

After avacopan: endpoint integrity and glucocorticoid-sparing care in antineutrophil cytoplasmic antibody-associated vasculitis

Dear Editor,

The problem that made avacopan appealing does not go away with avacopan. Glucocorticoid toxicity remains an unmet need in ANCA-associated vasculitis (AAV), especially in older, frail, infection-prone, metabolically vulnerable, or renally impaired patients. The clinical ambition that made an oral C5a receptor antagonist attractive, to induce remission while limiting cumulative glucocorticoid damage, remains valid. What has changed is not the need for glucocorticoid-sparing care, but the evidentiary confidence that avacopan can be used to provide it.

That distinction matters. ADVOCATE initially reported non-inferiority for remission at week 26 and superiority for sustained remission at week 52, with rituximab or cyclophosphamide, followed by azathioprine, as background therapy (1). However, the article reporting those findings was subsequently retracted (2). The avacopan episode should not be understood primarily as the ordinary uncertainty that may accompany approval in a rare disease when the evidentiary case rests heavily on a single pivotal trial. That limitation is real, but it does not capture what was at stake. What made the case different was the integrity of the endpoint itself: after a non-significant original analysis, the FDA reported that unblinded personnel selected nine ADVOCATE participants for post-database-lock readjudication, including five avacopan-treated patients whose outcomes changed from “not in sustained remission” to “sustained remission,” thereby compromising the credibility of the reported superiority finding (3). EMA similarly concluded that the benefit-risk balance could no longer be sustained because avacopan’s benefits were no longer proven to outweigh its risks (4).

The clinical response should therefore be neither therapeutic nihilism nor uncritical continuity. Physicians adopted avacopan because it addressed a real problem. In daily practice, the patients most harmed by glucocorticoids are often those in whom AAV is hardest to treat: patients with kidney failure, diabetes, osteoporosis, frailty, cardiovascular risk, or previous serious infections. Losing confidence in avacopan does not eliminate their vulnerability; it removes one proposed solution.

For patients currently receiving avacopan, the message in Europe is practical: no

new patients should start treatment, and those already treated should be switched to alternative options, with reassessment of disease activity, organ involvement, remission status, relapse/infection risk, and liver biochemistry (4, 5). This transition should be structured, while avoiding an automatic return to steroid excess. Established remission-induction strategies with rituximab or cyclophosphamide remain the therapeutic backbone (6, 7). Glucocorticoid minimization should continue through evidence-based tapering, careful phenotyping, early response assessment, and individualized risk balancing. PEXIVAS and LoVAS support reduced-dose glucocorticoid strategies in appropriate contexts, while reminding us that tapering must reflect disease severity, the induction regimen, and the patient’s phenotype (8, 9).

The lesson from avacopan is sharper than the lesson from a negative or underpowered trial. Biological plausibility, regulatory approval, and clinical need cannot compensate for compromised outcome ascertainment. Real-world cohorts and pharmacovigilance data may still help define patterns of use, vulnerable subgroups, and safety signals; however, they cannot substitute for a reliable pivotal efficacy signal once that signal has been materially questioned (10).

The problem that made avacopan appealing remains unsolved. The task now is not to abandon glucocorticoid-sparing care in AAV, but to pursue it with greater evidentiary discipline: transparent endpoint adjudication, prospective safety surveillance, conditional guideline recommendations when certainty is limited, and a refusal to let therapeutic appeal substitute for trustworthy data. For the clinician at the bedside, the aim remains unchanged: to control vasculitis early, protect organs, prevent relapse, and reduce the damage caused by both the disease and its treatment. After avacopan, glucocorticoid-sparing care remains the goal; endpoint integrity is the condition for trusting that path.

E.A. LEIVA-MURILLO, MD, MSc

Department of Internal Medicine, Hospital
Clínic de Barcelona, University of Barcelona,
Spain.

Please address correspondence to:

Enmanuel A. Leiva-Murillo

Department of Internal Medicine and
Systemic Diseases,

Hospital Clínic de Barcelona,

University of Barcelona,

C/ Villarroel 170, 08036 Barcelona, Spain.

E-mail: ealeiva@clinic.cat

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