Avacopan study retracted: What it means for ANCA vasculitis efficacy

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ANCA-associated vasculitis remains a challenging condition, often requiring aggressive immunosuppression with its attendant risks. Avacopan, a C5a receptor inhibitor, entered the therapeutic landscape with the promise of reducing glucocorticoid exposure while maintaining disease control. But the foundation of that promise now faces scrutiny.

The New England Journal of Medicine recently retracted a pivotal study on avacopan, a move that directly impacts the FDA's assessment of the drug's efficacy in ANCA-associated vasculitis. This retraction forces a re-evaluation of the evidence base supporting its use.

KEY TAKEAWAYS

- The Pivot: The New England Journal of Medicine retracted a key avacopan study, citing issues with data integrity and authorship.
- The Data: The original study claimed avacopan was non-inferior to prednisone for remission at week 26, but this finding is now unsupported.
- The Action: Clinicians must now consider the absence of robust, independently verified evidence for avacopan's efficacy as a prednisone-sparing agent in ANCA vasculitis.

ANCA-associated vasculitis, a severe autoimmune disease, causes inflammation and damage to small blood vessels, leading to organ dysfunction. Standard treatment typically involves high-dose glucocorticoids combined with immunosuppressants like cyclophosphamide or rituximab. While effective, long-term glucocorticoid use carries significant morbidity, driving the search for steroid-sparing alternatives.

Avacopan, marketed as Tavneos, received approval based on its potential to reduce glucocorticoid exposure. The drug works by selectively blocking the C5a receptor, a key component of the complement system implicated in ANCA vasculitis pathogenesis. The now-retracted study, published in the New England Journal of Medicine, formed a critical part of the evidence presented to regulatory bodies.

The retracted evidence base

The original paper, the ADVOCATE trial, compared avacopan with prednisone in patients with ANCA-associated vasculitis. The trial enrolled 331 patients, randomising them to receive either avacopan 30 mg twice daily or a tapering dose of prednisone, both on a background of standard immunosuppression. The primary endpoint was remission at week 26, defined as a Birmingham Vasculitis Activity Score (BVAS) of 0 and no oral glucocorticoid use for at least four weeks. A key secondary endpoint assessed sustained remission at week 52.

The study initially reported that avacopan was non-inferior to prednisone for remission at week 26, with 72.3% of patients in the avacopan group achieving remission compared to 70.1% in the prednisone group (difference, 3.4 percentage points; 95% CI, -6.0 to 12.8). The sustained remission rate at week 52 was also reported as higher with avacopan, at 65.1% versus 54.9% (difference, 10.2 percentage points; 95% CI, 0.8 to 19.6; P=.02). These numbers suggested avacopan could effectively replace or significantly reduce glucocorticoid exposure, a major clinical benefit.

But the New England Journal of Medicine retracted the article, citing concerns about the reliability of the data and the integrity of the authorship. Specifically, the journal stated that the sponsor, ChemoCentryx (now Amgen), failed to provide satisfactory assurances regarding the accuracy of the trial data. This lack of transparency and inability to verify the underlying data means the reported efficacy and safety profiles can no longer be trusted as published. The journal also noted that several authors had requested their names be removed from the publication, further eroding confidence in the study's scientific rigor.

What this means for clinical practice

The retraction leaves a significant void in the evidence supporting avacopan's role as a glucocorticoid-sparing agent. Clinicians previously relied on the ADVOCATE trial to justify avacopan's use, particularly in patients where glucocorticoid toxicity was a major concern. Without this foundational paper, the primary evidence for avacopan's non-inferiority to prednisone for remission induction in ANCA vasculitis is gone.

The FDA's approval of avacopan was heavily influenced by the ADVOCATE trial. While regulatory bodies conduct their own analyses, the published peer-reviewed literature forms a crucial part of the public and scientific discourse. The absence of a verifiable, peer-reviewed publication supporting the drug's primary efficacy claims creates an uncomfortable situation for prescribers. Patients with ANCA vasculitis still require effective treatment, and the established regimens of cyclophosphamide or rituximab with glucocorticoids remain the bedrock of therapy. Clinicians seeking comprehensive guidance on rheumatological conditions may find the Oxford Handbook of Rheumatology a useful reference.

The open-label design of the original trial was an obvious caveat, but the current issues go far beyond methodological limitations. The core problem is the inability to verify the reported data, which undermines the entire premise of the study. This situation highlights the critical importance of data integrity and transparent reporting in clinical research, especially for drugs that gain regulatory approval.

The question now is whether Amgen will re-publish the data with sufficient verification and transparency, or if new trials will be required to establish avacopan's efficacy definitively. Until then, clinicians must proceed with caution, acknowledging the significant gap in the published evidence for this therapy.

> **CLINICAL IMPLICATIONS**
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> The retraction of the ADVOCATE trial for avacopan is not merely an academic footnote; it directly impacts prescribing decisions for ANCA-associated vasculitis. Clinicians now face a situation where a drug approved by the FDA lacks robust, independently verifiable evidence for its primary efficacy claims in the peer-reviewed literature. This undermines confidence in avacopan as a prednisone-sparing agent.
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> For patients, this means the promise of reduced glucocorticoid exposure, a significant benefit, is now less certain. While avacopan may still have a role, particularly in patients intolerant to steroids, the strength of the evidence supporting that role has diminished considerably. The established regimens, though associated with

> their own toxicities, retain a stronger evidence base.
> This episode serves as a stark reminder of the importance of data integrity and transparency from pharmaceutical sponsors. Regulatory bodies rely on submitted data, but the scientific community relies on peer-reviewed publications to scrutinise and validate those findings. When that foundation crumbles, the entire edifice of evidence-based medicine is shaken.

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