Review Article

Efficacy of novel monoclonal antibody belimumab in the treatment of lupus nephritis

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ABSTRACT

Recently introduced into the market, belimumab (Benlysta) is a monoclonal antibody that has potential clinically efficacious applications for the treatment of lupus nephritis. Lupus nephritis is a major complication of systemic lupus erythematosus (SLE) that can lead to significant illness or even death without proper intervention and treatment. With vast implications through a novel mechanism, belimumab offers a new standard of treatment for physicians in the complications associated with SLE, specifically lupus nephritis. By targeting B cell signaling and maturation, belimumab is able to mitigate the underlying pathological complications surrounding SLE. Phase 3 clinical trials with belimumab have depicted clinically efficacious applications, suggesting belimumab as a revolutionary breakthrough in the treatment armamentarium for practicing clinicians. This article explains the precise mechanism of action of belimumab on the soluble protein BlyS that plays a major role in the pathogenesis of lupus nephritis. In addition, the extensive pharmacokinetics and clinical implications are exemplified in this review with belimumab's comparison with standard therapeutic guidelines for the treatment of lupus nephritis.

Key words: BAFF, belimumab, BlyS, lupus nephritis, monoclonal antibody

INTRODUCTION

Systemic lupus erythematosus (SLE) is a multifaceted autoimmune disease driven by auto-reactive immune cells, in particular B cells that target multiple organ systems leading to severe complications. B-lymphocyte stimulator (BlyS) and its receptors (TACI, BCMA and BAFF-R) remain the focal point of therapeutic targets for SLE therapy as autoimmune B cell stimulation and maturation play a major role in the pathogenesis of the disease. SLE may include a variety of disease entities, such as isolated cutaneous lupus, undifferentiated connective tissue disease, mixed connective tissue disease and drug-induced lupus.[1] There are many ongoing therapeutic clinical trials in SLE patients with different mechanisms of cellular action, such as classic immunosuppression, cell depletion, antigen-specific immunomodulation and targeting of antigen-non-specific, immune-activating molecules.[1] New immune cell-targeted therapies are now available that are specifically designed to block cellular pathways involved in disease pathogenesis. SLE immunology, pathogenesis and laboratory evaluation, as well as updated treatment options,

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are integral items of knowledge for practicing health care providers.[1]

A main complication of SLE is nephritis, formally known as lupus nephritis that is classified as a secondary form of glomerulonephritis. Up to 60% of adults with SLE have some form of kidney involvement later in the course of the disease.[2] Corticosteroids are the major conventional option for patients with mild lupus nephritis. For more severe cases, high-dose prednisone, methylprednisolone, mycophenolatemoefitil (MMF), cyclophosphamide (CYC), azathioprine (AZA) and even cyclosporine have been used in clinical practice.[2] Exploration of alternative therapies is ongoing. Healthcare practitioners should be knowledgeable regarding several aspects of autoimmune disorders, especially SLE and lupus nephritis.[3] The patients have diverse symptoms and may present in different specialty clinics of the hospital. This review discusses various aspects of SLE, its pathogenesis, role of accelerated atherosclerosis, proinflammatory cytokines and therapeutic approaches. The role of vascular endothelial growth factor (VEGF) is also discussed. VEGF plasma levels have been associated with disease activity, classification of severity, side-effect profiling, diagnostics, current treatment options and prognosis as well as future therapeutic approaches.[3]

Pharmacology of belimumab

The recently approved belimumab, a monoclonal antibody, effectively targets the soluble form of BlyS and has shown clinically significant reductions in SLE disease activity and major flares.[4] Belimumab's mechanism of action is based on the known pathological functions of Blys, a tumor necrosis factor (TNF) super family ligand. Blys plays a critical role in the development and homeostasis of B lymphocytes. Under pathological conditions (i.e. SLE), B lymphocytes produce the auto-antibodies responsible for the clinical features of SLE. By inhibiting Blys, belimumab is able to effectively block this pathological pathway.[5]

An interesting mechanism unique to belimumab is its action in the bone marrow as well as through inhibition of the transition of a plasma cell to a long-lived plasma cell, which hinders the formation of prolonged antibody memory.[6] Additionally, in the secondary lymphoid tissue, belimumab is able to block BlyS-mediated maintenance of germinal center reaction, preventing the progression of B cells to high-affinity memory cells.[7] Also unique to belimumab is its ability to block BlyS-induced T cell secretion of interferon-gamma (INF-γ) and interluekin-2 (IL-2) as well as IL-2-dependent proliferation of T cells that occur as a result of BlyS activation.[7,8]

Equally important, belimumab may also produce an action in the spleen by blocking BlyS-mediated transition of immature B cells from the T1 to T2 stage, preventing the eventual generation of mature B cells. The T1 to T2 transition is a key checkpoint for negative selection of B cells; hence, explaining the novel logic of belimumab's mechanism of action.[9] The TNF super family ligand BlyS, along with a proliferation-inducing ligand (APRIL), regulates B cell maturation, function and survival. Thus, a novel mechanism to block this ligand signaling pathway could have potentially revolutionary therapeutic effects in the treatment of lupus nephritis. Treatment with belimumab may lead to an increase in apoptosis and depletion of autoreactive B cells present in many autoimmune diseases, further validating its novel versatility as a therapeutic entity.

Immunology and pathogenesis surrounding SLE therapy

Upon exposure to a particular antigen, several antigen-presenting cells, including monocytes, macrophages, neutrophils and dendritic cells, produce BlyS in response to interleukin-10 and IFN-γ.[10] This stimulation is characteristic of the innate immune response that eventually leads to the development of the adaptive immune response, which eventually gives rise to T cells and B cells.[10] The actual transition from the innate to the adaptive immune response is unknown; however, the presence of NK cells could be a potential indicator of this shift.[8] B cell activating factor (BAFF) has also been proposed to play a major role in the distinction and transition from the innate to the adaptive response in addition to its role as a positive regulator of B cell development and maturation. As an immunostimulant, BAFF is necessary for maintaining normal immunity.[11] Therefore, depletion of soluble BAFF with belimumab therapy can lead to remarkably inadequate levels of BAFF, resulting in the failure of B cell activation and their ability to produce sufficient immunoglobulin. The final result will lead to an immunosuppressed state due to the lack of B cell presence, which may elucidate to be efficacious in SLE patients who have a high degree of autoreactive B cells.[11] BAFF, also known as BlyS, is able to effectively bind to B cells leading to the initiation of downstream signaling of B cell maturation and survival. BlyS binds to a multifaceted system of receptors known as BCMA and BAFF-R, with its primary target at BR-3 and, to a lesser extent, transmembrane activator and CAML (calcium modulating cyclophilin ligand) interactor (TACI).[12] Targeting these mechanisms and downstream signaling of BlyS binding to BR3 activating relcomponent B (RelB) and nuclear factor NF-kappa B p100 (NF-kB2) in the eventual end target of Bcl-2-related survival factors for B cells can have a significant therapeutic benefit in the treatment of lupus nephritis. A recent paper reviewed the link between NF-κB and SLE, including B cell development, signaling and cytokines, which play a crucial role in the pathogenesis of SLE and T cell development, a key player in T cell activation.[9] Dendritic cells have been shown to promote tolerance or immunity to antigens. Furthermore, the study identified polymorphisms and NFkB as being linked

with SLE. The paper also included the role of Toll-like receptors (TLRs) in the pathogenesis of SLE.[9]

TLR-9 and vascular endothelial growth factor (VEGF) levels in human kidneys from lupus nephritis patients have been elucidated.[13] The study analyzed glomerular and tubular expression of both TLR-9 and VEGF in biopsies from human subjects with lupus nephritis and normal controls. This is the first study that investigated the combined expression of TLR-9 and VEGF, which could be an important tool for understanding the role of TLR-9 and VEGF in lupus nephritis, with insights into the early detection and targeted treatment of this disease.[13]

The soluble form of BlyS enables belimumab to inhibit the intracellular signaling cascade through all three BlyS-binding receptors (TACI, BCMA and BAFF-R), in effect leading to inhibition of B cell proliferation and antibody production. The endpoint of downstream intracellular signaling leads to the activation of transcriptional regulatory factors such as Re1A and Re1B, which can regulate the expression of antiapoptotic proteins, including Bcl-2, A-1, Bcl-XL and Mc1-1.[6] Through selective binding of BlyS through BlyS-targeted therapies, we are able to see decreased formation of these anti-apoptotic proteins, allowing increased regulation of auto-antibody B cells that are present in high serum concentrations in lupus nephritis patients.[14]

Pharmacokinetic parameters and multi-centered clinical trials

Belimumab (Benlysta; Human Genome Sciences Inc. and GlaxoSmithKline), a human IgG1λ monoclonal antibody, was approved by the Food and Drug Administration in 2011 for the treatment of active SLE in patients currently receiving standard therapy (e.g. glucocorticoids, antimalarials, immunosuppressants and non-steroidal anti-inflammatory drugs [NSAIDs]). Standard dosing is currently 10 mg/kg IV injection on Days 0, 14 and 28, and then every 28 days thereafter. The onset of action insofar as B cell suppression is 8 weeks, with clinical manifestations in 16 weeks. The volume of distribution is 5.29 L, with an elimination half-life of 19.4 days.[15]

Belimumab has been shown to decrease the levels of activated and naïve B cells as well as plasma cells. However, it has not been elucidated to deplete memory B cells. The maintenance of the memory B cell lines is dichotomous insofar as clinical utility. Advantages of memory B cell conservation include protective qualities stemming from the continuation of influenza, pneumococcus and tetanus antibody production. A disadvantage of memory B cell conservation is the innate possibility of this cell line initiating a redevelopment of cell progeny that subsequently secrete auto-antibodies thus reinvigorating the pathogenic causation of SLE.[10] Despite this innate risk of resurgent SLE, belimumab has been elucidated to cause significant reductions in severe flares, decreased concurrent prednisone dose, greater normalized C3 levels, decreased prevalence of patients with positive anti-ds DNA antibody assay, decreased proteinuria and increased mean SF-36 scores.[16,17]

Phase II placebo controlled trials have shown belimumab to be a generally well-tolerated drug, with an incidence of adverse events and laboratory abnormalities similar to those of placebo control groups.[18] The most common adverse events were infusion reactions, typical of any IV drug route, and these were comparable to the placebo injection. Notably, patients receiving belimumab, as compared with placebo control, experienced greater incidence rates of infections, especially with concomitant administration of mycophenolatemofetil (MMF) treatment at baseline.[18] In a long-term continuing study of belimumab, the observed mortality rate (0.4/100 patient years) is less than the standard rate (1.63/100 patient-years) currently manifested in the literature for SLE patients, suggesting an advantage over conventional treatment options.[18]

A Phase III clinical trial of belimumab identified reduction in severe flares and decreased steroid use, which may subsequently lead to reduced long-term damage, decreased disease costs and improved Health Related Quality of Life (HRQOL).[19] BLISS-76, a 76-week long second phase III clinical trial of belimumab for the treatment of SLE, was conducted primarily in North America and Europe. The study participants were SLE patients receiving a stable regimen, defined as prednisone, or equivalent, 7.5–40 mg/day, or combined 0–40 mg/day with antimalarial drugs, NSAIDs and/or immunosuppressive therapy for at least 30 days before the first belimumab dose. Clinical endpoints included the Safety of Estrogens in Lupus Erythematosus National Assessment version of the SLE Disease Activity Index (SELENA-SLEDAI), the Physician's Global Assessment, the British Isles Lupus Assessment Group Index (BILAG) and the SLE Flare Index. Each of these markers was evaluated every 4 weeks. Other conditions monitored included adverse events, vital signs, concomitant medications and lab/pregnancy test results.[19] The SELENA-SLEDAI score at week 52 was the primary efficacy endpoint. The SRI response rate was defined as >4 point reduction in this score, no new BILAG A organ domain score, no more than one new BILAG B score and no worsening of the Physician's Global Assessment Score compared with baseline. Belimumab 10 mg/kg resulted in more SRI responders at week 52 compared with placebo, while the 1 mg/kg group, although numerically greater than placebo, did not manifest statistically significant results. BLISS-52, a counterpart to BLISS-76 conducted in Latin America, Asia-Pacific and Eastern Europe, found statistically significant SRI rate increases for belimumab 1 mg/kg compared with placebo at Week 52. Other efficacy endpoints were found to be similar to those in BLISS-76.[17]

Clinical trials performed on belimumab were conducted with concomitant standard therapy. As a result, the dearth in data on the efficacy of standalone treatment makes a case for further investigational studies. The exact niche for belimumab insofar as concomitant use in SLE treatment remains unclear. There is a strong need for head-on comparative studies in order to more effectively gauge the clinical efficacy of belimumab in the treatment of both naïve and experienced patients.

Belimumab is unlike any of the current standard therapies outlined for the treatment of lupus nephritis and can potentially address some of the unmet needs for many patients who cannot bear the toxic effects of many of the immunosuppressants (i.e. methotrexate, azathioprine, rituximab, etc.).[20] When to initiate belimumab therapy in addition to which patients' initiation of therapy would be most beneficial is a recurrent predicament, troubling many physicians. In both phase III trials aforementioned, patients' baselines were noted and the patients included in both trials were those with clinical disease activity that interferes with the quality of life or, as mentioned previously, those patients who could not tolerate the toxic effects of primary immunosuppressive therapy; however, when to initiate therapy is still an art based on clinical judgment.[20] Current guidelines put forth by the American College of Rheumatology [Figure 1] and the European League against Rheumatism do not specify the use of belimumab in patients with SLE.[21,22] However, consideration is based solely on the two phase III clinical trials. With more clinical experience, both patients and healthcare practitioners will eventually have a stronger foundation of both the advantages and disadvantages put forth by this new treatment. Thus, belimumab may potentially find its role in the therapeutic armamentarium for primary treatment of lupus nephritis.

CONCLUSION

By understating the precise mechanism and functions of BlyS, as well as its effects on B cell proliferation, maturation and survival, the clinician will be better suited to engage in decisive therapeutic options for lupus nephritis therapy. Autoreactive B cells play a critical role in the severe inflammation and resulting tissue damage present in lupus nephritis patients. Belimumab is able to successfully block the initial production of B cell stimulation and signaling for maturation, which remains a popular area of research in part due to the focal role B cells play in the pathogenesis of SLE. Renal involvement remains the single most common cause of morbidity and a major cause of mortality in SLE patients, accounting for the vast amount of concern of current prescribers in regard to treatment modalities for lupus nephritis secondary to SLE.[17] Physicians now have more options beside the standard immunosuppressive therapy via a new mechanism that may eventually prove to be a true game changer, significantly increasing the rates of meeting therapeutic goals and improving the quality of life in patients with SLE. Furthermore, the degree of proteinuria is an important diagnostic tool in determining the extent of declining renal function as a result of the nephritis brought about as a complication of SLE. Decreasing the extent and rate of proteinuria is an exceptional progression for a patient not only due to the kidney salvaging effects but also due to the positive cardiovascular event risk that is now significantly

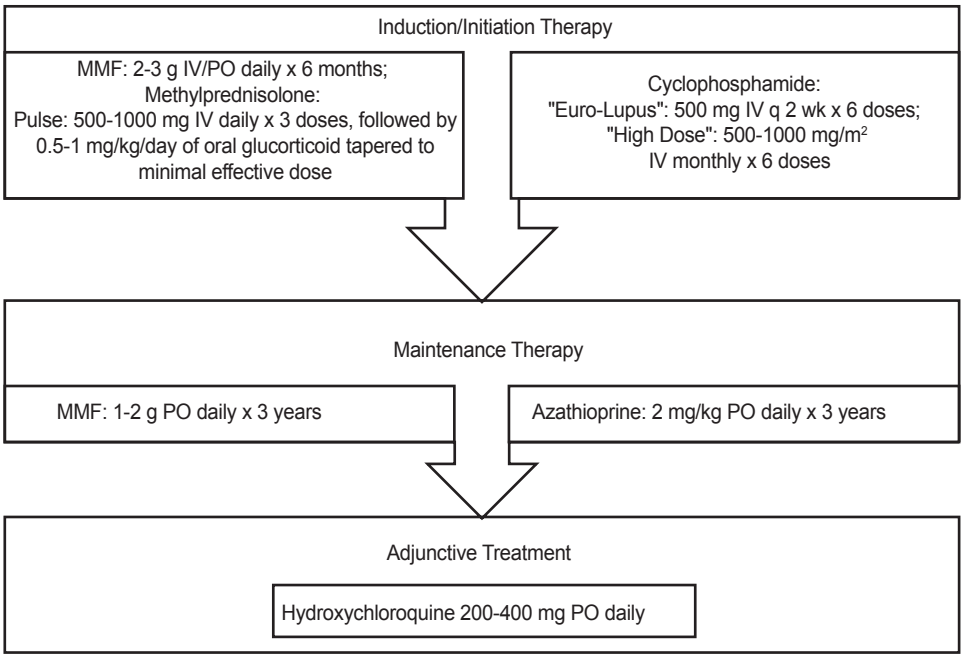

Figure 1: Standard pharmacological treatment for systemic lupus nephritis as per the American College of Rheumatology guidelines

Table 1: BLISS-52 (*n*=865) comparative analysis after 52 weeks

	SLE responder index at week 52	SLE responder index at week 76	SELENA-SEDAI reduction of ≥4	% of patients with no new BILAG* flares	% of patients with no worsening by PGA
Belimumab 1 mg/kg (*n*=288)	51.4%**	NR	53.1%**	78.8%	78.8%**
Belimumab 10 mg/kg (*n*=290)	57.6%**	NR	58.3%**	81.4%**	79.7%**
Placebo + standard therapy (*n*=287)	43.6%	NR	46%	73.2%	69.3%

*BILAG: British isles lupus activity group. **Indicates statistical significance (*P*<0.05) vs. placebo. SLE=systemic lupus erythematosus, SELENA-SEDAI=Safety of Estrogens in Lupus Erythematosus National Assessment version of the SLE Disease Activity Index, PGA=Physician's global assessment

Table 2: BLISS-76 (*n*=819) comparative analysis after 76 weeks

	SLE responder index at week 52	SLE responder index at week 76	SELENA-SEDAI reduction of ≥4	% of patients with no new BILAG* flares	% of patients with no worsening by PGA
Belimumab 1 mg/kg (*n*=271)	40.6%	39.1%	42.1%**	NR	NR
Belimumab 10 mg/kg (*n*=273)	43.2%**	38.5%	41.1%**	NR	NR
Placebo + standard therapy (*n*=275)	33%	32.4%	33.8%	NR	NR

*BILAG: British Isles lupus activity group. **Indicates statistical significance (*P*<0.05) vs. placebo. SLE=systemic lupus erythematosus, SELENA-SEDAI=Safety of Estrogens in Lupus Erythematosus National Assessment version of the SLE Disease Activity Index, PGA=Physician's global assessment

decreased. A recent article published data claiming that belimumab may in fact have positive effects on the extent of proteinuria. In the BLISS trials [Table 1], patients with baseline proteinuria >0.2 g/24 h had numerically or significantly greater median percent reductions in proteinuria during weeks 12–52 than those treated with placebo.[17] The ability of belimumab to reduce proteinuria is a significant accomplishment for SLE therapy and physicians now have another tool to aid in the management of the kidney complications associated with SLE.

The BLISS-76 [Table 2] and BLISS-52 phase III trials evinced strong evidence supporting the use of belimumab as adjuvant therapy in the treatment of SLE. Both trials are limited in scope of practice insofar as the fact that belimumab monotherapy was not studied. Monotherapeutic efficacy of belimumab in SLE patients is a currently unexplored area of research. Furthermore, the exclusion criteria of both studies included pediatric populations and those with severe active lupus nephritis. As a result, belimumab's efficacy in these populations is currently unknown. The study designs also prevented comparison of any specific standard of care. Finally, it is necessary to note that neither trial was carried out with a large enough n value nor for a sufficient period of time to identify any long-term adverse drug reactions that may be possible during belimumab therapy.

SLE is a challenging disease with current therapy aimed to restore the imbalance of a dysregulated immune system and, with the recent approval of belimumab, this monoclonal antibody may prove to be a revolutionary tool in the therapeutic management of lupus nephritis and significantly reduce the underlying inflammation present in these patients. Although pooled data from the phase III clinical trials depicted adequate safety profiles, an extended post-marketing surveillance is warranted as this will better define the safety profile and guide safety decisions for physician prescribing. Belimumab has set the stage for a new mechanism of targeted therapy in SLE and, with future clinical surveillance, this drug may become a viable option in the therapeutic management of lupus nephritis.

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