic target.
- Although murine, chimeric, humanized and fully human antibodies have all been considered in SLE, most recent trials aim at employing antibodies carrying the least immunogenicity (eliminating mouse components) to achieve longer-term efficacy.
- Since clinical trials suggested that the blockade of B-lymphocyte stimulator can have beneficial effects on disease in some SLE patients, belimumab (anti-B-lymphocyte stimulator) will probably be approved for SLE therapy in a near future.
- Although very effective in other rheumatic disease, treatment with TNF inhibitors has given disappointing results in clinical trials in SLE.
- While preliminary, recent studies on the use of interferon and IL-6 blockade hold promise as new therapeutics in SLE.

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Table 1

Antibody-based therapies in ongoing clinical trials in systemic lupus erythematosus.

Target cytokine	Agent	Trade name	mAb type	Phase	Clinical trials ID	Year of completion, sponsor
BLyS	Belimumab	Benlysta	Human	I	NCT00657007	2003, Human Genome Sciences
				II	NCT00071487	2006, Human Genome Sciences
				III	NCT00424476	2009, Human Genome Sciences
				II	NCT00583362	2010, Human Genome Sciences
				III	NCT00724867	2010, Human Genome Sciences
				III	NCT00712933	2010, Human Genome Sciences
				III	NCT00410384	2010, Human Genome Sciences
				II	NCT00732940	2012, Human Genome Sciences
				II/III	NCT00573157	2010, EMD Serono
				II/III	NCT00624338	2011, EMD Serono
				I	NCT00541749	NA, Genentech
				II	NCT00962832	2012, Genentech
IFN- α	rhUMab IFN- α		Human	I	NCT00482989	2007, MedImmune LLC
				I	NCT00657189	2010, MedImmune LLC
				II	NCT01031836	2010, MedImmune LLC
IFN- γ	AMG 811		Human	II	NCT01031836	2011, Astra Zeneca
				I	NCT00818948	2011, Amgen
IL-6	Tocilizumab	Actemra	Humanized	I		

BLyS: B-lymphocyte stimulator; mAb: Monoclonal antibody; NA: Not applicable.