Chapter 13: Pauci-immune focal and segmental necrotizing glomerulonephritis

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INTRODUCTION

This chapter makes treatment recommendations for adults with pauci-immune focal and segmental necrotizing GN with or without systemic vasculitis, and with or without circulating ANCA. The cost implications for global application of this guideline are addressed in Chapter 2.

13.1: Initial treatment of pauci-immune focal and segmental necrotizing GN

13.1.1: We recommend that cyclophosphamide and corticosteroids be used as initial treatment. (*1A*)

13.1.2: We recommend that rituximab and corticosteroids be used as an alternative initial treatment in patients without severe disease or in whom cyclophosphamide is contraindicated. (*1B*)

13.2: Special patient populations

13.2.1: We recommend the addition of plasmapheresis for patients requiring dialysis or with rapidly increasing SCr. (*1C*)

13.2.2: We suggest the addition of plasmapheresis for patients with diffuse pulmonary hemorrhage. (*2C*)

13.2.3: We suggest the addition of plasmapheresis for patients with overlap syndrome of ANCA vasculitis and anti-GBM GN, according to proposed criteria and regimen for anti-GBM GN (see Chapter 14). (*2D*)

13.2.4: We suggest discontinuing cyclophosphamide therapy after 3 months in patients who remain dialysis-dependent and who do not have any extrarenal manifestations of disease. (*2C*)

BACKGROUND

Small-vessel vasculitis encompasses a group of diseases characterized by necrotizing inflammation of the small vessels: arterioles, capillaries, and venules. They are characterized by little or no deposition of immune complexes in the vessel wall (pauci-immune). Medium or large vessels may occasionally be involved. Pauci-immune small vessel vasculitides include granulomatosis with polyangitis (Wegener's), microscopic polyangiitis, and Churg-Strauss syndrome. The characteristic kidney lesion in these conditions is pauci-immune focal and segmental necrotizing and crescentic glomerulonephritis (NCGN). Active pauci-immune small-vessel vasculitis is typically associated with circulating ANCA (ANCA vasculitis). NCGN may also occur without extrarenal manifestations of disease.

The clinical manifestations associated with NCGN include microscopic hematuria with dysmorphic red blood cells and red cell casts, and proteinuria that is usually moderate (1–3 g/d). Pauci-immune NCGN is frequently associated with a rapidly declining GFR over days or weeks. A minority of patients may present with a more indolent course with asymptomatic microscopic hematuria and minimal proteinuria, which may progress over months.

Patients with systemic vasculitis may present with a variety of extrarenal clinical manifestations affecting one or several organ systems, with or without kidney involvement. Commonly involved systems are upper and lower respiratory tract, skin, eyes, and the nervous system. Severe pulmonary hemorrhage affects about 10% of patients with ANCA GN, and is associated with an increased risk of death.[704] The need to treat extrarenal vasculitis may impinge on treatment choices for renal vasculitis.

About 90% of patients with small-vessel vasculitis or pauci-immune NCGN have ANCA, directed primarily to the neutrophil granule proteins myeloperoxidase (MPO) or proteinase 3 (PR3).

The treatment recommendations in this guideline derive from studies of patients with ANCA vasculitis and/or GN. About 10% of patients presenting with signs and symptoms of microscopic polyangiitis, granulomatosis with polyangitis (Wegener's), or pauci-immune NCGN are persistently ANCA-negative. These patients are treated similarly to ANCA-positive patients, although no study has focused specifically on the treatment of ANCA-negative patients.

RATIONALE

- Without therapy, ANCA vasculitis with GN is associated with very poor outcomes.
- There is high-quality evidence for treatment with corticosteroids and cyclophosphamide that has dramatically improved the short- and long-term outcomes of ANCA vasculitis associated with systemic disease.
- Immunosuppressive therapy may not be appropriate in patients with severe NCGN already requiring dialysis.
- All patients with extrarenal manifestations of disease should receive immunosuppressive therapy regardless of the degree of kidney dysfunction.

Table 30 | Recommended treatment regimens for ANCA vasculitis with GN

Agent	Route	Initial dose
Cyclophosphamide[a]	i.v.	0.75 g/m^2 q 3–4 weeks. Decrease initial dose to 0.5 g/m^2 if age >60 years or GFR <20 ml/min per 1.73 m^2. Adjust subsequent doses to achieve a 2-week nadir leukocyte count >3000/mm^3.
Cyclophosphamide[b]	p.o.	1.5–2 mg/kg/d, reduce if age >60 years or GFR <20 ml/min per 1.73 m^2. Adjust the daily dose to keep leucocyte count >3000/mm^3.
Corticosteroids	i.v.	Pulse methylprednisolone: 500 mg i.v. daily × 3 days.
Corticosteroids	p.o.	Prednisone 1 mg/kg/d for 4 weeks, not exceeding 60 mg daily. Taper down over 3–4 months.
Rituximab[c]	i.v.	375 mg/m^2 weekly × 4.
Plasmapheresis[d]		60 ml/kg volume replacement. *Vasculitis*: Seven treatments over 14 days If diffuse pulmonary hemorrhage, daily until the bleeding stops, then every other day, total 7–10 treatments. *Vasculitis in association with anti-GBM antibodies*: Daily for 14 days or until anti-GBM antibodies are undetectable.

ANCA, antineutrophil cytoplasmic antibody; GBM, glomerular basement membrane; GFR, glomerular filtration rate; GN, glomerulonephritis; i.v., intravenous; p.o., orally.
[a]Given with pulse and oral steroids. An alternative i.v. cyclophosphamide dosing schema is 15 mg/kg given every 2 weeks for three pulses, followed by 15 mg/kg given every 3 weeks for 3 months beyond remission, with reductions for age and estimated GFR.[705]
[b]Given with pulse and oral steroids.
[c]Given with pulse and oral steroids.
[d]Not given with pulse methylprednisolone. Replacement fluid is 5% albumin. Add 150–300 ml fresh frozen plasma at the end of each pheresis session if patients have pulmonary hemorrhage, or have had recent surgery, including kidney biopsy.

- There is high-quality evidence that plasmapheresis provides additional benefit in those with severe NCGN.
- There is low-quality evidence that plasmapheresis provides additional benefit for diffuse pulmonary hemorrhage.
- There is evidence that rituximab is not inferior to cyclophosphamide in induction therapy.

Recommended treatment regimens are shown in Table 30.

Without therapy, ANCA vasculitis with GN is associated with very poor outcomes. Treatment with corticosteroids and cyclophosphamide has dramatically improved the short- and long-term outcomes of ANCA vasculitis associated with systemic disease. Treatment with immunosuppressive therapy is therefore considered indicated in all cases of ANCA vasculitis and GN. The rare possible exception relates to patients with severe kidney-limited disease, in the absence of extrarenal manifestations of small-vessel vasculitis. Thus, in patients with severe pauci-immune NCGN requiring dialysis, the question arises as to whether the risks of therapy are greater than the likelihood of recovering kidney function, or whether there is a point beyond which immunosuppressive therapy is futile.

Cohort studies did not detect a level of kidney function below which therapy can be deemed futile, as remission occurred in about 57% of patients with a GFR of 10 ml/min or less at presentation.[706] Of 69 patients who presented dialysis-dependent at the beginning of the Methylprednisolone or Plasma Exchange (MEPEX) trial,[707] 44% were dialysis-independent at 12 months, and the point at which the chance of dying from therapy with plasmapheresis exceeded that of the chance of recovery was reached only in patients with severe tubular atrophy and injury of nearly all glomeruli.[708] This study suggests that, in the absence of extrarenal manifestations of disease, treatment is warranted in all but patients with extreme glomerular obsolescence and severe tubulointerstitial scarring. All patients with extrarenal manifestations of disease should receive immunosuppressive therapy, regardless of the degree of kidney dysfunction.

Disease Activity

Kidney manifestations of active GN are a progressive decline in kidney function, ongoing proteinuria with the continued presence of dysmorphic red cells in the urine, and red cell casts.

Remission is defined by the absence of manifestations of vasculitis and GN disease activity. For GN, it is defined as the absence of microscopic hematuria and a stable or improved proteinuria and GFR. Disease activity of ANCA vasculitis represents signs or symptoms attributable to active disease in any organ system.

Cyclophosphamide

The addition of cyclophosphamide to corticosteroids in induction therapy improved the remission rate from about 55% to about 85%, and decreased the relapse rate three-fold.[706,709]

Pulse i.v. and daily oral regimens for cyclophosphamide are associated with similar remission and relapse rates (Online Suppl Tables 96–99).[705] Considerations in choosing one approach over the other are: compliance, cost, cumulative dose of cyclophosphamide, frequency of leucopenia, and infection. For the same duration of therapy, patients in the i.v. pulse arm received about half the cumulative amount of cyclophosphamide as in the daily oral arm.[705] In a meta-analysis of four RCTs, pulse i.v. cyclophosphamide compared to daily oral cyclophosphamide was associated with less leucopenia (RR 0.53 95%CI 0.36-0.77; P = 0.0009), fewer infections (not significant), increased risk of relapse (RR 1.79, 95%CI 1.11-2.87; P = 0.02), and a trend toward an increased number of patient requiring renal replacement therapy.[710]

Based on the RCT of maintenance therapy comparing cyclophosphamide to azathioprine, the majority of patients (77%) achieved remission with oral cyclophosphamide by 3 months, and another 16% between 3 and 6 months.[711] Thus, the duration of continuous oral cyclophosphamide should usually be limited to 3 months, with a maximum of 6 months. Whether this duration of treatment applies to pulse i.v. cyclophosphamide is inferred, but not tested. The only study of a short (6-month) vs. long (12-month) course of cyclophosphamide was not powered to detect a difference in outcome.[712] A retrospective cohort analysis did not indicate that longer treatment with cyclophosphamide reduces the rate of relapse.[706]

Among patients who require dialysis, those who recover sufficient kidney function nearly always do so within the first 3 months of treatment.[708,709] Therefore, in patients who are still dialysis-dependent after 3 months and who have no evidence of ongoing extrarenal manifestations of active vasculitis, we suggest discontinuing cyclophosphamide therapy.

Pulse Methylprednisolone

The value of pulse methylprednisolone induction therapy has not been tested directly. The rationale for pulse methylprednisolone is related to its rapid anti-inflammatory effect. High-dose methylprednisolone may also contribute to a rapid reduction in ANCA-producing plasma cells. The only randomized evaluation of pulse methylprednisolone (3×1000 mg) was in the setting of the MEPEX trial, where it was compared to plasmapheresis as adjunctive therapy to oral corticosteroids and oral cyclophosphamide.[707] In that trial, pulse methylprednisolone was less efficacious than plasmapheresis in preserving kidney function. There are no data that 1000 mg daily for 3 days is better than 500 mg; this lower dose is widely used in clinical practice, and the higher dose may be associated with increased short- and long-term risks of infection and other complications of steroids.

Rituximab

Two RCTs examined rituximab as first-line induction therapy for ANCA vasculitis (Online Suppl Tables 100-102). In the RITUXVAS trial, 44 patients with newly diagnosed ANCA vasculitis were randomized 3:1 to either rituximab (375 mg/m^2 weekly $\times$ 4) in addition to cyclophosphamide (15 mg/kg i.v., 2 weeks apart for a total of two doses); or to cyclophosphamide (15 mg/kg i.v. every 2 weeks $\times$ 3, then every 3 weeks for a maximum total of 10 doses).[713] Both groups received the same regimen of methylprednisolone 1000 mg i.v. followed by oral corticosteroids. Rates of remission were similar (76% with rituximab group vs. 82% with cyclophosphamide), as were rates of serious adverse events.[713]

In Rituximab for the Treatment of Wegener's Granulomatosis and Microscopic Polyangiitis (RAVE), 197 patients were randomized to treatment with either rituximab (375 mg/m^2 infusions once weekly for 4 weeks) or cyclophosphamide (2 mg/kg/d orally) for months 1-3, followed by azathioprine (2 mg/kg/d orally) for months 4-6.[714] All patients received one to three i.v. pulses of methylprednisolone (1000 mg each) followed by the same oral corticosteroid regimen. There was no significant difference between the two treatment groups in rates of complete remission at 6 months, adverse events, or relapse rates. The RAVE trial excluded patients with severe alveolar hemorrhage or severe kidney dysfunction (SCr >4 mg/dl [>354 μmol/l]), so the role of rituximab for such patients remains unknown.

Rituximab shows equivalent efficacy to cyclophosphamide in initial therapy and the evidence does not suggest a difference in rates of adverse effects. However, analysis of the long-term outcomes, including safety, is still awaited. In addition, the very high cost of rituximab compared to cyclophosphamide limits its application from a global perspective.

Plasmapheresis

The addition of plasmapheresis to initial therapy with corticosteroids and cyclophosphamide is indicated for patients presenting with either advanced kidney failure (SCr >5.66 mg/dl [>500 μmol/l]) or with diffuse alveolar hemorrhage.

In a large, multicenter controlled trial,[707] 137 patients with a new diagnosis of ANCA vasculitis confirmed by kidney biopsy were randomly assigned to either seven treatments of plasmapheresis, or three doses of 1000 mg of i.v. methylprednisolone. Both groups received standard therapy with oral cyclophosphamide and oral prednisone followed by azathioprine for maintenance therapy. Plasmapheresis was associated with a significantly higher rate of kidney recovery at 3 months (69% of patients with plasmapheresis vs. 49% with i.v. methylprednisolone), and with dialysis-free survival at 12 months. Whether duration of plasmapheresis should be tailored to ANCA titers has not been studied.

Studies of plasmapheresis as adjunctive therapy in patients with SCr <5.66 mg/dl (<500 μmol/l) have not shown benefit, but were underpowered to provide definitive evidence.[715,716] A large RCT of adjunctive therapy with plasmapheresis is currently underway (clinicaltrials.gov identifier NCT00987389).

Plasmapheresis for Patients with Diffuse Alveolar Hemorrhage

The impact of plasmapheresis in patients with diffuse, severe alveolar hemorrhage is the reduction of mortality, based on retrospective case series.[716,717] Although the strength of supportive data is low (retrospective case series without controls), the impact of such treatment is high (less mortality).[709,718] Whether patients with "mild" alveolar hemorrhage (small focal infiltrate without or with mild hypoxemia) require plasmapheresis is unknown.

Patients with ANCA Vasculitis: Anti-GBM GN Overlap Syndrome

The recommendation for plasmapheresis, in addition to corticosteroids and cyclophosphamide for patients with both

circulating ANCA and anti-GBM antibodies, is based on the rationale for the treatment of anti-GBM GN. About one-third of patients with anti-GBM disease also have ANCA antibodies, usually directed against MPO. Patients with ANCA/anti-GBM overlap have a worse outcome than patients with ANCA vasculitis alone, or anti-GBM alone.[719]

MMF

There are insufficient data to support the use of MMF for induction therapy in ANCA vasculitis. Although small uncontrolled studies report remission rates similar to those reported with corticosteroids and cyclophosphamide,[720] relapses have been reported, despite continued use of MMF.[721]

The only controlled study to date of MMF (1.5-2 g/d) vs. cyclophosphamide (monthly i.v. pulse of 0.75-1 g/m^2) includes 35 patients from China,[722] four of whom were lost to follow-up (all in the cyclophosphamide group). When patients lost to follow-up were excluded from the analysis, the rates of remission were similar in the two groups. No data on follow-up beyond 6 months is provided in this study. A larger RCT of MMF vs. i.v. cyclophosphamide for induction treatment is currently underway (clinicaltrials.gov identifier NCT00414128).

13.3: Maintenance therapy

13.3.1: We recommend maintenance therapy in patients who have achieved remission. (*1B*)

13.3.2: We suggest continuing maintenance therapy for at least 18 months in patients who remain in complete remission. (*2D*)

13.3.3: We recommend no maintenance therapy in patients who are dialysis-dependent and have no extrarenal manifestations of disease. (*1C*)

13.4: Choice of agent for maintenance therapy

13.4.1: We recommend azathioprine 1-2 mg/kg/d orally as maintenance therapy. (*1B*)

13.4.2: We suggest that MMF, up to 1 g twice daily, be used for maintenance therapy in patients who are allergic to, or intolerant of, azathioprine. (*2C*)

13.4.3: We suggest trimethoprim-sulfamethoxazole as an adjunct to maintenance therapy in patients with upper respiratory tract disease. (*2B*)

13.4.4: We suggest methotrexate (initially 0.3 mg/kg/wk, maximum 25 mg/wk) for maintenance therapy in patients intolerant of azathioprine and MMF, but not if GFR is <60 ml/min per 1.73 m^2. (*1C*)

13.4.5: We recommend not using etanercept as adjunctive therapy. (*1A*)

BACKGROUND

The indications for maintenance therapy are not well defined. The goal of maintenance therapy is to decrease the incidence and severity of relapsing vasculitis. With the exception of a small trial with trimethoprim-sulfamethoxazole (see Rationale), no placebo-controlled RCT has studied the benefit of maintenance therapy, although RCTs have compared the efficacy of different maintenance regimens. Therefore, the likely benefit of maintenance therapy depends on the assessment of the risk of relapse, which differs among various subgroups of patients. For example, the risk of low-dose maintenance immunosuppression in a frail, elderly patient has to be weighed against the very high risk for such a patient of severe relapse. Maintenance immunosuppressive therapy is justified in patients at high risk of relapse, but the potential benefit of maintenance therapy may be low in patients who have a low likelihood of relapse.

RATIONALE

- There is moderate-quality evidence that maintenance therapy is required in those at high risk of relapse or who have received less than 6 months induction treatment with cyclophosphamide.
- There is low-quality evidence that the duration of maintenance therapy should be at least 18 months.
- There is moderate-quality evidence that azathioprine is the preferred maintenance immunosuppressive agent, being equivalent in efficacy to cyclophosphamide in an RCT with a more favorable adverse-effect profile.
- There is moderate-quality evidence that trimethoprim-sulfamethoxazole as an adjunct to maintenance therapy reduces the risk of relapse, but only in those with upper respiratory disease due to vasculitis.

Risk of Relapse

Based on cohort studies, risk factors for relapse include persistence of PR3-ANCA (compared to MPO-ANCA), history of upper respiratory tract disease (e.g., sinusitis, subglottic stenosis), or lower respiratory tract disease (e.g. alveolar hemorrhage, cavities, or nodules). Patients with any one of these three risk factors have an approximately 1.7-fold increased risk of relapse, and those with all three risk factors have an approximately 4.7-fold increased risk of relapse.[706]

Patients with persistent PR3-ANCA–positivity at the end of cyclophosphamide therapy have a 2- to 3-fold increased risk of relapse, compared to patients who are ANCA-negative at the end of initial therapy.[723] In addition, patients who are persistently PR3-ANCA–positive are significantly more likely to relapse within 5 years after diagnosis.[723] Among patients who achieved remission and were switched from cyclophosphamide to azathioprine, those who remained PR3-ANCA–positive at the time of the switch had a 2.2-fold increased risk of suffering a relapse when compared to patients who were PR3-ANCA–negative. No similar data are available for patients with MPO-ANCA.

It is unknown whether patients with none of the risk factors for relapse need maintenance immunosuppression. The risk-benefit ratio of maintenance therapy has not been evaluated in such patients. The tailoring of maintenance therapy, based on the risk factors of relapse, has not been tested in clinical trials.

Choice of Immunosuppressive Agent for Maintenance Therapy

The optimal total duration of corticosteroid therapy is unknown. Some studies have maintained patients on a low dose of prednisone (7.5 mg daily) for >12 months.[711] In other cohort studies, corticosteroids are tapered completely off by the end of 5 months if the patient is in remission.[706]

The best available data support the use of azathioprine 1-2 mg/kg/d for 6-18 months. This is inferred from an RCT of azathioprine vs. cyclophosphamide for the maintenance of remission.[711] Although not specifically designed to demonstrate the ability of azathioprine to prevent relapses (compared to placebo), the study established that introducing azathioprine after 3-6 months of cyclophosphamide, compared to continuing cyclophosphamide for 12 months, resulted in similar rates of relapse up to 18 months.

Maintenance therapy with azathioprine appears superior to MMF. In a large RCT of 155 patients with ANCA vasculitis, who attained remission with cyclophosphamide and corticosteroids, those randomized to MMF (2 g/d) vs. azathioprine (2 mg/kg/d) had a higher cumulative incidence of relapse (HR 1.7; $P = 0.02$).[724] We therefore recommend azathioprine as the first choice for maintenance therapy in ANCA vasculitis. However, we suggest using MMF in patients who are allergic to or intolerant of azathioprine.

In a placebo-controlled trial, the use of trimethoprim-sulfamethoxazole was associated with a decreased rate of upper airway-relapse.[725] The use of trimethoprim-sulfamethoxazole had no impact on the rate of relapse in other organs.

In a large prospective RCT, 12 months maintenance therapy with methotrexate (0.3 mg/kg/wk initially and progressively increased to 25 mg/wk) was compared to azathioprine (2 mg/kg/d) after induction of remission with cyclophosphamide and corticosteroids.[726] The study was not designed to demonstrate the superiority of methotrexate over azathioprine in preventing relapses, but to test the hypothesis that methotrexate would be safer than azathioprine. The rates of relapse were not significantly different between the azathioprine- and methotrexate-treated groups (36% and 33%, respectively; $P = 0.71$) with a mean randomization-to-relapse interval of 20.6 ± 13.9 months. Methotrexate was not associated with a higher rate of adverse events when compared to azathioprine (HR 1.65; 95% CI 0.65-4.18; $P = 0.29$). However, the severity of the adverse effects with the use of methotrexate was greater; therefore, it is not recommended in patients with a reduced GFR <30 ml/min per 1.73 m^2, and the dose should be adjusted in patients with a GFR <60 ml/min per 1.73 m^2.

The efficacy and safety of the tumor necrosis factor receptor–Fc fusion protein, etanercept, in the maintenance of remission among patients with granulomatosis with polyangitis (Wegener's) was evaluated in an RCT in which etanercept or placebo was added to a regimen of daily oral cyclophosphamide or methotrexate and corticosteroids. Etanercept did not reduce the rate or the severity of relapses, and was associated with a higher rate of solid tumors and is therefore not recommended.[727,728] Although not tested, we also do not recommend the use of other anti–tumor necrosis factor agents.

Duration of Maintenance Therapy

There are no direct data to support a recommendation for the duration of maintenance therapy. The suggestion of continuing maintenance therapy for 18 months in patients who remain in complete remission is inferred from the duration of maintenance therapy used in the CYCAZAREM trial.[711] Some cohort studies, but not others, have suggested a higher incidence of relapse in the first 18 months after induction therapy.

In retrospective analyses of patients with ANCA vasculitis, the relapse rates of vasculitis were about 60% lower in patients with ESRD, and infections almost twice as frequent among patients maintained on immunosuppressive agents with ESRD.[727,728] In addition, infections were an important cause of death in this population. Given the lower risk of relapse and higher risk of infection and death, the risk-benefit ratio does not support the routine use of maintenance immunosuppression therapy in ANCA vasculitis patients on chronic dialysis, in the absence of active extrarenal disease.

Continued maintenance therapy is associated with the risks of immunosuppression, bone marrow suppression (leucopenia, anemia, thrombocytopenia), and possibly increased risk of cancer, notably skin cancer.[284]

13.5: Treatment of relapse

13.5.1: We recommend treating patients with severe relapse of ANCA vasculitis (life- or organ-threatening) according to the same guidelines as for the initial therapy (see Section 13.1). (*1C*)

13.5.2: We suggest treating other relapses of ANCA vasculitis by reinstituting immunosuppressive therapy or increasing its intensity with agents other than cyclophosphamide, including instituting or increasing dose of corticosteroids, with or without azathioprine or MMF. (*2C*)

RATIONALE

- Relapse is associated with increased risk of ESRD.
- Relapse is associated with severe or life-threatening extrarenal damage.
- There is low-quality evidence that relapses are responsive to reintroduction or increased dosing of immunosuppression, but the preferred treatment regimen has not been defined.

Impact of Relapse

Relapse is defined as the occurrence of increased disease activity after a period of partial or complete remission. Thus, a relapse can manifest as a worsening of pre-existing disease

activity or the recurrence or development of active GN, or new signs or symptoms of vasculitis in any organ system.

Severe relapse is defined as life- or organ-threatening relapse. Examples of life-threatening relapse include diffuse alveolar hemorrhage and severe subglottic stenosis. Examples of organ-threatening disease are active GN, or a retro-orbital mass threatening vision.

In a cohort study, patients who had a relapse of GN were 4.7 times more likely to progress to ESRD compared to those who did not relapse. This increased risk of ESRD associated with relapse was independent of age, gender, race, ANCA specificity, and kidney function at the time of initial biopsy.[706]

Relapses respond to immunosuppression with corticosteroids and cyclophosphamide with a similar response rate as the initial disease.[709] The repeated use of cyclophosphamide should be based on the severity of the relapse, taking into account the cumulative dose previously received by the patient. Severe relapses should be treated with cyclophosphamide, corticosteroids and plasmapheresis (when indicated) as described in Section 13.1 and Table 30.

Although a "safe" dose of cyclophosphamide has not been precisely determined, a recent retrospective study suggests that the risk of malignancy (other than nonmelanoma skin cancer) increases with cumulative doses of cyclophosphamide above 36 g.[284] Therefore, for patients who have received, or are approaching a 36 g cumulative dose of cyclophosphamide, we suggest treating subsequent relapses with a rituximab-based regimen.

For patients with a relapse that is not severe (as defined earlier), immunosuppressive therapy should be increased while avoiding, if possible, more cyclophosphamide. If such a relapse occurs when the patient is not receiving maintenance therapy, treatment may include the reinstitution of corticosteroids, azathioprine, or MMF, alone or in combination; however, there is no RCT evidence to support any of these regimens. In patients who suffer a relapse while on maintenance therapy with azathioprine or MMF, one treatment option is i.v. immunoglobulin. In an uncontrolled study, the addition of 6-monthly pulses of i.v. immunoglobulin (0.5 g/kg/d $\times$ 4 days) over background maintenance immunosuppression was associated with rates of complete or partial remission of 83% and 63% at 6 and 9 months, respectively.[729] In patients with kidney dysfunction, it is preferable to use a sucrose-free formulation of i.v. immunoglobulin in order to minimize the risk of osmotic-induced AKI.[730]

Rituximab was more effective than cyclophosphamide in treating patients with relapsing ANCA vasculitis (OR 1.40; 95% CI 1.03-1.91; $P = 0.03$).[714] Although more experience will be needed with the use of rituximab for treatment of severe relapses, and although the long-term safety of rituximab remains uncertain, its use in relapse may provide an opportunity to minimize cumulative dosage and avoid the potential long-term toxicity of cyclophosphamide.

13.6: Treatment of resistant disease

13.6.1: In ANCA GN resistant to induction therapy with cyclophosphamide and corticosteroids, we recommend the addition of rituximab (*1C*), and suggest i.v. immunoglobulin (*2C*) or plasmapheresis (*2D*) as alternatives.

BACKGROUND

Resistance is defined as the persistence of or appearance of kidney and/or systemic manifestation of vasculitis, while receiving treatment equal in intensity to initial immunosuppressive therapy. Kidney manifestations of resistance include the continued presence of dysmorphic erythrocyturia and red blood cell casts, and are associated with a progressive decline in kidney function. Disease resistance to corticosteroids and cyclophosphamide occurs in approximately 20% of patients.

RATIONALE

Adjunctive therapy with i.v. immunoglobulin (single course of a total of 2 g/kg) was evaluated in an RCT in patients with resistant ANCA vasculitis. Patients treated with i.v. immunoglobulin had a more rapid decline in disease activity (as measured by a 50% reduction in Birmingham vasculitis activity score) and C-reactive protein at 1 and 3 months, but there was no significant difference between the two groups after 3 months, with respect to disease activity or frequency of relapse.[731]

Several small, uncontrolled case series suggest a role for rituximab in resistant ANCA vasculitis.[732–734] In these reports, rituximab (375 mg/m^2 i.v. weekly $\times$ 4, or 500 mg i.v. weekly $\times$ 4 fixed doses), in conjunction with corticosteroids, resulted in remission in the majority of patients, and was generally well-tolerated.

There has been no trial of plasmapheresis in resistant ANCA vasculitis, but its value in this setting has been inferred from the MEPEX study, which demonstrated improved kidney outcome with plasmapheresis in patients with severe kidney dysfunction, and studies suggesting decreased mortality with plasmapheresis in patients with diffuse alveolar hemorrhage (see Recommendation 13.2.2).

13.7: Monitoring

13.7.1: We suggest not changing immunosuppression based on changes in ANCA titer alone. (*2D*)

RATIONALE

Available data mostly report the assessment of PR3-ANCA, with limited data for MPO-ANCA. The data do not support the contention that PR3-ANCA is clinically useful in predicting relapse and should not be used (alone) to alter immunosuppression.[735,736] A persistently positive PR3-ANCA, at the time of switch to maintenance therapy with azathioprine, is associated with a 2- to 3-fold increased risk of relapse, and warrants close follow up.[723] For patients who are in clinical remission but remain PR3-ANCA–positive after 3-4 months of cyclophosphamide and corticosteroids, continuing cyclophosphamide for up to 6 months may be

considered; however, there are no data on the risks or benefits of such an approach. If ANCA titers increase, it may be worth intensifying patient follow-up.

13.8: Transplantation

13.8.1: We recommend delaying transplantation until patients are in complete extrarenal remission for 12 months. (*1C*)

13.8.2: We recommend not delaying transplantation for patients who are in complete remission but are still ANCA-positive. (*1C*)

RATIONALE

No prospective data are available to assess the likelihood of recurrent ANCA vasculitis after kidney transplantation, or the impact of disease activity or that of a positive ANCA test at the time of transplantation, on patient outcome. The frequency of recurrent ANCA vasculitis after kidney transplantation has been assessed in several retrospective case series. These have revealed a frequency of relapse around 15-20%, although the frequency of recurrent pauci-immune necrotizing GN is only around 5%.[737,738] In the largest retrospective study of 107 kidney transplant recipients in the UK, relapses occurred in only 5% of patients.[739] By multivariate analysis, kidney transplantation within 12 months of achieving remission was associated with increased mortality; the causes of death were not related to recurrent vasculitis. ANCA positivity at the time of transplantation does not appear to affect graft or patient survival, or the frequency of relapse after transplantation.

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SUPPLEMENTARY MATERIAL

Supplementary Table 96: Evidence profile of IV vs. p.o. Cyc for ANCA vasculitis.

Supplementary Table 97: Existing systematic review of Induction with pulse Cyc vs. daily p.o. Cyc in patients with ANCA vasculitis.

Supplementary Table 98: Summary table of RCT examining induction with pulse Cyc vs. daily p.o. Cyc in patients with ANCA vasculitis (categorical outcomes).

Supplementary Table 99: Summary table of RCT examining induction with pulse Cyc vs. daily p.o. Cyc in patients with ANCA vasculitis (continuous outcomes).

Supplementary Table 100: Evidence profile of RCTs examining induction with rituximab vs. Cyc in patients with ANCA vasculitis.

Supplementary Table 101: Summary table of RCTs examining induction with rituximab vs. Cyc in patients with ANCA vasculitis (categorical outcomes).

Supplementary Table 102: Summary table of RCTs examining induction with rituximab vs. Cyc in patients with ANCA vasculitis (continuous outcomes).

Supplementary material is linked to the online version of the paper at http://www.kdigo.org/clinical_practice_guidelines/GN.php