How to Treat Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis

Authors: Aleksandra Zurowska, EMJ

Citation: EMJ Rheumatol. 2025;12[1]:28-32. https://doi.org/10.33590/emjrheumatol/JPSF7192

IN A HIGHLY anticipated session presented at the European Alliance of Associations for Rheumatology (EULAR) 2025 Congress, Benjamin Terrier, Professor at Université Paris Cité, France, delivered a comprehensive update on the ever-evolving management of anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitis (AAV). The session covered treatment strategies for granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA).

Drawing on data from recent landmark trials and guideline updates, Terrier aimed to answer some of the most pressing questions that clinicians face today: 'How to optimise glucocorticoid use?', 'When and how to deploy immunosuppressives?', and 'Where do new agents, like complement inhibitors, fit into the treatment landscape?'

ANTI-NEUTROPHIL CYTOPLASMIC ANTIBODY-ASSOCIATED VASCULITIS PATHOPHYSIOLOGY

Opening by briefly outlining the immunopathology of AAV, which includes GPA, MPA, and EGPA, Terrier explained that these small-vessel vasculitides are characterised by necrotising inflammation associated with ANCA, directed against either proteinase 3 (PR3) or myeloperoxidase (MPO). The disease is systemic and often involves multiple organs, such as the lungs and kidneys.

He mapped the pathophysiological sequence, in which ANCAs promote the release of inflammatory mediators by activating neutrophils, thereby activating the alternative complement pathway. Terrier stated that this cascade is responsible for tissue damage and multiple organ involvement. Treatments such as glucocorticoids, rituximab, cyclophosphamide, plasma exchange, and more recently, complement inhibition with avacopan, aim to intervene at various points along this cascade.

GLUCOCORTICOID USE: HOW LOW CAN WE GO?

Aiming to answer one of the most pressing questions in AAV ('How to safely reduce glucocorticoid use without compromising on disease control?'), Terrier reviewed two major studies: the PEXIVAS[1] and LoVAS[2] trials, which have informed current practice. He began with PEXIVAS,[1] which showed that a reduced-dose glucocorticoid regimen was non-inferior to standard dosing for preventing end-stage kidney disease or mortality, while significantly reducing the risk of serious infections.[1] The LoVAS study[2] used an even more aggressive steroid taper, and also demonstrated non-inferiority to standard dosing. However, nearly two-thirds of patients were unable to maintain a low-dose regimen, prompting dose adjustments.

Terrier explained that the current EULAR, American College of Rheumatology, and Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend reduced-dose glucocorticoid regimens as standard for induction therapy. However, he cautioned that in real-world

> **Terrier explained that the current EULAR, American College of Rheumatology, and Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend reduced-dose glucocorticoid regimens as standard for induction therapy**

settings, particularly in patients treated with rituximab or those with severe renal involvement, reduced steroid regimens may lead to suboptimal disease control. To illustrate this point, Terrier presented retrospective multicentre data from a study by Nagle et al.,[3] showing that in such patients, lower-dose regimens were associated with higher rates of treatment failure, albeit without an increased risk of end-stage kidney disease or mortality.

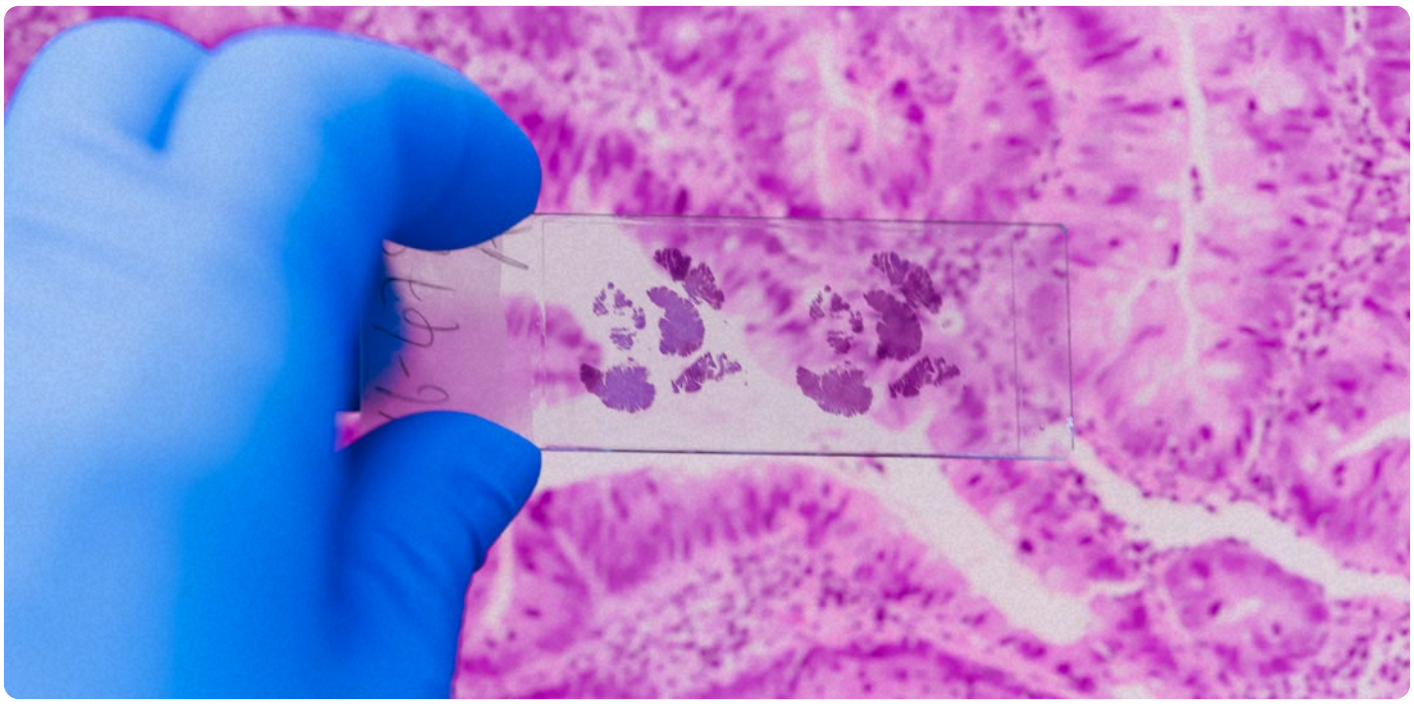
INDUCTION THERAPY: RITUXIMAB, CYCLOPHOSPHAMIDE, OR BOTH?

In severe GPA and MPA, induction therapy with rituximab and cyclophosphamide remains viable first-line options. The RAVE trial,[4] which established the non-inferiority of rituximab compared with cyclophosphamide, showed a subgroup analysis favouring rituximab in relapsing disease. Guidelines now recommend that in non-severe AAV, glucocorticoids should be combined with rituximab, rather than used alone. In patients with rapidly progressive renal involvement, especially where estimated glomerular filtration rate (eGFR) is significantly reduced, the data supporting rituximab are more limited. In such settings, a combination of rituximab and cyclophosphamide may be considered, with guidelines offering flexibility based on physician judgement and access to care.

Terrier noted that when combining rituximab and cyclophosphamide for severe disease, two doses of each agent at Days 1 and 15 is a practical and effective regimen, allowing early, intensive immunosuppression.

PLASMA EXCHANGE: STILL A ROLE IN SEVERE DISEASE?

The role of plasma exchange (PLEX) remains controversial. Earlier studies, such as MEPEX,[5] suggested that PLEX could reduce dialysis dependence in patients with very high serum creatinine. However, the PEXIVAS trial,[1] which included a broader population with a median creatinine of 330 µmol/L, found no overall benefit.



Terrier presented a meta-analysis, pooling data from a newer study by Walsh et al.[6] that suggested that PLEX may still benefit patients with severe renal impairment, particularly those with serum creatinine of >500 µmol/L. For this group, the number needed to treat to prevent one case of end-stage renal disease at 12 months was six, while the number needed to harm (i.e., cause a serious infection) was 14, suggesting a favourable risk–benefit ratio in select patients. Current guidelines recommend considering PLEX in patients with severe renal disease, though not in those with diffuse alveolar haemorrhage, unless associated with hypoxaemia.

AVACOPAN: A GLUCOCORTICOID-SPARING GAME CHANGER?

Terrier then turned to avacopan, a novel oral C5a receptor antagonist that targets the complement cascade. In the ADVOCATE trial,[7] avacopan was compared to a standard prednisone taper (alongside rituximab or cyclophosphamide) and achieved non-inferior remission rates at 26 weeks. At 52 weeks, avacopan demonstrated superiority in sustained remission rates and better preservation of kidney function.

While all patients in ADVOCATE received some background steroid (mean 2.5g over the year), avacopan enabled more rapid tapering, aligning with its mechanism of reducing complement-m§ediated inflammation.[7] Terrier emphasised that the true utility of avacopan lies in its potential to significantly reduce steroid burden, especially in patients at higher risk of steroid toxicity or with lower baseline eGFR.

At 52 weeks, avacopan demonstrated superiority in sustained remission rates and better preservation of kidney function

MAINTENANCE: RITUXIMAB STILL REIGNS

As Terrier stated, rituximab remains the gold-standard treatment for the maintenance of remission, with two regimens widely used: 500 mg every 6 months (MainRITSAN),[8] or 1g every 4 months (RITAZAREM).[9] EULAR guidelines recommend maintenance therapy for 2–4 years, depending on relapse risk. Factors associated with higher relapse rates include PR3-ANCA positivity; ear, nose, and throat involvement; and a history of multiple flares.

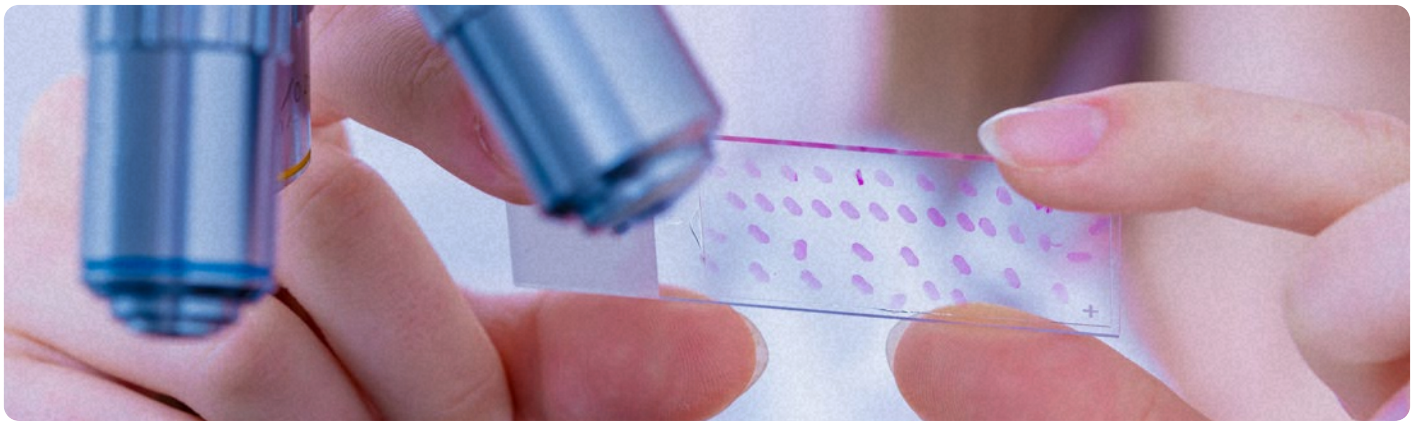
Terrier encouraged regular B cell monitoring during maintenance, especially in patients who appear to be under-responding. Anti-rituximab antibodies or incomplete B cell depletion may explain suboptimal responses, and monitoring can guide decisions around re-dosing or switching therapies.

EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS

Finally, Terrier addressed EGPA, which differs significantly in its pathophysiology and management from GPA and MPA. EGPA is often ANCA-negative and dominated by eosinophilic inflammation, asthma, and ENT involvement. Cardiac and neurological complications can also be prominent.

> **EGPA is often ANCA-negative and dominated by eosinophilic inflammation, asthma, and ENT involvement**

For non-severe EGPA, glucocorticoids remain first-line. For severe disease, conventional immunosuppressants, such as cyclophosphamide, are still recommended. Although the new REOVAS trial,[10] which investigated rituximab in severe EGPA, was negative, it showed potential as an alternative option. Biologic therapies targeting eosinophils have transformed treatment of relapsing/refractory EGPA. Mepolizumab, an anti-IL-5 monoclonal antibody, showed superiority over



placebo in the MIRA trial.[11] The more recent MANDARA study[12] demonstrated that benralizumab was non-inferior to mepolizumab. While not tested at diagnosis or in patients with severe cases, both are now recommended for patients with relapsing, eosinophil-driven disease.[12] Terrier cautioned that while anti-IL-5 therapies are highly effective for asthma, their impact on nasal polyposis is modest. He urged clinicians to optimise local ear, nose, and throat treatments before switching therapies and to avoid unapproved agents such as dupilumab, which has been associated with disease flares in EGPA.

CONCLUSION

Terrier concluded the enlightening session with a practical set of take-home messages: glucocorticoid reduction is feasible and desirable, despite requiring close monitoring, particularly in rituximab-treated patients or those with severe renal involvement; rituximab remains a mainstay for both induction and maintenance therapy; PLEX maintains its role in select patients with very advanced kidney disease; complement inhibition with avacopan is a valuable glucocorticoid-sparing alternative, especially in patients with low eGFR; and finally, EGPA treatment should be tailored by distinguishing between vasculitic and eosinophilic disease drivers to help guide the use of cyclophosphamide, rituximab, or biologics targeting IL-5.

References

1. Walsh et al. Plasma exchange and glucocorticoids in severe ANCA-associated vasculitis. N Engl J Med. 2020;382:622-31.
2. Furuta S et al; LoVAS Collaborators. Effect of reduced-dose vs high-dose glucocorticoids added to rituximab on remission induction in anca-associated vasculitis: a randomized clinical trial. JAMA. 2021;325(21):2178-87.
3. Jayne DR et al; European Vasculitis Study Group. Randomized trial of plasma exchange or high-dosage methylprednisolone as adjunctive therapy for severe renal vasculitis. J Am Soc Nephrol. 2007;18(7):2180-8.
4. Stone JH et al. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. N Engl J Med. 2010;363:221-32.
5. Walsh M et al; European Vasculitis Study Group (EUVAS). Long-term follow-up of patients with severe ANCA-associated vasculitis comparing plasma exchange to intravenous methylprednisolone treatment is unclear. Kidney Int. 2013;84(2):397-402.
6. Walsh M et al; Plasma exchange and glucocorticoid dosing for patients with ANCA-associated vasculitis BMJ Rapid Recommendations Group. The effects of plasma exchange in patients with ANCA-associated vasculitis: an updated systematic review and meta-analysis. BMJ. 2022;376:e064604.
7. Jayne et al. Avacopan for the treatment of ANCA-associated vasculitis. N Engl J Med. 2021;384:599-609,
8. Guillevin L et al. Rituximab versus azathioprine for maintenance in ANCA-associated vasculitis. N Engl J Med. 2014;371(19):1771-80.
9. Walsh M et al. Rituximab for the maintenance of remission in ANCA-associated vasculitis: results of the RITAZAREM trial. Lancet Rheumatol. 2020;2(5):e295-305.
10. Dutertre M et al. Long-term efficacy of remission-induction regimens for eosinophilic granulomatosis with polyangiitis. Abstract 0854. ACR Convergence 2023, 10-15 November, 2023.
11. Weschler et al. Mepolizumab or placebo for eosinophilic granulomatosis with polyangiitis. N Engl J Med. 2017;376:1921-32.
12. Weschler et al. Benralizumab versus mepolizumab for eosinophilic granulomatosis with polyangiitis. N Engl J Med. 2024;390:911-21.

EULAR 2025

Abstract Reviews

Discover cutting-edge advances in rheumatology through novel abstracts unveiled at the EULAR 2025 Congress. Hear from leading experts as they share fresh insights and clinical perspectives shaping the future of the field.