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Maintenance therapy in ANCA-associated vasculitis: who needs what and for how long?

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ABSTRACT

Anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitides (AAV) are severe chronic auto-immune diseases in which the small vessels are inflamed. Nowadays, in the majority of patients disease can be brought into remission with cyclophosphamide and corticosteroids. However, depending on disease characteristics, patients with AAV have a risk of 29-60% to experience relapses of disease within 5 years despite maintenance therapy with less toxic agents, such as azathioprine, methotrexate or mycophenolate mofetil. More recently, rituximab has been found effective in both induction and maintenance of remission in AAV. This review discusses the different aspects of maintenance therapy in AAV based on reported cohorts and studies, including the different agents, therapy duration, efficacy or lack thereof and future directions. Finally, recommendations are made who to treat and for how long.

INTRODUCTION

The last quarter of the previous century has seen a tremendous development in the understanding and treatment of the diseases that we now commonly denote as anti-cytoplasmic antibody associated (ANCA) vasculitis. Following the observation of neutrophil-specific antibodies in association with segmental necrotizing glomerulonephritis in the early 1980s (1), van der Woude et al. described autoantibodies producing a diffuse granular cytoplasmic staining of neutrophils, so-called C-ANCA, in patients with Wegener's granulomatosis (2). A few years later, perinuclear staining of alcohol-fixed neutrophils (P-ANCA) was described predominantly in patients with microscopic poly-angiitis and renal limited small vessel vasculitis (3). Many subsequent studies at first focused on the pathogenesis of ANCA-associated diseases and reported that ANCA could activate neutrophils and monocytes resulting in a release of inflammatory constituents, suggesting a direct pathogenic role (4), and finally proved the pathogenic potential of these antibodies in a myeloperoxidase(MPO)-ANCA animal model (5)

Since then, finding a better treatment paradigm became a dominant focus of different studies. Due to the introduction of cyclophosphamide combined with high dose steroids in the 1960's (6), these diseases changed from progressive and often fatal to modifiable and treatable and thereby became more chronic conditions with unpredictable periods of relapse in about 25-40% of patients (6,7). Still, mortality and morbidity are substantial due to either disease or toxicity of prolonged courses of immunosuppressive treatment.

Many studies have addressed this toxicity–problem: avoidance of prolonged cyclophosphamide by a staged approach, limiting induction treatment to 3-6 months and followed by a longer period of less-toxic therapy with azathioprine to maintain disease remission, proved to be successful (7). By this scheme, remission was and is achieved in over 90% of patients (8).

Although initial disease control is obtained, the efficacy of these therapies on subsequent relapse is still not clear (9-11). This review focuses on maintenance therapy in ANCA associated vasculitis in order to answer the question who needs what maintenance therapy and for how long.

Relapses- definition

As remission is a clinical definition (defined by absence of manifestations of vasculitic disease activity) and not a pathophysiological one, so is relapse with a large variation in severity (9). It can be defined as new or worsened manifestation of ANCA-associated vasculitis after a period of partial or complete remission requiring a change in therapy which could be classified as minor and major, according to the absence or presence of threatened vital organ function (11-13).

Noteworthy, relapses can sometimes be triggered or preceded by and coincide with infection or malignancy, but more important, these important clinical phenomena can mimic relapse, so attention must be paid for a thorough differential diagnosis.

Relapses- prediction of risk

Because about 30-50% of patients experience a relapse within five years after diagnosis (12) ,the ability to predict risk of relapse and thus reserve potentially toxic therapy for those who are most likely to benefit, would be highly desirable (14).

A lot of studies addressed this topic and provided evidence that the risk of relapse is influenced by both disease and patient characteristics and also choice of therapy.

Patients with granulomatosis with poly-angiitis (GPA) have a relapse risk within 5 years of up to 60% versus 29% in microscopic poly-angiitis (MPA) (9). The presence of proteinase-3 (PR3)-ANCA (12,15), respiratory tract disease (in particular alveolar haemorrhage) and prior relapse have a significantly higher likelihood of relapses with increased risk of ~ 1.7 fold for each risk factor (16,17). In contrast, patients with higher serum creatinine levels and those who remain dependent of renal replacement therapy are at substantially lower risk of relapse of up to 60% less (12,18,19).

The presence of a positive ANCA at the time of remission increases the risk of relapse > 2 fold (13). The value of serial measurement of ANCA titre during follow up is still controversial (20,21) . Rises in ANCA titre occur prior to relapse in many patients but sensitivity and specificity of these rises are too low to guide therapy in individual patients (19,20) .

It has been suggested that relapse risk is more likely related to the organs that are affected than to the overall severity or aggressiveness of the vasculitis. This has been proven for respiratory tract involvement. For cardiovascular involvement this association is less clear and, but since cardiovascular involvement is uncommon and difficult to diagnose, it may have been underestimated in earlier studies (12).

Several genetic factors have been associated with AAV; only very few have been identified as related to disease course or to risk factors for relapse. Human leucocyte antigen (HLA)-DR antigens were thought to be weakly associated with increased relapse rate but it was unclear whether this was due to the class II antigens itself or due to linkage with polymorphism located close to class II genes (22). In a large genome-wide association study, both major-histocompatibility-complex (MHC) and non-MHC were found to be genetically associated with the antigenic specificity of ANCA. On this ground, GPA and MPA are supposed to be genetically distinct which may explain the different clinical spectrum and outcomes (23).

Previously, patients treated for only a few months were found to be likely to relapse, which led to recommendation of continuing immunosuppressive therapy (14). Recently, based on long-term follow-up data of a randomized trial, it has been suggested that a longer

duration of cyclophosphamide for induction remission was related to less relapses, a finding also reported by an older observational study (24,25)
Initial use of methotrexate (MTX) or intravenous cyclophosphamide (HR, 0.50; 95% CI, 0.26-0.93; P=0.029) has been associated with higher relapse rates than oral cyclophosphamide (26). There are some conflicting data on plasma exchange: the recently published long-term data of the methylprednisolone versus plasma exchange (MEPEX) showed a reduced number of relapses in the plasma exchange-group compared with high-dose prednisolone, 14.4% vs 20.5% (27); however, in a smaller retrospective study on plasmapheresis rescue therapy, an unexpected higher number of relapses was found (58%) during follow- up of 10 years (28). Early withdrawal of glucocorticoids is associated with higher relapse rate compared with long-term steroid regimes (43% versus 14%) as was found in a large meta-analysis of 13 studies with over 900 patients (29). Addition of sulfamethoxazole-trimethoprim (co-trimoxazole) to other immunosuppressive agents during remission, however, was associated with overall reduced relapse rates (30).
There might be a relation between infection- induced activation of neutrophils and monocytes/macrophages and subsequent development of disease activity since target antigens of ANCA are expressed and released by these cells (1,14). Several cases of subsequent events and also seasonal variations in incidence of disease, suggesting possible viral influences, have been described. It has even been hypothesized that the site of infection might even determine the location of active vasculitis (21). At last, nasal carriage of Staphylococcus aureus has been pointed out as a significant risk factor (RR 7.2) for the occurrence of relapse in GPA(31).

Relapses- consequences
Severe relapses could cause death or at least extensive organ damage as measured by vasculitis damage index (VDI), for instance due to stenotic/occlusive or aneurysmal changes of vessels, diffuse alveolar haemorrhage or subglottic stenosis (20,31). Over time, in a large cohort of patients, severe damage occurred in > 50% of patients and was mostly due to renal and cardiac involvement; however, the strongest predictors for cumulative organ damage were baseline organ damage and elevated erythrocyte sedimentation rate (ESR) (25).
In renal involvement, every renal relapse is associated with a decrease in estimated glomerular filtration rate (eGFR in ml/min per 1.73m2) of 8-12 ml/min (34). Additionally, patients who have a renal relapse with overt and active glomerulonephritis are also 4.7 times more likely to progress to end-stage renal disease, compared with those who do not experience a relapse, independent of other risk factors such as age, ANCA specificity or initial kidney function (16).

Relapsing ear, nose and throat disease-activity may lead to progressive subglottic and tracheal stenosis independent of therapy. These patients require frequent surgical intervention, and the clinician should remain vigilant for progression of disease (35).
Next to life- or organ- threatening events, the price for retreatment or prolonged courses of immunosuppression to prevent or cure relapse could be high due to side effects of these toxic treatment regimes. In the short-term, cyclophosphamide can induce haemorrhagic cystitis but most important, prolonged courses of leucopenia and associated infections are important contributors to morbidity (10). In the long-term, the risk of malignancy (in particular bladder cancer, leukaemia and lymphoma) increases with cumulative cyclophosphamide dose above 36 g, although a safe dose has not been determined (34). Furthermore, the risk of infertility (> 50% of women in childbearing age) should be taken into account when deciding on treatment of relapses (37).
Azathioprine, MTX and low dose glucocorticoids are usually the mainstay of long term maintenance therapy, next to mycophenolate mofetil (MMF). Most reported side events are gastro-intestinal complaints (abdominal pain, diarrhoea) and (viral) infections, but also mucositis and hepatotoxic effect have been described (10,36). Definitely, the use of glucocorticoids is associated with a wide range of metabolic, gastro-intestinal and psychiatric adverse events (10); the prolonged treatment with moderate to high doses of glucocorticoids significantly contribute to diffuse cumulative organ damage of any significance, for instance considerable weight gain, bone diseases and fractures (10,25).

Relapses- impact on quality of life (QOL)

ANCA associated vasculitis patients are exposed to long-term toxic therapies, suffer from accumulated organ damage and at risk for potentially life-threatening relapses. However, quality of life (QOL) is reported to be similar to other chronic conditions and of all this aforementioned threats, fatigue was the most important contributor and major determinant to poor QOL (37,38). QOL measurements also reported sleeping problems, perhaps due to uncertainty and fear about the relapsing nature of the disease, and neurological manifestations (often resulting in pain, sensory disturbance and functional disability) as important in defining QOL, next to old age and high current prednisolone dose (37,38). These factors can partially be associated with poor disease control and therefore can be regarded as potentially modifiable; however, the actual impact of relapses on QOL has not been reported.

Relapses- prevention

Because the consequences of retreatment of relapses are huge in terms of probable increase in both morbidity and mortality, a lot of studies addressed the issue of prevention of relapse. However, to demonstrate the efficacy of a medication, a study must include

a population at risk of relapse that is followed over a sufficiently long period of time. For a disease with a annual incidence in Northern Europe of 11-16 cases per million and a prevalence of 177 cases per million (10,35) , this is a difficult goal and there are only a few randomized trials comparing different medications (Table 1). What evidence has been delivered?

In 1990, Cohen Tervaert et al proved the need for maintenance therapy in order to prevent relapse by comparing pre-emptive immunosuppressive therapy based on rising ANCA-titres to patients who were only treated if there was a clinical relapse. Those who were treated pre-emptively experienced significantly less relapses, $P < 0.05$. Of note, those patients who were treated based on clinical relapse received a higher cumulative cyclophosphamide dose, than those who were treated pre-emptively (14).

In 2003, the randomized trial of cyclophosphamide versus azathioprine during remission in ANCA positive systemic vasculitis (CYCAZEREM) demonstrated in 155 patients that withdrawal of cyclophosphamide after induction of remission and substitution of azathioprine was safe and did not increase relapse rates. Duration of azathioprine-use was ~ 12 months (from +/- 6 to 18 months after initial therapy). Patients with severe renal involvement and serum creatinine > 500 umol/l were excluded from this trial (7).

Based on a few small studies and the known superior effect in treatment of systemic lupus erythematosus (SLE), MMF was studied as alternative to azathioprine in maintenance therapy in AAV (36)(Figure 1). Treatment duration was 42 months. Surprisingly, MMF was less effective because relapses were more common in the MMF group compared to azathioprine ($P= 0.03$); adverse events did not differ. The authors stated that MMF should not be considered as first line for maintenance therapy, although in might be considered in refractory cases of AAV (36).

Co-trimoxazole (800 mg sulfamethoxazole and 160 mg trimethoprim) was given twice daily for 24 months during and after treatment with cyclophosphamide and prednisolone and especially reduced the number of relapses involving the upper airways ($P= 0.03$). Although 20% of patients stopped treatment prematurely because of side effects, these were generally mild (30).

Due to the known effect in rheumatoid arthritis (RA) and based on smaller studies, MTX was also compared with azathioprine in maintenance therapy, especially addressing safety-issues during 15 months after diagnosis (39,40). Although in a smaller study, the number of renal relapse was high under methotrexate maintenance therapy (41), in this randomized trial the drug appeared to be similar to azathioprine in maintaining remission but also for the toxicity profile. However, although no differences were found in severe and less severe adverse events, the authors warn to adjust the dose to renal function and advise to avoid it in patients with severe renal impairment (39).

Due to increased understanding in pathogenesis of AAV and also the known effects in other rheumatic diseases, tumour necrosis factor-α (TNF-α) inhibitors were also introduced in

Table 1 Overview of randomized clinical trials of maintenance therapy in AAV.

	Inclusion	Induction	Maintenance
Cohen Tervaert et al, 1990 N= 20	Biopsy proven WG, in partial or complete remission		Depending on significant rise in ANCA: CYC 1 mg/kg/day + pred 30 mg/day N=9 or no maintenance N=11.
Stegeman et al, 1994 N=81	WG in remission	Various	CYC + pred according to protocol + Co-trimoxazol 960 mg twice weekly N=41 Placebo N=40
CYCAZEREM Jayne et al, 2003 N=144	Newly diagnosed WG/MPA/RLGN seCreat < 500 umol/l.	Cyc oral 2 mg/kg Pred 1 mg/kg	Cyc 1.5 mg/kg/day + pred N= 73 AZA 2 mg/kg/day + pred N=71
WGET WGET research group, 2005 N= 180	Newly diagnosed and flares, BVAS > 3	Severe: CYC 2 mg/kg + pred 0.5-1 mg/kg Limited: MTX 0.25 mg/kg/wk + pred 0.5-1 mg/kg	MTX max 25 mg/wk AZA 2 mg/kg/day +/- Etanercept 25 mg twice weekly N=89 with ETA N=91 without
WEGENT Pagnoux et al, 2008. N=126	WG/MPA	CYC i.v 0.6 mg/0.6 x m2 first two weeks, thereafter 0.7 mg/m2 every three weeks. Pred 1 mg/kg/day	AZA 2.0 mg/kg/day N=63 MTX 0.3 mg/kg/wk N=63

	Duration	Relapse	AE's
		CYC/pred N=0 No treatment: N=9 (82%), of which 6 within 3 months after ANCA-rise.	Mild. No differences between groups. Death N=1 (no treatment).
	Treatment 24 months. FU 24 months	Patients in remission Co-trim: 82% Without Co-trim: 60% P 0.40 In patients with respiratory tract disease P 0.03	Co-trim: N=8, 20% (medication discontinued) Placebo: N=2, 5% Death N=1 (placebo)
	Treatment 18 months	CYC: N=10, 13.7% AZA: N=11, 15.5% P 0.65	CYC: N=7, 10% AZA: N=8, 11% P 0.94 Death N=1.
	Treatment 12 months + tapering, FU 27 months.	ETA: N=51, 57.3% Without ETA: N=52, 57.1% P 0.54	ETA: 56.2% Without ETA: 57.1% P 0.90 Death ETA: N=4, Without ETA: N=2
	Treatment 15 months FU 29+/- 13 months	AZA: N=23, 37% MTX: N=21, 33% P 0.71	AZA: N=29, 46% MTX: N=35, 56% P 0.29. Death N=1 (MTX)

Table 1 Continued

	Inclusion	Induction	Maintenance
Metzler et al, 2009 N= 20	Generalized WG in complete or partial remission	CYC Pred	Stepwise approach in use of Leflunomide: N=20 -100 mg for 3 days - 20 mg/day for 12 weeks - 100 mg for 2 days - 30 mg/day for 12 weeks If necessary: - 40 mg/day for 12 weeks Optional: continuation for two consecutive years
Metzler et al, 2007 N=54	Generalized WG Exclusion: leucopenia < 4 mmol/l and seCreat > 115 umol/l,	CYC 2 mg/kg/day Pred 1 mg/kg/day	MTX N= 28 - Wk 1-4: 7.5 mg/wk - Wk 5-8: 15 mg/wk - Wk 8: 20 mg/wk Leflunomide: N=26 -100 mg for 3 days - 20 mg/day for 4 weeks - > 4 weeks: 30 mg/day
IMPROVE Hiemstra et al, 2010 N=156	Newly diagnosed AAV (WG/MPA)	CYC 1.5-2 mg/kg/day Pred 1 mg/kg/day	AZA 2 mg/kg/day N=80 MMF 2000 mg/day N=76

treatment for ANCA-associated vasculitis (42). Etanercept or placebo was added to standard maintenance regimen with either cyclophosphamide or methotrexate and glucocorticoids during 12-15 months. No differences were found in number of flares, but six cases of solid tumours were detected in the etanercept group. It was hypothesized that the combination of cyclophosphamide and TNF-a inhibition heightens the risk of cancer. Therefore, this drug is no longer recommend and also other TNF-a inhibition is advised not to use (42).

Duration	Relapse	AE's
Treatment 52 weeks (1.75-2.5 years)	N=9 (45%)	N= 20, 8.3 AE's per patient.
Study was ended prematurely by the advisory board. Aimed treatment duration 24 months (12 patients in each arm) Median FU 21 months (1-24)	MTX: N=13 (46%) LEF: N=6 (23%) P 0.09	MTX: N=17 LEF: N= 34 (1.3 per patient) P= 0.09 Death: ..
Treatment mean 39 months (0.66-53.6) FU 42 months	AZA: N=30, 37% MMF: N=42, 55% P 0.03	AZA: N=13, 16% MMF N=8, 7.5% P 0.12 Death N=2 (1 AZA, 1 MTX)

Since in RA the use of leflunomide seems to approach the potency of MTX, this drug was also studied as maintenance agent in AAV, especially since it does not accumulate in renal failure and does not cause leucopoenia (43). Relapse risks were equal or even better compared with standard agents (a controlled trail comparing MTX versus leflunomide was terminated early because of major relapse rate in MTX group) but there was a adverse event rate reported of up to 8.3 per patient (43,44).

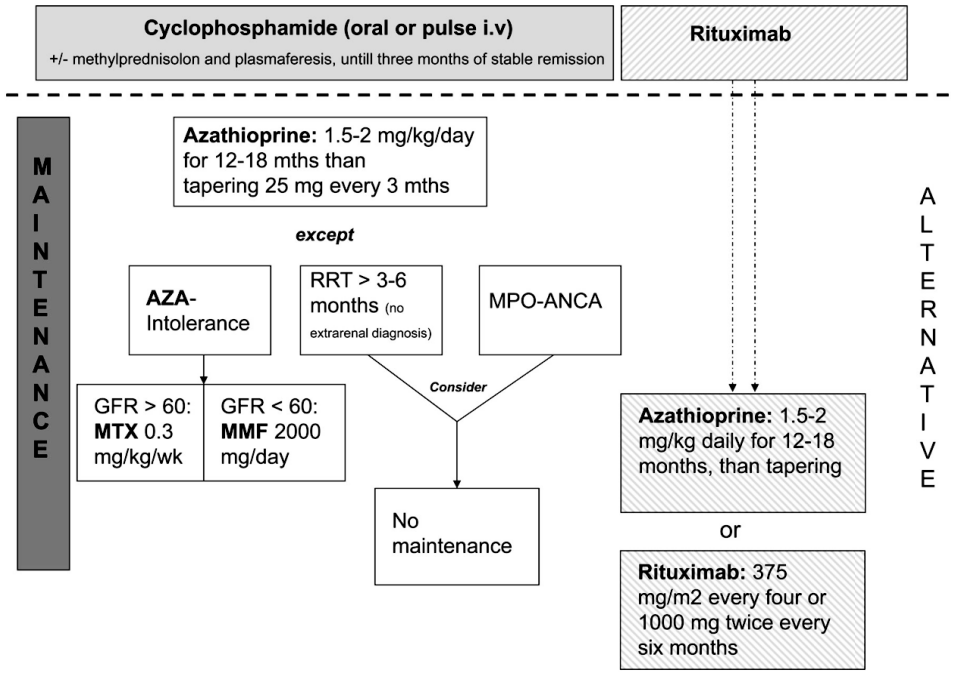

Figure 1 Proposed flow chart for maintenance treatment in AAV

Relapses- duration of maintenance therapy

The strategy of discontinuing maintenance therapy after 18-24 months was chosen as Committee consensus by analogy with the results of the aforementioned clinical trials (45). This duration may be somewhat arbitrary, especially when keeping in mind that in surveys on outcome reported median disease-free survival is 21.8 (range 9.8-27) months after diagnosis (46). Moreover, it is also known that most relapses happen during tapering or after discontinuing drugs.

The data of a large multi-centre study comparing short-term and long-term courses of azathioprine maintenance therapy are not yet published (REMAIN) but in a prospective study of 126 patients with PR3-ANCA- associated vasculitis, in a subgroup of patients who remained ANCA positive at time of remission (n=44) no difference in relapse rate was found for longer duration of azathioprine up to 48 months (47). This may raise questions about the effect of azathioprine maintenance effect at all. This same question about maintenance rose after the rituximab for induction-remission trail (RAVE). The rituximab-arm received no additional treatment but had the same outcomes on relapse rate at 18 months of follow up (48) (Table2).

Also, it has been suggested that a specific subset of patients who do not carry any risk factor for relapse (e.g. MPO-ANCA, no respiratory tract involvement) do no require any maintenance therapy at all (11). However, specific markers allowing reliable identification of low relapse risk have to be studied further to make clear statements about this topic.

Relapses- new developments

Although nowadays given a prominent role in induction therapy and refractory disease, present knowledge on rituximab- maintenance therapy is scarce but promising. After its first description in 2001 in ANCA-associated vasculitis, it was initially used for patients who were refractory to common immunosuppressants or relapsing under treatment (49). In two prospective randomized controlled studies, rituximab turned out to be as effective as cyclophosphamide at inducing remission (48,50,51), so both the Food and Drug Administration (2011) and the European Medicines Agency (2013) approved its use for the induction treatment of adults with GPA and MPA (49). The recently published prospective maintenance of remission using rituximab in systemic ANCA-associated vasculitis trial (MAINRITSAN) also demonstrates its efficacy in maintenance of remission (52).

Nevertheless, treatment regimens and dosages vary throughout the different studies and the most efficient scheme for both induction and maintenance has not been determined yet (52-54). One of the great advantages is the preservation of ovarian function; therefore its use can be considered in young women whose pregnancy wish is not yet fulfilled (38,51). Furthermore, a positive issue regarding the use of rituximab is the possibility to withdraw concomitant immunosuppressants and reduction of daily prednisolone-dose (54).

Safety issues are minimal but mainly consists of long-lasting severe infections (due to hypogammaglobulimia and loss of humoral immunity); guidelines recommend checking immunoglobulin levels before and after treatment (10,49,51). Complications of long-term outcome after rituximab, for instance late onset neutropenia (LON) has to be further studied, so close monitoring seems needed when rituximab is prescribed combined with other immunosuppressive therapies (49,54).

Another recent development is the use of intravenous abatacept, CTLA4 (cytotoxic T-lymphocyte associated protein 4 also known as CD 152) -IgG which is able to inhibit T-cell activation by blocking CD28 to its ligand, which may have impact on the GPA disease pathogenesis. In a small open label trial, this treatment was added in 20 patients with non-severe relapsing GPA and showed good results in both disease remission as prednisolone discontinuation and was well tolerated (55).

Another potential maintenance agent could be belimumab, an anti-BLyS (B-lymfocyte stimulator) monoclonal antibody, that inhibits B-cell activation. A large industry driven Phase III study is currently recruiting participant and aims to enrol 400 patients to evaluate efficacy and safety in remission maintenance by adding belimumab to azathioprine during approximately 3 years of follow up *(Clinical trials.gov. NCTO1663623)*

Table 2 Overview of trials in AAV and rituximab for maintenance therapy.

Besada et al, Norwegian GPA cohort study, 2013 N=35 Retrospective	GPA as registered in Nordnorsk Vaskulittregister.	Various prior to first RTX infusion. RTX 1gr i.v twice a weeks apart + methylprednisolone 125 mg.
Charles P et al, French vasculitis study group, 2014. N=80 Retrospective	AAV as defined by Chapel Hill nomenclature and Histological confirmation or ANCA detected. RTX as first-line, second- line or maintenance.	Induction with RTX: four different protocols, most frequently chosen 375 mg/m2 for 4 weeks. 25% concomitant immunosuppression.
Pendergraft WF et al, 2014. N=172.	Clinical/laboratory features with GPA/MPA or other forms of vasculitis together with PR3- or MPO-ANCA by ELISA	Various
Smith RM et al, 2012 N= 73.	GPA/MPA with refractory/ relapsing disease Exclusion: RTX as first line or FU < 6 months	Various

Pre-emptive RTX 1gr i.v twice a weeks apart or 1 gr bi-annually	FU since first RTX infusion: 47 months(2-88)	N=9 (23%), relapse rate of 6.6/100 patient years	Severe infections N=9 (26%) RTX discontinuation N=13 (37%) Death N=2.
Maintenance with RTX: 'several different regimes', N=64; most frequently chosen 375 mg/m2 every 6 months 13% concomitant immunosuppression	Median FU 18 months (IQR 12-37)	N=18 (23%) With RTX maintenance N=10 (20%) Without RTX maintenance therapy N=8 (44%) P 0.002	N=22 Infections N=12 (15%) Death N=5
Prior RTX: 1000 mg every 4 months. Other induction-protocol: RTX 1gr i.v twice a week apart, afterwards 1000 mg every 4 months	Median remission maintenance FU-time 2.1 years.	N=35 (20%), no statistical difference for prior treatment, for ANCA-specificity other ..	All AE's: N=121 Reguiring hospitalization: N=84 - infections: N=22 - disease-related: N=7 - Other: N=52 Death: N=10.
A: RTX 375 mg/m2 BSA 4 times or 1000 mg twice a week apart. Thereafter only at relapse. N=28 B: RTX 1000 mg twice a week apart, followed by 1 gram every 6 months for two years N=45 C: patients of group A, switching to routine retreatment N=19	Treatment FU A: 18 months (7-102) B: 40 months (4-61) C: 55 months (19-62) Long term FU	During two-years treatment A: N=19 (73%) B: N=5 (12%) C: N=2 (11%) During 4-years FU A: N=21 (81%) B: N=11 (26%) C: N= 10 (46%) P < 0.001 and P= 0.001	A: N=9 (28%), 16 events B: N=21 (47%), 45 events C: N= 7 (37%), 20 events P= 0.326 and P =0.984 Death: N=4 (groups?)

Table 2 Continued

Carvin-Ceba et al 2010 N= 53	GPA/MPA Refractory disease	Methylprednisolone Prednisolon 1 mg/kg/day RTX i.v 375 mg/m2 BSA during 4 weeks Or RTX i.v 1 gr twice every two weeks

RECOMMENDATIONS

Maintenance therapy: what to choose?

For patients who received standard cyclophosphamide for remission-induction, the use of azathioprine 2 mg/kg/day is most rationale, combined with low dose steroids, e.g. 10 mg/day (9). Duration should be close to 12 months, than tapering the dose by 25 mg every 3 months until discontinuation. Glucocorticoid doses can be reduced gradually after 6-18 months with the aim of discontinuing (based on individual patient responses) (20). Since azathioprine can cause considerable myelosuppression in patients who have low thiopurine methyltransferase (TPMT), the enzyme responsible for conversion of azathioprine to its active metabolites, routine testing is recommended in all guidelines (10,11,56)

Although associated with a higher relapse rate, mycophenolate mofetil (2000 mg/day) may be the best agent of choice in the case of allergy/intolerance for azathioprine (36). Methotrexate (0.3 mg/kg/wk, progressively increasing to 25 mg/wk) could be another alternative agent but dose should be adjusted to renal function and is not recommended in patients with GFR < 30 ml/min per 1.73 m2 (40).

Rituximab for maintenance therapy is still experimental but results are hopeful; in young women with future pregnancy wish, the use of rituximab maintenance should at least be considered (51,57,58). Treatment schemes vary from bi-annually 375 mg/m2 BSA to 1000 mg every four months or only at relapse. Until today, there are no randomized trials that prove a certain dose or one scheme superior to another. A dosage of 375 mg/m2 BSA two weeks apart every 6 months is reported most often.

There is no place for TNF-a blockers in maintenance therapy for ANCA-associated vasculitis

RTX without pred when reconstitution of B-lymfocytes - in patients who never were ANCA positive - combined with a rise in PR3-ANCA - without a rise in PR3-ANCA but with a history of relapse. N=53	FU since first RTX infusion: 4.4 years (2.7-6.2)	53 patients with > 2 courses of RTX: N=32, 60%.	Infection episodes N=30 Infusion related episodes N=16. Death N=2

(13). On the basis of what is yet known, there is also no support to continue potentially toxic immunosuppression after 24 months (47,59).
As suggested in kidney disease improving global outcomes guidelines, in patients who present with end- stage renal disease without any other systemic disease-manifestations and who continue the need for renal replacement therapy after 3 months of treatment, based on evident lower relapse rates, maintenance therapy could be abated (11,18,19).
Also, as patients with MPO-ANCA associated vasculitis are far less likely to relapse, there is no evidence for subsequent toxic maintenance therapy after the first episode of disease, and therefore it could be considered to continue only a low dose of glucocorticoids 5-10 mg/day for 12 months.
Difficulty in maintaining remission probably relates to the difference between true pathophysiological remission and the absence of clear evidence of disease activity. ANCA-titres should be determined at every outpatient visit and, although the association of rising ANCA-titres and relapse is still debated, suspicion is warranted when ANCA-titres change from negative to positive or rises substantially between visits. However, escalating therapy or reinstating immunosuppressive therapy based on ANCA-titres alone is not encouraged. Careful attention must be paid to all possible long-term side effects of these toxic immuno-suppressive agents, especially for the increased risk of myelosuppression, infec-tions and cancer (bladder cancer, leukaemia and lymphoma).

In case of relapse

It is known that relapses respond to therapy with a similar response rate as the initial disease (59). The severity of possible relapse should guide choice of therapy. In case of

a severe relapse, cyclophosphamide should be reintroduced, given that the cumulative dose is not exceeding 36 g. In patients who approach or do exceed this amount of drugs, rituximab 1000 mg twice is recommended every 4-6 months to avoid long-term toxicity of cyclophosphamide. Treatment should be combined with glucocorticoids and plasmapheresis when necessary.

In relapses that are not severe, re-instating or increasing doses of the provided maintenance agent (azathioprine, MMF or MTX) combined with glucocorticoids could lead to remission of disease activity. The addition of four cycles of intravenous immunoglobulins (0.5 g/kg/day) could be considered, but there is not enough evidence to recommend standard use for relapse in ANCA-associated vasculitis (60).

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