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Review

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What Has Changed in the New Guidelines in the Treatment of ANCA-Associated Vasculitis?

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ABSTRACT

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a rapidly progressing disease with high mortality and morbidity. There is necrotizing inflammatory involvement in small vessels associated with autoantibodies against proteinase-3 (PR3) and myeloperoxidase (MPO-ANCA). Mortality rates are significantly higher within the first year. Causes that increase mortality include rapid deterioration in serum creatinine and glomerular filtration rate, pulmonary hemorrhage, delay in treatment, and adverse events related to treatments. Kidney and other organ involvement also affect the treatment protocol and dose. Kidney Diseases Improving Global Outcomes (KDIGO) has been providing treatment management guidelines for glomerulonephritis, including AAV-related glomerular involvement, since 2012. The most recently published glomerulonephritis treatment guideline in 2021 highlights the emphasis on rapid reduction of the glucocorticoid dose through controlled studies. With the approval of the complement 5a antagonist avacopan (CCX 168) in AAV, KDIGO has recently published separate guidance for AAV treatment management. This article discusses AAV treatment recommendations and changes in the 2024 guideline.

Keywords: ANCA-Associated Vasculitis, Avacopan, Glomerulonephritis, Vasculitis

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INTRODUCTION

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a serious, often life-threatening disease associated with autoantibodies against proteinase 3 (PR3-ANCA) and myeloperoxidase (MPO-ANCA).[1] There is necrotizing inflammation in small vessels with little or no immune complex deposition. End-stage kidney disease (ESKD) and early death continue to be common in AAV patients presenting with decreased kidney function or pulmonary hemorrhage.[2] A mortality study was published with data obtained from the United Kingdom General Practice Research Database.[3] According to this study, despite current treatment, deaths due to vasculitis, infection, and kidney failure in patients with Granulomatosis with Polyangiitis (GPA) increased ninefold in the first year compared to the control population. Although the risk was at its lowest between the first year and the 8th year, this rate increased again from the 8th year. The development of ESKD has been observed in an average of 4.6 ± 4.4 years, and this rate has been reported to be 15%-38%.[4] The European Vasculitis Study Group (EUVAS) investigated the impact of vasculitis activity and adverse events on 1-year mortality.[5] In the study, the biggest threat in the first year of treatment in patients with AAV was reported to be drug-related adverse events.

Kidney involvement and treatment have a significant impact on survival and long-term prognosis in AAV.[2] AAV-glomerulonephritis (AAV-Gn) is more common in

microscopic polyangiitis (MPA) and GPA, and is less common in eosinophilic granulomatous polyangiitis (EGPA). Kidney involvement is in the form of focal and segmental necrotizing crescentic glomerulonephritis. There is a decrease in glomerular filtration rate (GFR) within days. In AAV-Gn, the decrease in GFR can be seen together with vasculitic involvement of non-kidney organs, especially pulmonary alveolar hemorrhage. Assessment of the involvement of all relevant organ systems is summarized in the Birmingham vasculitis activity score (BVAS), allowing the clinician to assess the severity of the disease.[6] Extrarenal organ involvement, as well as the decrease in GFR, also affects the treatment protocol decision.

Kidney Diseases Improving Global Outcomes (KDIGO) published the first guideline for the treatment management of glomerulonephritis, including AAV-Gn, in 2012, the discussion conference in 2017, and the final guideline in 2021. The complement 5a receptor (C5aR) antagonist avacopan (CCX168) was first approved for the treatment of severe AAV by the Food and Drug Administration (FDA) in Japan in September 2021 and subsequently in the United States in October 2021.[7] With the approval of the European Medicines Agency (EMA), KDIGO accelerated its work to publish a new guideline in the treatment of AAV, and the new guideline was published in 2024.[8]

DIAGNOSIS

No changes have been made to the diagnosis section of the KDIGO 2024 clinical practice guideline for AAV management.[9] Practical recommendation 9.1.1: In case of positive MPO- or PR3-ANCA serology with a clinical picture compatible with small vessel vasculitis, immunosuppressive treatment should be started without waiting for kidney biopsy or its results, especially in patients whose condition deteriorates rapidly. Kidney biopsy is the gold standard in the diagnosis of AAV-Gn. It should be done as soon as the patient's general clinical condition improves. Practical recommendation 9.1.2: Patients with AAV should be treated in centers experienced in AAV management. Definition of a center experienced in AAV management: availability of adequate serological and histological tests for rapid diagnosis; must be experienced in induction, remission treatments (all treatment methods including rituximab and plasma exchange), and management of complications must have access to intensive care unit and acute hemodialysis.

MAIN POINTS

- Morbidity and mortality increase in anti-neutrophil cytoplasmic antibody-related vasculitis, especially in the presence of a rapid decrease in glomerular filtration rate or pulmonary hemorrhage, and in case of delay in treatment.
- Drug-related adverse events affect the treatment of the disease and the patient's quality of life. For this reason, one of the points emphasized in the guideline is the rapid reduction of the glucocorticoid dose.
- In recent articles, it is emphasized that rituximab and glucocorticoid treatment should be preferred over cyclophosphamide and glucocorticoid treatment in induction treatment and relapse treatment. The combined use of rituximab and cyclophosphamide is also among the recommendations.
- Avacopan has received both FDA and EMA approval for the treatment of anti-neutrophil cytoplasmic antibody-related vasculitides and has taken its place in the guidelines for induction therapy. It has been reported in studies that the mechanism of action in the disease will be effective in reducing the glucocorticoid dose.
- Along with new recommendations for induction and relapse treatments, it is also recommended in this guideline that treatment for anti-neutrophil cytoplasmic antibody-related vasculitis be administered in experienced and well-equipped centers.

PROGNOSIS

In the prognosis phase, at 9.2.1 Survival and 9.2.2 Kidney prognosis and response to treatment, no recommendations or practical application recommendations are made in the new guideline. While the 2021 guideline uses the expression practical application recommendation 9.2.3.1: "Persistence of ANCA positivity, increase in ANCA levels, and change in ANCA from negative to positive are only a modest predictor of future disease recurrence and should not be used to guide treatment decisions." In the relapse heading, this statement has been changed to "Continuation of ANCA positivity, increase in ANCA levels, or change in ANCA from negative to positive may be predictive of disease recurrence in the future and should be taken into account when making treatment decisions," in the KDIGO 2024 guideline (Table 1).

TREATMENT

Induction Therapy

The main point of change in the KDIGO 2024 clinical practice guideline for AAV management has been in remission induction treatment. Recommendation 9.3.1.1 in the KDIGO 2021 guideline, "We recommend the use of glucocorticoids in combination with cyclophosphamide or rituximab as initial treatment of new-onset AAV (1B)," has been updated to rituximab or cyclophosphamide in the KDIGO 2024 guideline. Practical application recommendation 9.3.1.2 in the KDIGO

Table 1. Changes in the New Guideline for the Assessment of Prognosis

KDIGO 2021	KDIGO 2024
9.2.3.1: Persistence of ANCA positivity, increase in ANCA levels, and change in ANCA from negative to positive are only a modest predictor of future disease recurrence and should not be used to guide treatment decisions.	9.2.3.1: Continuation of ANCA positivity, increase in ANCA levels, or change in ANCA from negative to positive may be predictive of disease recurrence in the future and should be taken into account when making treatment decisions.

2021 guideline: "There is limited evidence supporting rituximab and glucocorticoids in patients presenting with markedly decreased or rapidly decreasing GFR (SCr >4 mg/dL [>354 µmol/L]). Cyclophosphamide and glucocorticoids are preferred for induction therapy in these patients. The statement "The combination of rituximab and cyclophosphamide may also be considered in these patients." has been updated to "In this case, both cyclophosphamide and glucocorticoids and the combination of rituximab and cyclophosphamide should be considered" in the KDIGO 2024 guideline. The RAVE (Rituximab in ANCA-Associated Vasculitis) study, published in 2010, is the first controlled study showing that rituximab treatment is noninferior to cyclophosphamide treatment in the management of AAV.[10] The RAVE study showed that rituximab and glucocorticoid could be alternatives to cyclophosphamide and glucocorticoid in induction treatment and were also superior in the treatment of relapse. In the RAVE study post-hoc analysis published in 2016, patients were evaluated separately as PR3-AAV and MPO-AAV.[11] In PR3-AAV, complete remission at 6 months was more common in the rituximab group than in the cyclophosphamide and azathioprine group. In relapse cases, remission rates at 6, 12, and 18 months were again found to be in favor of rituximab. No relationship between treatment medication and remission was observed in MPO-AAV patients. No changes were made to practical application recommendations 9.3.1.3 and 9.3.1.4. However, the use of rituximab is more prominent than the use of cyclophosphamide due to its contribution to the reduction of the glucocorticoid use. In AAV patients with serum creatinine value (SCr) >4 mg/dL, the statement "The combination of two intravenous (IV) cyclophosphamide pulses with rituximab should be considered" as in 9.3.1.2. Although the criteria for per oral (PO) or IV use of cyclophosphamide in AAV do not change in the 2024 guideline, the experience of the center providing the treatment, the sociocultural and socioeconomic status of the patients, and environmental factors such as COVID-19 affect them. The statement "Discontinue immunosuppressive treatment after 3 months in patients who continue dialysis and do not have symptoms of extrarenal disease" in practical application recommendation 9.3.1.5 has been changed to "discontinuation should be considered" in the 2024 guideline. The oral glucocorticoid reduction recommendations in Practical Application Recommendation 9.3.1.6 were left the same. In AAV, there is now a stronger emphasis on a more rapid reduction of the glucocorticoid dose. New guideline is based on the phase 4, multicenter low-dose glucocorticoid vasculitis induction study (LoVAS).[12] In the study, patients were randomized to receive 4 doses of 375 mg/m^2/week rituximab along with reduced dose prednisolone (0.5 mg/kg/day) or high dose prednisolone (1 mg/kg/day). It led to a similar remission rate in both groups at 6 months. The frequency of serious infections has decreased. Although the study has limitations, it ultimately supports the "accelerated low glucocorticoid dose schedule" used in the plasma exchange and glucocorticoids in the treatment of AAV (PEXIVAS) study (Table 2).[13]

Table 2. Prednisolone Tapering Regimen for AAV

Week	<50 kg	50-75 kg	>75 kg
1	50	60	75
2	25	30	40
3-4	20	25	30
5-6	15	20	25
7-8	12.5	15	20
9-10	10	12.5	15
11-12	7.5	10	12.5
13-14	6	7.5	10
15-16	5	5	7.5
17-18	5	5	7.5
19-20	5	5	5
21-22	5	5	5
23-52	5	5	5
>52	Physician's clinical practice		

In the practical application point 9.3.1.7 of the KDIGO 2024 guideline, the use of the new molecule C5aR antagonist avacopan as an alternative to glucocorticoids is emphasized. The statement "Patients at high risk of glucocorticoid toxicity are likely to receive the most benefit from avacopan. Patients with lower GFR may benefit from greater GFR improvement." is used. The basis of these statements is the results of the ADVOCATE (Avacopan in the Treatment of ANCA-Associated Vasculitis) Working Group. In phase 3 studies dated 2021, avacopan 30 mg tablet 2×1/day PO dose with the use of rituximab or cyclophosphamide and glucocorticoid with the use of rituximab or cyclophosphamide were compared.[14] When the study results were examined, it was seen that it was not only non-inferior to the standard care treatment at the 26th week but non-inferior or even superior at the 52nd week. Additionally, the rate of adverse effects was observed to be lower than in the glucocorticoid regimen. In the post hoc analysis of the ADVOCATE study published by Cortazar et al, AAV patients with GFR <20 mL/min/1.73 m^2 were again evaluated for 52 weeks.[15] Initial GFR values were 17.6 and 17.5 mL/min/1.73 m^2 in the avacopan and prednisone groups, respectively. Post-treatment GFR increase was seen as 16.1 and 7.5 mL/min/1.73 m^2, respectively. The doubling rate in GFR was found to be 40.7% and 13%, respectively. Albuminuria improved more quickly in the avacopan group than in the prednisone group, but the final magnitude of improvement was the same in both groups. Although the study had limitations, the results were accepted as meaningful by the KDIGO 2024 committee to support the results of previous studies.

Another vital treatment model is plasma exchange. A change was also made in the plasma exchange decision. Implementation point 9.3.1.8 in 2021: "Consider plasma exchange in patients with SCr >5.7 mg/dL (500 µmol/L) requiring dialysis or with

rapidly increasing SCr, patients with diffuse alveolar hemorrhage, and patients with hypoxemia." statement was revised as "Consider plasma exchange for patients with SCr >3.4 mg/dL (>300 µmol/L), patients requiring dialysis, or patients with rapidly increasing SCr, patients with diffuse alveolar hemorrhage, and patients with hypoxemia." in 2024. In the 2007 study conducted by the EUVAS comparing methyl prednisolone and plasma exchange, newly diagnosed AAV patients confirmed by kidney biopsy and SCr >5.7 mg/dL were included in the study. Patients were randomly assigned to receive 3000 mg IV methyl prednisolone versus the plasma exchange group. Both groups received standard care treatment with oral cyclophosphamide and oral prednisolone. The primary endpoint, the rate of remaining dialysis-free at 3 months, was reported to be 49% in the prednisolone group and 69% in the plasma exchange group.[16] The PEXIVAS study published in 2020 reported that plasma exchange did not delay AAV-related kidney failure and death.[13] In the meta-analysis of 9 studies with 1060 patients published in 2022, Walsh et al[17] stated that plasma exchange reduces the risk of ESKD in 12 months, has no effect on all-cause mortality, but increases the risk of serious infections. For ESKD and death in AAV patients: SCr >500 µmol/L represents the high-risk group, 300-500 µmol/L represents the medium-high risk group, 200-300 µmol/L represents the low-intermediate risk group, ≤200 µmol/L represents the low-risk group. The absolute risk reduction of kidney failure up to 12 months in the serum creatinine 300-500 µmol/L group was 4.6% (95% CI: 1.2%-6.8%) and 6% in patients with SCr above 5.7 mg/dL (500 µmol/L). Therefore, plasma exchange should be considered in patients with SCr above 3.4 mg/dL (300 µmol/L) or in those with alveolar hemorrhage and hypoxemia, where early mortality is high. The recommendation "Application point 9.3.1.10: Addition of plasma exchange for patients with AAV and anti-glomerular basement membrane (GBM) overlap syndrome" remains unchanged in the 2024 guideline (Table 3).

Table 3. Changes in the New Guideline in Induction Therapy

KDIGO 2021	KDIGO 2024
9.3.1.1: We recommend that glucocorticoids in combination with cyclophosphamide or rituximab be used as the initial treatment of new-onset AAV (1B).	9.3.1.1: The priority order of molecules to be used in combination with glucocorticoids in the initial treatment of AAV has changed to rituximab or cyclophosphamide (1B).
9.3.1.2: In patients presenting with markedly reduced or rapidly declining GFR (SCr >4 mg/dL [>354 µmol/L]), there are limited data to support rituximab and glucocorticoids. Cyclophosphamide and glucocorticoids are preferred for induction therapy. The combination of rituximab and cyclophosphamide can also be considered in this setting.	9.3.1.2: In the same case, it changed to "both cyclophosphamide and glucocorticoids or the combination of rituximab and cyclophosphamide can be considered"
9.3.1.5: Discontinue immunosuppressive therapy after 3 months in patients who remain on dialysis and who do not have any extrarenal manifestations of disease.	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.
	9.3.1.7: Avacopan may be used as an alternative to glucocorticoids. Patients with an increased risk of glucocorticoid toxicity are likely to receive the most benefit from avacopan. Patients with lower GFR may benefit from greater GFR recovery.
9.3.1.8: Consider plasma exchange for patients with SCr >5.7 mg/dL (500 µmol/L) requiring dialysis or with rapidly increasing SCr, and in patients with diffuse alveolar hemorrhage who have hypoxemia.	9.3.1.9: In the recommendation in 9.3.1.8, only the serum creatinine value changed to >3.4 mg/dL (>300 µmol/L).

Maintenance Therapy

The statement "recommendation 9.3.2.1: After remission induction, we recommend maintenance treatment with rituximab or azathioprine and low-dose glucocorticoids (1C)" under the title of maintenance treatment in AAVs has not changed. However, the statement "practical practice recommendation 9.3.2.1: Following cyclophosphamide induction, either azathioprine plus low-dose glucocorticoids or rituximab without glucocorticoids should be used to prevent relapse" was removed from the 2024 guideline (Table 4). However, the point of application "following rituximab induction, most patients should receive maintenance immunosuppressive therapy" remained unchanged. Imprecise statements for "Practical application recommendation: 9.3.2.3: Optimal duration of azathioprine plus low-dose glucocorticoids" and "9.3.2.4: Optimal duration of rituximab maintenance therapy" were given in the single practice recommendation in the KDIGO 2024 guideline as "The optimal duration of remission treatment is between 18 months and 4 years after remission induction." In the MAINRITSAN (Maintenance of Remission using Rituximab in Systemic ANCA-associated Vasculitis) study, in which azathioprine + glucocorticoid therapy was evaluated against rituximab for the maintenance of remission, AAV patients received rituximab 500 mg intravenously at 6, 12, and 18 months; azathioprine at 2 mg/kg/day for 12 months, 1.5 mg/kg/day for 6 months, and 1 mg/kg/day for 4 months before discontinuing.[18] In new-onset disease, after cyclophosphamide induction, maintenance with rituximab reduced the risks of major recurrence compared with azathioprine. The RITAZAREM (Rituximab in the Treatment of ANCA-Associated Renal Vasculitis) study is an evaluation of the

Table 4. Changes in the New Guideline in Maintenance Therapy

KDIGO 2021	KDIGO 2024
9.3.2.1: Following cyclophosphamide induction, either azathioprine plus low-dose glucocorticoids or rituximab without glucocorticoids should be used to prevent relapse.	9.3.2.1: Removed
9.3.2.3: The optimal duration of azathioprine plus low-dose glucocorticoids is not known but should be between 18 months and 4 years after induction of remission.	9.3.2.2: The new guideline states that "The optimal duration of remission therapy is between 18 months and 4 years after induction of remission."
9.3.2.4: The optimal duration of rituximab maintenance is not known, but studies to date have evaluated a duration of 18 months after remission. There is no role for the routine use of an oral glucocorticoid or oral immunosuppressive with rituximab maintenance.	9.3.2.4: Removed

sustainability of remission with maintenance rituximab or azathioprine after rituximab induction therapy in AAV patients.[19] It has been shown to reduce the risk of major and minor recurrence in studies lasting at least 36 months. In the MAINRITSAN3 study, after 18 months of maintenance treatment, patients were randomized to continue rituximab or placebo every 2 years. Rituximab maintenance reduced the number of relapses compared to placebo.[9] If patients with AAV were in stable remission after cyclophosphamide + glucocorticoid induction followed by azathioprine + glucocorticoid maintenance therapy, those who received maintenance therapy until 18-24 months after diagnosis were called the standard group, and those who received up to 48 months were called the continuation group.[20] The primary endpoint of the study was the assessment of the risk of recurrence up to 48 months. The risk of recurrence was less and kidney survival was better in the continuation group. Practical application points also included in the 2021 guideline: "When discontinuation of maintenance treatment is considered, the risk of relapse should be taken into account and patients should be informed about the need for immediate intervention if symptoms recur" and "considering mycophenolate mofetil or methotrexate as an alternative for maintenance treatment in patients with azathioprine intolerance (Methotrexate should not be used for patients with GFR <60 mL/min/1.73 m^2)" has not been changed in the 2024 guideline.

Relapsing Disease

AAV patients with recurrent (life- or organ-threatening) disease should undergo re-induction, preferably with rituximab. Treatment of recurrence usually consists of repeating induction therapy. If repeating the cyclophosphamide protocol is considered, it should be ensured that the total dose the patient will receive does not exceed 36 grams in terms of the risk of cancer development.[21] It was reported in the RAVE study that rituximab treatment had better complete remission rates, especially in relapses of PR3-AAV cases.[11] In the RITAZAREM and MAINRITSAN studies mentioned in maintenance treatment, it was also reported that rituximab maintenance treatment was effective in reducing the risk of relapse.

REFRACTORY DISEASE AND TRANSPLANTATION

In the 2024 guideline for AAV treatment, no changes were made to the refractory disease title and transplantation recommendations. Factors contributing to difficulty in treatment include delay in diagnosis, drug insufficiency or intolerance, and accompanying diseases. It is important to note that the progression of kidney failure may reflect chronic damage. A kidney biopsy should be considered to evaluate whether active disease or chronic change is due to ongoing kidney disease activity.

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