Maintaining remission in granulomatosis with polyangiitis (Wegener's)

Since the introduction of combined immunosuppressive therapy with oral cyclophosphamide (CYC) and glucocorticosteroids in the 1970s, the outcome of antineutrophil cytoplasmic antibody-associated vasculitides, for example, in granulomatosis with polyangiitis (Wegener`s), improved dramatically. However, the long-term follow-up of patients treated with CYC plus glucocorticosteroids has revealed high treatment-related morbidity and mortality and a high relapse rate (up to 50%), often re-requiring CYC and glucocorticosteroids. Today, according to the European League Against Rheumatism recommendations for the management of small- and medium-vessel vasculitis, the treatment paradigm for severe courses of granulomatosis with polyangiitis consists of CYC for the induction of remission, followed by a less-toxic maintenance therapy for the prevention of relapses. Azathioprine, methotrexate, leflunomide and mycophenolate mofetil proved efficacy for maintaining remission in randomized controlled trials. However, despite clear improvements achieved by the use of maintenance strategies, frequent relapses are still a major concern in the care for granulomatosis with polyangiitis patients, and reliable biomarkers indicating patients at risk of relapse are lacking. The question on the optimal duration of the treatment for remission maintenance has also not yet been answered.

KEYWORDS: azathioprine ▪ granulomatosis with polyangiitis (Wegener`s) ▪ leflunomide ▪ long-term outcome ▪ maintenance of remission ▪ methotrexate

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Learning objectives

Upon completion of this activity, participants should be able to:

- Describe recommendations for induction of remission in patients with GPA, and likely outcomes of recommended therapy
- Describe overall recommendations for maintenance of remission in patients with GPA, and medications shown to be effective for this indication
- Describe adverse events and warnings associated with medications used to maintain remission in patients with GPA, and possible alternatives

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Granulomatosis with polyangiitis (GPA; Wegener's), microscopic polyangiitis (MPA) and Churg Strauss syndrome (CSS) are systemic necrotizing vasculitides and associated with antineutrophil cytoplasmic antibodies (ANCAs). They typically affect small- to medium-, rarely large-, sized blood vessels. Despite profound differences in clinical appearance and genetic background [1] they are often subsumed under the term 'ANCA-associated vasculitides' (AAV). The incidence of AAV is approximately 10–12 cases per million inhabitants per year [2], with GPA being the most frequent diagnosis with approximately eight new cases in Germany and most of the northern European countries, whereas, compared with GPA, the incidence of MPA seems to be higher in southern European countries and in Japan. With the introduction of combined immunosuppressive therapy with oral cyclophosphamide (CYC) and glucocorticosteroids (GCs), survival improved but was still substantially reduced when compared with the general population, mainly due to high treatment-related morbidity and mortality (e.g., MDS, hemorrhagic cystitis, carcinoma, infections and infertility) and relapse rates of up to 50% often requiring repeated courses of CYC and GCs [3–7]. Very recently, normalization of life expectancy in a large monocentric cohort of GPA from a vasculitis referral centre was reported for the first time [6]. The basis for this success was a further improvement of diagnostic and therapeutic options, for example, leading to increased awareness of GPA and earlier diagnosis. Treatment can now often be initiated in less-severe stages of the disease. Therefore, patients in the 'localized stage' of GPA (symptoms restricted to the upper and/or lower respiratory tract), which only very recently has been widely accepted as a distinct and frequently persistent disease stage [8], or the 'early systemic stage' (generalized course without immediately life- or organ-threatening manifestations, e.g., without significant kidney involvement) can often be prevented from progressing to severe generalized life-threatening diseases. With respect to therapeutic strategies, the most important advance was the amelioration of maintenance of remission protocols. Given the high relapse rates after induction of remission, CYC was formerly used for prolonged periods of time. Today according to the European League Against Rheumatism (EULAR) recommendations for the management of small- and medium-vessel vasculitis, the treatment paradigm for severe courses of GPA consists of CYC – either as oral therapy or as dose-saving and less-aggressive pulses – for the induction of remission, followed by a less-toxic maintenance therapy for the prevention of relapses [9]. The proof-of-concept study for this idea was the CYCAZAREM trial [10], showing that azathioprine was not inferior to low-dose daily oral cyclophosphamide regarding relapse rates. In this study (and all other studies for maintenance of remission), only patients with GPA and MPA were included.

The situation gets more complex when recent definitions of remission are considered, for example, those proposed by EULAR/EUVAS, which include an upper limit of the GC dose. In most patients, absence of disease activity can be achieved by highly potent immunosuppression but many patients fail to have their GC doses reduced below, for example, 7.5 mg per day. In our experience, even medium and low GC doses are associated with substantially increased risks of infections and other related side effects. Other patients achieve a state of low disease activity ('grumbling disease') with no further need for intense immunosuppression but also without being in remission. Those patients are usually also switched to medium potent agents to enable further reduction of GC doses. In the following review, different options

for remission maintenance in GPA are presented and discussed (Table 1).

Methotrexate

The first successful use of methotrexate (MTX) for induction of remission in GPA was reported 40 years ago [11]. It then took more than 30 years until the first randomized trial compared MTX with oral CYC for induction of remission in early systemic AAV. The NORAM trial proved the noninferiority of MTX compared with daily oral CYC for induction of remission in this subset of AAV [12]. Several studies have been undertaken to find out whether MTX may also be used as a drug for maintenance of remission.

In 1996, in an open-label study, it was observed that the relapse rates in GPA patients treated with MTX (0.3 mg/kg bodyweight [BW] weekly) alone (n = 22) or in combination with low-dose GC (median 3 mg/day, n = 11) as maintenance of remission therapy were 14% after a median of 16 months (range: 5–30) and 9% after a median of 20 months (range: 4–34), respectively [13]. It is worth noting that the median previous induction therapy with oral CYC was 27 and 22 months (up to 112 months), respectively. Side effects in this study were rare and resolved in 11 out of 12 patients after adaptation of the MTX dose. In this study, the MTX groups (without and with low-dose GCs) were compared with a maintenance therapy with cotrimoxazole, also without (n = 24) and with low-dose GCs (n = 8) in an uncontrolled manner. In the latter two subgroups, the relapse rates were conspicuously higher, at 48 and 100%, respectively. In a further study by the NIH in 1999, Langford *et al.* report on 31 GPA patients who received MTX maintenance therapy for a median of 16 months (range: 4–49) after remission with oral CYC (plus GCs) was achieved, mostly after 3 months [14]. The MTX dose target was 0.3 mg/kg BW orally per week, with a starting dosage not exceeding 15 mg per week and a subsequent increase of up to 20–25 mg per week. After a median of 13 months (range: 10–15 months) from remission only five patients (16%) relapsed. There was noconcomitant GC medication at that time. Two patients had to stop MTX because of suspected MTX pneumonitis. All patients had received pneumocystis prophylaxis with cotrimoxazole and no patient developed an opportunistic infection. Comparing those patients with their historical data on 60 patients continuously treated with daily oral CYC for at least 1 year after achieving remission the authors found similar relapse rates. When extending the follow-up to 32 months the same group reported in 2003 that 22 out of 42 GPA patients (52%) relapsed under the same MTX regimen [15]. In 16 signs of glomerulonephritis were observed, in six as a *de novo* manifestation. The median time from remission to relapse was 15 months (range: 5–60). At the time of relapse, GC had been ceased for a median time of 9 months in all patients. Comparable relapse rates were seen in a trial in 71 patients (mean dose 22.5 mg MTX weekly intravenous [iv.] with an equivalent dose of folic acid after 24 h) over a median follow-up of 25 months [16]. A total of 55 of these 71 patients (77.5%) were on low-dose GC, (median: 5.9 mg/day) at the start

Table 1. Therapies for maintenance of remission in granulomatosis with polyangiitis and/or antineutrophil cytoplasmic antibody-associated vasculitides.

Drug	Dosage	Caveats	Comment	Level of recommendation	Category of evidence
Methotrexate	0.3 mg/kg BW per week	Impaired kidney function	sc. or iv. application is preferable plus folic acid on the next day	A	Ib
Azathiorpine	2 mg/kg BW per day	TPMT deficiency No combination with allopurinol	Possible bone marrow toxicity in long-term use	A	Ib
Leflunomide	20–40 mg per day	Can induce or aggravate hypertension Can cause neuropathy	Extreme long half-life time, needs to be washed out in case of cessation	A	Ib
Mycofenolate mofetil	2–3 g per day	Decreased plasma levels when combined with PPI	Clearly inferior to the three drugs mentioned above	B	IIc
Rituximab	1 g on day 1 and 14 iv.; or 375 mg/m^2 on day 1, 8, 15, 22 iv.	Possible reactivation of virus-hepatitis Problematic in HIV-positive patients	Can decrease IgG levels, especially when used after cyclophosphamide	C	III

BW: Bodyweight; iv: Intravenous; PPI: Proton pump inhibitor; sc.: Subcutaneous; TPMT: Thiopurine-S-methyltransferase.

of MTX. In total, 26 patients (36.6%) developed a relapse after a median of 19.4 months. Again, the majority of the patients (65.4%) had ceased their GC medication at the time of relapse and 16 of the 26 relapsers had signs of renal activity with an increase in serum creatinine in 14; one patient developed rapid progressive glomerulonephritis and died. No serious adverse events occurred. All of these studies were uncontrolled and the direct comparison is often difficult because of different definitions used for remission and relapse and different concomitant therapy.

Leflunomide

In a multicenter blinded randomized controlled trial, MTX was compared with leflunomide (20–40 mg per day) for maintenance of remission; 28 patients received MTX (20 mg per week orally plus low-dose GCs [median 5 mg/day]) after induction of remission with CYC [17]. Within 6 months, 13 of the 28 MTX patients relapsed, seven were major relapses requiring CYC again, four with glomerulonephritis and two with pulmonary hemorrhage. Interim analysis showed that, compared with the leflunomide group, major relapses were significantly more frequent with MTX ($p = 0.037$), resulting in premature termination of this study. However, the frequency of serious side effects was higher in the leflunomide group and led to discontinuation (hypertension, peripheral neuropathy and leukopenia) in four patients, whereas no patients had to cease using MTX because of side effects.

Azathioprine

The idea of substituting CYC with less-toxic agents for the purpose of maintaining remission in AAV was first formally proven in a multicenter unblinded randomized study, the so-called CYCAZAREM trial conducted by the European Vasculitis Study Group (EUVAS) [10]. After remission was achieved with 3–6-month oral CYC medication, the patients were randomly assigned to receive either azathioprine (AZA) 2 mg per kg BW daily or 1.5 mg CYC per day. The latter group was switched to AZA after a total of 12 months. The primary end point was relapse. At 18 months, eleven relapses had occurred in the 71 patients assigned to the AZA group compared with ten relapses in the 73 patients treated with prolonged oral CYC, proving the noninferiority of AZA. There was also no significant difference regarding adverse events between both groups. This trial demonstrated that AZA may be used as a CYC-sparing substance without losing efficiency. The likely positive effects on long-term toxicity could not be proven owing to the limited observation period.

In 2008, the French vasculitis study group published a multicenter prospective open-label study to compare AZA (2 mg/kg BW per day) with MTX (0.3 mg BW up to 25 mg weekly plus folic acid) over 12 months for remission maintenance in AAV after induction of remission with CYC pulses [18]. Each group comprised 63 patients; in both groups 76% of the patients had GPA, and the others had MPA. The primary end point of this study was an adverse event requiring discontinuation of the drug or leading to death. The primary hypothesis was that MTX would be less toxic than AZA. After a mean study period of 29 months (±13 months) there was no significant difference in the incidence of side effects. Patients with fewer than 250 $CD4^+$ T lymphocytes per millilitre received a pneumocystis prophylaxis with cotrimoxazole in the AZA group, and with pentamidine aerosol in the MTX group. In total, 23 out of 63(36.5%) patients in the AZA group and 21 out of 63 patients (33.3%, not significant) in the MTX group relapsed; 73% of them experienced the relapse after discontinuation of the study drug after 12 months. In the MTX group, two cases of MTX pneumonitis occurred. In conclusion, AZA and MTX seem to be equally safe and effective.

Mycophenolate mofetil

After its introduction in the field of organ transplant medicine and positive results in an SLE trial [19], mycophenolate mofetil (MMF) was also increasingly used for maintenance, and sometimes even for induction of remission in AAV. As smaller studies showed efficiency for induction [20] and maintenance [21] of remission, a well-designed randomized controlled trial comparing MMF with AZA was performed by the EUVAS Group (IMPROVE) [22]. After induction of remission with standard CYC therapy, patients were randomly assigned to receive either AZA 2 mg/kg BW per day or MMF of at least 2000 mg per day. The primary end point was relapse-free survival. After a median follow-up of 39 months, 42 out of 76 patients in the MMF group relapsed versus 30 out of 80 patients in the AZA group, resulting in a hazard ratio of 1.69 ($p = 0.03$) for MMF. With no significant differences in adverse event rates, this trial clearly demonstrated the inferiority of MMF when compared with AZA.

Glucocorticoids

A current meta-analysis of recent large controlled trials including patients with GPA and MPA [23]

showed that the concomitant GC regimen may also influence the risk of relapse: the relapse rate was significantly higher in those patients who had a scheduled stop of GCs within the first 12 months of treatment (43%) as opposed to those who remained on low-dose steroids beyond 1 year of treatment (14%). To date, no data from trials primarily evaluating different GC regimens exist. An ongoing EUVAS VCRC trial is testing two different GC regimens for induction of remission.

Rituximab

Rituximab (RTX), a chimeric monoclonal antibody directed against the B-cell-specific antigen CD20, has recently been proven to have equal efficiency in induction of remission in generalized AAV (including GPA) in two randomized controlled studies comparing it with CYC [24,25]. A substantial number of observational studies investigating the efficacy of RTX in refractory AAV and/or GPA have been published in the past few years [26–29], most of which reported high rates of remission (>80%). A very recent analysis, however, indicated less effectiveness on the granulomatous manifestations of GPA [30]. Recently, an uncontrolled retrospective study investigated the efficacy of RTX as maintenance therapy in 39 patients with AAV [31]. A total of 20 out of these 39 AAV patients had 2 years of follow-up. Patients received either two 1000-mg RTX infusions in a 2-week interval (n = 35) or four weekly infusions with 375 mg/m² (n = 4). All patients were scheduled to receive a single 1000-mg dose every 4–6 months. Thirty of the 39 patients had involvement of the ENT tract and were classified as GPA, the other patients had MPA. Twenty-four patients were positive for PR3-ANCA and 15 for MPO-ANCA. Disease duration before starting RTX varied widely, with a median of 67 months. Seventeen of the 39 patients were in complete remission (Birmingham Vasculitis Activity Score [BVAS]/GPA: 0), the other patients had a partial remission with a median BVAS/GPA of 2. The indications for initiation of RTX were heterogeneous, including rising or persistently high ANCA, CYC and GC toxicity. At the end of follow-up (after at least 20 months), three patients experienced nonlife-threatening or nonorgan-threatening flare. The percentage of patients on additional immunosuppressive therapy decreased from 87 to 41% at month 12 ($p < 0.001$) and to 30% at month 24 ($p = 0.002$). Recently, two controlled studies have been started investigating RTX versus AZA as maintenance therapy in relapsing AAV.

Etanercept

There is some evidence that TNF-α may be centrally involved in the pathogenesis of AAV. Uncontrolled trials of TNF-blocking agents suggested efficacy in AAV, including GPA [32], and led to a placebo-controlled randomized trial of etanercept (ETA) in 174 patients [33]. ETA or placebo was given as an add on to standard therapy – that is, CYC or MTX for induction and MTX or AZA for maintenance of remission. The primary end point, sustained remission for at least 6 months, was reached in 69.7% in the ETA group versus 75.3% in the placebo group ($p = 0.39$). Six solid cancers occurred in the ETA group versus none in the placebo group ($p = 0.01$). In conclusion, ETA adds no benefit to standard maintenance therapy, but might increase the risk of severe adverse events [34].

Conclusion & future perspective

The optimal maintenance of remission regimen in GPA and other AAVs still remains a matter of debate. The relapse rate in GPA patients is twice as high as those of MPA patients [10]; however, apart from PR3-ANCA positivity, normal renal function and pulmonary involvement [23,35], no further predictors of relapse could yet be identified and evaluated. According to recent work by McKinney and colleagues, a CD8 T-cell transcription signature might bear the potential to predict relapses in AAV and other autoimmune diseases [36]. Prospective evaluation of these findings is planned in the context of an EUVAS trial. Changes of the ANCA titer are certainly not predictive of relapses, as shown in a recent subanalysis of a large placebo-controlled randomized therapeutic trial in GPA patients in the USA [37]. Likewise, there are no reliable biomarkers that could guide the initial choice of drug for maintenance therapy. What can be concluded from existing evidence is that AZA and MTX are equipotent and seemingly comparably safe. Therefore, both can be regarded as first-choice drugs. Comorbidities and comedications must be taken into account: MTX may not be used in patients with reduced kidney function – that is, a glomerular filtration rate of 50 ml/min or lower – if the use of one of the equipotent alternatives is possible. It also may interact with, for example, cotrimoxazole. Its hematotoxicity is low, especially when substitution with folinic acid is abided. AZA confers a higher long-term risk for hematotoxicity, the blood count and – in our experience – as a sensitive parameter the MCV should be monitored. It cannot be combined with allopurinol and up to 10% of Caucasians

lack activity of the thiopurine methyltransferase owing to gene mutations leading to an increased risk of bone marrow suppression. Conception and pregnancy might be safe under AZA; however, MTX is associated with high rates of fetal malformation. Therefore, age, family planning and the eventual need for contraception must be taken into account.

Leflunomide is less well investigated. The existing data suggest that it may be as effective as MTX and AZA. It can be seen as a second-line drug. Besides its potential to induce or worsen high blood pressure, peripheral neuropathy is the most important adverse event, which often is difficult to differentiate from neuropathy due to active vasculitis.

Judging by the available data, MMF seems to be less effective than MTX, AZA and LEF. It should be regarded as a reserve drug that should only be used if the other three medium potent immunosuppressants have failed or cannot be used for other reasons.

Finally, the account of RTX cannot yet be estimated. First published data suggest that it might be a potent drug not only for induction, but also for maintenance of remission. However, to date, no controlled trials exist and safety issues are yet to be resolved. It might be speculated that otherwise than in rheumatoid arthritis the incidence of secondary immunodeficiency, with low immunoglobuline levels is increased, especially in CYC pretreated patients.

Another important question regarding maintenance therapy is the optimal duration, and there is no clear answer yet. As a secondary result of the NORAM study [12], an extraordinarily high relapse rate (69.5% in the MTX induction group and 46.5% in the CYC induction group) following complete termination of the immunosuppressive therapy after 1 year was observed. Thus, it must be concluded that, at least in GPA patients, who represented the vast majority in the NORAM trial, maintenance therapy should be continued beyond 12 months, especially when induction of remission was achieved without CYC. Thus, the EULAR guidelines recommend a duration of maintenance therapy of at least 18 months [9]. The British Society for Rheumatology guidelines recommends continuous immunosuppression in GPA for up to 5 years [38]. This question will also be addressed in another trial of the European Vasculitis Study Group EUVAS. Furthermore, the optimal dose and duration of concomitant GC use is also yet to be determined. In conclusion, despite maintenance of remission strategies, the relapse rate in GPA remains high, and reliable biomarkers for the identification of patients at risk of relapse are still lacking.

Executive summary

- Granulomatosis with polyangiitis (GPA) is characterized by a variable spectrum of disease courses, ranging from persisting localized forms to life-threatening severe extremes – for example, the pulmorenal syndrome.
- Owing to the introduction of glucocorticosteroids (GCs) and cyclophosphamide (CYC) for the induction of remission, acute survival even in severe courses of GPA can be achieved in the majority of patients, thus shifting the actual clinical problem to the still high relapse rates.
- As long-term use of CYC is associated with substantial morbidity, current concepts aim to shorten the period of CYC use to 3–6 months, followed by less aggressive medication after reaching remission.
- In randomized controlled trials, azathioprine (AZA) and methotrexate (MTX) proved to be equally potent in maintaining remission.
- Leflunomide may be superior to MTX in terms of maintenance of remission; however, this advantage is outweighed by a substantial increase in adverse event rates. Mycophenolate mofetil is less effective than AZA.
- In patients with a glomerular filtration rate <50 ml/min, MTX should be used with caution; AZA and leflunomide are alternatives in this situation.
- A long-term low-dose GC medication seems to contribute to maintenance of remission. Given the relatively low rate of adverse events with daily GC doses of 5 mg and below, cessation of GC might be disadvantageous.
- Preliminary data from uncontrolled trials suggest that repeated applications of rituximab might also be effective in maintaining remission. Controlled trials on this topic are on their way.
- As the result of a randomized controlled trial, etanercept is not useful for maintenance of remission in GPA.
- To date, no biomarkers are available to identify patients at risk of relapse.

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Maintaining remission in granulomatosis with polyangiitis (Wegener's)

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Activity evaluation: where 1 is strongly disagree and 5 is strongly agree.	1	2	3	4	5
The activity supported the learning objectives.					
The material was organized clearly for learning to occur.					
The content learned from this activity will impact my practice.					
The activity was presented objectively and free of commercial bias.					

1. Your patient is a 72-year-old male diagnosed with severe granulomatosis with polyangiitis (GPA; Wegener's disease). Based on the review by Drs. Reinhold-Keller and Moosig, which of the following statements about recommendations for induction of remission in patients with GPA and likely outcomes of recommended therapy is most likely correct?

- ☐ **A** Acute survival rates are poor when glucocorticosteroids (GC) and oral cyclophosphamide (CYC) are used together to induce remission
- ☐ **B** Treatment-related morbidity and mortality are low for GC and CYC
- ☐ **C** Relapse rates with GC and CYC are about 15%
- ☐ **D** The European League Against Rheumatism (EULAR) recommends CYC for about 3–6 months to induce remission, followed by less toxic maintenance treatment to prevent relapses

2. Based on the review by Drs. Reinhold-Keller and Moosig, which of the following statements about recommendations for maintenance of remission and likely outcomes in the patient described in question 1 is most likely correct?

- ☐ **A** Currently available maintenance strategies are highly effective in preventing relapses
- ☐ **B** Randomized trials have shown efficacy of azathioprine (AZA), methotrexate (MTX), leflunomide, and mycophenolate mofetil (MMF) for maintaining remission
- ☐ **C** Controlled randomized trials have shown that AZA is significantly more effective than MTX in maintaining remission
- ☐ **D** MMF is significantly more effective than AZA in maintaining remission

3. Based on the review by Drs. Reinhold-Keller and Moosig, which of the following statements about adverse events and warnings associated with medications used to maintain remission in patients with GPA, and possible alternatives, would most likely be correct?

- ☐ **A** Leflunomide has a superior safety profile
- ☐ **B** AZA is contraindicated in patients with GFR <50 ml/min
- ☐ **C** There is a relatively low rate of adverse events with daily GC doses of 5 mg or less
- ☐ **D** Controlled trials have shown that rituximab and etanercept are useful to maintain remission in GPA