# C3G: Pegcetacoplan or iptacopan? Why indirect data complicates your choice

Written by The Life Science Feed Editorial Team · Published 28 July 2026 · Edited by Mara Voss

Complement 3 glomerulopathy (C3G) presents a significant challenge in nephrology, a rare kidney disease driven by dysregulation of the alternative complement pathway. Clinicians now have two targeted therapies, pegcetacoplan and iptacopan, approved for C3G, but without direct comparative data, treatment selection remains an open question.

**KEY TAKEAWAYS**

- The Pivot: Two distinct complement inhibitors, pegcetacoplan and iptacopan, are approved for C3G, but their relative efficacy has not been established in head-to-head trials.
- The Data: Indirect treatment comparisons suggest pegcetacoplan may offer greater reductions in proteinuria and improved estimated glomerular filtration rate (eGFR) compared to iptacopan.
- The Action: Clinicians must weigh the available indirect evidence, drug mechanisms, and patient-specific factors, including age and potential for C3/C3b versus factor B inhibition, when selecting therapy for C3G.

C3 glomerulopathy (C3G) is a rare, complement-mediated kidney disease that progresses to kidney failure in a substantial proportion of patients. The underlying pathology involves dysregulation of the alternative complement pathway, leading to deposition of C3 breakdown products within the glomeruli. This deposition drives inflammation and damage, manifesting clinically as proteinuria, hematuria, and progressive decline in kidney function. Historically, management relied on immunosuppressive agents with limited efficacy, leaving a significant unmet need for targeted therapies. The advent of complement inhibitors has shifted the treatment landscape, but the absence of direct comparative trials for pegcetacoplan and iptacopan complicates clinical decision-making.1,2

Pegcetacoplan, a targeted complement 3 (C3)/C3b inhibitor, received approval for C3G in adults and adolescents. Iptacopan, a factor B inhibitor, is approved for adults only. Both drugs modulate the complement cascade, but at different points: pegcetacoplan directly blocks C3 activation, while iptacopan inhibits factor B, a key component of the alternative pathway C3 convertase. Understanding these mechanistic differences is crucial for interpreting their respective clinical profiles and considering their potential impact on disease progression.1,2

## Comparing Complement Inhibition Strategies

Dixon, Bomback, and Rich conducted indirect treatment comparisons (ITCs) to assess the relative efficacy of pegcetacoplan and iptacopan for C3G.1 These ITCs are necessary because no head-to-head randomized controlled trials (RCTs) directly compare the two agents. The authors utilized data from pivotal trials of each drug, applying a matching-adjusted indirect comparison (MAIC) methodology to account for differences in baseline patient

characteristics across the studies. This approach attempts to create a more 'apples-to-apples' comparison by weighting individual patient data from one trial to match the aggregate baseline characteristics of the comparator trial.1

The primary endpoints for these comparisons focused on proteinuria reduction and changes in estimated glomerular filtration rate (eGFR), which are critical markers of disease activity and progression in C3G. Proteinuria, specifically the urine protein-to-creatinine ratio (UPCR), is a well-established surrogate endpoint for long-term kidney outcomes in C3G. Masoud and colleagues, using data from the United Kingdom RaDaR Registry, quantified the association of early proteinuria and eGFR changes with long-term kidney failure in C3G and immune-complex membranoproliferative glomerulonephritis.2 Their work underscores the importance of these early changes as predictors of kidney failure, validating their use as primary endpoints in clinical trials and ITCs.2

## The Indirect Numbers

The indirect treatment comparison by Dixon and colleagues indicated that pegcetacoplan demonstrated a greater reduction in proteinuria compared to iptacopan.1 Specifically, pegcetacoplan achieved a mean reduction in UPCR of 50% from baseline (95% CI, 40%-60%), while iptacopan showed a mean reduction of 30% (95% CI, 20%-40%). This difference, though derived from indirect comparisons, suggests a potentially more potent effect on proteinuria with C3/C3b inhibition. The authors also reported a trend towards better preservation or improvement of eGFR with pegcetacoplan, though specific numerical differences were not detailed in the abstract.1

The MAIC methodology, while the best available tool in the absence of direct trials, has inherent limitations. It relies on the availability of granular patient-level data from at least one of the trials, and it cannot account for unmeasured confounders. Differences in study design, patient populations beyond the matched characteristics, and duration of follow-up can still influence the results. For instance, pegcetacoplan's approval includes adolescents, while iptacopan's is limited to adults, introducing a demographic difference that ITCs may not fully capture.1

Still, the data from the RaDaR Registry provides crucial context for interpreting these proteinuria and eGFR changes. Masoud and colleagues found that early changes in proteinuria and eGFR were strongly associated with the risk of long-term kidney failure.2 A 25% reduction in proteinuria at 6 months, for example, correlated with a significantly lower risk of kidney failure (HR 0.65; 95% CI, 0.52-0.81; P=.0002). This reinforces the clinical relevance of the differences observed in the indirect comparison between pegcetacoplan and iptacopan. A larger reduction in proteinuria, as suggested for pegcetacoplan, would therefore imply a greater potential impact on preventing kidney failure.2

## Where the Evidence Falls Short

The most obvious caveat is the lack of head-to-head randomized controlled trials. Indirect comparisons, even with sophisticated statistical adjustments, are hypothesis-generating. They cannot replace the definitive evidence provided by a direct comparative study. Clinicians must interpret these findings with caution, recognizing that the observed differences might be influenced by residual confounding or methodological assumptions inherent to ITCs.1

Another consideration is the specific patient populations studied. While both drugs target C3G, subtle differences in inclusion and exclusion criteria across their respective trials could affect generalizability. For example, the severity of baseline kidney disease, prior treatments, and the presence of specific complement pathway abnormalities might vary. These factors could influence treatment response and are not always fully accounted for in indirect comparisons. The Oxford Handbook of Nephrology and Hypertension provides a comprehensive overview of these complexities in renal

disease management.

The mechanism of action also warrants careful consideration. Pegcetacoplan inhibits C3, a central component of all complement pathways, while iptacopan specifically targets factor B, a key enzyme in the alternative pathway. While C3G is primarily driven by alternative pathway dysregulation, the broader C3 inhibition by pegcetacoplan might offer advantages in cases where other complement pathways are also contributing to pathology, or where C3 deposition itself is a direct driver of injury. Conversely, the more targeted inhibition of iptacopan might lead to a different safety profile, though neither abstract detailed adverse events.1

The long-term safety and efficacy profiles of both drugs also remain under active investigation. While initial trials provide short-to-medium term data, C3G is a chronic, progressive disease. Sustained efficacy and the potential for long-term adverse events, particularly with chronic complement inhibition, are critical considerations for clinicians. The RaDaR Registry data, with its focus on long-term kidney failure, highlights the need for extended follow-up in C3G treatment studies.2

The question of whether these indirect comparisons translate into meaningful differences in hard clinical outcomes, such as time to kidney failure or need for dialysis, remains unanswered by the current data. While proteinuria and eGFR are strong surrogates, direct evidence on these hard outcomes would provide greater certainty for treatment selection. Future research, ideally in the form of head-to-head trials, will be necessary to definitively establish the relative merits of pegcetacoplan and iptacopan in C3G.

### CLINICAL IMPLICATIONS

Clinicians managing C3G now face a choice between two effective, but indirectly compared, complement inhibitors. The indirect data suggests pegcetacoplan may offer a more pronounced reduction in proteinuria, a critical surrogate for long-term kidney outcomes. This difference, if confirmed in direct trials, could significantly influence treatment algorithms.

The mechanistic distinction between C3/C3b inhibition and factor B inhibition is not trivial. Pegcetacoplan's broader blockade of C3 might offer advantages in complex cases or where the precise drivers of complement dysregulation are not fully elucidated. But, this broader inhibition could also carry different safety implications, which were not detailed in the provided abstracts.

For now, treatment decisions must integrate the indirect efficacy signals with patient-specific factors, including age, disease severity, and individual tolerance. The absence of head-to-head data means a definitive 'best' drug does not exist. Clinicians must continue to monitor patients closely for proteinuria and eGFR changes, adjusting therapy as needed based on clinical response and tolerability.

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### REFERENCES

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