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Treatment of ANCA-Associated Vasculitis, Where to Go?

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Abstract The introduction of (oral) cyclophosphamide (CYC) in the treatment of ANCA-associated vasculitides (AAV) has strongly improved prognosis but the side effects of long-term CYC treatment are serious. A number of recent randomized controlled studies have shown that the cumulative dose of CYC can be strongly reduced in the treatment of AAV or even reduced to zero. Maintenance treatment can be performed with azathioprine (AZA), or methotrexate (MTX) in case of intolerance, although the intensity and duration of maintenance treatment is still under discussion. More insight into the mechanisms involved in relapsing disease might allow individualized treatment. Induction of remission can be achieved in cases of mild disease expression with MTX but requires maintenance treatment to prevent relapses. Generalized disease can be treated with pulses of i.v. CYC or, possibly, with MMF. However, recent studies demonstrate the efficacy of RTX in inducing remission without the concomitant use of immunosuppressives. Corticosteroids are part of treatment in all regimens but the intensity and duration of steroid treatment is still being discussed. In life-threatening disease, the adjunctive efficacy of plasma exchange has been demonstrated and its usefulness in less severe disease is under investigation. Taken together, there are, indeed, alternatives for CYC in AAV.

Keywords ANCA-associated vasculitis · Treatment · Granulomatosis with polyangiitis · Microscopic polyangiitis · Rituximab

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Introduction

The antineutrophil cytoplasmic autoantibody (ANCA)-associated vasculitides (AAV) comprise granulomatosis with polyangiitis (GPA, formerly Wegener's granulomatosis), microscopic polyangiitis (MPA) including its renal limited form (idiopathic pauci-immune necrotizing crescentic glomerulonephritis, and Churg–Strauss syndrome [1]). These diseases, in particular GPA and MPA, have a very poor prognosis if left untreated. Mortality in GPA was described as 63 % (35 out of 56 patients) at 6 months after diagnosis [2]. The introduction of (oral) cyclophosphamide (CYC) by the pioneering work of Fauci et al. at the National Institute of Health (NIH), USA, has dramatically improved survival [3]. Oral CYC was used in GPA both for induction and maintenance treatment. A regimen of (in most cases) oral CYC with glucocorticoids at the NIH resulted in marked improvement of 91 % of 158 GPA patients with 75 % of patients achieving complete remission [4]. However, 50 % of patients achieving remission relapsed, 13 % of patients died, 86 % of patients had serious irreversible morbidity resulting from the disease, and 42 % of patients suffered from irreversible side effects of treatment [4]. Long-term oral CYC was especially associated with hemorrhagic cystitis and bladder cancer (with a cumulative risk of 5 % after 10 years follow-up increasing to 16 % after 15 years [5]). In addition, opportunistic infections, particularly during leukopenia resulting from CYC, and infertility were frequently observed. In the NIH series, 46 % of patients (73 out of 158) experienced 140 episodes of serious infection during CYC treatment [4]. Thus, although prognosis was strongly improved by the introduction of oral CYC, the serious side effects of CYC in conjunction with the far from optimal efficacy prompted the search for alternative treatment modalities. In this review, I will discuss these various

modalities and suggest that we might abandon CYC for the treatment of AAV in the near future.

Do We Need Cyclophosphamide for Induction of Remission?

As mentioned, the introduction of oral CYC has dramatically improved survival in AAV. Nevertheless, side effects of oral CYC are considerable, significant morbidity and damage still occur and relapsing disease is frequent. Therefore, reduction in dosage or abandonment in general of CYC for induction of remission in AAV, if possible, would be welcome.

Oral or Pulse Cyclophosphamide?

The first step to reduce the dosage of CYC consisted of replacing oral CYC by pulse intravenous CYC for induction of remission. In the so-called CYCLOPS study, 149 patients with AAV and non-life-threatening renal involvement were randomized to either daily oral CYC (2 mg/kg) or pulse i.v. CYC (15 mg/kg, three times every 2 weeks, thereafter every 3 weeks until remission), both arms with prednisone [6]. Azathioprine (AZA) was given after remission was obtained in both arms. No difference was observed in time to remission and proportion of patients reaching remission (87.7 % vs. 88.1 %). Thirteen out of 76 patients relapsed after induction of remission with i.v. CYC compared to 6 out of 73 patients in the oral group (NS). The cumulative dose of CYC was significantly lower in the i.v. group compared to the oral group (8.2 g vs. 15.9 g, $p<0.001$), and less leukopenia occurred in the i.v. group. Long-term follow-up [7] disclosed significantly more relapses in the i.v. group, but outcome in terms of endstage renal failure, serum creatinine, duration of immunosuppression or adverse events was not different between both groups. This study shows that i.v. CYC can replace oral CYC for induction of remission in generalized AAV.

Can CYC be Replaced by Mycophenolate Mofetil?

A randomized controlled trial comparing mycophenolate mofetil (MMF) with intravenous pulse CYC for induction of remission (acronym MYCYC, coordinated by the European Vasculitis Study Group (EUVAS)) is still underway. Small open series, however, have shown that MMF in a target dose of 2 g daily is effective in inducing remission of AAV with moderate renal involvement [8, 9]. Stassen et al [10] used MMF (2 g daily with corticosteroids) for induction of remission in 32 consecutive patients with AAV who relapsed and could not be treated with CYC. Twenty-five (78 %) patients reached complete remission and in all but one of the remaining patients, partial remission after 12 months. MMF was tapered by 500 mg every 3 months in patients in remission. This resulted in the frequent occurrence of relapses (relapse-free survival at 1, 3, and 5 years was 63, 38, and 27 %, respectively). In a small controlled study [11] MMF was as effective as i.v. CYC in Chinese MPA patients with renal involvement. Thus, awaiting the results of the MYCYC trial, MMF may be used for induction of remission in patients with non-life-threatening AAV who cannot tolerate CYC.

Methotrexate for Induction of Remission

In milder cases of AAV, methotrexate (MTX) has been used for induction of remission. In a controlled trial, 100 patients with active AAV but without critical organ manifestations and a serum creatinine <150 μmol/l, were randomized either to oral CYC (2 mg/kg) or MTX (20–25 mg/week) in combination with prednisone in both arms [12]. Drugs were tapered after induction of remission and withdrawn at 12 months. The percentage of patients reaching remission at 6 months was not different between both arms (89.8 % for MTX, 93.5 % for CYC). Relapses at 18 months were, however, more frequent in the MTX-arm (69.5 %) than in the CYC-arm (46.5 %) with a shorter time to remission in the MTX group. The high relapse rate in both arms is undoubtedly due to the lack of long-term maintenance treatment in this study. With respect to adverse events, leukopenia was more frequent in the CYC group and liver function disturbances in the MTX group. Thus, in milder cases of AAV, MTX can be used but relapses are frequent.

Rituximab, a New Player?

More recently, rituximab (RTX) has been used for induction of remission in AAV [13, 14]. In the so-called RAVE study, 197 patients with severe GPA or MPA, either at first presentation or at the time of relapse, were included. Patients got 1–3 g i.v. methylprednisolone and were randomized either to RTX (375 mg/m^2 i.v. weekly for 4 weeks) or oral CYC (2 mg/kg/day), both in combination with prednisone. Steroids were tapered and the primary endpoint was complete remission off prednisone at 6 months. Sixty three out of 98 (64 %) patients on RTX reached the primary endpoint versus 52 out of 99 (53 %) patients on CYC. This led to the conclusion that RTX is not inferior to CYC for induction of remission. In relapsing patients, RTX was even superior to CYC (66.7 % reaching the primary endpoint on RTX versus 42.0 % on CYC, $p=0.01$). There were no significant differences between both arms in adverse events. Thus, RTX is at least as effective for induction of remission of severe GPA and MPA as oral CYC. This has led to registration of RTX for induction of remission of AAV by the FDA. Interestingly in this study, no maintenance treatment was applied in the

RTX group whereas the CYC group received maintenance treatment with AZA. At 18 months after study entry, no differences in relapse rate were observed between both arms [15]. As expected, more relapses occurred in PR3-ANCA-positive patients than in MPO-ANCA patients. More relapses were also seen in patients included with a relapse than in patients included with a new diagnosis of AAV.

Another controlled study has also shown the potential of RTX to induce remission in severe cases of AAV [14]. In this study, 44 patients with newly diagnosed AAV and (severe) renal involvement were randomized, in a 3:1 ratio, either to RTX (375 mg/m^2 i.v. weekly for 4 weeks), with two i.v. pulses of CYC, or to pulse i.v. CYC (as in the CYCLOPS study), with corticosteroids in both arms. The primary endpoint was sustained remission at 12 months. There was no difference in the number of patients reaching the primary endpoint between both arms (76 % in the RTX group and 82 % in the CYC group had sustained remission at 12 months). Also, no differences were observed in mortality, severe adverse events, and renal function at 12 months.

The above-mentioned studies show that RTX can be used for induction of remission in patients with severe AAV, even in those with impaired renal function at presentation. In addition, many open series have demonstrated that RTX could be effective in cases of AAV refractory to conventional treatment [16, 17]. This has led to recommendations for the use of RTX in AAV [18, 19]. The general conclusion from these overviews is that RTX is an effective therapy in refractory AAV and that the drug is as effective as CYC in newly diagnosed cases. However, in view of the relatively short observations on RTX, long-term follow-up is needed to get a better insight into efficacy and safety in the long run.

Adjunctive Treatment in Life-Threatening Disease

Do we need more intensive treatment in patients with AAV who present with life-threatening disease, in particular renal failure and respiratory insufficiency? It is common use to start with i.v. methylprednisolone, 1 g on 1–3 consecutive days, in patients with severe AAV at presentation. Also, plasma exchange has been suggested as an additive way to remove pathogenic substances including ANCA in life-threatening disease. In a randomized controlled study, the adjunctive efficacy of seven plasma exchanges was compared with that of methylprednisolone (1 g i.v. on 3 consecutive days) [20]. Patients with newly diagnosed AAV and a serum creatinine of >500 μmmol/l were included (n=137). At 3 months, 69 % of patients on plasma exchange compared to 49 % on methylprednisolone (p=0.02) were alive and dialysis independent (primary outcome). Plasma exchange reduced the risk of endstage renal disease from 43 to 19 % at 12 months as compared with methylprednisolone.

Currently, the adjunctive effect of plasma exchange is being evaluated in patients with newly diagnosed or relapsing AAV with severe vasculitis but not just renal or respiratory insufficiency. This study, called PEXIVAS, will also evaluate different corticosteroid regimens.

Current recommendations for induction of remission in AAV as based on EULAR and British Society for Rheumatology (BSR) recommendations [19, 21] are given in Table 1.

Table 1 EULAR and BSR recommendations for induction of remission in ANCA-associated vasculitis (21,19)

Disease category	Definition	Drug	Dose
Generalized	Renal or other organ-threatening disease, s-creatinine <500 μmmol/l	CYC	Oral, 2 mg/kg[a] or i.v., 15 mg/kg/2 weeks 3 times, then every 3 weeks[a]
		RTX	375 mg/m^2/week, 4 times
Early systemic	Without organ-threatening or life-threatening disease	MTX as alternative to CYC/RTX	15 mg/week increasing to 20–25 mg/week, oral or s.c.
Severe	Renal or other vital organ failure, s-creatinine >500 μmmol/l	plasma exchange as adjunctive therapy to CYC or RTX	7 times
Refractory	Progressive disease unresponsive to CYC and glucocorticoids	RTX	375 mg/m^2/week, 4 times
		IVIG	2 g/kg over 5 days
		MMF	2 g/day
		15-deoxy-spergualin	0.5 mg/kg/day till leucocytes at 3×10^9/l, again when leucocytes at $\geq4\times10^9$/l, six cycles
		ATG	
		Infliximab	

All regimens include oral corticosteroids, frequently with methylprednisolone

CYC cyclophosphamide, *RTX* rituximab, *MTX* methotrexate, *IVIG* intravenous immunoglobulin, *ATG* anti-thymocyte globulin

[a] Dose adjustments based on age and renal function, cytopenia, in particular, leukopenia

Maintenance of Remission

As mentioned before, the cumulative dose of CYC is a critical factor for the development of side effects such as bladder cancer, myelosuppression, and infertility. In the original NIH approach, oral CYC was continued for at least 1 year after induction of complete remission and then tapered by 25 mg decrements every 2 to 3 months until discontinuation but doses was increased when symptoms reappeared [4]. As remission was reached within 6 months in most cases, accumulation of CYC usage particularly occurred during maintenance treatment. So, the question was whether maintenance treatment with CYC could be replaced by maintenance azathioprine treatment.

Azathioprine Instead of Cyclophosphamide for Maintenance

The EUVAS compared CYC with AZA for maintenance treatment of patients with AAV [22]. Patients with active AAV with renal involvement or other threatened loss of function of a vital organ were included and remission was induced with oral CYC (2 mg/kg/day) and prednisolone (1 mg/kg/day with tapering). Patients received at least 3 months of induction treatment with oral CYC and prednisolone. At remission, patients were randomized either for oral CYC (1.5 mg/kg/day) or AZA (2 mg/kg/day), both with 10 mg of prednisolone. After 12 months of maintenance treatment all patients continued with AZA (1.5 mg/kg/day) and 7.5 mg of prednisolone. Primary end point was the occurrence of relapses within 18 months from study entry. This study showed, firstly, the efficacy of the induction regimen with oral CYC as 93 % (144 out of 155) of patients reached remission, although seven patients (5 %) died during the first 3 months. Secondly, no differences were seen in the occurrence of relapses between both arms: 10 relapses occurred in the CYC group (13.7 %) and 11 relapses in the AZA group (15.5 %), $p=0.65$. No differences were seen in severe adverse events between both arms during the study period. Also, renal function at the end of the study and disease activity scores were not different between both arms. This so-called CYCAZAREM study shows that, during a period of 12 months, AZA is as effective as CYC for maintenance of remission without differences in side effects. However, a few remarks have to be made. First, long-term follow-up is necessary to demonstrate that AZA is, indeed, as efficacious for persisting remission and restoration of renal function as oral CYC. Secondly, long-term follow-up is also required for assessment of late side effects of treatment such as bladder cancer, myelodysplasia, and other malignancies, as well as assessment of cumulative damage. These data are eagerly awaited. Nevertheless, the results of this study have led to the replacement of CYC by AZA for maintenance treatment of AAV.

Is Methotrexate Effective for Maintenance of Remission?

As AZA still may have undesired adverse events in some patients, the question arises whether AZA can be replaced by MTX as maintenance treatment of AAV. The French Vasculitis Study Group addressed this question [23]. Patients with active AAV, that is GPA or MPA, were included. Induction treatment consisted of intravenous pulses of CYC in combination with corticosteroids (three times 1 g of methylprednisolone followed by oral prednisone, 1 mg/kg/day with tapering after 3 weeks). After remission had been achieved, patients were randomized to either AZA (2 mg/kg/day) or MTX (0.3 mg/kg/week increasing to 25 mg/week) for a period of 12 months after which drugs were discontinued. Primary end point was an adverse event requiring discontinuation of the drug or death; secondary endpoints were severe adverse events and relapses. In this study, 79 % (126 out of 159) of patients reached remission. After 12 months of maintenance treatment, there were no differences between both arms in primary endpoint (7 patients had to stop AZA versus 11 patients, including one death, in the MTX group, $p=0.21$). Also, no differences were observed in the secondary end points (severe adverse events in 5 out of 63 patients in the AZA group versus 11 out of 63 patients in the MTX group; 23 relapses in the AZA group versus 21 relapses in the MTX group, most relapses occurring after discontinuation of the drugs). So, again, during short-term follow-up, MTX appears as effective as AZA for maintenance of remission whereas a slight tendency seems present for more adverse events during MTX treatment. We may conclude from this study that MTX can be used for maintenance

Table 2 EULAR and BSR recommendations for maintenance of remission in ANCA-associated vasculitis [19, 21]

Drug	Dose	Comment
AZA	2 mg/kg/day for 12 months, thereafter 1.5 mg/kg/day	As effective as oral CYC (1.5 mg/kg/day) for 12 months
MTX	up to 25 mg/week	As effective as AZA (2 mg/kg/day) for 12 months
RTX	1 g i.v. every 4–6 months	RCT (comparison with AZA) in progress
Co-trimoxazole	960 mg, twice daily	Adjunctive therapy in patients with recurrent (upper) airway relapses and chronic carriage of *S. aureus*

Low dosage prednisolone with tapering was included in the majority of studies.

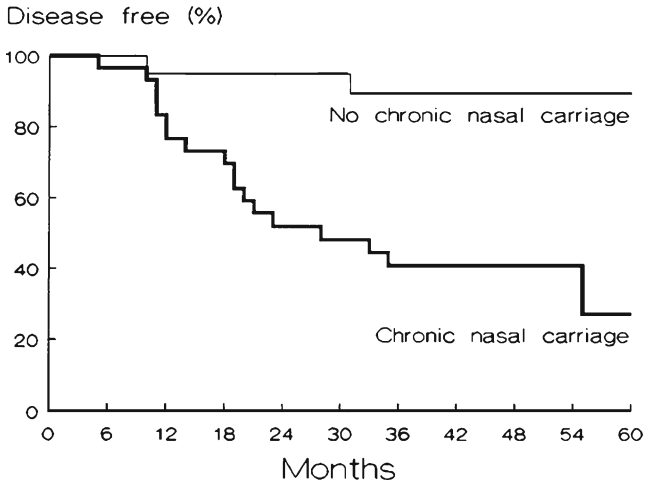

Fig. 1 Disease-free interval and carrier status. Disease-free interval of 57 patients with GPA grouped according to *Staphylococcus aureus* carrier status. The time of the disease-free interval was counted from the beginning of the most recent period of disease activity (either initial diagnosis or relapse; $p<0.001$). From Ref. [29], with permission

treatment of AAV in patients who cannot tolerate AZA. Nevertheless, long-term follow-up is needed for a definite conclusion as to the potency of MTX versus AZA for keeping patients in remission and for evaluation of side effects of drugs and damage. In this respect, an open series study in which MTX was used for maintenance treatment demonstrated a relatively high relapse rate of 36.6 % after 20 months with more than half of the relapses affecting the kidney [24].

Is Mycophenolate Mofetil an Alternative for Azathioprine?

MMF has been suggested, at least in one study [25], to be more efficacious than AZA for maintenance treatment in lupus nephritis. So the EUVAS group started a study to compare MMF with AZA for maintenance treatment in AAV [26]. Induction treatment in this study consisted of CYC (either orally or as intravenous pulses) in combination with corticosteroids. At remission, patients were randomized to either AZA (2 mg/kg/day for 12 months, 1.5 mg/kg/day for another 6 months, thereafter 1 mg/kg/day for another 24 months) or MMF (2 g/day for 12 months, 1.5 g/day for another 6 months, thereafter 1 g/day for another 24 months). Surprisingly, relapses were more common in the MMF-arm (42 out of 76 patients) than in the AZA-arm (30 out of 80 patients, $p=0.03$). Other outcome measures such as renal function and cumulative damage did not differ. This study demonstrates that AZA is the preferred drug for maintenance treatment in AAV but its efficacy is still not optimal as a substantial number of patients still relapse.

Rituximab for Maintenance of Remission?

In view of the limited efficacy of AZA to maintain remission in AAV, different approaches are being considered. Rituximab, a chimeric monoclonal antibody directed against the CD20 molecule on B-lymphocytes, has been used for induction of remission in AAV, as discussed before, and proven at least as effective as oral CYC in a large randomized controlled trial [13]. In this trial, patients who achieved remission on oral CYC were switched to AZA for maintenance of remission whereas patients achieving remission on rituximab did not receive any maintenance treatment. Interestingly, no differences in relapse-free remission were observed at 18 months after inclusion between both arms (preliminary data, [15]). However, also in this study, percentages of relapsing patients were still high in both arms. This

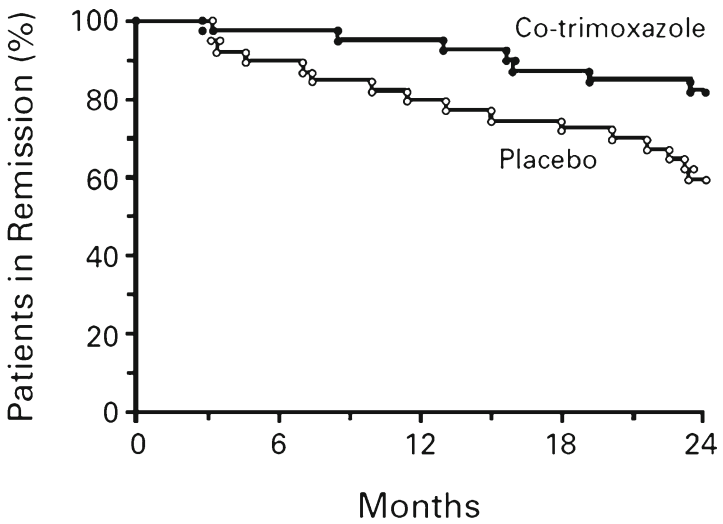

Fig. 2 Disease-free interval from the start of co-trimoxazole or placebo treatment to relapse in patients with GPA. The difference in the disease-free interval between the co-trimoxazole group and the placebo group was statistically significant (by the log-rank test) at 24 months (relative risk of relapse, 040; 95 % confidence interval, 017 to 0.98). From Ref. [33], with permission

prompted the use of rituximab as maintenance treatment in AAV. In a retrospective analysis, Rhee et al [27] reported their experience with rituximab maintenance treatment (1 g i.v. every 4 months) in 39 patients with AAV. They showed that this approach allowed discontinuation of immunosuppressives and corticosteroids in a substantial number of patients without the occurrence of relapses. These data are in line with the preliminary data from the Mayo Clinic [Specks U, personal communication] demonstrating the potential of intermittent rituximab administration to prevent the occurrence of relapses in patients with AAV, particularly in those at risk for relapsing disease (see later). However, prospective controlled trials with long-term follow-up are needed to show not only the efficacy but also the safety of intermittent rituximab administration for maintaining patients with (relapsing) AAV in remission. Currently, an international randomized controlled trial (RITAZAREM) has been started to compare rituximab with AZA for maintaining remission in AAV.

In conclusion, we can abandon CYC as a drug for maintaining remission in AAV (Table 2). AZA appears as the drug of choice with, if not tolerated, the possibility to replace it with MTX. However, many patients still relapse, particularly when these drugs are tapered or discontinued. Future trials should demonstrate if rituximab is more effective than AZA or MTX for keeping patients into remission. Long-term safety of rituximab may, however, be an issue. Otherwise, more insight into the factors that underlie the occurrence of relapses is necessary. This insight will have therapeutic consequences such as the selection of those patients who need long-term maintenance treatment (personalized medicine). A discussion on risk factors for relapse follows in the next paragraph.

Risk Factors for Relapse in AAV

As mentioned, relapses are frequent in AAV but not every patient has relapsing disease. Knowing which patients are at high risk of relapse would certainly influence decisions on duration and level of maintenance treatment. Relapses occur more frequently in patients with PR3-ANCA compared to those with MPO-ANCA which corresponds with a diagnosis of GPA versus a diagnosis of MPA [28]. Furthermore, relapsing disease is associated with chronic nasal carriage of *Staphylococcus aureus* and with persistence of ANCA after induction of remission [29] (Fig. 1). Also, upper-airway, lung-, and heart involvement are associated with relapse [28, 30] whereas a serum creatinine level >200 μmol/l at the time of diagnosis is associated with a reduced risk of relapse [31]. The association of relapsing disease with PR3-ANCA-positive GPA with involvement of the respiratory tract suggests that factors triggering relapse are residing in the (upper) airways. In this respect, the role of *S. aureus* is intriguing [32]. Here, the potential of maintenance treatment with co-trimoxazole to strongly reduce the occurrence of relapses is highly relevant [33] (Fig. 2).

In conclusion, based on the data presented, there is a rationale to individualize maintenance treatment in AAV. Patients with GPA with persisting or recurrent upper-airway involvement and chronic nasal carriage of *S. aureus* can be selected for maintenance treatment with co-trimoxazole. Ongoing maintenance treatment (with AZA or RTX) should be considered for PR3-ANCA patients with recurrent relapses.

References

1. Jennette JC, Falk RJ, Andrassy K et al (1994) Nomenclature of systemic vasculitides. Proposal of an international consensus conference. Arthritis Rheum 37:187–192
2. Walton EW (1958) Giant-cell granuloma of the respiratory tract (Wegener's granulomatosis). Br Med J 2(5091):265–270
3. Fauci AS, Katz P, Haynes BF, Wolff SM (1979) Cyclophosphamide therapy of severe systemic necrotizing vasculitis. N Engl J Med 301:235–238
4. Hoffman GS, Kerr GS, Leavitt RY et al (1992) Wegener granulomatosis: an analysis of 158 patients. Ann Intern Med 116:488–498
5. Talar-Williams C, Hijazi YM, Walther MM et al (1996) Cyclophosphamide-induced cystitis and bladder cancer in patients with Wegener granulomatosis. Ann Intern Med 124:477–484
6. De Groot K, Harper L, Jayne DR (2009) Pulse versus daily oral cyclophosphamide for induction of remission in antineutrophil cytoplasmic antibody-associated vasculitis: a randomized trial. Ann Intern Med 150:670–680
7. Harper L, Morgan MD, Walsh M et al (2011) Pulse versus daily oral cyclophosphamide for induction of remission in ANCA-associated vasculitis: long-term follow-up. Ann Rheum Dis. Nov 29, [Epub ahead of print]
8. Joy MS, Hogan SL, Jennette JC, Falk RJ, Nachman PH (2005) A pilot study using mycophenolate mofetil in relapsing or resistant ANCA small vessel vasculitis. Nephrol Dial Transplant 20:2725–2732
9. Silva F, Specks U, Kalra S, Hogan MC, Leung N, Sethi S, Fervenza FC (2010) Mycophenolate mofetil for induction and maintenance of remission in microscopic polyangiitis with mild to moderate renal involvement—a prospective, open-label pilot trial. Clin J Am Soc Nephrol 5:445–453
10. Stassen PM, Tervaert JW, Stegeman CA (2007) Induction of remission in active anti-neutrophil cytoplasmic antibody-associated vasculitis with mycophenolate mofetil in patients who cannot be treated with cyclophosphamide. Ann Rheum Dis 66:798–802
11. Han F, Liu G, Zhang X et al (2011) Effects of mycophenolate mofetil combined with corticosteroids for induction therapy of microscopic polyangiitis. Am J Nephrol 33:185–192
12. De Groot K, Rasmussen N, Bacon PA et al (2005) Randomized trial of cyclophosphamide versus methotrexate for induction of remission in early systemic antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheum 52:2461–2469
13. Stone JH, Merkel PA, Spiera R et al (2010) Rituximab versus cyclophosphamide for ANCA-associated vasculitis. N Engl J Med 363:221–232
14. Jones RB, Tervaert JW, Hauser T et al (2010) Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. N Engl J Med 363:211–220

15. Specks U, Stone JH, for the RAVE-ITN Research Group (2011) Long-term efficacy and safety results of the RAVE trial. Clin Exp Immunol 164(suppl 1):65
16. Rutgers A, Kallenberg CG (2011) Refractory disease in antineutrophil cytoplasmic antibodies associated vasculitis. Curr Opin Rheumatol 24:245–251
17. Guillevin L, Mahr A (2011) Rituximab to treat ANCA-associated vasculitis. Rev Med Interne 32:591–593
18. Holle JU, Gross WL (2011) Rituximab in AAV: when and how to use it. Nat Rev Rheumatol 7:566–567
19. Guerry MJ, Brogan P, Bruce IN et al (2012) Recommendations for the use of rituximab in anti-neutrophil cytoplasm antibody-associated vasculitis. Rheumatology (Oxford) 51:634–643
20. Jayne DR, Gaskin G, Rasmussen N et al (2007) Randomized trial of plasma exchange or high-dosage methylprednisolone as adjunctive therapy for severe renal vasculitis. J Am Soc Nephrol 18:2180–2188
21. Mukhtyar C, Guillevin L, Cid MC et al (2009) European Vasculitis Study Group. EULAR recommendations for the management of primary small and medium vessel vasculitis. Ann Rheum Dis 68:310–317
22. Jayne D, Rasmussen N, Andrassy K et al (2003) European Vasculitis Study Group. A randomized trial of maintenance therapy for vasculitis associated with antineutrophil cytoplasmic autoantibodies. N Engl J Med 349:36–44
23. Pagnoux C, Mahr A, Hamidou MA et al (2008) Azathioprine or methotrexate maintenance for ANCA-associated vasculitis. N Engl J Med 359:2790–2803
24. Reinhold-Keller E, Fink CO, Herlyn K, Gross WL, De Groot K (2002) High rate of renal relapse in 71 patients with Wegener's granulomatosis under maintenance of remission with low-dose methotrexate. Arthritis Rheum 47:326–332
25. Dooley MA, Jayne D, Ginzler EM et al (2011) Mycophenolate versus azathioprine as maintenance therapy for lupus nephritis. N Engl J Med 365:1886–1895
26. Hiemstra TF, Walsh M, Mahr A et al (2010) Mycophenolate mofetil vs azathioprine for remission maintenance in antineutrophil cytoplasmic antibody-associated vasculitis: a randomized controlled trial. JAMA 304:2381–2388
27. Rhee EP, Laliberte KA, Niles JL (2010) Rituximab as maintenance therapy for anti-neutrophil cytoplasmic antibody-associated vasculitis. Clin J Am Soc Nephrol 5:1394–1400
28. Pagnoux C, Hogan SL, Chin H et al (2008) Predictors of treatment resistance and relapse in antineutrophil cytoplasmic antibody-associated small-vessel vasculitis: comparison of two independent cohorts. Arthritis Rheum 58:2908–2918
29. Stegeman CA, Cohen Tervaert JW, Sluiter WJ et al (1994) Association of nasal carriage of *Staphylococcus aureus* and higher relapse in Wegener's granulomatosis. Ann Intern Med 120:12–17
30. Pierrot-Deseilligny Despujol C, Pouchot J, Pagnoux C, Coste J, Guillevin L (2010) Predictors at diagnosis of a first Wegener's granulomatosis relapse after obtaining complete remission. Rheumatology (Oxford) 49:2181–2190
31. Walsh M, Flossmann O, Berden A et al (2012) Risk factors for relapse of antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheum 64:542–548
32. Tadema H, Heeringa P, Kallenberg CG (2011) Bacterial infections in Wegener's granulomatosis: mechanisms potentially involved in autoimmune pathogenesis. Curr Opin Rheumatol 23:366–371
33. Stegeman CA, Cohen Tervaert JW, de Jong PE, Kallenberg CGM (1996) Trimethoprim-sulfamethoxazole (co-trimoxazole) for the prevention of relapses of Wegener's granulomatosis. N Eng J Med 335:16–20