EDITORIAL

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Beating B Cells in Lupus Nephritis

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Despite years of intensive research, the optimal treatment for lupus nephritis remains a considerable challenge. The nature of lupus nephritis requires a multidisciplinary approach and a shared decision-making process with patients. Systemic lupus erythematosus (SLE) patients where evidence of kidney involvement is present: glomerular hematuria and /or cellular casts, proteinuria > 0.5 g every 24 hours or urine protein to creatine ratio (UPCR) higher or equal to 500 mg/g and unexplained decreases in glomerular filtration rate (GFR), should be considered for a kidney biopsy. Cyclophosphamide (CYC) or mycophenolate mofetil (MMF) along with corticosteroids are frequently used for active lupus. Despite receiving standard treatment, only around 50% of patients achieve a complete remission and about 22% of patients still experience renal failure at 15 years.[1] Additionally, such medications have been associated with serious long-term side effects including increased risk of infections, diabetes and infertility. As a result, investigators are working towards better and safer medicines by targeting key cellular drivers.

Immune complex deposition within the glomeruli or autoantibodies that bind to glomerular antigens are pivotal mechanisms underlying lupus nephritis.[2] Depletion of B cells, which secrete these pathogenic autoantibodies, using rituximab (a chimeric monoclonal antibody directed against CD20) was approved by Food and Drug Administration (FDA) in 2006 for use in RA and it was the first example of targeted therapy for lupus nephritis.(Rituximab has shown efficacy for SLE in open-label studies and real-life settings, but did not achieve its primary endpoints in 2 large clinical trials. Two hundred fifty seven patients with moderate to severe non-renal systemic lupus erythematosus participated in the EXPLORER trial, which studied the effectiveness and safety of rituximab. In addition to conventional immunosuppressive medications, patients were randomised to receive either rituximab (n = 169) or a placebo (n = 88). The 2 arms of the trial showed no significant reduction in clinical activity compared with baseline.[4] The second trial evaluated the efficacy and safety of rituximab in subjects with class III or IV lupus nephritis (LUNAR trial). One hundred forty four patients were randomly assigned to receive either two courses (administered on days 1, 15,168 and 182) of rituximab (1000 mg) or placebo. The primary end point was renal response status at week 52. Rituximab therapy led to a greater reduction in anti-dsDNA and C3/C4 levels, but it did not improve clinical outcomes after 1 year of treatment.[5] However, a post hoc analysis of the LUNAR trial, showed that patients in the rituximab-treated arm who attained full depletion were more likely to experience a complete response.[6] A post hoc analysis of the LUNAR trial also revealed a trend toward the benefit in African-American and Hispanic patients.[7] This was particularly important because black ethnicity has been linked to an inability to deplete B cells.[8]

Besides rituximab, other fully humanized monoclonal antibodies targeting B cells have been evaluated in SLE. In a phase III trial with 381 patients who had severe lupus nephritis, ocrelizumab (anti-cd20 humanized monoclonal antibody) was assessed. Due to an increased incidence of serious infections in the treatment arm, this trial was stopped early.[9] Obinutuzumab is another humanized anti-CD20 monoclonal antibody that has been studied in a phase II clinical trial in lupus nephritis (NOBILITY). The results show that patients who received obinutuzumab as opposed to a placebo saw higher frequencies of complete and partial renal responses.[10] Finally, the fully human monoclonal antibody ofatumumab has demonstrated encouraging benefits in smaller groups of lupus nephritis patients.[11] These last two medications may be especially useful for patients in whom rituximab has been effective, but infusion reactions have forced withdrawal or for those in whom rituximab treatment did not completely deplete B cells.

Belimumab, a human IgG1 mAb directed at B cell–activating factor (BAFF), a B cell survival factor that also promotes the development of autoreactive B cells, was the first licensed therapy for lupus after a gap of 50 years. Belimumab was previously shown to improve control of non-renal lupus. Two large double-blind phase III RCTs, BLISS-52 (n=865) and BLISS-76 (n=819) received IV belimumab 1, 10 mg/kg, or placebo at weeks 0, 2, 4 and then every 4 weeks.[12,13] All patients were required to be on stable doses of corticosteroids and other immunosuppressants. The primary endpoint in both trials was the Systemic Lupus Erythematosus responder Index (SRI)-4 at week 52, defined as ≥4 point reduction in the Safety of Estrogens in Lupus Erythematosus National Assessment-Systemic Lupus Erythematosus

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Disease Activity Index (SELENA-SLEDAI) score, no new British Isles Lupus Activity Group (BILAG) A organ domain score and ≤ 1 new BILAG B score, and no worsening in Physicians Global Assessment (PGA) score. In BLISS-52, a higher proportion of patients in BEL 1 mg/kg and 10 mg/kg arms than in the placebo arm experienced an SRI-4 response at week 52.[12,13] Post hoc analyses involving patients in BLISS-52 and BLISS-76 who had proteinuria at baseline showed decreased proteinuria and a lower incidence of renal flares in patients who received belimumab.[14] These positive findings were followed by a trial to assess the efficacy and safety of belimumab combined with conventional therapy in patients with active lupus nephritis. In the BLISS-LN study, 448 patients with proliferative or membranous lupus nephritis on induction therapies with glucocorticoid and either cyclophosphamide- or MMF-containing regimens, were randomized to have belimumab or placebo.[15] Belimumab or placebo was added to these induction protocols as biweekly infusions for 2 years. The original primary outcome for this study, complete, partial, or no kidney response, was changed 5 years after the commencement of the trial, to "primary efficacy renal response" (PERR), which comprised a urine protein-to-creatinine ratio of <0.7, an eGFR within 20% of the preflare value or ≥60 mL/min per 1.73 m^2, and no use of rescue therapy.[15] More patients in the belimumab group than in the placebo group achieved a PERR by 24 weeks, and the benefit was maintained to 104 weeks (43% versus 32%). Treatment was also associated with an increase in complete kidney response as originally defined (30% versus 20% at 104 weeks). Treatment with belimumab was accompanied by greater normalization of disease biomarkers, including levels of anti–double-stranded DNA antibodies, anti-C1q antibodies, C3, and C4. The rate of infections was similar in patients who received belimumab or placebo. Taken together BLISS-LN supported the prolonged use of biological agents as add-on therapy to conventional background immunosuppression.[15]

Sequential treatment with rituximab followed by belimumab has recently been evaluated for lupus nephritis in a phase 2A, open-label, single arm proof-of-concept study.[16] The anti-BAFF monoclonal antibody belimumab, which was administered right after rituximab, was hypothesized to lead to a more prolonged B cell depletion, based on observations that high BAFF levels post-rituximab could be limiting its effectiveness in some patients with SLE.[17] The CALIBRATE study (NCT 02260934) was a phase 2 multi-center, randomized, controlled, open-label trial comparing belimumab after rituximab compared to rituximab alone. Forty-three patients with active proliferative LN despite conventional therapy received iv rituximab (1000 mg), cyclophosphamide (750 mg) and methylprednisolone (100 mg) at weeks 0 and 2 and an initial prednisolone dose of 40 mg/day with taper to 10 mg/day by week 12. Conventional immunosuppressants such as mycophenolate were stopped from randomization. At week 4, half of the patients were randomized to belimumab (10 mg/kg iv at weeks 4, 6, 8 and every 4 weeks). The addition of belimumab to rituximab and CYC was safe in patients with refractory LN. Clinical efficacy was not improved with rituximab and CYC combined with belimumab when compared with B cell depletion therapy alone. There was no difference in renal response at weak 48 in subjects who received anti-CD20 therapy followed by anti-BAFF therapy compared with anti-CD20 therapy alone.[18]

Although the BEAT-Lupus trial was not designed to exclusively test LN patients, this phase II, randomized placebo-controlled UK based trial of 52 patients included 20 with active LN patients. Participants received rituximab (two infusions, two weeks apart) and then randomized to receive monthly belimumab infusions or placebo in addition to standard of care. BEAT Lupus met the primary end point, a significant reduction in serum IgG anti-double stranded DNA antibody levels at 52 weeks, and a key secondary endpoint, a reduction by 3-fold in the risk of severe flares in patients treated with belimumab. Belimumab did not increase the risk of infections or severe adverse events, supporting the idea that combination biologic therapy may be a safe and potentially efficacious treatment for refectory SLE. A post hoc analysis revealed that belimumab treatment outperformed placebo with respect to the percentage of patients with renal involvement who experienced a full renal response (and no new renal flare).[19]

These results continue to support exploration of B cell therapies for SLE. The combination of belimumab after rituximab brings hope for the treatment of lupus nephritis, but given the variation in response between patients, it will be crucial to identifying predictors of response to enable a personalized medicine approach as well as identify how to induce and then sustain remission.

■ Ethical Disclosures

Conflicts of Interest: For BEAT LUPUS TRIAL: GSK Grant funding and provision of study drug belimumab, payment made to our institution

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