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Lupus (S Manzi, Section Editor)

Belimumab: Where Are We Three Years After FDA Approval?

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Opinion statement

Belimumab, a B cell modulator that inhibits soluble BlyS, was the first agent approved by the FDA for systemic lupus erythematosus (SLE) in over 50 years. Although its licensed indication is broad, only 5 % of lupus patients in the USA have been prescribed the agent since its introduction in 2011. This is largely a consequence of uncertainties relating to length/duration of treatment; long-term safety especially concerning mental health issues; response in patients with nephritis, central nervous system disease, and pediatric lupus; efficacy among African-Americans; and perceived lack of pharmacoeconomic benefits. Over 95 % of post-approval-treated patients reside in the USA. Nonetheless, belimumab has turned out not only to be remarkably safe and well tolerated but is also associated with clear cut clinical improvement in approximately 70 % of individuals who have been treated. Its principal benefits are observed in patients with moderate to severe disease with mucocutaneous, musculoskeletal, constitutional, and/or serositis manifestations who are not responsive or unable to decrease their corticosteroid dose, as well as those who are intolerant to or in whom methotrexate, mycophenolate mofetil, or azathioprine are not effective or contraindicated. Work on its use as induction therapy for recent onset lupus is a promising avenue for investigation.

Introduction

In 1948, only half of all patients with systemic lupus erythematosus (SLE) survived 2 years or more [1]. The advent of corticosteroids, immune suppression, dialysis, transplantation, autoantibody, and serologic testing as well as newer antihypertensive agents and antibiotics improved the 10-year survival rate to 90 % by the 1980s [2]. Since that time, longevity has not changed. All too many lupus patients succumb to complications of accelerated atherogenesis, infection, and other factors after 20–30 years [3]. Studies have shown that the ACR/SLICC

damage index inexorably increases in most patients who feel well and have minimal clinically apparent activity [4]. Patient reported outcomes are significantly impaired and the quality of life in SLE patients has stagnated over the last 20 years. The divorce rate of lupus patients in their 20s and 30s has been estimated to be 50 % within 5 years of diagnosis [5]. The above factors clearly demonstrate an unmet need in the way lupus patients are managed. Only one targeted therapy, belimumab, is approved by the Food and Drug Administration for managing SLE. This article details the insights that have been derived in the 3 years since its introduction.

History

A series of papers identified a 285 amino acid protein member of the TNF ligand superfamily in 1999, which ultimately became known as BlyS (B lymphocyte stimulator) or BAFF (B cell activating factor) [6–8]. Stohl's group at the University of Southern California was the first to demonstrate increased levels in rheumatic disorders, especially SLE in 2001 [9]. This led to the development of belimumab, a fully humanized IgG1-lambda monoclonal antibody that binds to soluble BLyS and inhibits binding to its receptors, thus decreasing disease activity. A phase I dose-escalation, randomized, double-blind, placebo-controlled study of 70 patients with mild to moderate SLE demonstrated evidence for naïve B cell reduction, and safety was completed in 2003 but not published until 2008 [10]. Belimumab was only modestly effective for rheumatoid arthritis, and further development for this indication was halted [11].

Mechanism of Action and Immune Effects

BLyS is a growth factor required for B cell survival, maturation, and activation. BLyS is present on maturing B cells but is not present in the bone marrow or mature B (memory) cells. Constitutive overexpression of BLyS leads to lupus-like disease in normal mice. BlyS levels are elevated in about half of all lupus patients, and this roughly correlates with disease activity. Binding between belimumab and BLyS prevents its attachment on B cells which leads to apoptosis, and the BLyS-anti-BLyS structure is cleared by the reticuloendothelial system. Belimumab has a half-life of 17 days and takes about five half lives to become clinically effective [12••].

Mostly post hoc analyses of pooled data from the phase II and phase III pivotal trials (see below) demonstrated in the approved 10 mg/kg dose the following statistically significant findings [13•]:

a. normalization of C3 complement in approximately 40 % of patients
b. change from positive to negative anti-dsDNA antibody assay in about 15 %
c. normalization of immunoglobulin levels in half (IgG and IgM levels tended to initially decrease by 20–40 %)
d. decreases in numbers of naïve and activated B cells and plasma cells

There was also greater positive to negative conversion rates for anti-SM, anti-cardiolipin, and anti-ribosomal P antibodies. No change in memory B cells and T cell populations has been reported.

Treatment with belimumab did not affect the ability of patients with SLE to maintain antibody titers to previous pneumococcal, tetanus, or influenza immunizations, but the levels of response were decreased in a minority of treated patients [14].

Pivotal Trials

A phase II and two phase III "registration studies" including 2133 SLE patients provided the FDA with enough documentation to approve belimumab in March 2011. An additional approximately 800 SLE and RA patients studied using a subcutaneous (as opposed to intravenous preparation) delivery system, enrolled in the phase I trial, or in the abovementioned RA studies enhanced the "corpus" of belimumab experience at the time of its approval to nearly 3000 subjects.

The sponsor of belimumab at the time (Human Genome Sciences) was well aware of the minefield of prior lupus trial disasters, many of which mandated rigid, clinical impractical dosing regimens of corticosteroids and using poorly validated outcome measures. A double-blind, placebo-controlled, dose-ranging phase II was conducted in 449 SLE patients [15]. Patients with a minimum SLEDAI score of 4 were randomized into three dosing regimens and placebo with a background community standard of care wherein low to moderate dose corticosteroids, nonsteroidals, antimalarials, and immune suppressive therapies were allowed. Although the primary endpoints (change in SLEDAI score at week 24 and time to first flare) were not met, at week 24, patients who were antinuclear antibody positive (71 % of the group at screening) had significant reductions in prednisone dose and flares in the 10 mg/kg (as opposed to 4 and 1 mg/kg) dosing. Post hoc analyses informed the sponsors on how to improve upon the effort. The pivotal phase III trials thus used only the 10 mg/kg dose, required a minimum SLEDAI score of at least 6, and mandated antinuclear antibody positivity on screening. Adhering closely to the 2005 FDA Guidance Document, two nearly identical trials (BLISS-52 and BLISS-76) were initiated [16, 17]. The only real differences were geographical (BLISS-52 was conducted mostly in Asia, eastern Europe, and Latin America and BLISS-76 in the USA and western Europe) and duration (52 versus 76 weeks). A metric was derived known as the SLE Responder Index (SRI) retrospectively identified patients who did well in the phase II trial [18]. This mandated at least a four-point improvement in the SLEDAI, no more than a 10 % decrease in the physician global assessment (PGA), and the development of no new BILAG organ domains. One thousand six hundred eighty-six participants enrolled in the studies (patients were dosed at week 0, 2, and 4 and monthly thereafter) and significantly improved outcomes were found in the SRI in both trials. Most patients who responded did so between week 8 and week 26. However, the differences were relatively modest, with only a 9–14 % difference between the arms and background standard of care. This criticism is partly countered with the acknowledged difficulty in lowering the SLEDAI score by four points. There were no safety signals compared to control groups

concerning serious infection experience, malignancy, or adverse reactions.

Post-approval Studies: Clinical Observations

Funded by the Sponsors (Human Genome Sciences or GlaxoSmithKline)

Numerous retrospective analyses have been performed on patients who participated in the pivotal trials. However, the reader should be cautioned that the clinical trial patients in these publications represent an artificial cohort of individuals with very specific phenotypes. Only 10–15 % of patients in a lupus community practice would have been eligible for receiving belimumab under similar circumstances.

1. Patients who have greater disease activity, anti-dsDNA, and low complement or were taking corticosteroids at entry have a greater chance of responding to belimumab [19]. More organ systems involvement was associated with decreased flare rates [20].
2. Patients with musculoskeletal and mucocutaneous BILAG and SELENA-SLEDAI domains had the best response rates [21•].
3. Two hundred sixty seven patients with mild renal involvement (those with nephrosis or azotemia were excluded from study entry) did as well as other study patients, especially if they were also taking mycophenolate [22] and had no increased adverse events.
4. Pooled safety data demonstrated no increased rate of malignancy, infection, or adverse events compared to the non-belimumab group. There were more suicides in the treated group that was not significant. Ongoing trials will include mental health inventories [2, 23•].
5. An open label 7-year longitudinal continuation study of phase II, BLISS-52, and –76 patients demonstrated sustained efficacy, improvements in fatigue and quality of life, fewer flares (by SLE Flare Index or BILAG-A or B flares), improved Physicians' Global Assessment, persistent normalization of complement and anti-dsDNA, steroid sparing effects, less immune suppressive use, and no new safety signals. Seventy five percent of pregnancies were successful [24•].

Ongoing trials will address pregnancy, mental health, pediatric lupus, subcutaneous injection, immunization issues, and serious nephritis and how well the drug works in African-Americans. The latter was initiated because due to geography, there were proportionately very few African-Americans in the BLISS-52 study. The BLISS-76 enrolled a disproportionate number of Caucasians as a consequence of rapid enrollment in private practice sites. By the time academic Institutional Review Boards could approve the study, negotiate with Contract Research Organizations (CROs), and implement contracts and grants and deal with liability issues, this heavily African-American group of SLE patients was 6–12 months behind in enrollment. Even though 33 % with SLE in the USA are estimated to be African-American, they only constituted 14 % of the BLISS-76 enrollment, and the numbers were not large enough to come to any

conclusions [17]. Nevertheless, there is no evidence that African-Americans respond differently to belimumab than anybody else. The sponsors are also underwriting open label follow up initiatives to examine more realistic community experience with the drug (e.g., SABLE).

There are preliminary suggestions that belimumab improves primary Sjogren's syndrome (20 % with SLE have secondary Sjogren's), and studies have been initiated in vasculitis [25].

Studies Not Directly Controlled by the Sponsor

Real-world, unbiased experience with the drug has been hampered by small numbers and high discontinuation rates. Although the majority of patients in the pivotal studies opted for open label follow-ups, it has been estimated that fewer than half of the 15,000 patients given the drug in a practice setting were still receiving infusions a year later. This is probably due to site inexperience, poor dissemination of information regarding which patients are the best candidates due to marketing constraints on the sponsor, and interruptions in reimbursement in clinical settings. Although the pivotal trials excluded patients on other biologics, cyclophosphamide, individuals with central nervous system or renal disease, those under the age of 18, or on high doses of steroids, many of these individuals have since been treated with belimumab. Some of the preliminary insights include the following:

1. Over 500 patients followed by 60 community rheumatologists for 24 months had similar outcomes to that reported in the pivotal trials with marked reduction in steroid use. Half of the patients experienced a 50 % improvement based on physician's impression. This group had a large African-American participation rate [26].
2. Of 1189 SLE patients in 15 centers who are members of the Lupus Clinical Trials Consortium (LCTC), 5.7 %, or 68 received belimumab. Most of the 44 patients who remained on the drug for a year had clinical improvement but it was not steroid sparing [27].
3. A group of 115 belimumab-treated patients from 16 academic SLE clinical practices were followed after a year. The majority (58 %) improved by 6 months based on mostly subjective measures. Favorable responses are noted at 3 months [28].
4. Two post hoc analyses suggest that belimumab and mycophenolate mofetil are synergistic, especially in lupus nephritis [29, 30].

Two cases of progressive multifocal leukoencephalopathy in patients receiving belimumab have been reported [31]; both individuals were also taking mycophenolate mofetil and had been on other immune suppressive agents.

The Approved Label: Subtexts, Safety, and Time Does Not Stand Still

When belimumab was approved in March 2011, the indication section of the package insert stated (and still stands when most recently revised in April 2014: "Benlysta is…indicated for the treatment of adult patients with active, autoantibody positive systemic lupus erythematosus who are receiving standard

therapy. Limitations of use: The efficacy of benlysta has not been evaluated in patients with severe active lupus nephritis or severe active central nervous system lupus. Benlysta has not been studied in combination with other biologics or intravenous cyclophosphamide. Use of benlysta is not recommended in this situation" [32]. The reader should be aware of the following caveats:

1. Careful reading should take into account that since March 2011, post-approval real-world experience has included patients who have severe renal disease and severe active central nervous system were receiving other targeted therapies and/or intravenous cyclophosphamide as well as pediatric patients. No untoward complications have been reported. Simply because the sponsor has not updated the label, does not mean that if the clinical setting is appropriate, belimumab *cannot* be used. The labeling does not use the word "contraindicated," but instead "not recommended" simply because specific clinical settings were exclusions for participation in clinical trials and there was no accrued experience with certain lupus phenotypes. Controlled trials are underway to study the agent in children and severe renal disease as well as with other targeted therapies.
2. In the phase II trial, African-Americans performed as well as other patients. BLISS-52 and BLISS-76 did not enroll enough patients to comment on EFFICACY, but there were no SAFETY issues [16, 17]. In our experience, many African-American lupus patients had impressive improvements on belimumab. The EMBRACE trial, which is underway, should definitively address this issue.
3. For unclear reasons, the label mentions a potential increased risk for malignancy with belimumab. In fact, there were FEWER malignancies in the belimumab group in the pivotal trials than among control patients receiving community standard of care [32].
4. Only 13 % of patients who participated in the pivotal trials were premedicated, and the use of premedication was discretionary. There have been occasional reports of infusion reactions, adverse reactions, and anaphylaxis and the labeling documents their occasional but not statistically significant occurrence. Only one anaphylactic fatality among 15,000 patients has been reported, and this attribution is questionable (the patient was on multiple other agents and the reaction occurred almost 24 h after the infusion). Anecdotally, several centers have used the following strategies to minimize infusion reactions:
    a. Premedication with a combination of loratadine and acetaminophen. Diphenhydramine can be used in patients at increased risk.
    b. Infusing patients over 2 h rather than 1 h.

The Future of Belimumab: Where Do We Go From Here?

In 2012 and again in 2013, the UK-based National Institute for Health and Care Excellence (NICE) concluded that "despite some evidence for its clinical effectiveness, the health benefits…(of belimumab)… are outweighed by the significant costs of the drug" [33]. As a consequence, belimumab is not available for general

Table 1. Summary of Community Experience With Belimumab

A. Favorable effects of belimumab
Constitutional symptoms and improved quality of life measures
Cutaneous disease
Musculoskeletal disease
Mild renal disease
Reduction of flare rates
Steroid sparing
No statistically significant increase in malignancy, serious infections, or serious adverse events compared to community standard of care
No new organ domain involvement
No safety signals in open label follow up studies to 7 years
Relative safety with pregnancy
Improvement in complement and anti-dsDNA
Safety with killed vaccines
B. Unknowns with belimumab treatment
Response in African-Americans
When to stop treatment if patients are doing well
Concurrent use with biologics, cyclosporine, or cyclophosphamide
Whether or not to premedicate patients to prevent reactions
How long patients should be treated before discontinuing therapy for lack of response
Mental health concerns
Use with central nervous system disease and patients with BILAG A or B hematologic, cardiopulmonary, ophthalmologic, or gastrointestinal domains
Effects on the immune system
Safety with live vaccines
Induction therapy for early lupus
Use in disease flares vs chronic, stable disease

use in Europe. In retrospect, the sponsors made a strategic miscalculation in their presentation: assuming that individuals receiving the drug would need it indefinitely. Can belimumab be used as an "induction therapy" or perhaps as maintenance for a limited period of time (1–2 years) after improvement is noted. The following initiatives are underway to address these concerns:

1. The sponsors will be looking at flare rates among patients who received open label extension belimumab after completing the pivotal phase II or III trials and are withdrawn from the drug.
2. The Alliance for Lupus Research is finalizing a protocol for using belimumab as induction therapy for early SLE that includes only 1–2 years of therapy.
3. The Immune Tolerance Network is also studying a rituximab/belimumab combination protocol (CALIBRATE) for active lupus nephritis that involves short term use.
4. IRBIS (International Registry of Biologics in SLE), partially underwritten by industry and the Systemic Lupus International Collaborating Clinics (SLICC) will follow patients at academic sites who discontinue belimumab.
5. Real-world post-marketing surveys will focus on disease activity and flares among patients who discontinue belimumab for any reason.

6. Data mining from patients in the pivotal and other industry sponsored studies will assess different biomarkers to ascertain which group of lupus patients do best with belimumab.
7. Is belimumab effective and safe if given subcutaneously?

Conclusion

In summary, belimumab is a useful, safe disease modifying agent for some patients with SLE. Its use may be best suited for chronic stable active disease or in combination with other agents for flares. Among these patients, its cost effectiveness is probably best suited for a yet to be determined specific period of time until less expensive therapies can maintain improvement or a low level of disease activity. Pharmacoeconomic studies that look into the cost-benefit ratios of short versus long-term use as well as subcutaneous delivery are in preparation (Table 1).

Compliance with Ethics Guidelines

Conflict of Interest
Daniel Wallace is a consultant for GlaxoSmithKline.

Human and Animal Rights and Informed Consent
Human studies done by authors (but no animal studies).
This article does not contain any studies with animal subjects performed by any of the authors. With regard to the authors' research cited in this paper, all procedures were followed in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 2000 and 2008.

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