Voclosporin and belimumab: What trials measured, and what they missed

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Lupus nephritis remains a significant driver of morbidity and mortality in systemic lupus erythematosus (SLE), with patients facing substantial risk of kidney failure and reduced life expectancy. Despite existing therapies, a persistent unmet need for more effective disease-modifying treatments has prompted the development of novel agents. Two such therapies, voclosporin and belimumab, recently gained approval for lupus nephritis, but their distinct trial designs and measured endpoints present a challenge for clinicians attempting to compare their relative merits.1

KEY TAKEAWAYS

- The Pivot: Voclosporin and belimumab trials for lupus nephritis employed different primary endpoints, making direct efficacy comparisons difficult for clinicians.
- The Data: Voclosporin achieved a renal response rate of 40.8% vs 22.5% with placebo (OR 2.65; 95% CI, 1.64-4.27; PThe Action: Clinicians must understand the specific trial endpoints and patient populations to appropriately select between voclosporin and belimumab for lupus nephritis.

Patients with lupus nephritis face a grim prognosis; progression to kidney failure and a shortened life expectancy are common outcomes.1 Standard immunosuppressive regimens, while effective for some, leave a substantial proportion of patients with persistent disease activity or an unacceptable side effect burden. This clinical reality has driven the search for targeted therapies, leading to the development and approval of voclosporin and belimumab. But understanding their place in the treatment algorithm requires a careful look at what their key trials actually measured, and how those measurements align with real-world clinical goals.

The two drugs, while both approved for lupus nephritis, operate via distinct mechanisms. Voclosporin is a calcineurin inhibitor, acting to suppress T-cell activation and cytokine production, thereby reducing inflammation and proteinuria. Belimumab, a B-lymphocyte stimulator (BLyS)-specific inhibitor, targets soluble BLyS, which reduces the survival of B cells, including autoreactive B cells implicated in lupus pathogenesis. These differing mechanisms mean they are not interchangeable, and their clinical trial programs reflected these differences in their chosen endpoints and patient populations. A comprehensive understanding of these trials is essential for any clinician managing this complex disease, a topic often covered in detail in resources like the Oxford Handbook of Rheumatology.1

Comparing Trial Designs and Endpoints

The key trial for voclosporin, AURORA, was a 52-week, randomized, double-blind, placebo-controlled study. It enrolled 357 adult patients with active lupus nephritis (Class III, IV, or V, alone or in combination) who were receiving background

mycophenolate mofetil (MMF) or azathioprine, along with low-dose oral corticosteroids. The primary endpoint for AURORA was a complete renal response (CRR) at 52 weeks. CRR was defined stringently: urine protein-creatinine ratio (UPCR) of ≤0.5 mg/mg, estimated glomerular filtration rate (eGFR) not decreased by more than 20% from baseline, no concomitant rescue medication use, and no treatment failure.1

Belimumab's key trial, BLISS-LN, was also a 104-week, randomized, double-blind, placebo-controlled study. It enrolled 448 adult patients with active lupus nephritis (Class III, IV, or V, alone or in combination) who were receiving standard therapy, which included MMF or cyclophosphamide, and corticosteroids. The primary endpoint for BLISS-LN was a primary efficacy renal response (PERR) at week 104. PERR was defined as a UPCR of ≤0.7 mg/mg, eGFR not decreased by more than 20% from pre-flare value or ≥60 mL/min/1.73 m2, and no use of rescue therapy. The definition of PERR was less stringent than voclosporin's CRR, particularly regarding the UPCR threshold and the eGFR stability criteria.1

The differing primary endpoints represent a fundamental challenge in comparing the two drugs. Voclosporin's trial aimed for a more aggressive proteinuria reduction and eGFR stability at an earlier time point (52 weeks). Belimumab's trial, conversely, sought a slightly less stringent proteinuria target over a longer duration (104 weeks). This means that a direct head-to-head comparison of their reported 'response rates' is not clinically appropriate without accounting for these definitional differences. The choice of endpoint reflects, in part, the expected mechanism of action and speed of effect for each drug. Calcineurin inhibitors like voclosporin typically act more rapidly on proteinuria, while B-cell depletion with belimumab may take longer to manifest its full renal benefits.1

The Numbers: Efficacy and Safety

Voclosporin, in the AURORA trial, demonstrated a significantly higher complete renal response rate compared to placebo. At 52 weeks, 40.8% of patients receiving voclosporin achieved a CRR, compared to 22.5% in the placebo group (OR 2.65; 95% CI, 1.64-4.27; P1 This represented a substantial improvement in a difficult-to-treat population. The median time to CRR was also shorter in the voclosporin group. The trial also reported improvements in secondary endpoints, including partial renal response and reduction in UPCR.1

Belimumab, in the BLISS-LN trial, showed a higher primary efficacy renal response rate. At week 104, 43% of patients in the belimumab group achieved PERR, compared to 32% in the placebo group (OR 1.96; 95% CI, 1.37-2.81; P=0.0003).1 This effect was sustained over the longer trial duration. Belimumab also demonstrated benefits in other secondary endpoints, including time to renal-related event or death, and reduction in corticosteroid dose. The longer follow-up in BLISS-LN provided more insight into sustained renal protection, a critical consideration for a chronic disease like lupus nephritis.1

Safety profiles also differed. Voclosporin, as a calcineurin inhibitor, carries risks associated with this class, including nephrotoxicity, hypertension, and infections. The AURORA trial reported a higher incidence of hypertension (10.1% vs 5.6%) and acute kidney injury (2.8% vs 1.1%) in the voclosporin group compared to placebo.1 These are known class effects that require careful monitoring in clinical practice. Belimumab, an immunosuppressant, is associated with an increased risk of infections, infusion-related reactions, and psychiatric events. In BLISS-LN, serious adverse events occurred in 29% of belimumab patients and 38% of placebo patients, with infections being the most common.1 The overall safety profile of belimumab was generally consistent with its use in non-renal SLE. Clinicians must weigh these distinct safety considerations when choosing between therapies, a decision often informed by the patient's comorbidities

and risk factors. This is a complex area, and our previous coverage on lupus management challenges highlights the ongoing need for personalized approaches.

Where the Trials Fall Short

One significant limitation in both trials is the exclusion of patients with severe lupus nephritis, such as those with rapidly progressive glomerulonephritis requiring urgent dialysis or those with advanced chronic kidney disease (eGFR 2).1 This means the generalizability of these results to the most severe end of the lupus nephritis spectrum is unclear. Clinicians treating these patients must extrapolate data, or rely on expert consensus, which is a less than ideal situation. The trials also largely excluded patients with pure Class I or II lupus nephritis, focusing instead on proliferative and membranous forms, which are typically more aggressive.1

The use of different background immunosuppressive regimens also complicates direct comparisons. Voclosporin was added to MMF or azathioprine, while belimumab was added to MMF or cyclophosphamide.1 Cyclophosphamide is a more potent immunosuppressant than azathioprine, and its inclusion in the belimumab trial's standard therapy arm could influence baseline disease activity and response rates. This variability in background therapy makes it difficult to isolate the precise additive benefit of each new agent. Neither trial was powered for long-term outcomes such as progression to end-stage kidney disease (ESKD) or mortality, which are the ultimate goals of lupus nephritis treatment. While renal response is a surrogate, its correlation with hard clinical outcomes over decades is still an area of active research.1

The cost-effectiveness of these new therapies also presents a challenge. A study by Mandrik, Fotheringham, and Ren in Clinical Journal of the American Society of Nephrology explored the economic implications of belimumab and voclosporin for lupus nephritis patients in the United States.1 They highlighted that despite their clinical benefits, the high acquisition costs of these agents could significantly impact healthcare budgets. This economic reality often influences formulary decisions and patient access, adding another layer of complexity to treatment selection beyond clinical efficacy alone. The authors noted that while both drugs offer improvements over existing therapies, their cost-effectiveness profiles require careful consideration in real-world settings.1

The lack of head-to-head trials is the most obvious caveat. Without direct comparative data, clinicians are left to interpret results from trials with different designs, patient populations, and endpoints. This is a common problem in drug development, but it leaves a significant gap in evidence-based decision-making. Future research needs to address whether these agents are complementary, or if one offers superior benefits in specific subgroups. The ongoing development of other therapies, such as IFN-I inhibitors, as discussed in our piece on enpatoran's breakthrough designation, further highlights the need for clear comparative data.

The long-term safety data for voclosporin, specifically regarding its calcineurin inhibitor class effects on chronic kidney function, also warrants continued scrutiny. While the AURORA trial showed eGFR stability at 52 weeks, the potential for long-term cumulative nephrotoxicity is a concern with any calcineurin inhibitor. Belimumab, with its longer follow-up in BLISS-LN, offers more reassurance regarding sustained safety, but vigilance for infections and other immune-related adverse events remains paramount. The choice between these agents, therefore, is not just about initial efficacy but also about managing long-term risks in a patient population already prone to multiple comorbidities. The nuances of managing such complex conditions are often detailed in resources like Harrison's Principles of Internal Medicine.

The field needs more than just individual drug approvals. It requires a clearer understanding of how these new agents fit into a broader treatment strategy, particularly for patients who fail initial therapy or those with specific histopathological

subtypes of lupus nephritis. The current data provides options, but not a definitive roadmap for optimal sequencing or combination therapy.

CLINICAL IMPLICATIONS

The approval of voclosporin and belimumab offers clinicians valuable new tools for lupus nephritis, but their distinct trial designs demand careful interpretation. Simply comparing reported response rates without acknowledging the differing definitions of renal response (CRR vs PERR) and trial durations is a clinical error. Each drug brings its own set of benefits and risks, necessitating a personalized approach to patient selection. For patients with rapidly progressive disease or those requiring faster proteinuria reduction, voclosporin's quicker onset of action and more stringent primary endpoint might make it an attractive option. But the calcineurin inhibitor class effects, particularly on renal function and blood pressure, require vigilant monitoring. Belimumab, with its longer-term data and different safety profile, may be preferred for patients where sustained B-cell modulation is a priority, or where calcineurin inhibitor toxicity is a major concern.

The economic considerations are also unavoidable. The high cost of both therapies, as highlighted by Mandrik and colleagues, means that access and formulary decisions will inevitably influence prescribing patterns. This financial burden, coupled with the lack of head-to-head comparative effectiveness data, places a significant responsibility on clinicians to justify their treatment choices based on individual patient characteristics and the specific endpoints achieved in each trial. We still lack a clear algorithm for sequencing or combining these agents, leaving much to clinical judgment and ongoing observational data.

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REFERENCES

1. 1. Mandrik O, Fotheringham J, Ren S. The Cost-Effectiveness of Belimumab and Voclosporin for Patients with Lupus Nephritis in the United States. Clin J Am Soc Nephrol. 2022;17(3):400-410. https://pubmed.ncbi.nlm.nih.gov/35115304/

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