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Remission maintenance in ANCA-associated vasculitis: does one size fit all?

Alvise Berti [1,2] and Ulrich Specks [2]

AFFILIATIONS:

[1]*Rheumatology Department, Santa Chiara Hospital and Department of Cellular, Computational and Integrative Biology (CIBIO), University of Trento, Trento, Italy.*

[2]*Division of Pulmonary and Critical Care Medicine, Mayo Clinic College of Medicine and Science, Rochester, MN, USA*

Please address correspondence to:
Dr. Ulrich Specks, MD,
Chair, Division of Pulmonary & Critical Care Medicine
Connor Group Foundation Professor of Medicine,
Mayo Clinic College of Medicine and Sciences
200 First St SW,
Rochester, MN 55905
Phone: (507) 284-4348
Fax: (507) 266-4372
Email: specks.ulrich@mayo.edu

ORCID: Alvise Berti 0000-0002-7831-921X

ABSTRACT

Introduction: The majority of the patients with anti-neutrophil cytoplasmic autoantibody (ANCA) associated vasculitis (AAV) achieve remission with effective induction therapy. Therefore, prevention of relapses and avoiding long-term damage and treatment-related toxicity are major challenges.

Areas covered: This review provides an update on maintenance therapy in AAV, emphasizing the available treatment options for granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA). A PubMed search was conducted for relevant literature. Among the spectrum of all patients with AAV, those at higher risk of relapse have recently been identified. Clinical trials have yielded robust results about various options for maintenance of remission including common disease-modifying anti-rheumatic drugs (DMARDs, i.e. azathioprine, methotrexate and mycophenolate mofetil) and rituximab (RTX). However, outcomes of these studies are not easy to compare.

Expert opinion: Regardless of the treatment used, patients presenting with an anti-proteinase-3 ANCA, relapsing GPA have a substantially higher risk of relapse compared to patients with newly diagnosed MPA or positive anti-myeloperoxidase ANCA. While the efficacy of common DMARDs for remission maintenance is heterogeneous, the role of RTX seems particularly promising for the high risk patients, although the most appropriate dose and timing of retreatment with RTX remain under controversial. Low-dose glucocorticoid use for remission maintenance versus complete discontinuation also remains under investigation.

KEYWORDS: ANCA-associated vasculitis; ANCA; RAVE; Rituximab; Azathioprine; Maintenance therapy; vasculitis

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ARTICLE HIGHLIGHTS BOX

- Patients with relapsing GPA with PR3-ANCA are at higher risk for relapse compared to newly-diagnosed, MPO-positive patients with MPA.

- For remission maintenance, the conventional DMARDs (i.e AZA, MTX and MMF) may be insufficient for patients with high relapse risk, whereasRTX seems to be more effective.

- A tailored administration of RTX has been shown to be superior to RTX at fixed scheduled, closely monitoring ANCA titers and B cells.

- In newly diagnosed MPO-ANCA positive patients with MPA, a shorter maintenance therapy or perhaps observation alone may suffice after induction therapy.

- Early GC withdrawal during follow-up in AAV is still debated, but lower dosing of GC during remission induction of AAV seems advantageous

1. INTRODUCTION

Granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA) are severe systemic immune-mediated diseases characterized by inflammation of small- and medium-sized vessels (1). Both syndromes are characterized by the presence of circulating anti-neutrophil cytoplasmic autoantibody (ANCA) directed against either proteinase 3 (PR3) or myeloperoxidase (MPO) in the majority of patients. These autoantibodies are thought to be key pathogenic triggers of neutrophil and monocyte activation which are the essential causes of necrotizing small vessel injury in GPA and MPA (2, 3).

Since treatment with cyclophosphamide (CYC) combined with high doses of glucocorticoids (GC) was introduced in the 1960s, the survival of patients with GPA and MPA has improved considerably (7). Today, these severe life-threatening conditions with a mortality in excess of 90% if untreated, represent manageable, chronically relapsing conditions in which toxicity associated with acute and long-term use of immunosuppressive agents is responsible for the majority of acute mortality and long-term morbidity (4-7).

Overall, reported relapse rates range between 25-70% over a 10-year follow-up period for patients with AAV who have achieved remission (8, 9). However, this data is not homogeneous and may influenced by specific characteristics of patients studied and treatments used. For instance, patients with GPA have an increased relapse rate compared to patients with MPA (10). Similarly, patients with PR3-ANCA are at higher risk for relapse compared to patients with MPO-ANCA, and patients presenting with a relapse are at higher risk for subsequent relapses than newly diagnosed patients (11, 12).

In keeping with the relapsing nature of AAV, treatment can be divided into an initial remission induction phase requiring the short-term use of effective high dose immunosuppressive therapy, followed by a remission maintenance phaserelying on the long-term

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use of less toxic treatment options (13). Both phases are essential to obtain disease control and to minimize disease and treatment-related organ damage and morbidity.

To date, several clinical trials have specifically addressed the maintenance of remission in AAV. However, the various trials have been designed differently, often enrolling different patient populations and applying different definitions for the assessment of outcomes. Being aware of these details is essential to understand their potential impact on reported results, and ultimately to translate the trial findings into daily clinical practice properly.

To identify relevant publications a literature search was conducted using PubMed using a combination of the following search terms: "ANCA-associated vasculitis", "maintenance therapy", "rituximab", "azathioprine", "mycophenolate mofetil", "methotrexate", "randomized controlled trial" "glucocorticoids". Articles in English were reviewed. Abstracts of unpublished trials and studies considered relevant for this review but not retrieved by our research in PubMed were also added.

2. DEFINITION OF REMISSION

Remission is a clinical definition implying (i) the absence of any inflammatory activity attributable to GPA or MPA, (ii) the fact that these syndromes are currently not curable, but (iii) have an inherent risk for relapses. Most reports on treatment efficacy in AAV use remission as the principal outcome measure, and the reported rate of remission achieved with induction therapy ranges from 70% to more than 90% (11, 14-16). In most trials, the definition of disease activity and remission rely primarily on the presence or absence, respectively, of symptoms, radiographic or laboratory test abnormalities attributable to inflammatory disease activity. To facilitate the conduct and comparability of clinical trialsdisease activity scoring tools such as the several iterations of the Birmingham Vasculitis Activity Score have been validated, and their

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use is widely accepted (BVASv.3). A score of 0 on these instruments reflects the absence of all measurable disease activity.

Where definitions of clinical outcomes and the use of the term remission vary most is with respect to the dose of GC used at the time of a measured activity score of 0, when after initiation of therapy the score of 0 occurs, and for how long the score of 0 is maintained without upgrade of immunosuppressive therapy; the term "sustained" remission is used variably to indicate that remission lasted for at least 6-12 months. For instance, in the Wegener's Granulomatosis Etanercept Trial (WGET), the first multicenter trial of a biologic agent in GPA, remission was defined as BVAS/WG=0, regardless of GC dose, achieved at any time, resulting in an overall reported remission rate of 91% (15). However, the primary outcome of that trial was "sustained" remission defined as remission (BVAS/WG=0) lasting at least 6 months, a goal that was achieved by only 72% of the WGET cohort (15). In the Rituximab versus Cyclophosphamide for AAV (RAVE study) remission was again defined as BVAS/WG of 0 regardless of GC dose, but the primary outcome was defined as complete remission, i.e. BVAS/WG=0 and prednisone dose of 0 mg by 6 months after enrollment. The primary outcome as defined was achieved by 64% of patients assigned to the RTX group and and by 53% assigned to the CYC group (14). The secondary outcome defined as BVAS/WG=0 with an allowed prednisone dose of less than 10 mg/d by 6 months was achieved by 71% and 62%, respectively (18). However, 77% (RTX group) and 71% (CYC group) achieved complete remission (BVAS/WG=0 and GC=0) at any time during follow-up, and remission (BVAS/WG =0), regardless of GC dose or when or for how long it was achieved or for how long it was maintained, was achieved by 90% of patients in both treatment arms (11, 14). In the Rituximab versus Cyclophosphamide in ANCA-Associated Renal Vasculitis (RITUXVAS) study, the

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primary outcome was yet another one: "sustained remission at 12 months" defined as a BVAS of 0 achieved with induction therapy and maintained to month 12 regardless of GC dose (17). This outcome was achieved by 76% of patients in the RTX treatment group (n=33) and 82% in the CYC treatment group (n=11), which was not significantly different (17). As illustrated by these examples, attention must be paid to the specific definitions of outcomes and the use of the term remission when comparing results from different trials.

3. RELAPSE AS A MAJOR OUTCOME

Disease relapses put patients at risk for cumulative organ damage from recurrent disease activity as well as from toxicities of high-dose immunosuppressive therapy required to restore remission. Consequently, recognized major outcomes of clinical trials in AAV include risk of any relapse, risk of severe relapse and time to relapse during follow-up (8, 9). Moreover, how to best maintain remission effectively with the least amount of cumulative toxicity has been the focus of clinical trials in AAV since the 1990's.

Once the combination of GC and CYC had been established as an effective combination to induce and maintain remission, the toxicities associated with their long-term and repeated use were quickly recognized (8, 18). Also, when the association of GPA and MPA with ANCA was discovered in the 1980's (19-21), ANCA titers were found to be correlated with disease activity, and titer increases were thought to portend an increased relapse risk (22, 23).

An early randomized controlled trial (RCT) demonstrated that patients at risk for relapse had a lower cumulative exposure to CYC and GCs when they were treated preemptively with low dose oral CYC rather than being treated only when relapses occurred (24). However, well

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recognized concerns about malignancy and infertility risks associated with increasing cumulative CYC doses, prompted the vasculitis community to search for effective alternatives (13, 25).

Another RCT investigated the use of trimethoprim-sulfamethoxazole 800/160 twice daily for relapse prevention in GPA (26). The rationale for this trial was based on observations that respiratory tract infections were associated with an increased relapse risk and that trimethoprim-sulfamethoxazole showed efficacy in inducing remission in patients with refractory disease or disease limited to the respiratory tract (11, 13, 14, 26, 27). This trial demonstrated that trimethoprim-sulfamethoxazole 800/160 twice daily was independently associated with prolonged disease-free survival and a reduction of the incidence of respiratory and non-respiratory tract infections (26). Even though the number of patients that remained in remission at 24 moths was only moderately superior in the treatment group compared to the placebo group (82% versus 60%), this study highlighted that a maintenance treatment was needed in order to prevent relapses in GPA.

4. CONVENTIONAL DISEASE-MODIFYING ANTIRHEUMATIC DRUGS (DMARDs) FOR MAINTENANCE TREATMENT

Because of the concerns about toxicities of long-term CYC use, conventional DMARDs were subsequently introduced as replacements of CYC for maintenance of remission following remission induction with GC and CYC. The three agents that have been studied most thoroughly for this purpose in several RCTs in AAV are azathioprine (AZA), methotrexate (MTX), and mycophenolate mofetil (MMF) (**Table 1**).

MTX had been proposed as a remission maintenance agent in lieu of continued CYC use based on results from an open-label, prospective, standardized treatment trial conducted at the NIH in 31 patients with GPA (28). A more recent, single-center, open-label trial on a small

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number of patients showed similar relapse frequency and relapse free-survivial between AAV patients treated with CYC or MTX for 12 months after achievement of remission (31). However, the higher level of evidence for MTX comes from the NORAM (Nonrenal Wegener's Granulomatosis Treated Alternatively with Methotrexate) trial, an RCT designed to investigate MTX as an alternative to oral CYC as an induction treatment for patients with newly diagnosed early systemic AAV (29). Approximately 90% of patients achieved remission with either MTX or CYC at 6 months, both in addition to GC. Although the trial was not powered to detect differences between treatments in clinical subsets of patients, MTX seemed to be less effective that CYC in patients with extensive disease or pulmonary involvement (29). Between month 6 and 12, treatment was tapered in each group to complete withdrawal, GC included. Of note, 89 of 95 patients studied were diagnosed with GPA (the majority of cases cytoplasmic-ANCA (C-ANCA) positive), and only 6 patients had MPA. After remission was achieved, the MTX regimen was associated with more relapses compared to the CYC regimen at month 18 (69.5% vs 46.5%), and the time-to-relapse was longer in the CYC group than in MTX group (15 vs 13 months, p=0.023) (29). Interestingly, the slope of the Kapan Meier curves representing the time-to-first-relapse are similar in both MTX and CYC groups, mirroring the pharmacodynamics of MTX and CYC, and declining sooner for MTX (approximately 1 month after stopping the treatment) and later for CYC (approximately after 3 months). Overall, this trial supported the concept of the need for continuated immunosuppressive therapy beyond 12 months in GPA as the early withdrawal of maintenance treatment results in disease relapse.

In 2003, the Cyclophosphamide or Azathioprine as a Remission Therapy for Vasculitis (CYCAZAREM) trial demonstrated in patients with newly diagnosed generalized AAV that the introduction of AZA after induction of remission with CYC was as effective as continuing CYC

for the maintenance of remission (9). Notably, patients with severe renal involvement were excluded from this trial (serum creatinine > 500umol/L).

The French Vasculitis Study group conducted an RCT comparing MTX to AZA for maintenance of remission following successful induction of remission with intravenous bolus CYC and GC in newly diagnosed patients with GPA (Comparison of Methotrexate or Azathioprine as Maintenance Therapy for ANCA-Associated Vasculitides, WEGENT) (30). Patients were treated with MTX or AZA for 12-month period of maintenance therapy, and then both agents were withdrawn over a period of 3 months. In addition to AZA and MTX, the protocol allowed the use of prednisolone at a daily dose of 5-12.5 mg, a fact which may not be entirely negligible and could have contributed to the observed efficacy of both agents. At 12 months of follow-up, the rates of relapse-free-survival and adverse events were the same in both groups, leading to the conclusion that the choice of MTX versus AZA for remission maintenance should be guided by patient-specific factors. Following withdrawal of the maintenance agents, the rate at which relapses occurred increased in both treatment arms, raising questions about the wisdom of dose reductions of DMARDs after 1 year of disease remission.

Although AZA remains a staple for the maintenance of remission in AAV in the everyday clinical practice, its efficacy for prevention of relapse has been recently been challenged (see below), and the treatment duration remains unclear. A prospective phase 3 RCT showed that an extended duration of AZA for maintenance of remission (48 months instead of 24 months) may reduce the risk of relapse, albeit patients treated for 48 months had a higher rate of severe adverse events (79). However, another prospective RCT focusing on PR3-AAV revealed only a limited effect of prolonged AZA therapy on the prevention of relapses when AZA was tapered starting 48 months after diagnosis instead of 12 months after diagnosis (80). These

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results were confirmed in a post hoc analysis of combined data from 6 prospective trials showing that AZA used for maintenance for more than 18 months after diagnosis had no significant influence on subsequent relapse-free survival, in contrast to other factors including induction therapy (intravenous bolus versus oral CYC) or ANCA specificity (PR3-ANCA versus MPO-ANCA or ANCA negative) (32).

Given the efficacy of MMF reported for systemic lupus erythematosus treatment and for preventing transplanted organ rejection, and the positive preliminary results from phase 2 trials investigating MMF for both induction of remission and maintenance in patients with AAV with mild to moderate renal disease (33, 34), an open-label phase 3 RCT, called International Mycophenolate Mofetil Protocol to Reduce Outbreaks of Vasculitides (IMPROVE), was conducted to assess the role of MMF on the prevention of relapses (35). The IMPROVE study was conducted in patients with newly diagnosed AAV with renal involvement, and patients were randomized to receive AZA (starting at 2 mg/kg/d) or MMF (starting at 2000 mg/d) and maintained on prednisolone daily 5-15 mg after induction of remission with CYC, either oral or intravenous, ± plasma exchange. Patients randomized to MMF experienced a higher number of relapses compared to those who received AZA (p=0.03). Based on these trial results MMF is considered to be a second line maintenance agent reserved for patients who do not tolerate MTX or AZA. It is of note that while there was no difference between baseline features of the two treatment groups at baseline (when patients were randomized), the C-reactive protein was significantly higher in the MMF group compared to the AZA arm (3.00 mg/L, IQR 0.88-9.25 versus 1.80 mg/L, IQR 0.00-5.20; p=0.04) (35). This may imply that the higher relapse rate in the MMF group, which was observed early after the switch from CYC, may have been the result

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of less well controlled disease activity at the time of switch in the MMF group compared to the AZA group, rather than being related to true differences in efficacy between the two agents.

The results of the recently published MYCYC trial which compared CYC to MMF for remission induction followed by AZA for remission maintenance indicated a higher relapse rate in the patients receiving induction therapy with MMF compared to CYC. This difference is most likely the result of the well-recognized fact that the effects of CYC on the immune system are more protracted than those of either MMF or MTX (29) (81).

Regardless of the maintenance regimen chosen, all patients should be closely followed in order to promptly identify relapses (13). The decision to taper and withdraw the maintenance treatment in patients with AAV should be tailored to each individual patient's overall risk profile. This is particularly important for patients with renal involvement and impairment of renal function as renal survival rapidly worsens with each subsequent renal flare, and the overall survival of patients depends on the renal function at 6 months after initiation of therapy (36, 37).

5. THE INTRODUCTION OF RITUXIMAB FOR AAV AND THE DEFINITION OF THE RELAPSING PHENOTYPE

To target remission maintenance therapy appropriately to individual patients, i.e. treating those at high risk for relapse while avoiding unecessary exposure to immunosuppressive agents in patients at low risk for relapse, several studies have aimed to identify (i) clinical subsets of patients with different treatment response and relapse risk within the spectrum of AAV, and (ii) biomarkers of imminent relapse (reviewed in: (38, 39)).

Several studies have shown that the ANCA type (PR3-ANCA versus MPO-ANCA) is a major independent determinant of relapse risk, with PR3-ANCA being associated with a high relapse risk, whereas MPO-ANCA is associated with a low relapse risk (10) (11, 12).

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The RAVE trial had shown that there was non-inferiority of efficacy for remission induction with RTX versus CYC followed by AZA for the entire cohort of patients as well as the for the subsets of patients presenting with major renal involvement or alveolar hemorrhage (14, 40). At the same time RTX was superior to CYC/AZA for remission induction in the subset of patients enrolled into the trial with a severe disease relapse rather than a new diagnosis as well as patients in the PR3-ANCA positive patient subset (14, 41). The subsequent detailed analysis of the 18-month follow-up data on protocolized therapy in the RAVE trial provided additional valuable information of relevance for the planning of remission maintenance therapy (11). Overall, 74% of patients achieved complete remission at any time (BVAS/WG=0 and GC dose=0 mg), and there was no difference between treatment arms (11). Thirty percent of these relapsed within a following achievement of complete remission (11). Although no imbalance was found in proportions of patients achieving complete remission after induction treatment between PR3-AAV and MPO-AAV, the relapse rate differed significantly between these two groups, confirming that patients with PR3-ANCA have an increased risk of relapse compared to patients with MPO-ANCA, regardless of renal involvement (11). Similarly, when patients were separated by clinical diagnosis, patients with GPA patients had a higher risk of relapse compared to patients with MPA. Finally, patients with relapsing disease upon enrollment had a higher risk of relapse compared with newly diagnosed patients (11). These three risk factors are not independent from each other, but rather define a clinical phenotype which is more prone to relapse, the PR3-ANCA positive patient with GPA prone to relapse (9, 11, 12, 42-44) (**Figure 1**). In fact, when GPA/PR3-AAV/relapsing patients (n=52) were compared to all the others (n=94) (11), there was a clear separation in relapse-free-survival (p=0.0016). When the group of GPA/PR3-AAV/relapsing patients (n=52) were further devided by treatment received (RTX

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versus CYC/AZA), there was no difference in relapse rate. Thus, disease phenotype, for which the ANCA type is the best surrogate biomarker, defines the relapse risk.

Notably, in the RTX arm of the RAVE trial, patients received no additional treatment during follow-up. Consequently, following B-cell reconstitution, the patients randomized to the RTX treatment could be considered as receiving no maintenance therapy. Indeed, there was no severe relapse in the RTX treatment group prior to B-cell reconstitution. However, after B-cell reconstitution, the relapses occurred at the same rate as in the CYC/AZA group where patients received AZA for remission maintenance for the entire 18 months of protocolized treatment. For newly-diagnosed patients with MPA and MPO-ANCA, the group with the lowest relapse risk, there was also no difference in relapse numbers or rate between the treatment groups. Taken together, these results add to the questions about the efficacy of AZA for remission maintenance in patients at high risk for relapse (30, 31).

The observations that different disease phenotypes diplay different responses to RTX compared to CYC and a different relapse risk suggest a different underlying pathophysiology for GPA/PR3-AAV and MPA/MPO-AAV. This concept is further supported by the results from genome wide association (GWAS) studies, which showed a different genetic background for GPA/PR3-AAV and MPA/MPO-AAV (45-47). In the first GWAS study on AAV (45), polymorphisms for the major inhibitor of PR3 (alpha-1 antitrypsin) as well as for PR3 were identified in PR3-AAV patients, in addition to differences in human leukocyte antigen associations between PR3-AAV and MPO-AAV. Recently, a SNP in the regulatory region of the BAFF gene (TNFSF13B) has been found to be associated with poor response to RTX, which was limited to PR3-AAV (49). Additional support for the hypothesis of different pathophysiology between GPA/PR3-AAV and MPA/MPO-AAV comes from the finding of substantially different

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cytokine profiles found at times of active disease in these two groups (48). Of note, in the GWAS study and the cytokine analysis as well as the relapse analysis in the RAVE cohort, the separation of groups was clearer when patients were classified for ANCA type rather than by clinical diagnosis (11,12).

In summary, while the initial response to remission induction therapy seems to be the same for patients with PR3-ANCA and MPO-ANCA or GPA and MPA, the ANCA-type, a biomarker available at the time of diagnosis, is the most significant predictor of subsequent relapse risk which has its roots in different underlying pathophysiology.

This raises the question, whether PR3-ANCA only broadly defines a general high relapse risk for defined clinical subsets of patients within the spectrum of AAV, or whether changes in titer can also be used as predictors of imminent relapses during follow-up of individual patients, and thus guide therapy.   The question about the clinical utility of serial ANCA-testing during follow-up of patients GPA goes back to time of the discovery of ANCA and has remained controversial ever since (21-23). A thorough meta-analysis concluded that there was only a weak association between ANCA titer rises and subsequent relapses, and that treatment decisions for individual patients should not be based on changes in ANCA titer (50). It is of note, that all the studies included in this analysis were baed on data obtained from patients who were treated with conventional immunosuppressive agents (CYC, AZA, MTX, MMF). Consequently, the prevalent use of RTX may force a revision of this generalizing conclusion.

In fact, in the RAVE trial, significantly more patients became PR3 ANCA-negative after RTX than after CYC therapy (50% versus 17%, p=0.004) by the 6   month time point. In contrast, similar proportions of patients receiving RTX and CYC became MPO-ANCA-negative (40% versus 41%, p=0.95)(11). This observation prompted a detailed analysis of the 93 patients

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with PR3-ANCA who achieved complete remission in the trial to determine whether an increase in PR3-ANCA levels predicted severe relapses in patients with AAV and which factors affected the clinical utility of serial PR3-ANCA testing (51). It was found that PR3-ANCA titer increases were associated with relapse within one year after the increase in patients who were treated with RTX as well as those who had presented with renal involvement or alveolar hemorrhage (51). The latter observation confirmed a previous observation by Kemna et al. who also found ANCA titer increases to be most useful in patients with renal involvement (52).

6. RITUXIMAB FOR REMISSION MAINTENACE

Several authors advocated the use of RTX for maintenance of remission in refractory or relapsing patients based on data derived from sizable cohort studies (53-55). Given the positive results of the RAVE trial and the fact that relapses were almost always preceded by B cell repopulation in RTX-treated patients (11, 14), the idea of targeting B cells to maintain remission gained popularity. The results of the Maintenance of Remission using Rituximab in Systemic ANCA-associated Vasculitis (MAINRITSAN) trial, an RCT that showed superiority of RTX compared to AZA for remission maintenance following remission induction with GC and CYC in newly diagnosed patients, firmly established the efficacy of RTX for remission maintenance and led to an extension of the label for RTX by regulatory agencies (56).

Nevertheless, there is still some controversy about the best efficacy and safety balance of different proposed dosing regimen of RTX to maintain remission. Retreatment at fixed scheduled intervals as well as individually timed in different patients have been proposed (53-63) (**Table 2**). In 2010, Rhee and colleagues showed in a retrospective analysis that two 1 g doses of RTX given 2 weeks apart and repeated every 4 months in patients with AAV in complete or partial remission appeared safe and effective (54). Three patients (of the total of 39

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treated) experienced nonorgan-threatening flares, and each flare occurred after at least 20 months of follow-up. Albeit a remarkable proportion of patients experienced reduction in GC doses and concomitant cytotoxic therapy during the follow-up, 55% and 30% remained under GC and cytotoxic therapy, respectively, at 24 months. A subsequent analysis of an extended cohort of 172 patients confirmed the efficacy and safety of the fixed 4-month timing, with a median remission maintenance follow-up time of 2.1 years (57). Of note, most of the patients in this report received only a single 1 g doseof RTX every 4 months.

The MAINRITSAN trial results implied that an even lower dose of 500 mg given every 6 months for 24 months is effective and safe for remission maintenance (56). Over two years the In the MAINRITSAN trial, patients were randomized who had achieved remission with GC and CYC were randomizedto receive either 500 mg of rituximab on days 0 and 14 and at months 6, 12, and 18 after study entry or daily AZA until month 22 (56). The study concluded that a significantly higher proportion of patients treated with fixed, low-dose of RTX remained in sustained remission (at 28 months) compared with patients treated with AZA, which had been considered to be the standard of care at the time. Moreover, AZA-treated patients showed a decline in physical abilities when compared to RTX at month 24 (64), and the use of RTX for remission maintenance was deemed cost-efftive when considering the cost of care associated with treatment of relapses and subsequent renal damage (65).

Retreatment of patients with an induction regimen dose of RTX to prevent relapse or at first warnings of relapse instead of maintenance with low dose of RTX is another approach that was tried more than a decade ago. Patients were initially retreated with the complete dose of RTX (375mg/m2 1 week apart for 4 weeks or two 1 g doses, 2 weeks apart) (57, 66). The individually timed approach is based on patients own past relapse history and B cell and ANCA

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levels measurements, relying on the concept that relapse risk is low as long as B cells remain depleted and as long as PR3-ANCA remain undetectable or at their nadir. The time of B cell reconstitution and associated or subsequent PR3-ANCA titer increase and relapse is highly variable between individual patients but fairly consistent within an individual patient, providing the rationale for close monitoring of ANCA titers and B cells (11, 51, 53). Particularly in chronically relapsing patients with PR3-AAV an individually timed retreatment with RTX based on increases of PR3-ANCA titers and/or B cells following remission induction with RTX was shown to be very effective and safe (53). This approach aims to individualize the treatment, allowing patients to experience B cell reconstitution between retreatments and prolonging the intervals between retreatments often substantially. Although the frequency of long term hypogammaglobulinemia with or without infections among patients who received RTX is still not fully characterized (59, 67, 68), a prolonged fixed-interval RTX may induce hypogammaglobulinemia in the long term in predisposed individuals. Only retrospective cohort studies have been published so far, with different incidence, predictors and outcomes. During induction with RTX, there is a preferential decline in ANCA titers relative to total IgG levels (mean rate around 50% compared to 6%, respectively) (59). New significant hypogammaglobulinemia (IgG level of <400 mg/dl) during maintenance treatment occurred in 4.6% of the patients, serious infections were rare (0.85 per 10 patient-years, 95% CI 0.66, 1.1) and were independently associated with an IgG level of <400 mg/dl (59). Interestingly, the IgG concentrations prior to and at the time of rituximab correlated with the nadir of IgG post rituximab, while prior CYC use only weakly correlated (68). Another study showed instead that high dose of concomitant CYC treatment, low CD4 cell count and a significant drop in total IgG after the first RTX round were significant risk factors for severe infection (61). Overall, severe

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infections may occur irrespective of hypogammaglobulinemia, while trimethoprim–sulfamethoxazole prophylaxis reduced the risk (82).

Whether the individually timed retreatment approach can prevent the development of hypogammaglobulinemia remains unclear. However, at least for some patients it provides opportunities to update needed vaccinations, which are ineffective during times of B cell depletion.

The MAINRITSAN2 trial was designed to compare the efficacy and safety of the redosing of RTX either scheduled every 6 months or individually time-based on ANCA-positivity and/or titer (reappearance after being negative, indirect immunofluorescence-determined≥2-dilution–titre increase and/or at least doubled ELISA PR3 or MPO arbitrary units) and/or reappearance of circulating CD19 B cells (> 0/mm^3) assessed every 3 month for the maintenance of remission AAV. The results showed that the rate of relapse was not statistically different between the two dosing regimens, and the median number of RTX infusions was lower in patients treated with individually tailored compared to fixed-schedule RTX regimens (69). In this trial, more that 2/3 of patients had a diagnosis of GPA and were newly diagnosed at inclusion. Almost 50% of the patients were PR3-ANCA positive at diagnosis in both tratement arms, and about 25% were positive at inclusion (after induction treatment). Interestingly, 18 out of the 21 patients who relapsed had GPA, 12 had PR3-ANCA (verusus 3 MPO-ANCA, 4 ANCA negative and 2 ANCA positive of unknowns specificity), and 12 out of 21 had newly diagnosed AAV. Although this trial did not stratify patients for disease subsets it nevertheless confirmed that relapses are associated with PR3-ANCA/GPA. Based on these trial results and our own clinical experience we recommend that patients at high risk of relapse should receive long-term maintenance therapy with RTX and favor to individually time RTX retreatments based on B-cell

reconstitution and ANCA seroconversion data. Another recently completed RCT of which the results are eagerly awaited compares the efficacy and safety of retreatment with a 1 g dose of RTX scheduled every 4 months to AZA as maintenance therapy. This trial called Rituximab Vasculitis Maintenance Study (RITAZAREM; registered with ClinicalTrials.gov, no. NCT01697267)(70) targeted only patients with relapsing AAV in whom remission was restored with GC in combination with RTX.

Another B cell targeted approach was evaluated with the Belimumab in Remission of Vasculitis (BREVAS) trial which showed that the anti-BLyS agent belimumab 10 mg/kg every 28 days alongside azathioprine (2 mg/kg per day) and low dose GC (≤10 mg/day) for the maintenance of remission in AAV did not reduce the risk of relapse compared to placebo (71). However, the researchers found that none of the 14 patients with RTX-induced remission who subsequently received belimumab experienced vasculitis relapses, suggesting that induction with RTX may influence relapse risk during follow-up more than maintenance with belimumab. Alternatively, belimumab given after rituximab may induce long-lasting remission because it leads to long-lasting B cell depletion, a concept that is further investigated in the Rituximab and Belimumab Combination Therapy in PR3 ANCA-associated vasculitis (COMBIVAS) trial.

7. GLUCOCORTICODIS REDUCTION AND RELAPSE RISK DURING FOLLOW-UP

One area of significant debate relates to the long-term use of low dose GC for maintenance of remission in AAV and other chronic autoimmune-inflammatory diseases, particularly because of concerns about the toxicities associated with cumulative doses of GC

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therapy (5-7). If low doses of prednisolone or equivalents can prevent relapses in AAV remains unsolved. A recent meta-analysis which evaluating published studies in AAV that reported the duration of low dose GC therapy and the number of relapses concluded that that longer courses of GCs are associated with fewer relapses (72), suggesting that an earlier GC withdrawal leads to a higher relapse risk. However, the studies in which GC were not stopped comprised mostly newly diagnosed patients, whereas in the studies in which GC were withdrawn early included more than 50% of patients with relapsing disease. Consequently, observed difference between the groups may have been driven by differences in inherent relapse risk of the patients included in the different studies reviewed rather than being attributable to different durations of GC use.

To settle this debate, the Assessment of Prednisone In Remission Trial (TAPIR, registered with ClinicalTrials.gov, no. NCT01933724) was designed, in which patients who achieved remission are randomized to continued low dose GC use (5 mg of daily prednisolone or equivalents) or to complete discontinuation of GC therapy, with or without a stable dose of DMARDs.

It is worth mentioning here that minimizing the GC exposure is one the major areas of investigation in AAV. To this end, several trials have either recently contributed novel data or are expected to provide new insights once completed. In light of the results of the phase II trial on the novel, orally-administered, selective complement C5a receptor inhibitor, avacopan, that was shown to be non inferior to standard of care in in replacing high-dose glucocorticoids (83), a phase III RCT investigating the efficacy and safety of avacopan in comparison to a standard GC regimen for remission induction is ongoing (registered with ClinicalTrials.gov, no. NCT02994927).

The trial Abatacept for the Treatment of Relapsing, Non-Severe, Granulomatosis With Polyangiitis (ABROGATE, registered with ClinicalTrials.gov, no. NCT02108860) focuses on non-severe, relapsing GPA and aims to assess the efficacy of abatacept to achieve sustained GC-free remission (73-75).

Both the Plasma Exchange and Glucocorticoids for Treatment of ANCA-Associated Vasculitis (PEXIVAS, registered with ClinicalTrials.gov, no. NCT00987389) and the Rituximab Vasculitis Maintenance Study (RITAZAREM, registered with ClinicalTrials.gov, no. NCT01697267) trials also compared the efficacy and safety of two different dosing regimens of GC therapy during remission induction. The preliminary PEXIVAS trial results indicate that the accelerated GC tapering regimen is as effective as standard higher dosed GC therapy for remission induction and subsequent maintenance, and that the accelerated GC taper was associated with a significantly lower number of infections (Abstract no. 361, The 19th International Vasculitis and ANCA Workshop, Philadephia, 2019).

8. CONCLUSION

In conclusion, patients presenting with relapsing, PR3-ANCA GPA have a substantially higher risk of relapse compared to patients with newly diagnosed, MPO-ANCA MPA regardless of the treatment chosen.

Among other DMARDs, RTX seems particularly promising for the high risk patients, although the most appropriate dose and timing of retreatment with RTX is not yet fully elucidated. Similarly, the use of low-dose GCs for remission maintance versus complete discontinuation remains to be defined.

9. EXPERT OPINION

The concept of maintenance therapy in AAV is clearly linked to the relapsing nature of the disease, and the identification of the patients with a "high risk profile". Overall, reported relapse rates range between 25-70% over a 10-year follow-up period for patients with AAV who have achieved remission. Despite the differences in clinical trial populations and tested regimens, evidence is accumulating that the disease phenotypes directly affect the outcome and the probability of relapse. Several studies including long-term data of the RAVE trial showed that patients presenting with a relapsing disease, a clinical diagnosis of GPA and positive PR3-ANCA have the highest risk of relapse, whereas patients with a new diagnosis of MPO-positive MPA have a low relapse risk. This insight in phenotyping disease in subsets of patients with different prognosis will have to be validated and compared in future clinical trials, in order to be prospectively confirmed on larger cohorts. Of note, different genetic backgrounds and cytokine profiles have been observed in different subsets of patients, with a clearer separation of groups when patients were classified by ANCA type rather than by clinical diagnosis.

The conventional DMARDs (i.e AZA, MTX and MMF) are widely used to maintain remission following induction of remission with CYC. However, these treatments may be insufficient for "highest risk" patients. RTX seems to be more effective for remission maintenance in these patients, but the best dosing and timing of retreatments with RTX for this purpose remains to be established.

An individually timed retreatment approach with RTX based on the patient's personal relapse history and B cell and ANCA levels measurements, relying on the concept that relapse risk is low as long as B cells remain depleted and as long as PR3-ANCA remain undetectable or at their nadir maybe preferable as it has the potential to reduce cost (frequency of retreatments) and increase safety (prevention of hypogammaglobulinemia and opportunity for vaccinations). The

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time of B cell reconstitution and associated or subsequent PR3-ANCA titer increase and relapse is highly variable between individual patients but fairly consistent within each individual patient, providing the rationale for close monitoring of ANCA titers and B cells.

For patients at low risk for relapse, namely newly diagnosed MPO-ANCA positive patients with MPA, a shorter maintenance therapy or perhaps even careful observation may suffice following successful remission induction therapy.

Early GC withdrawal during follow-up in AAV is still debated, and recent trials have either already documented that lower dosing of GC during remission induction of AAV is advantageous or aim to provide new data that may lead to substantial cumulative GC dose reductions or avoidance altogether.

Future prospective studies will clarify the best way to stratify AAV patients for treatment including remission maintenance therapy based on clinical phenotype and biomarkers.

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entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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TABLES AND IMAGES

Table 1. Overview of the most relevant clinical trials providing information about maintenance of remission in AAV.

Clinical Trial (RCT)	Ref.	Name of the trial	Year	N. of Patients	Phase	Information	Regimens	Relevance
Cohen Tervaert JW et al.	(24)	Prevention of relapses in Wegener's granulomatosis by treatment based on antineutrophil cytoplasmic antibody titer	1990	58	REMISSION	Prospective, multicenter, randomized, open-label, placebo-controlled trial	Oral CYC (1-2mg/kg/day) plus daily 30 mg prednisolone for 3-9 months or any treatment except if clinical relapses	Reduced relapse rate in patients assuming pre-emptive therapy (CYC) than untreated patients Patients pre-emptively treated took less CYC than controls
Dutch Co-trimoxazole Wegener Study	(26)	Trimethoprim–Sulfamethoxazole (Co-Trimoxazole) for the Prevention of Relapses of Wegener's Granulomatosis	1996	81	REMISSION	Prospective, multicenter, randomized, double-blind, placebo-controlled trial	Co-trimoxazole (800 mg of sulfamethoxazole and 160 mg of trimethoprim) twice daily or placebo for 24 months, in addition to usual patient medication	Co-trimoxazole reduces the incidence of relapses in patients with Wegener's granulomatosis in remission
CYCAZAREM	(9)	Cyclophosphamide or azathioprine as a remission therapy for vasculitis	2003	155	REMISSION	Prospective, multicenter, randomized, open-label placebo-controlled trial	Oral CYC (1.5 mg/kg/day) or a AZA (2 mg/kg/day), both plus daily oral prednisolone (7.5-10mg)	AZA is effective as CYC in maintenance of remission
NORAM	(29)	Nonrenal Wegener's Granulomatosis Treated Alternatively with Methotrexate	2005	95	INDUCTION	Prospective, multicenter, randomized, open-label placebo-controlled trial	Oral CYC (2 mg/kg/day) or oral MTX (20–25 mg/week), both plus daily prednisolone (7.5-0mg)	MTX less effective for induction of remission in patients with extensive disease and pulmonary involvement than CYC; Both treatment arms showed the usefulness of continuation of immunosuppressive treatment beyond 12 months
WGET	(15)	Wegener's Granulomatosis Etanercept Trial Wegener's	2005	174	REIMISSION	Prospective, multicenter, randomized, double-blind, placebo-controlled trial	Etanercept 50 mg weekly + standard therapy versus placebo plus standard therapy	Sustained remission and relapse rate not different in both groups; Solid cancer development in the Etanercept group
WEGENT	(30)	Comparison of Methotrexate or Azathioprine as Maintenance Therapy for ANCA-Associated Vasculitides	2008	159	REIMISSION	Prospective, multicenter, randomized, open-label placebo-controlled trial	AZA (2.0 mg/kg/day) or MTX (0.3 mg/kg/week, progressively increased to 25 mg per week) for 12 months, both plus daily prednisolone (5-12.5mg)	MTX is not superior to AZA for maintenance of remission; Efficacy and safety of the two treatments are similar
CYCLOPS	(76)	Randomized trial of daily oral versus pulse Cyclophosphamide as therapy for ANCA-associated Systemic Vasculitis	2009	148	INDUCTION	Prospective, multicenter, randomized, open-label	Pulse CYC (15 mg/kg every 2 to 3 weeks), or daily oral CYC	In both regimens equal proportions of patients had remissions, but the pulse

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					placebo-controlled trial	(2mg/kg/day), both plus daily oral prednisolone (1 mg/kg – 5 mg)	regimen seemed safer (less leukopenia); Study was not powered to detect differences in relapse rate.
IMPROVE	(35)	International Mycophenolate Mofetil Protocol to Reduce Outbreaks of Vasculitides	2010	156	REIMMISSION	Prospective, multicenter, randomized, open-label placebo-controlled trial	AZA (2 mg/kg/day) or MMF (2000 mg/day), both plus daily prednisolone (5-12.5 mg)	MMF less effective than AZA for maintaining disease remission ; MMF and AZA are equally safer in AAV patients
RAVE	(14)	Rituximab in ANCA-Associated Vasculitis	2013	197	REMISSION/INDUCTION	Prospective, multicenter, randomized, double-blind, double-dummy, non-inferiority, placebo-controlled trial	RTX (375 mg/m(2)/week for 4 weeks) or oral CYC (2 mg/kg/day, 3 to 6 months) followed by placebo-AZA in RTX treated patients and AZA (2 mg/kg/day, 12 to 15 months) in CYC-treated patients. Prednisolone was tapered off in both groups once that remission was achieved.	Single course of RTX was as effective as continuous conventional CYC/AZA therapy for the induction and maintenance of remissions over the course of 18 months.
RITUXIVAS	(66)	Rituximab versus Cyclophosphamide in ANCA-Associated Renal Vasculitis	2015	44	REMISSION/INDUCTION	Prospective, multicenter, open-label, two-group, parallel-design, randomized trial	RTX (375 mg/m(2)/week for 4 weeks) with two intravenous CYC pulses (15 mg/kg) at first and third RTX infusions, or intravenous CYC (15 mg/kg) followed by AZA (2 mg/kg/day) in CYC-treated patients.	At 24 months, rates of the composite outcome of death, end-stage renal disease and relapse did not differ between groups. In the RTX group, B cell return was associated with relapse.
MAINRITSAN	(56)	Maintenance of Remission using Rituximab in Systemic ANCA-associated Vasculitis	2014	115	REIMMISSION	Prospective, multicenter, randomized, nonblinded trial	After CYC induction, RTX 500 mg on days 0 and 14 and at months 6, 12, and 18 after study entry versus daily AZA until month 22	Low dose RTX is superior to AZA for maintenance of remission
MAINRITSAN 2	(69)	Maintenance of Remission using Rituximab in Systemic ANCA-associated Vasculitis 2	2018	162	REIMMISSION	Prospective, multicenter, randomized, open-label, controlled trial	After induction, RTX 500 mg at randomization, with RTX reinfusion only when CD19+B lymphocytes or ANCA had reappeared or ANCA titre rose markedly based on trimestrial testing until month 18 versus fixed scheduled RTX 500 mg (on days 0 and 14 , then 6, 12 and 18 months after the first infusion)	AAV relapse rates did not differ significantly between individually tailored and fixed-schedule rituximab regimens. Individually tailored-arm patients received fewer rituximab infusions.
BREVAS	(71)	Belimumab in Remission of Vasculitis	2019	105	REIMMISSION	Prospective, multicenter , randomized , double-	After induction with CYC or RTX, patients received AZA 2 mg/kg/day, oral	Belimumab plus azathioprine and glucocorticoids for the maintenance of remission in

					blind, placebo-controlled study	glucocorticoids, and placebo/intravenous belimumab 10 mg/kg	AAV did not reduce risk of relapse.
MYCYC	(81)	Mycophenolate Versus Cyclophosphamide in ANCA Vasculitis	2019	140	REMISSION/INDUCTION	Prospective, multicenter , randomized , double-blind, placebo-controlled study	After induction with CYC (intravenous, 15mg/kg for 3 to 6 months, 6-10 doses) or MMF (2-3g/day for 3-6 months), patients received AZA (2 mg/kg/day). Both arms received the same oral glucocorticoid regimen.	There is a higher relapse rate in patients receiving induction therapy with MMF compared to CYC. In PR3-ANCA patients, relapses occurred in 24% of the CYC group and 48% of the MMF group (p<0.05).

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Table 2. Overview of the most relevant studies (non-RTC) assessing RTX for the maintenance of remission in AAV.

Study	Ref.	Name of the Study	Year	N. of Patients	Phase	Information	Regimens	Relevance
Rhee EP et al.	(54)	Rituximab as maintenance therapy for anti-neutrophil cytoplasmic antibody-associated vasculitis.	2010	39	REMISSION	Retrospective, multicenter, cohort study	RTX (1gr) 2 weeks apart and every 4 months in patients with AAV, in addition to standard of care	RTX maintained remission and allowed the withdrawal of prednisone and cytotoxic immunosuppression in a remarkable number of patients
Mansfield N. et al.	(77)	Prolonged disease-free remission following rituximab and low-dose cyclophosphamide therapy for renal ANCA-associated vasculitis.	2011	23	REMISSION/INDUCTION	Prospective, single center, open label, cohort study	RTX (1gr) 2 weeks apart in case of relapse, in addition to maintenance with AZA (2.0 mg/kg/day) and prednisone	A RTX-based CYC-sparing regimen (CycLowVas) is effective in induction of renal AAV. Retreatment within severe relapse is also effective
Smith RM et al.	(55)	Rituximab for remission maintenance in relapsing antineutrophil cytoplasmic antibody-associated vasculitis.	2012	92	REMISSION	Retrospective, single-center, cohort study	RTX (1 gr) every 6 months or RTX (1 gr 2 weeks apart) if relapse occurs, both plus standard maintenance therapy and glucocorticoids	Two-year, fixed-interval RTX re-treatment is associated with a reduction in relapse and a more prolonged remission during follow-up
Cartin Ceba et al.	(53)	Rituximab for remission induction and maintenance in refractory granulomatosis with polyangiitis (Wegener's): ten-year experience at a single center.	2012	53	REMISSION/INDUCTION	Observational, single-center, open-label, cohort study	RTX (375 mg/m(2)/week for 4 weeks) or RTX (1gr) 2 weeks apart in case of relapse and/or PR3-ANCA flare and/or B cell reconstitution	RTX appeared to be effective and safe for the induction and maintenance of remission in patients with chronic relapsing GPA
Besada E.	(61)	Long-term efficacy and safety of pre-emptive maintenance therapy with rituximab in granulomatosis with polyangiitis: results from a single centre.	2013	35	REMISSION/INDUCTION	Retrospective, single-center, cohort study	Maintenance with RTX (1 gr every 6 months or 1 gr 2 weeks apart annually), associated with daily prednisone (5–10 mg) and/or other immunosuppressants (AZA, MTX, MMF, CYC)	Long-term pre-emptive RTX maintenance was efficacious in reducing the risk for relapse; After 4 years, 37% of GPA patients discontinued RTX maintenance due to infections and hypogammaglobulinaemia
Pendergraft WF 3rd et al.	(57)	Long-term maintenance therapy using rituximab-induced continuous B-cell depletion in patients with ANCA vasculitis.	2014	172	REMISSION	Retrospective, single-center, cohort study	In most of the patients 1 gr of RTX (rarely 1 gr 2 weeks apart) every 4 months	Long-term AAV control using continuous B-cell depletion
Charles P et al.	(63)	Rituximab for induction and maintenance treatment of ANCA-associated vasculitides: a multicentre retrospective study on 80 patients.	2014	80	REMISSION/INDUCTION	Retrospective, multicenter, cohort study	RTX (mainly 6 month interval; several regimens); with or without (60%) other immunosuppressive therapies	RTX able to induce remission and maintain remission better than other agents ; Relapse-free survival was longer for patients receiving RTX maintenance therapy
Calich AL et al	(62)	Rituximab for induction and maintenance therapy in granulomatosis with	2014	66	REMISSION/INDUCTION	Retrospective, single-center, cohort study	Maintenance with RTX (500 mg) every 6 months for 18 months, associated with glucocorticoids	Maintenance treatment with low doses of RTX in a routine time-based protocol

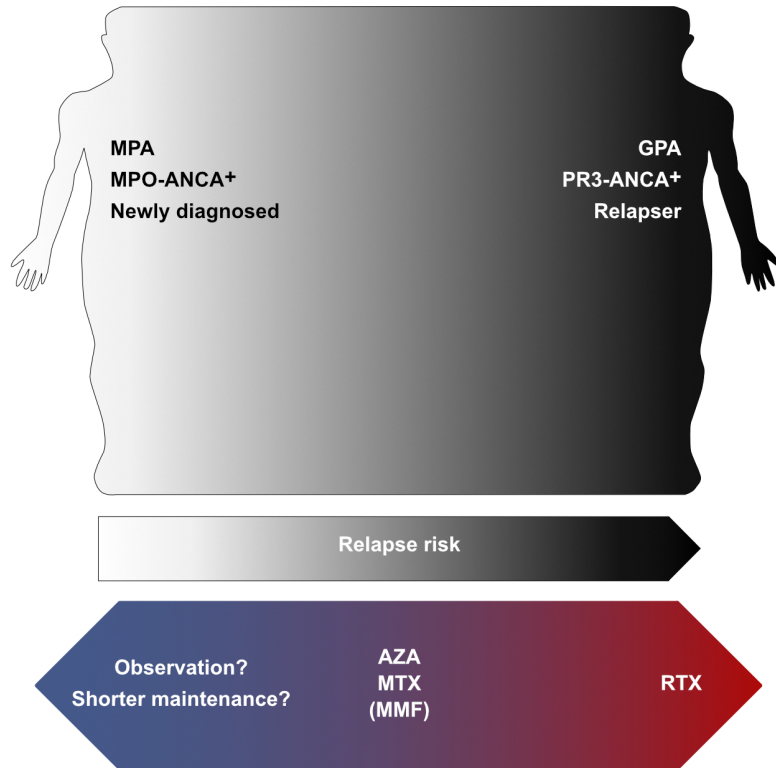|							
		polyangiitis (Wegener's). Results of a single-center cohort study on 66 patients.					was safe and associated with low rates of relapse on treatment
Azar L. et al.	(78)	Rituximab with or without a conventional maintenance agent in the treatment of relapsing granulomatosis with polyangiitis (Wegener's): a retrospective single-center study.	2014	89	REMISSION/INDUCTION	Retrospective, single-center, cohort study	RTX (4 weekly doses of 375 mg/m(2) intravenously or 2 fixed doses of 1gr 2 weeks apart) in addition to MMF, AZA, MTX and/or glucocorticoid	RTX is an effective induction – remission agent; The addition of a conventional maintenance agent to RTX and glucocorticoids decreased the incidence of relapse
Alberici F et al.	(60)	Long-term follow-up of patients who received repeat-dose rituximab as maintenance therapy for ANCA-associated vasculitis.	2015	69	REMISSION/INDUCTION	Retrospective, single-center, cohort study	RTX (1 gr) every 6 months for 24 months , plus steroid (and in 9% additional immunosuppression)	Fixed-interval RTX is safe and effective in maintenance of remission for in relapsing/refractory AAV
Timlin H et al.	(58)	Rituximab for remission induction in elderly patients with ANCA-associated vasculitis	2015	31	REMISSION/INDUCTION	Retrospective, single-center, cohort study	RTX (1gr 2 weeks apart or 375 mg/m(2)/week for 4 weeks) plus steroid in case of relapse	RTX is effective for remission induction in elderly patients with AAV
Cortazar FB et al.	(59)	The effect of continuous B cell depletion with rituximab on pathogenic autoantibodies and total IgG levels in ANCA vasculitis.	2016	239	REMISSION/INDUCTION	Retrospective, single-center, cohort study	RTX 1gr every 4 months for 2 years, followed by a 1 gr dose IV every 6 months, with or without low-dose ($\leq$ 7.5 mg/day) prednisone	RTX causes a preferential decline in ANCA titers relative to total IgG levels; Despite prolonged RTX maintenance therapy, IgG levels remain essentially constant and serious infections were rare
Puèchal X. et al	(84)	Rituximab for induction and maintenance therapy of granulomatosis with polyangiitis: a single-centre cohort study on 114 patients	2019	114	REMISSION/INDUCTION	Retrospective, single-center, cohort study	RTX four infusions (375 mg/m2 of body surface area; 1/week) or two 1 g infusions, 2 weeks apart, with low-dose ($\leq$ 10 mg/day) prednisone at month 6	RTX induction and low-dose preemptive maintenance can effectively and safely induce sustained remission in GPA in a real-life setting.

Figure 1. Current maintenance therapies for AAV in relation to relapse risk and patient disease phenotypes: different approaches may be advocated for different risk profiles. After induction therapy and baseline stratification for the risk of relapse, several approaches

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for keeping disease in remission can be undertaken. Patients should be repeatedly evaluated during remission: during follow-up the patients can move from left to right (i.e. because of first flair occurrence or, more rarely, because granulomatous manifestations could appear afterwards), increasing the risk of future relapse.

Figure Legend: *MPA, microscopic polyangiitis; GPA, granulomatosis with polyangiitis; MPO+, myeloperoxidase positive ANCA-associated vasculitis; PR3+, proteinase-3 positive ANCA-associated vasculitis; RTX, Rituximab; AZA, Azathioprine; MTX, Methotrexate; MMF, Mycofenolate Mofetil.*

Maintenance therapy and disease phenotypes

MPA
MPO-ANCA+
Newly diagnosed

GPA
PR3-ANCA+
Relapser

Relapse risk

Observation?
Shorter maintenance?

AZA
MTX
(MMF)

RTX

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