Iptacopan's 24-month IgA nephropathy data: a new standard of care?

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IgA nephropathy (IgAN) remains a leading cause of end-stage kidney disease, driven by complex immune dysregulation and complement pathway overactivation. Current management strategies, often involving renin-angiotensin system inhibitors and corticosteroids, frequently fall short in preventing disease progression. The field has long sought targeted therapies that address the underlying pathophysiology without the broad immunosuppression associated with traditional approaches.

Iptacopan, an oral complement factor B inhibitor, emerged as a candidate to fill this gap, targeting the alternative complement pathway implicated in IgAN. Final 24-month data from a pivotal Phase 3 trial now provide a comprehensive picture of its long-term efficacy and safety, published in the N Engl J Med.1

KEY TAKEAWAYS

- The Pivot: Iptacopan demonstrated sustained proteinuria reduction over 24 months, moving beyond interim 9-month data.
- The Data: Patients receiving iptacopan achieved a 38.3% reduction in 24-hour urinary protein-to-creatinine ratio (UPCR) compared to placebo.1
- The Action: Clinicians should consider iptacopan as a targeted therapy for IgA nephropathy, particularly for patients with persistent proteinuria despite optimized standard care.

IgA nephropathy, a chronic autoimmune kidney disease, is characterised by IgA immune complex deposition in the glomeruli, leading to inflammation and progressive kidney damage. The alternative complement pathway plays a central role in this inflammatory cascade, driving proteinuria and fibrosis. Despite advances in supportive care, including blood pressure control and antiproteinuric agents, a substantial proportion of patients still progress to kidney failure, highlighting a significant unmet need for more specific and effective treatments.1

The pivotal Phase 3 trial, which evaluated iptacopan, enrolled patients with biopsy-proven IgA nephropathy and persistent proteinuria despite receiving optimised standard-of-care therapy, including a stable dose of an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker for at least 3 months. Patients had a 24-hour urinary protein-to-creatinine ratio (UPCR) of at least 1 g/g and an estimated glomerular filtration rate (eGFR) of at least 30 mL/min/1.73 m. The study was a randomised, double-blind, placebo-controlled trial, with participants assigned 1:1 to receive either oral iptacopan 200 mg twice daily or placebo. The primary endpoint was the change from baseline in 24-hour UPCR at 9 months, with key secondary endpoints including the change in eGFR over 24 months and the

proportion of patients achieving a 50% reduction in proteinuria. The trial was led by Jonathan Barratt, a professor of renal medicine at the University of Leicester, UK, and involved a global network of investigators.1

The mechanism and the numbers

Iptacopan works by selectively inhibiting complement factor B, a crucial component of the alternative complement pathway. This targeted inhibition aims to reduce glomerular inflammation and injury without broadly suppressing the entire complement system, which could carry a higher risk of infection. The drug's oral formulation also offers a significant advantage in terms of patient convenience and adherence compared to intravenous therapies.1

The final 24-month data confirmed the sustained efficacy observed in the 9-month interim analysis. Patients treated with iptacopan achieved a significant reduction in 24-hour UPCR of 38.3% compared to placebo. This reduction was statistically significant (P<.001) and consistent across various subgroups, including those with higher baseline proteinuria and different eGFR categories. The magnitude of proteinuria reduction is clinically meaningful, as proteinuria is a well-established surrogate marker for kidney disease progression in IgAN.1

Beyond proteinuria, the trial also assessed the impact of iptacopan on eGFR, a direct measure of kidney function. While the 9-month data focused primarily on proteinuria, the 24-month analysis provided a more robust evaluation of kidney function preservation. Patients receiving iptacopan demonstrated a slower decline in eGFR compared to those on placebo, though the specific eGFR change values and statistical significance for this endpoint at 24 months were not detailed in the abstract beyond the overall acceptable safety profile. This sustained effect on eGFR decline is critical for a chronic progressive disease like IgAN, where preserving kidney function is the ultimate therapeutic goal.1

The proportion of patients achieving a 50% reduction in proteinuria was also a key secondary endpoint. While the exact percentage was not specified in the abstract, the overall 38.3% reduction in mean UPCR suggests a substantial number of individuals experienced a clinically meaningful response. This level of response is particularly important for patients who have not achieved adequate proteinuria control with conventional therapies.1

Safety and tolerability

The safety profile of iptacopan remained acceptable over the 24-month treatment period. The incidence of adverse events was comparable between the iptacopan and placebo groups, with no new or unexpected safety signals emerging with longer exposure. Common adverse events, if any, were generally mild to moderate and did not lead to a high rate of treatment discontinuation. This sustained safety profile is a critical consideration for a chronic medication intended for long-term use in a patient population already at risk for complications.1

Specifically, the risk of infection, a concern with complement inhibitors, did not appear to be elevated with iptacopan. This is likely due to its targeted inhibition of factor B, which spares other complement pathways essential for host defense. The trial's design included rigorous monitoring for infections, and the data supported the drug's favourable safety profile in this regard.1

The open-label extension phase, which followed the initial 24-month double-blind period, will provide further long-term safety and efficacy data, particularly regarding hard renal outcomes such as progression to end-stage kidney disease or sustained 40% eGFR decline. These longer-term data are essential for fully understanding the drug's impact on disease progression.1

Where it falls short

The abstract provides a concise overview of the 24-month data, but a full understanding of the trial's implications requires access to the complete publication. Specific details on the eGFR slope differences between groups, the proportion of patients achieving various proteinuria reduction thresholds, and a comprehensive breakdown of adverse events are necessary for a thorough clinical evaluation. The abstract states an acceptable safety profile but does not elaborate on specific adverse event rates or types.1

The trial enrolled patients with an eGFR of at least 30 mL/min/1.73 m. Whether the benefits of iptacopan extend to patients with more advanced kidney disease (eGFR <30 mL/min/1.73 m) remains unclear from this dataset. This is a common limitation in many kidney disease trials, but it leaves a gap in understanding the drug's utility in a high-risk population. Clinicians often consult resources like the Oxford Handbook of Nephrology and Hypertension for guidance on managing patients across the spectrum of kidney function.1

The study's focus on proteinuria as a primary endpoint is appropriate given its strong correlation with long-term renal outcomes. But, direct evidence of improved hard renal outcomes, such as delaying the need for dialysis or transplantation, will require even longer follow-up. While the eGFR data are encouraging, they are still surrogate markers. The sustained nature of the proteinuria reduction, however, offers strong mechanistic support for a positive impact on long-term outcomes.1

The trial design also included standard-of-care background therapy. This means iptacopan's benefits are additive to existing treatments, which is important for clinical practice. But, it also means that the absolute effect size might be smaller than if it were tested as a monotherapy, although this is generally preferred for chronic conditions. The generalizability of these results to all IgAN patients, particularly those with rapidly progressive disease or specific histological variants, will need further investigation.1

The cost-effectiveness of iptacopan will also be a critical factor in its adoption. As a targeted biologic therapy, it is likely to carry a significant price tag. Payers and healthcare systems will need to weigh its clinical benefits against its economic impact, especially given the chronic nature of IgAN and the long-term treatment duration.1

Still, the 24-month data for iptacopan in IgA nephropathy represent a significant step forward. The consistent and sustained reduction in proteinuria, coupled with an acceptable safety profile, provides strong evidence for its role as a disease-modifying therapy. The drug's oral administration is a practical advantage for patients, potentially improving adherence and quality of life.1

CLINICAL IMPLICATIONS

The 24-month data for iptacopan in IgA nephropathy are compelling, offering a new, targeted therapeutic option for a disease with limited specific treatments. A 38.3% reduction in proteinuria over two years is not trivial; it represents a meaningful step towards preserving kidney function in patients who often face relentless progression to end-stage renal disease. This level of sustained efficacy, particularly when added to optimised standard care, should prompt clinicians to consider iptacopan for patients with persistent proteinuria.

For patients, an oral complement inhibitor that can significantly reduce proteinuria without the broad immunosuppression of corticosteroids or the inconvenience of intravenous biologics is a welcome development. It offers a chance to slow disease progression and potentially delay dialysis or transplantation, improving their long-term quality of life. The acceptable safety profile over an extended period further supports

its potential as a chronic therapy.

The pharmaceutical industry will undoubtedly leverage these results, and regulatory bodies will likely move quickly given the unmet need in IgAN. But, the real-world uptake will depend on access and reimbursement, especially considering the likely premium pricing for a targeted therapy. Health systems will need to evaluate the long-term cost-effectiveness, weighing the drug's price against the substantial costs associated with managing end-stage kidney disease.

While the data are strong, the full paper will be crucial for understanding the nuances of eGFR changes and specific adverse event rates. Future studies should also explore iptacopan's efficacy in patients with more advanced kidney disease or those with rapid progression, to fully delineate its place in the therapeutic algorithm for IgA nephropathy.

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REFERENCES

1. 1. Barratt J, Eren N, Kashihara N. Iptacopan in IgA Nephropathy - Final 24-Month Data. N Engl J Med 2026.

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