JHPOR | Journal of Health Policy & Outcomes Research

Belimumab therapy in systemic lupus erythematosus – the clinical expectations and burdens

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Keywords:
clinical trials, responder index, systemic lupus erythematosus, belimumab, BAFF, BLyS

DOI: 10.7365/JHPOR.2014.5.4
JHPOR, 2014, 1, 46-51

ABSTRACT

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease with serious organ involvement and unpredictable outcome. In 1990s B-cell activating factor (BAFF), which induces B cell maturation, survival, switch-class recombination and high-affinity antibodies production was discovered. The intensive research proven the importance of BAFF in SLE pathogenesis in both murine models and humans. In 2011 belimumab, human monoclonal antibody specific for soluble BLyS (B-lymphocyte stimulator) was approved for active, seropositive SLE treatment in add to standard of care therapy. Belimumab is the first target, biologic therapy formally approved for SLE. To overcome the complexity and heterogeneity of SLE the new rules in clinical trial design were done: restrict inclusion criteria involving only seropositive patients with active disease and implementation of a novel, composed responder index. Despite the success, new medication rises some efficacy concerns: modest clinical effect, no data provided for treatment of lupus nephritis or central nervous system involvement and very high cost.

INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune disease, with the wide range internal organ involvement, that cause significant morbidity, increased mortality rate and diminished quality of life. Due to its heterogeneity, lack of universal biomarkers and unpredictable course of flares and remissions, it is difficult to construct and to achieve primary end-points in SLE clinical trials. After 50 years of failures in 2011 US Food and Drug Administration (FDA) approved first new, target therapy in SLE – belimumab, which is monoclonal antibody neutralizing BAFF (B-cell activating factor). This review paper presents arguments advocating this therapy from pathogenic and clinical point of view and on the other hands explains its limitations.

LYMPHOCYTES B, BAFF AND APRIL SYSTEM IN SLE

B cells play a critical role in autoimmunity and SLE pathogenesis. Under normal conditions B cells develope in the bone marrow and in the peripheral lymphoid organs. Their differentiation into memory cells and antibody secreting plasma cells is mainly antigen-dependent and needs both co-stimulation from T cells, cytokine environment and B-cells survival factors [1]. One of them is BAFF also commonly known as BLyS (B-lymphocyte stimulator). It is a 285 amino-acid type-II transmembrane protein member of tumor necrosis factor (TNF) superfamily, subsequently cleaved a soluble 17-kD biologically active protein (also known as TNF superfamily member 17 – TNFSF17). BAFF was first described

PRIMARY CERVICAL CANCER CONSTITUTES A VAST MAJORITY OF CASES OF UTERINE CANCER AND DEVELOPS OVER MANY YEARS FROM PRECANCEROUS LESIONS KNOWN AS CERVICAL INTRAEPITHELIAL NEOPLASIA (CIN)

in 1999 by three independent groups, and since the very first descriptions was suspected to play a critical role in human B-cells immunity, both in physiology and pathology [2-5]. BAFF binds to three receptors on B cells: BCMA (B cell maturation), TACI [transmembrane activator and CALM (calcium modulator and cyclophilin ligand) interactor] and BAFFR (BAFF receptor also known as BR3).

The major source of systemic BAFF are myeloid-lineage cells: monocytes, dendritic cells, macrophages and neutrophils and bone-marrow–derived radiation-resistant stromal cells. Also expression of BAFF by follicular Th cells in germinal centers, is necessary for the development of antigen-specific high affinity B cells [6]. BAFF mainly circulates in trimeric forms. As well multimeric forms of BAFF were described (in ex. clusters of 60-merics), however their influence on in vivo immune response remains to be elucidated. The main importance is now related to function of soluble, trimeric forms. Both, in humans and mouse, BAFF contributes in B cell survival, differentiation of immature B cells to mature B cells, to Ig class switch and antigen specific antibody production, leading to generation of high affinity antibodies [7-10]. Moreover some studies on mouse models suggest that autoreactive B cells have a greater dependency on BAFF then non-autoreactive B-cells populations [11].

The other important player in B cells homeostasis is a proliferation inducing ligand known as APRIL. It is a 250-amino acid member of the TNF ligand super family (TNFSF13), which shares homology with BAFF. APRIL is released only in soluble form and binds to two receptors, TACI and BCMA, but not to BAFFR, leading to more pronounced influence of APRIL on plasma cells [12]. From practical point of view it is important to remember that soluble BAFF inhibition does not influence on APRIL function by TACI and BCMA.

Due to its properties it is not surprising that BAFF is associated with SLE. In animal models Baff-transgenic mice developed severe B cell hyperplasia, hypergammaglobulinemia, multiple autoantibodies, immune-complexes and immune deposition in kidneys [13-16]. An association of BAFF levels and human SLE also has been documented. The preliminary results indicated that serum BAFF level was elevated in the patients with SLE, and the increased BAFF in SLE existed in the soluble form, which is cleaved from cell surface [17, 18]. The serum BAFF level correlated with serologic abnormalities, including dsDNA titer, however did not correlate with disease activity and severity. However there was a suggestion that the disease activity tools and small number of patients were not sufficient to confirm relation. In the study which included over 200 SLE subjects association between a greater increase in the BLyS level from the previous visit

and a greater increase in the SELENA-SLEDAI (SLE Diseases Activity Index) score at the subsequent visit, and between an elevated BLyS level at the previous visit and a greater SELENA-SLEDAI score at the subsequent visit, demonstrate a relationship between circulating BLyS levels and SLE disease activity [19]. Almost 50% and 61% of patients have manifested persistently or intermittently elevated serum BLyS and blood BLyS mRNA phenotypes, respectively in longitudinal observation [20]. In Cheema at al. study BLyS levels correlated inversely with nephrotic-range proteinuria in SLE patients [18]. This results lend support to the notion that inhibition of BAFF/APRIL axis is therapeutic targeting in SLE and lead to further progress in the area. Despite belimumab, monoclonal antibody that inhibits soluble BAFF, three other type of molecules are in clinical development – atacicept, fusion protein which targets BAFF and APRIL, blisibimod (peptibody) and tabalumab, monoclonal antibody, both target membrane and soluble BAFF [21].

BELIMUMAB IN SLE

Belimumab (Benlysta) is a first BAFF antagonist approved by FDA. It is a human IgG1 mAb that neutralizes soluble BAFF [21]. However its way from bench to bedside was somehow bumpy [23]. In 2003 a phase I clinical trial (70 lupus patients enrolled) documented safety of the drug [24]. A phase II clinical trial in SLE with mild and moderate disease activity confirmed that therapy was safe, but the efficacy end-points were not met. Belimumab was administered intravenously initially at day 0, 14, 28 and then every 28 days. SELENA SLEDAI and SELENA SLEDAI Flare Index were used for the activity assessment. There was no significant improvement in the disease activity except of patients who were ANA (antinuclear antibodies) or dsDNA positive on study entry [25]. In 2009 novel evidence-based systemic lupus erythematosus responder index (SRI) was described, based on belimumab phase II SLE trial and demonstrated its potential utility. It demonstrated the ability to define a responder index based on improvement in diseases activity without worsening in overall condition or the development of significant disease activity in new organ system [26]. Subsequently SRI was implemented as an outcome measure in both pivotal belimumab studies. In a phase III study which was conducted in 90 centers in Latin America, Asia Pacific and Eastern Europe (Romania and Russia), only unequivocally seropositive patients, with active disease (score ≥ 6 at screening on SELENA SLEDAI) were included. They have to be on a stable treatment regimen with fixed doses of prednisolone or standard of care therapy (SOC): non-steroidal anti-inflammatory, antimalarials or immunosuppressive, at least 30 days before the first study dose. It is necessary to underscore that on study design the changes to SOC therapy was restricted after 16 weeks for immunosuppressant medications and after 24 weeks for antimalarials.

The main clinical exclusion criteria were severe lupus nephritis and central nervous system involvement. To the BLISS-52 study 1266 patients were screened and 847 randomly assigned in 1:1:1 ratio to placebo, or belimumab 1 mg/kg, or 10 mg/kg. The study drug was administered by iv infusion on days 0, 14, 28 and then every 28 days until week 48. The primary efficacy endpoint was the response rate at week 52, assessed by SRI [27]. A responder was defined as having a reduction of at least 4 points in the SELENA SLEDAI score, no new British Isles Lupus Assessment Group index A organ domain score (BILAG), no more than 1 new BILAG B organ domain score and no worsening in Physician Global Assessment (PGA) score (increase<0.3) at week 52 compared with the baseline. At week 52 primary end-point was achieved. Significantly greater responses were noted starting from week 16 for dose 10 mg/kg (except week 20) and from week 28 for dose 1 mg/kg. Moreover the proportions of patients with at least a 50% reduction in prednisone dose were significantly greater with belimumab 10 mg/kg at every visit from weeks 24 to 52. Use of prednisone was significantly greater in the placebo group then in the belimumab group (10 mg/kg) from week 12 to 52. The reduction in risk of flares was shown by the increase of median time to flare, and the risk of moderate to severe flares was significantly reduced in the belimumab group. Early in the study, starting form week 4 and 8 belimumab improved serum complement concentration and decreased dsDNA titer.

MOREOVER THE CLINICAL RESPONSE ASSESSED BY SRI IS A COMPOSITE INDEX INCLUDING SEVERAL INDEPENDENT TOOLS OF ACTIVITY ASSESSMENT WHICH ARE NOT ROUTINELY USED IN THE REAL LIFE. IT MAKES DIFFICULT FOR CLINICIANS TO ASSESS RESPONSE AND MAKE DECISIONS FOR TREATMENT CONTINUATION OR DISCONTINUATION.

The BLISS-76 study, the second study which led to belimumab approval for SLE, included 826 patients from US and Europe. Similarly to BLISS-52 primary end-points were achieved by week 52, but SRI did not differ significantly between groups in week 76 [28].

The safety profile of belimumab was similar to that of placebo, with no differences between trial arms in any studies.

Pooled analysis of this trials revealed benefits of belimumab (10 mg/kg) in the mucocutaneus, musculoskeletal, CNS and vascular organ domains [29]. Also at the post-hoc analisys among the 267 patients with renal involvement at baseline from BLISS-52 and BLISS-76, those receiving mycophenolate mofetil or with serologic activity at baseline had greater renal organ disease improvement with belimumab than with placebo [30]. It seems that the most important predictors for benefits from belimumab treatment are high disease activity at baseline, dsDNA positivity, hipocomplementemia and high dose of steroids [31].

Lately data of the total belimumab exposure over 7 years (double-blind and open-label periods) and 1746 patient-years were published. SLE response rates at week 52 in autoantibody-positive patients: was in placebo, 29%; and in belimumab, 46% ($p < 0.05$). In the continuation study, 57% of auto-antibody-positive patients had an SRI response by year 2 and 65% by year 7; severe flares occurred in 19% with placebo and 17% with belimumab during the first year, with the annual rate declining to 2%-9% during years 2-7. Anti-dsDNA autoantibodies in patients positive for them at baseline had a progressive decline of 40%-60% from baseline over 2-7 years with belimumab. Corticosteroid use decreased over time with ≥ 50-55% reduction in median dose during years 5-7. Serious and overall annual adverse events rates, including infections, were generally stable or decreased during 7-year treatment [32].

Finally belimumab (Benlysta) is approved only as an add-on therapy for SLE in adults with a positive auto-antibody test whose disease is still highly active despite standard treatment. Despite the hopes for approval of new drug, some practical concerns have been raised, limiting the clinicians enthusiasm.

LIMITATIONS OF BELIMUMAB THERAPY IN SLE

A first area of concern is the limited target group- only patients with seropositive SLE but with exclusion of more severe and debilitating organ involvement: active lupus nephritis and central nervous system. All the completed and published studies with belimumab excluded such patients.

The second problem is the prolonged time for the response assessment. The time necessary for initial treatment is as long as 6-12 months, both for responders and non-responders. In the latter it means at least 6 month of really expensive, biologic treatment that does not give any clinically significant benefits. In case of responders there are another issues – doubts if there is no loss of efficacy on prolonged treatment, as response from 52 weeks, was no longer present 24 week later in BLISS-76 study [33]. It can be due to the BAFF independent autoimmunity pathogenic pathway that can occurre in patients with the prolonged BAFF inhibition.

Moreover the clinical response assessed by SRI is a composite index including several independent tools of activity assessment which are not routinely used in the real life. It makes difficult for clinicians to assess response and make decisions for treatment continuation or discontinuation. Another aspect is a clear explanation for patients what benefits can be expected from this chronic treatment in their health status or particular, specific symptoms. It seems to be mostly intuitive. On the other hand in the real life possibility to reduce glicocorticosteroids dose, and to avoid glicocorticosteroid-related damage, can be important argument for treatment, for both, the patient and the clinician. The next argument, important for remitting-relapsing patients can be prolong time between moderate or severe flares, which lead to hospitalization and cytotoxic treatment induction.

On the other hand if any benefits for belimumab treatment is achieved the next concern is the time of discontinuation. There are no any available data to support this decision but on the it is not reasonable to continue belimumab life-long.

Taking all of this into consideration due to unfavorable estimates of cost effectiveness belimumab is still not recommended by NICE for SLE treatment [34]. Additional economic studies involving the real cost of SLE treatment and clinical data regarding belimumab treatment and discontinuation are needed to change this recommendation. Future research may define the specific clinical manifestations related to abnormalities in BAFF/APRIL system, what might help to stratify patients with SLE into subgroups that are more likely to respond for anty-BAFF therapy [35]. ■

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