KDOQI US Commentary on the KDIGO 2024 Clinical Practice Guideline for the Management of Antineutrophil Cytoplasmic Antibody (ANCA)–Associated Vasculitis

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The Kidney Disease Outcomes Quality Initiative (KDOQI) convened a work group to review the KDIGO 2024 Clinical Practice Guideline for the Management of Antineutrophil Cytoplasmic Antibody (ANCA)–Associated Vasculitis. The KDOQI work group reviewed the Kidney Disease: Improving Global Outcomes (KDIGO) guideline statements and practice points and provided perspective for implementation within the context of clinical practice in the United States. Overall, the KDOQI work group agrees with the majority of the KDIGO guideline statements. Throughout this commentary, the KDOQI work group provides clarifications and additional areas for consideration when implementing these practice points.

Complete author and article information provided before references.

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KDOQI Commentaries are not peer reviewed by AJKD because they reflect the views and recommendations of the responsible KDOQI Commentary work group and they are reviewed and approved by KDOQI leadership and the NKF Scientific Advisory Board. This article was prepared by a KDOQI Commentary work group comprising Salem Almaani, Isabelle Ayoub, and Duvuru Geetha.

Introduction

Antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis (AAV) is a group of small vessel vasculitides with several clinical phenotypes: granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis. The kidneys are involved in more than 70% of cases of GPA and MPA (ANCA-associated glomerulonephritis, ANCA-GN).[1] Histologically, ANCA-GN presents as a pauci-immune necrotizing and crescentic glomerulonephritis whereas it often presents clinically as a rapidly progressive glomerulonephritis (RPGN). ANCA-GN is one of the main contributors to morbidity and mortality in AAV and influences the therapeutic approach. Several clinical trials have been conducted in patients with AAV, but the majority of trials excluded patients with eosinophilic granulomatosis with polyangiitis. Thus, the recommendations for management are limited to patients with GPA and MPA.

Review and Approval Process for this Commentary

The KDOQI Leadership selected members of the KDOQI work group based on their clinical and research expertise as well as their interest in the guideline process and experience taking care of people with ANCA–associated vasculitis. KDOQI work group members reviewed recent literature and provided commentary on the KDIGO guideline recommendations. The work group discussed the guideline via teleconference, and all work group members and KDOQI leadership reviewed and approved the commentary. This review and commentary follow the same order and numbering scheme used in the KDIGO guideline.[2] All KDIGO guideline practice points and recommendations are reproduced although commentary is not provided for each. The KDOQI work group agrees with the practice points and recommendations for which it has provided no commentary. For those guideline recommendations that may have implications for clinical care in the United States, we present comments and discuss their clinical utility and implementation. All material is reproduced with permission of KDIGO.

9.1. Diagnosis

Practice Point 9.1.1: In the case of a clinical presentation compatible with small-vessel vasculitis in combination with positive myeloperoxidase (MPO)- or proteinase 3 (PR3)-ANCA serology, waiting for a kidney biopsy to be performed or reported should not delay starting immunosuppressive therapy, especially in patients who are rapidly deteriorating.

Commentary and Clinical Utility

The KDOQI work group agrees with this practice point, which was retained from the 2021 KDIGO guideline for the management of glomerular diseases (see Figure 1 in the guideline for additional guidance). ANCA-GN frequently presents as RPGN, and timely initiation of immunosuppressive therapy is crucial for rapid

amelioration of inflammation and maintenance of kidney function.

Kidney biopsy is the gold standard for confirmation of diagnosis and adds prognostic value.[3] However, in the presence of a compatible clinical presentation of small vessel vasculitis and positive ANCA serologies, which should be tested in all patients and are positive in ~90% of cases of GPA and MPA,[1] treatment should not be delayed until kidney biopsy results are available.

Similar to the 2021 guideline, the 2024 KDIGO guideline lacks a discussion of drug-induced AAV, which can be caused by drugs such as hydralazine, propylthiouracil, cocaine adulterated with levamisole, and minocycline. Drug-induced AAV is characterized by high-titer myeloperoxidase (MPO)-ANCA positivity, dual MPO- and proteinase 3 (PR3)-ANCA positivity, and discordance of ANCA type by immunofluorescence and enzyme-linked immunosorbent assay (ELISA); it is often associated with the presence of other autoantibodies such as antihistone antibodies and antinuclear antibody (ANA).

The 2024 KDIGO guideline did not include a discussion of infection-associated glomerulonephritis with ANCA positivity, which can present clinically similarly to ANCA-GN and is often associated with positive ANCAs, especially in patients with endocarditis-associated glomerulonephritis.[4]

Implementation and Challenges

ANCA-GN is characterized by rapid clinical deterioration over days to weeks if left untreated. Kidney biopsy is essential for confirmation of diagnosis and should be expedited in centers that lack timely testing of ANCA serologies. Additionally, in centers where antigen-specific testing is not available, positive ANCA testing using immunofluorescence can be used for initiation of therapy in patients with a compatible clinical presentation.

Practice Point 9.1.2: Patients with ANCA-associated vasculitis (AAV) should be treated at centers with experience in AAV management.

Commentary

We agree with this practice point that was retained from the 2021 KDIGO guideline. We acknowledge the need for multidisciplinary expertise in vasculitis, given the rarity of this disease, the need for rapid diagnosis, and the complexities of initiating and managing immunosuppressive therapy and its complications. However, we also acknowledge that there are a limited number of centers with such expertise.

9.2. Prognosis

9.2.1. Survival

No recommendations or practice points.

9.2.2. Kidney Prognosis and Remission

No recommendations or practice points.

9.2.3. Relapses

Practice Point 9.2.3.1: The persistence of ANCA positivity, an increase in ANCA levels, or a change in ANCA from negative to positive may be predictive of future disease relapse and should be considered when making treatment decisions.

Commentary

We agree with this point, which has been retained from the 2021 KDIGO guideline. The relationship between ANCA titer and disease relapse is variable and can be influenced by many factors such as ANCA type, method of measurement (immunofluorescence vs antigen-specific testing), induction agent, and disease phenotype.

Clinical Utility

Several studies have reported the relationship between ANCA titers and risk of relapse. In the REMAIN trial, persistence of ANCA positivity was associated with relapse risk, independently from ANCA type or disease phenotype.[5] In PR3-ANCA patients treated with rituximab, disappearance of ANCAs was associated with long-lasting remission.[6] A meta-analysis of several studies demonstrated a modest predictive ability of ANCA titers on the risk of relapse that varied according to the type of ANCA (better for MPO/pANCA).[7] However, in a single-center study, the rise in ANCA titer was a strong predictor of subsequent relapse in patients with kidney disease.[8] Analysis from the RAVE trial demonstrated that a rise in ANCA titer was predictive of relapse in patients treated with rituximab, particularly in patients with kidney disease or alveolar hemorrhage.[9] Although ANCA monitoring alone is not helpful to guide treatment decisions, it can help in relapse prediction and identify patients who need close monitoring for relapse.[10] Nonetheless, treatment decisions should be informed by the clinical status of the patient in conjunction with other pertinent diagnostic studies confirming disease activity.

Implementation and Challenges

The utility of serial ANCA monitoring has considerable challenges. These include a lack of assay standardization, the absence of well-defined thresholds that reflect or forecast a disease relapse, and uncertainty regarding the optimal frequency of monitoring.

9.3. Treatment

9.3.1. Induction

Recommendation 9.3.1.1: We recommend that glucocorticoids in combination with rituximab or cyclophosphamide be used as initial treatment of new-onset AAV *(1B)*.

Commentary and Clinical Utility

The work group agrees with this recommendation that was retained from the 2021 KDIGO guideline (see also Fig 6 in this commentary). This recommendation is based on the RAVE and RITUXIVAS trials, which demonstrated that induction therapy with cyclophosphamide or rituximab (alone or in combination with 2 doses of cyclophosphamide) were similar in efficacy and adverse event rates.[11,12] We also agree with the accompanying comment that the best evidence is available for patients with new-onset disease as rituximab was superior to cyclophosphamide for remission induction in patients with relapsing disease and PR3-ANCA positivity.[11,13] Additionally, we agree that there are limited available data for induction therapy with single-agent rituximab in patients with severe kidney involvement (defined as a serum creatinine > 4 mg/dL); patients with a serum creatinine exceeding this threshold were excluded from participation in the RAVE trial. Based on the RAVE and RITUXIVAS trial results, cyclophosphamide and rituximab are both effective for remission induction in AAV, with rituximab preferred for relapsing disease and those with PR3-ANCA, and cyclophosphamide (alone or in combination with rituximab) preferred for those presenting with severe kidney failure.

Patient preference should also be considered when choosing an induction agent. A patient panel on the American College of Rheumatology ANCA guideline committee preferred rituximab over cyclophosphamide.[14] It is also important to clarify the dosing of rituximab for remission induction. The US Food and Drug Administration approved 4 weekly doses of 375 mg/m^2, but 2 doses of 1,000 mg rituximab given 2 weeks apart have been shown in systematic review and meta-analysis to be equally effective,[15] and choosing between these 2 dosing regimens should be guided by patient preference.

The 2024 KDIGO guideline did not make any recommendations for use of mycophenolate mofetil (MMF) for induction therapy but suggested it as an alternative to cyclophosphamide in patients with non-life-threatening disease without RPGN, in whom it was as effective as cyclophosphamide for remission induction.[16,17] However, in the MYCYC trial, MMF resulted in a higher relapse rate, especially in patients with PR3-ANCA, suggesting that MMF can be an alternative to cyclophosphamide primarily in patients with MPO-ANCA with mild to moderate kidney disease in whom avoidance of cyclophosphamide and rituximab is desirable.[16] Methotrexate also was noninferior to cyclophosphamide for remission induction of nonsevere extrarenal disease but resulted in a higher relapse rate.[18] The induction therapy of choice should therefore be guided by patient age, new onset/relapsing disease, ANCA serotype, severity of kidney dysfunction, and patient preference.

Implementation and Challenges

A recent analysis of AAV treatment patterns in patients from the Rheumatology Informatics System for Effectiveness (RISE) Registry, who are treated mainly by community rheumatologists, showed that in the United States rituximab was the most prescribed induction agent and cyclophosphamide the least prescribed induction agent.[19] However, using rituximab as an induction agent may be associated with delays depending on availability and insurance coverage. By contrast, cyclophosphamide is generally widely available, and treatment delays are less likely.

Practice Point 9.3.1.1: A practical treatment algorithm for AAV with kidney involvement is given in Figure 6.

Commentary and Clinical Utility

The 2021 KDIGO guideline stratified treatment for AAV based on disease severity; however, the 2024 guideline removed this stratification, likely due to the fact that ANCA-GN represents organ-threatening disease. For consideration of plasma exchange, the updated algorithm sets a threshold for organ-threatening kidney disease at serum creatinine level > 3.4 mg/dL (compared to serum creatinine > 5.7 mg/dL in the 2021 guideline). This recommendation was largely based on a meta-analysis of 7 trials (including PEXIVAS) that found a minimal absolute risk reduction in rates of end-stage kidney disease (ESKD) at 12 months in patients with serum creatinine < 3.4 mg/dL (300 μmol/L). This meta-analysis found an absolute risk reduction of ESKD rates at 12 months of 4.6% and 16% in patients with a presenting serum creatinine of 3.4-5.7 mg/dL (300-500 μmol/L) and >5.7 mg/dL (500 μmol/L), respectively.[20]

The potential benefit of using plasma exchange in these patients should be weighed against the risk of infections. The absolute risk increase of infection at 12 months in patients with a presenting serum creatinine of 3.4-5.7 mg/dL (300-500 μmol/L) and >5.7 mg/dL (500 μmol/L) were 8.6% and 13.5%, respectively. The new algorithm also recommends the use of cyclophosphamide or a combination of cyclophosphamide and rituximab in patients with severe disease (see Practice Point 9.3.1.2). In addition, the algorithm recommends consideration of the C5a-receptor antagonist avacopan as an alternative to glucocorticoids based on the ADVOCATE trial, which found avacopan to be noninferior to glucocorticoids at 6 months and superior at 12 months for achieving remission.[21]

For maintenance therapy, the algorithm suggests azathioprine or rituximab, with consideration for a preferred choice depending on certain clinical conditions (Fig 13 of the KDIGO guideline). Based on results of the MAINRITSAN trial, rituximab would be preferred after cyclophosphamide induction[22]; observational studies suggest effectiveness of rituximab for remission maintenance after rituximab induction.[23] Additionally, the RITAZAREM trial demonstrated the superiority of rituximab compared with azathioprine for remission maintenance in patients with relapsing AAV induced with rituximab.[24] Thus, we suggest using rituximab as the first-line maintenance agent and azathioprine as the second line for maintenance of remission.

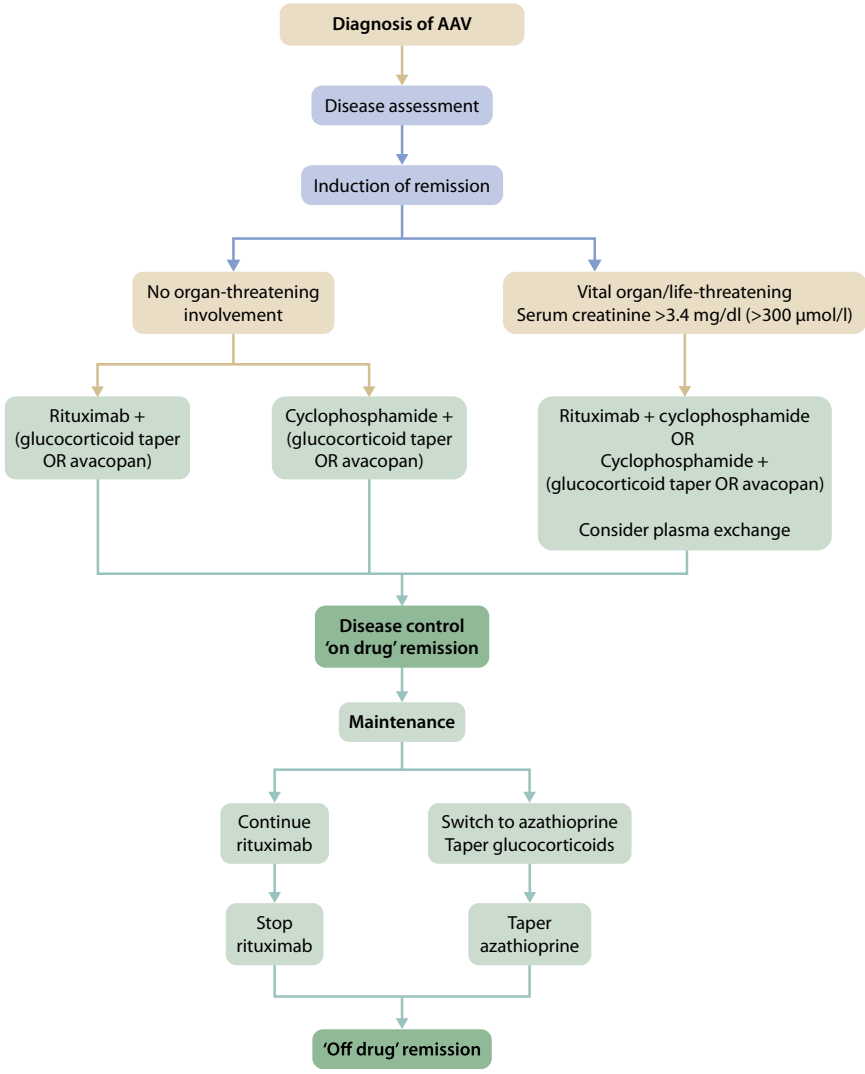

Figure 6. Practical treatment regimen for AAV. Abbreviations: AAV, ANCA-associated vasculitis; ANCA, antineutrophil cytoplasmic antibody.

Implementation and Challenges

Although the goal of induction therapy is to achieve remission, we lack a robust and uniform definition of remission. The Birmingham Vasculitis Activity Score (BVAS)[25] is used in clinical trials to assess disease activity, with BVAS of 0 or 1 used to define remission. However, the BVAS score is seldom used in day-to-day patient care, and clinicians typically rely on a combination of clinical symptoms and laboratory/imaging criteria to assess remission status. Unlike lupus nephritis, an end point for kidney remission in AAV is not currently utilized. Clinicians typically rely on stabilization of serum creatinine and resolution of hematuria and proteinuria. It is important to note, however, that the significance of persistent hematuria and proteinuria is unclear. In a post hoc analysis of RAVE and WGET, more than 40% of patients who achieved remission after induction had persistent hematuria for at least 6 months, and this was associated with higher risk of kidney relapse.[26] Other trials showed that proteinuria and hematuria after remission induction are associated with ESKD and/or death and kidney relapse, respectively.[27] There is a clear need for better biomarkers of disease activity/damage to help customize therapy for patients.

> Practice Point 9.3.1.2: In patients presenting with markedly reduced or rapidly declining glomerular filtration rate (GFR) (SCr >4 mg/dl [>354 µ mol/l]), there are limited data to support rituximab and glucocorticoids. Both cyclophosphamide and glucocorticoids, and the combination of rituximab and cyclophosphamide can be considered in this setting.

Commentary

We agree with this recommendation. This population of patients has a high risk of progression to kidney failure and a high mortality rate. A combination of glucocorticoids

Rituximab preferred	Cyclophosphamide preferred
• Children and adolescents • Premenopausal women and men concerned about their fertility • Frail older adults • Glucocorticoid-sparing especially important • Relapsing disease • PR3–ANCA disease	• Rituximab difficult to access • Severe GN (SCr >4 mg/dl [354 μmol/l]), combination of 2 intravenous pulses of cyclophosphamide with rituximab can be considered

Figure 7. Factors for consideration when choosing between rituximab and cyclophosphamide for induction therapy of AAV. Abbreviations: AAV, ANCA-associated vasculitis; ANCA, antineutrophil cytoplasmic antibody; GN, glomerulonephritis; PR3, proteinase 3; SCr, serum creatinine.

and cyclophosphamide has the best evidence for efficacy in this population and therefore is preferred. Treatment with a combination of glucocorticoids, cyclophosphamide, and rituximab is also reasonable because the results of the RITUXIVAS trial and other observational studies conducted in the United Kingdom and United States demonstrated excellent rates of remission and patient survival.[28,29]

Implementation and Challenges

This group of patients represents the most severe AAV phenotype and should be managed in a dedicated vasculitis or glomerulonephritis clinic. In hospitalized patients, the therapies described previously can be implemented without major hurdles. However, when the patient is discharged, follow-up with physicians with expertise in management of AAV is critical to ensure close monitoring of renal recovery, identification of refractory or relapsing disease, management of therapy-related adverse events, adjustment of the immunosuppressive regimen, and long-term care.

Practice Point 9.3.1.3: Considerations for choosing between rituximab and cyclophosphamide for induction therapy are given in Figure 7.

Practice Point 9.3.1.4: Considerations for choosing the route of administration of cyclophosphamide are given in Figure 8.

Commentary and Clinical Utility

Practice Point 9.3.1.3 was retained from the 2021 KDIGO guideline, and Figure 7 in this commentary lists the factors that make a rituximab- or a cyclophosphamide-based regimen preferable. The list excludes patient preference and medication nonadherence, both of which should be considered when choosing between therapeutic regimens. Figure 7 lists glucocorticoid-sparing as a factor for preferring rituximab, but the evidence for this preference is lacking. In the RAVE trial, glucocorticoid dosing was similar between the cyclophosphamide and rituximab arms; and a subgroup analysis of the PEXIVAS trial demonstrated that use of standard-dose glucocorticoids compared with reduced-dose glucocorticoids in rituximab-treated patients had a favorable effect on the primary outcome of death and kidney failure.

Figure 7 also suggests the use of rituximab in frail older adults; however, there are limited data to support this suggestion because most reported observational studies likely suffer from confounding by indication. Importantly, studies in the elderly population have demonstrated improved survival when treated with "standard" immunosuppression with cyclophosphamide or rituximab.[30,31] Treating clinicians should be cognizant of the need for cyclophosphamide dose adjustment and monitoring for bone marrow suppression in the elderly population.[32]

Figure 8 in this commentary, which depicts considerations for choosing the route of administration of cyclophosphamide, lists factors that might influence the choice of providing cyclophosphamide intravenously or as an oral formulation. Both delivery routes are effective for remission induction, and both need meticulous monitoring for adverse events. We agree that intravenous cyclophosphamide may be preferred in patients who already have

Intravenous cyclophosphamide	Oral cyclophosphamide
• Patients who already have a moderate cumulative dose of cyclophosphamide • Patients with lower white blood cell counts • Ready access to an infusion center • Adherence may be an issue	• Cost is an important factor • Access to an infusion center difficult • Adherence is not an issue

Figure 8. Considerations for the route of administration of cyclophosphamide for AAV. AAV, ANCA-associated vasculitis. Abbreviations: ANCA, antineutrophil cytoplasmic antibody.

received a moderate cumulative dose of cyclophosphamide, in patients with lower white blood cell counts, or where poor adherence might be an issue. Intravenous cyclophosphamide may also be preferred in younger patients who can suffer from gonadal toxicity. Although lack of access to an infusion center may make oral cyclophosphamide preferable, the CYCLOPS trial[33] used a 3-day (5 mg/kg/day) pulse of oral cyclophosphamide after the first 3 intravenous doses; this route of administration can be a consideration in patients where a lower cumulative dose of cyclophosphamide is needed. Lastly, individual physician and patient preferences should be taken into consideration.

Practice Point 9.3.1.5: Consider discontinuation of immunosuppressive therapy after 3 months in patients who remain on dialysis and who do not have any extrarenal manifestations of disease.

Commentary and Clinical Utility

This practice point is consistent with the 2021 KDIGO guideline. We suggest that withdrawal of immunosuppression in patients with renal-limited vasculitis should be considered 3 to 6 months after starting dialysis, given the low chance of renal recovery, high risk of infection, and low risk of extra renal relapse.[34,35] In patients with extrarenal manifestations, treatment should be tailored to extrarenal disease.

Implementation and Challenges

Patients with AAV with severe kidney involvement resulting in the need for dialysis are often hospitalized early in their disease journey. It is important for these patients to have disposition pathways that ensure close follow-up with a nephrologist who has expertise in the care of AAV.

Practice Point 9.3.1.6: Recommendations for oral glucocorticoid tapering are given in Figure 9.

Commentary and Clinical Utility

The recommended glucocorticoid regimen in the 2024 KDIGO guideline, which has been retained from the 2021 guideline, is based on body weight. Because glucocorticoids are a major contributor to morbidity and mortality in the AAV population, efforts toward dose reduction have been pursued. The PEXIVAS and LoVAS trials were the main trials to explore the efficacy of a reduced-glucocorticoid approach in patients with AAV.[36,37] We agree with the recommendation to adopt a reduced-dose glucocorticoid regimen; however, we note that only 15% of patients in the PEXIVAS trial received induction with rituximab, so the efficacy and safety of reduced-dose glucocorticoid in this group requires further study. For this reason, when using reduced-dose glucocorticoids, we suggest close monitoring of kidney function during the first 4 weeks for patients receiving rituximab for induction therapy and in those presenting with organ-threatening kidney involvement.

We also note that there are alternative strategies that can reduce the glucocorticoid burden in patients with AAV; the ADVOCATE trial demonstrated that the use of avacopan, a C5a receptor blocker, had similar efficacy to high-dose glucocorticoids at week 26 and had superior efficacy at week 52 when used in combination with rituximab or cyclophosphamide. The use of avacopan was also associated with a decreased relapse rate, better preservation of estimated glomerular filtration rate (GFR), reduced glucocorticoid toxicity, and improved quality of life.[21] Additionally, treatment with a combination regimen of rituximab and cyclophosphamide was useful in reducing oral glucocorticoid therapy to less than 2 weeks in 2 small observational studies from the United Kingdom and Ireland.[38,39] Finally, the dose of pulse glucocorticoids continues to be based on local practice patterns and is not evidence based.

Practice Point 9.3.1.7: Avacopan may be used as an alternative to glucocorticoids. Patients with an increased risk of glucocorticoids toxicity are likely to receive the most benefit from avacopan. Patients with lower GFR may benefit from greater GFR recovery.

Commentary and Clinical Utility

This is a new practice point that was not included in the 2021 KDIGO guideline. The ADVOCATE trial demonstrated that the use of the C5a receptor blocker avacopan had similar efficacy to steroids for achieving remission at 26 weeks and was superior at 52 weeks.[21] In the avacopan arm, patients received glucocorticoids but at significantly reduced cumulative dose by two-thirds. The use of avacopan was expectedly associated with a lower rate of glucocorticoid-induced adverse effects (measured using the glucocorticoid toxicity index). Patients receiving avacopan experienced a larger increase in GFR, an effect that was consistent across different baseline GFR cutoffs, and a faster decrease in proteinuria.[40] Additionally, patients receiving avacopan also experienced a lower relapse rate.

We agree with this practice point with 2 comments. First, the ADOVCATE trial excluded patients who presented with estimated GFR < 15 mL/min/1.73 m^2, thus the data on efficacy in this population are limited. Second, around 60% of patients in ADVOCATE received rituximab for induction with no maintenance rituximab or steroids after 20 weeks, which likely confounds the observation for superior efficacy at 12 months and the decreased rate of relapse.

Implementation and Challenges

The use of avacopan may be limited by financial considerations and limited availability, especially for patients who

are hospitalized early in their disease course because many health care centers do not carry avacopan in their inpatient formulary. However, in a recent real-world evidence study on the use of avacopan, patients receiving avacopan >30 days after induction were still able to achieve a lower cumulative glucocorticoid dose when compared with patients who had received avacopan earlier, with a similar improvement in GFR albeit with a slower improvement in proteinuria.[41] Hence, avacopan use should still be considered in patients who are at a higher risk of developing glucocorticoid-related adverse effects and in patients with a low GFR, even after hospital discharge.

Practice Point 9.3.1.8: Recommendations for immunosuppressive dosing are given in Figure 10.

Practice Point 9.3.1.9: Consider plasma exchange for patients with 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.

Commentary and Clinical Utility

The serum creatinine cutoff used for this practice point has decreased from serum creatinine > 5.7 mg/dL (500 μmol/L) to serum creatinine > 3.4 mg/dL (>300 μmol/L). We agree with this practice point with 2 comments.

The rationale for decreasing the serum creatinine threshold for consideration of plasma exchange was discussed in our commentary on Practice Point 9.3.1.1 and is based on a meta-analysis of 7 trials (including PEXIVAS) that found a minimal absolute risk reduction in rates of ESKD at 12 months in patients with serum creatinine < 3.4 mg/dL (300 μmol/L).[20] This meta-analysis found a meaningful absolute risk reduction of ESKD rates at 12 months in patients presenting with a serum creatinine > 3.4 mg/dL (300 μmol/L). Treatment with plasma exchange should also consider the increased absolute risk of infections observed in patients with a serum creatinine of >3.4 mg/dL (300 μmol/L).

The practice point recommends plasma exchange in patients with alveolar hemorrhage and hypoxemia. However, a subgroup analysis of the PEXIVAS trial did not demonstrate any significant difference in rates of death or ventilator-free days between patients who received plasma exchange and patients who did not, albeit the number of patients with clinically significant alveolar hemorrhage was small.[42] Recent guidelines from the European League Against Rheumatism (EULAR)[43] and the American College of Rheumatology (ACR)[14] recommend against the routine use of plasma exchange in this population. The use of plasma exchange in these patients should be individualized and should consider the increase in risk of infections.

Practice Point 9.3.1.10: Add plasma exchange for patients with an overlap syndrome of ANCA-associated vasculitis and anti-glomerular basement membrane (GBM).

Commentary

This practice point has been retained from the 2012 and 2021 KDIGO guidelines. We agree with adding plasma exchange daily for 14 days or until antiglomerular basement membrane (anti-GBM) antibodies are undetectable.[44]

Implementation and Challenges

The plasma exchange regimens outlined in Figure 11 of the guidelines have been retained from the 2021 guideline. We agree with a dose of 7 treatments over 14 days in patients with glomerulonephritis and a daily treatment regimen for patients with concomitant anti-GBM disease. Expertise in plasma exchange procedure and knowledge of its applications and complications are needed. In patients whose kidney biopsy was performed in the prior week, it is important to consider fresh frozen plasma instead of albumin to minimize the risk of postbiopsy bleeding. In addition, the timing of medications should be adjusted based on the plasma exchange schedule. Intravenous cyclophosphamide can be given after a plasma exchange session, and plasma exchange should be held for 48 to 72 hours after rituximab infusion.

9.3.2. Maintenance Therapy

Recommendation 9.3.2.1: We recommend maintenance therapy with either rituximab, or azathioprine and low-dose glucocorticoids after induction of remission *(1C)*.

Commentary

The work group agrees overall with this recommendation, which was retained from the 2021 KDIGO guideline, with some clarifications. We agree that all patients should receive maintenance immunosuppressive therapy except for patients with kidney-limited disease who remain on dialysis after completing induction therapy. Although patients with MPO-ANCA demonstrated a low risk of relapse in the RAVE trial,[11] the REMAIN trial did not demonstrate that anti-MPO versus PR3 positivity was predictive of the relapse rate.[5] We therefore suggest that all patients be treated with maintenance immunosuppression if they are not receiving dialysis, regardless of the induction agent used.

The 2024 guideline does not explicitly recommend the use of rituximab or azathioprine as a first-line maintenance agent. Patients treated with rituximab demonstrated a lower relapse rate compared with those on azathioprine after induction therapy with cyclophosphamide[22] and rituximab.[24] Thus, in line with the EULAR[43] and ACR guidelines,[14] rituximab should be considered as a first-line agent in maintenance therapy, especially in patients with a high risk of relapse. Azathioprine can be considered as an alternative agent in patients with low IgG levels. When using

azathioprine, concomitant use of low-dose prednisone should be considered because this combination was favorable for relapse prevention in a meta-analysis of 13 trials[45] and is supported by the preliminary results of the TAPIR trial.[46] In the same trial, use of prednisone with rituximab maintenance did not seem to add any benefit and, given that prednisone therapy beyond 6 months is associated with increased infection risk,[47] we do not suggest its use in patients receiving rituximab maintenance.

Clinical Utility

Longitudinal management of patients with AAV includes many considerations. Preventing a relapse is critical to limiting morbidity and mortality. Patients with AAV are at high risk of infections, which are the main cause of death in the first year of therapy and contribute to long-term mortality.[48,49] Hence, there is the need to monitor for infections and ensure *Pneumocystis jirovecii* pneumonia (PJP) prophylaxis. Monitoring immunoglobulin levels is especially important in patients receiving maintenance rituximab, in particular after a combination of rituximab/cyclophosphamide for induction. AAV patients are also at a higher risk of cardiovascular disease than the general population, even if they achieve remission. Thus, aggressive screening and management of risk factors is of utmost importance.[50] For patients receiving azathioprine, thiopurine methyltransferase activity should be tested to identify patients at risk for bone marrow suppression, and complete blood cell count and liver function tests should be monitored along with surveillance for skin cancer.

Implementation and Challenges

The therapeutic approach to patients with AAV should balance the risk of relapses with the risk of adverse events. Maintenance therapy should be individualized, based on each patient's risk/benefit profile.

Practice Point 9.3.2.1: Following rituximab induction, maintenance immunosuppressive therapy should be given to most patients.

Commentary

The KDOQI work group suggests maintenance therapy be given to all patients following successful rituximab induction for the reasons highlighted previously under Recommendation 9.3.2.1.

Practice Point 9.3.2.2: The optimal duration of remission therapy is between 18 months and 4 years after induction of remission.

Commentary

This new practice point within the 2024 KDIGO guideline suggests a duration of maintenance therapy of 18 months to 4 years for all patients regardless of induction regimen. We agree with this recommendation with some clarification. The recommendation of longer therapy in patients maintained on azathioprine is based on the REMAIN trial, which found that extending maintenance therapy to 48 months (instead of 24 months) was associated with a lower risk of relapse and improved survival.[5]

The recommendation for extended rituximab therapy is based on the MAINRITSAN 3 trial, which found that extended maintenance with rituximab for a total of 46 months was associated with a superior relapse-free survival compared with placebo,[51] a finding that was powered by patients with PR3-ANCA. However, the patients enrolled in MAINRITSAN 3 had been participants in MAINRITSAN 2[52]; they received either a fixed-dose or tailored rituximab therapy before participating in MAINRITSAN 3, which likely confounded the findings. A pooled analysis of MAINRITSAN trials demonstrated similar major relapse-free survival between patients who received fixed-dose rituximab for 18 or 36 months and patients who received tailored rituximab for 18 months followed by fixed-dose rituximab for 18 months.[53] However, the patients who received tailored rituximab for 18 months followed by placebo had a higher rate of major relapse compared with the other rituximab regimens. In light of the evidence thus far, the duration of maintenance therapy should take into consideration relapse risk factors, the drug used, and the dosing regimen.

Practice Point 9.3.2.3: When considering withdrawal of maintenance therapy, the risk of relapse should be considered, and patients should be informed of the need for prompt attention if symptoms recur (Figure 12).

Baseline factors	Factors after diagnosis	Treatment factors
• Diagnosis of granulomatosis with polyangiitis • PR3–ANCA subgroup • Higher serum creatinine • More extensive disease • Ear, nose, and throat disease	• History of relapse • ANCA positive at the end of induction • Rise in ANCA	• Lower cyclophosphamide exposure • Immunosuppressive withdrawal • Glucocorticoid withdrawal

Figure 12. Factors that increase relapse risk for AAV. Abbreviations: AAV, ANCA-associated vasculitis; ANCA, antineutrophil cytoplasmic antibody; PR3, proteinase 3.

Commentary

This practice point has been retained from the 2021 KDIGO guideline and is accompanied by Figure 12 (found in this commentary), which lists factors that increase risk of relapse. We agree with the listed factors. In patients with ANCA-GN, a lower serum creatinine level is associated with a higher risk of relapse.[54] Relapse rates in patients with AAV remain high, with around 40% of patients experiencing a relapse with long-term follow-up regardless of induction regimen (cyclophosphamide or rituximab).[55,56]

Implementation and Challenges

Given the high risk of relapses, patients should ideally be evaluated at regular intervals in centers with expertise in the care of vasculitis because early recognition of a relapse and early therapeutic intervention are necessary to achieve long-term kidney health. In addition, although patients with higher serum creatinine levels are at a lower risk of relapse, their limited kidney reserve can make a relapse more catastrophic and result in initiation of kidney replacement therapy; thus, special consideration should be given to these patients when deciding to withdraw immunosuppression.

Practice Point 9.3.2.4: Consider mycophenolate mofetil (MMF) or methotrexate as alternatives to azathioprine for maintenance therapy in patients intolerant of azathioprine. Methotrexate should not be used for patients with a GFR <60 ml/min per 1.73 m^2.

Commentary

We agree with this practice point with 2 comments. First, rituximab was superior to azathioprine for prevention of relapse and should be considered first in patients who are intolerant to azathioprine.[22,53] Second, methotrexate was found to be of equal efficacy to azathioprine in the WEGENT trial[57] whereas in the IMPROVE trial MMF was found to be inferior to azathioprine in preventing relapses.[58] Hence, consideration of efficacy should be included for patients who are intolerant of azathioprine and rituximab.

Practice Point 9.3.2.5: Considerations for choosing rituximab or azathioprine for maintenance therapy are presented in Figure 13.

Commentary

This practice point has been retained from the 2021 KDIGO guideline and provides guidance on choosing between rituximab and azathioprine as the appropriate maintenance therapy (see also Fig 13 in this commentary). The work group discussed these factors under Recommendation 9.3.2.1 earlier.

Practice Point 9.3.2.6: Recommendations for dosing and duration of maintenance therapy are given in Figure 14.

9.3.3. Relapsing Disease

Practice Point 9.3.3.1: Patients with relapsing disease should be reinduced (Recommendation 9.3.1.1.), preferably with rituximab.

Commentary

This practice point has been retained from the 2021 KDIGO guideline. In the RAVE trial, rituximab was associated with a better relapse rate when compared with cyclophosphamide in patients with relapsing disease, even after adjustment for ANCA type.[11] A post hoc analysis of RAVE patients who relapsed after successfully achieving remission demonstrated that reinduction with rituximab achieved remission in >87% of patients regardless of their initial induction regimen.[59] The RITAZAREM trial demonstrated that rituximab induced remission in 91% of patients with relapsing GPA/MPA.[60]

9.4. Special Situations

9.4.1. Refractory Disease

Practice Point 9.4.1.1: Refractory disease can be treated by an increase in glucocorticoids (intravenous or oral), by the addition of rituximab if cyclophosphamide induction had been used previously, or vice versa. Plasma exchange can be considered.

Rituximab preferred	Azathioprine preferred
• Relapsing disease • PR3–ANCA disease • Frail older adults • Glucocorticoid-sparing especially important • Azathioprine allergy	• Low baseline IgG <300 mg/dl • Limited availability of rituximab

Figure 13. Considerations for using rituximab or azathioprine for AAV maintenance therapy. AAV, ANCA-associated vasculitis; ANCA, antineutrophil cytoplasmic antibody; IgG, immunoglobulin G; PR3, proteinase 3.

Commentary

This practice point has been retained from the 2021 KDIGO guideline. Refractory disease is defined as unchanged or increased disease activity after 4 weeks of treatment with standard induction therapy or <50% improvement in the BVAS score after 6 weeks. In a post hoc analysis of the RAVE trial, most patients (>85%) who suffered a severe flare or had uncontrolled disease achieved a remission with masked crossover.[61] Intravenous immunoglobulin can also be used as an adjunct in the treatment of patients with persistent disease.[62]

Implementation and Challenges

Before labeling disease as "refractory" or "persistent," it is essential to ensure the correct diagnosis and medication adherence. Patients with refractory disease should be referred to centers of expertise, both to confirm refractory vasculitis and determine further treatment decisions.

Practice Point 9.4.1.2: In the setting of diffuse alveolar bleeding with hypoxemia, plasma exchange can be considered in addition to glucocorticoids with either cyclophosphamide or rituximab.

Commentary

Diffuse alveolar hemorrhage is one of the life-threatening manifestations of AAV, occurring in 25% of patients with AAV.[63] Its management generally parallels the therapeutic approach used for active glomerulonephritis. The 2024 KDIGO guideline differs from the 2021 guideline in the phrasing "can be considered" instead of "should be considered." As mentioned in the commentary of Practice Point 9.3.1.9 earlier, subgroup analysis of the PEXIVAS trial did not demonstrate any significant difference in rates of death or ventilator-free days between patients who received plasma exchange and patients who did not, albeit the number of patients with clinically significant alveolar hemorrhage was small.[42] Recent guidelines from EULAR[43] and ACR[14] recommend against the routine use of plasma exchange in this population. Given the risk of infection, the decision to use plasma exchange should be individualized.

4.2. Transplantation

Practice Point 9.4.2.1: Delay transplantation until patients are in complete clinical remission for ≥6 months. The persistence of ANCA should not delay transplantation.

Commentary

This practice point has been retained from the 2021 KDIGO guideline. We favor delaying transplantation until patients have been in extrarenal remission for 12 months. In a cohort of patients with AAV, transplantation less than 1 year after achieving remission was associated with an increased probability of death, even after correcting for other variables.[64] Patients who are ANCA positive at the time of transplantation and those with a GPA phenotype are at a higher risk of relapse.[65] These patients should not be disqualified from kidney transplantation but should be monitored more closely for relapses.

Conclusion

The 2024 KDIGO guideline provides a comprehensive framework for the care of patients with AAV. The incorporation of complement inhibitors as an alternative to glucocorticoids in the AAV therapeutic strategy represents a major update over previous iterations. Additionally, the updated guideline has a more nuanced approach to the use of plasma exchange, acknowledging its potential risks and benefits. Taken together, the 2024 KDIGO guideline reflects the most recent advances in AAV and ANCA-GN therapies. However, given that AAV is a multisystem disease, taking a holistic approach to care that considers all organ systems involved remains the best way to serve patients.

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