Executive summary of the KDIGO 2024 Clinical Practice Guideline for the Management of ANCA–Associated Vasculitis

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In 2021, the Kidney Disease: Improving Global Outcomes (KDIGO) Guideline for the Management of Glomerular Diseases was published. KDIGO is committed to providing the nephrology community with periodic updates, based on new developments for each disease. For patients with anti-neutrophil cytoplasmic antibody (ANCA)–associated vasculitis (AAV), avacopan received regulatory approval in late 2021, leading to this KDIGO guideline update. In addition, the evidence supporting a lower-dose glucocorticoid induction regimen or even complete replacement of glucocorticoids has become stronger. Herein, an executive summary of the most important guideline changes from the AAV chapter is provided as a quick reference.

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In 2021, a major revision of the Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for the Management of Glomerular Diseases was published.[1] Since publication, important data concerning anti-neutrophil cytoplasmic antibody (ANCA)–associated vasculitis (AAV) have become available, prompting this guideline update. Probably the most significant development has been the approval of the C5a receptor inhibitor avacopan by the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA) as add-on therapy to standard-of-care for the treatment of AAV.[2,3] This development directly relates to the second major emerging novel approach to the treatment of AAV, namely, a reduction of systemic glucocorticoid exposure. Although the latter is obviously desirable, given the short- and long-term complications of glucocorticoids, it is less clear which patients need avacopan in order to allow for lower glucocorticoid dosages. At the same time, this new therapy adds significant cost to treatment, and long-term safety data are currently lacking.

This Executive Summary provides a brief snapshot of the updated guideline, but readers are encouraged to view the full chapter for detailed discussion and useful practice points (Supplementary Table S1; https://kdigo.org/guidelines/gd/).

No major changes have been made in sections related to diagnosis and assessment of prognosis of AAV (https://kdigo.org/guidelines/gd/). The most important update in the ANCA guideline relates to induction therapy. Recommendation 9.3.1.1, "**We recommend that glucocorticoids in combination with cyclophosphamide or rituximab be used as initial treatment of new-onset AAV (1B),**" did not change, but the discussion now places stronger emphasis on a more rapid reduction of glucocorticoid dose, based on the recent Low-Dose Glucocorticoid Vasculitis Induction Study (LoVAS), among others.[4] The study randomized patients with AAV to receive reduced-dose prednisolone (0.5 mg/kg/d) or high-dose prednisolone (1 mg/kg/d) plus 4 doses of 375 mg/m^2/wk rituximab. Reduced-dose glucocorticoids led to a similar remission rate, but the frequency of severe infections was

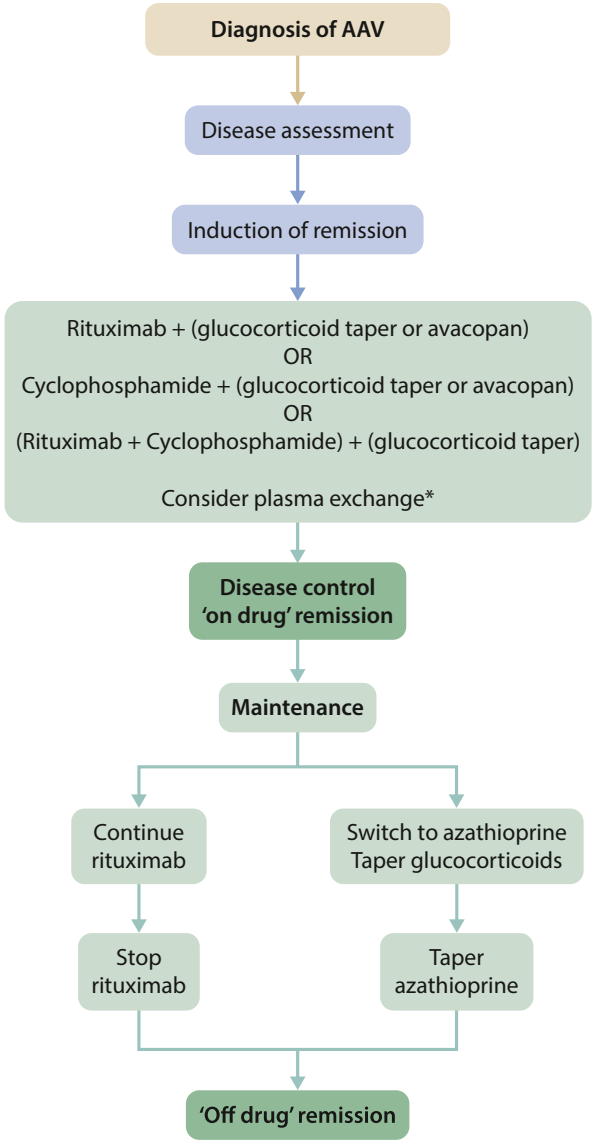

Figure 1 | Practical treatment regimen for antineutrophil cytoplasmic antibody–associated vasculitis (AAV). *Please see Practice Point 9.3.1.9 for details.

reduced. A limitation of the study is that it included only Japanese patients with predominantly myeloperoxidase (MPO)-ANCA-associated vasculitis. Nonetheless, these data support the "reduced-glucocorticoid dose" as used in the Plasma Exchange and Glucocorticoids for the Treatment of ANCA-Associated Vasculitis (PEXIVAS) trial.[5]

The most important change in AAV induction therapy is the availability of avacopan for AAV (Figure 1; **Practice Point 9.3.1.1 and Practice Point 9.3.1.7 in guideline**). Two placebo-controlled randomized controlled trials (RCTs) studied avacopan in AAV; one of the RCTs (A Phase 3 Clinical Trial of CCX168 [Avacopan] in Patients with ANCA-Associated Vasculitis [ADVOCATE]) had no serious methodological concerns,[6] but the other RCT (Clinical ANCA Vasculitis Safety and Efficacy Study of Inhibitor of C5aR [CLASSIC]) had a high dropout rate and changed the *a priori* primary outcome.[7] The certainty of the evidence for sustained remission and severe adverse events was graded as moderate, but the certainty of evidence for infections and discontinuation due to adverse events were graded as low. The Work Group considered the results of both randomized controlled trials (RCTs) when deciding to make avacopan a practice point rather than a recommendation. Patients with an increased risk of glucocorticoid toxicity are likely to benefit most from avacopan. Furthermore, a *post hoc* analysis of patients with low glomerular filtration rate (GFR) (<30 ml/min per 1.73 m^2) suggested greater GFR recovery with avacopan as compared to glucocorticoid therapy.[8]

Controversy still surrounds the value of plasma exchange in AAV patients with a severe clinical course. From the Public Review, approval for Practice Point 9.3.1.9. was relatively low, at 75%: "Consider plasma exchange for patients with serum creatinine (SCr) >3.4 mg/dl (>300 µmol/l), patients requiring dialysis or with rapidly increasing SCr, or patients with diffuse

alveolar hemorrhage who have hypoxemia." However, a 2022 meta-analysis concluded that there is a reduction of kidney failure at 12 months with plasma exchange, with no evidence of subgroup effects, but it comes at the cost of an increased risk of serious infections.[9] At present, the routine use of plasma exchange is not recommended for patients presenting with a GFR <50 ml/min per 1.73 m^2, but it can be considered in patients with more severe presentations (SCr >3.4 mg/dl [>300 μmol/l], especially if oliguric) or those with alveolar hemorrhage and hypoxemia, in whom early mortality is high. Plasma exchange should be used in patients with concomitant anti-glomerular basement membrane (GBM) disease. Conversely, plasma exchange is not required for therapy of diffuse alveolar hemorrhage in the absence of hypoxemia.

Maintenance therapy has not changed in the 2024 guideline update, and Recommendation 9.3.2.1 still states "**We recommend maintenance therapy with either rituximab, or azathioprine and low-dose glucocorticoids after induction of remission (1C)**." For both azathioprine and rituximab, the updated guideline now mentions an optimal duration of therapy of between 18 months and 4 years after the induction of remission. As a maintenance drug, rituximab can be dosed on a fixed schedule or upon reappearance of CD19+ B cells and/or ANCA, but dosing based on B cell counts led to fewer infusions and thus lower cost.[10,11]

Even in patients on kidney replacement therapy, extrarenal AAV can and does relapse, and a remission should be consolidated with maintenance therapy. In patients with kidney failure, anti-MPO positivity, and no extrarenal symptoms, long-term maintenance may not be necessary. In this situation, the need for (and length of) maintenance treatment should be assessed at an individual level.

There is no new information to guide clinical approaches to AAV in patients with relapsing or refractory disease, or after kidney transplantation; thus, the content of the 2021 guideline did not change. Finally, research recommendations from this 2024 guideline still call for RCTs that incorporate patient-reported outcomes, more prolonged long-term outcome studies, studies aimed at defining the role of rituximab in severe AAV, and studies conducted in ethnically diverse populations. Another area in which there is a large unmet need is the identification of biomarkers to better guide treatment. Hopefully, these future trials, if successful, will lead to yet another update of the KDIGO AAV guideline in the near-term.

DISCLOSURE

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SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary Table S1. Comparison of the 2021 and 2024 KDIGO Clinical Practice Guideline for the Management of Antineutrophil Cytoplasmic Antibody (ANCA)–Associated Vasculitis.

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