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Might maintenance therapy be discontinued once clinical remission is achieved in ANCA-associated vasculitis?

Dario Roccatello [a], Roberto Padoan [b,*], Savino Sciascia [a], Luca Iorio [b], Eithne Nic An Ríogh [c], Mark A. Little [c]

[a] University Center of Excellence on Nephrologic, Rheumatologic and Rare Diseases (ERK-Net, ERN-Reconnet and ERN-RITA Member) with Nephrology and Dialysis Unit and Center of Immuno-Rheumatology and Rare Diseases (CMID), Coordinating Center of the Interregional Network for Rare Diseases of Piedmont and Aosta Valley, San Giovanni Bosco Hub Hospital, ASL Città di Torino and University of Torino, Turin, Italy
[b] Rheumatology Unit, Department of Medicine DIMED, University of Padova, Padova, Italy
[c] Trinity Kidney Centre, Trinity Translational Medicine Institute, School of Medicine, Trinity College, Dublin, Ireland

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ABSTRACT

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) encompasses a group of rare, multisystem autoimmune disorders characterised by the occurrence of inflammation and damage to small blood vessels, leading to a wide range of clinical manifestations. They include granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA). Outcomes for patients with MPA and GPA have been transformed over recent years. However, the establishment of effective maintenance therapy aiming to balance the risks of disease relapse with those related to prolonged immunosuppression has become a clinical priority. This review aims to explore two differing perspectives on this unsolved problem. Pros and Cons of the following approaches will be discussed: "Biomarker-guided personalised approach on top of generic maintenance strategy guidelines" or "ANCA specificity-related personalised maintenance treatment after intensive B-cell depletion"?

1. Introduction

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) encompasses a group of rare, multisystem autoimmune disorders characterised by the occurrence of inflammation and damage to small blood vessels, leading to a wide range of clinical manifestations [1]. Small-vessel vasculitides include granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA) [2]. Criteria to classify AAV consider both clinical and laboratory parameters [3]. Recent genome-wide association studies revealed that proteinase 3 (PR3)-ANCA and myeloperoxidase (MPO)-ANCA associated vasculitis are genetically different. [4]. Consistent with this, PR3-AAV [5] is associated with a higher risk of relapse and consequently requires more ongoing immunosuppression to maintain disease remission [6].

In the last two decades, the successful conduct of high-quality, large, multi-center, randomized, controlled clinical trials established the standard of care for treatment of ANCA-associated vasculitis [7]. Outcomes for patients with MPA and GPA have been transformed over recent years, although premature mortality is still evident compared with the general population [8,9].

The establishment of effective maintenance therapy aiming to balance the risks of disease relapse with those related to prolonged immunosuppression has become a clinical priority [10]. International guidelines recommend maintenance therapy following induction of remission currently with repeat-dose rituximab (RTX) for at least 24–48 months, while azathioprine (AZA), mycophenolate mofetil (MMF) or methotrexate (MTX) are alternatives [11]. Results of a recent meta-analysis describing the outcomes of 7 randomized controlled trials (RCTs) including 752 patients with ANCA vasculitis [12] revealed that relapse-free survival was significantly worse with AZA, MTX, and mycophenolate mofetil (MMF) compared with RTX (hazard ratio [HR] respectively: 2.11, 95% CI: 1.19–3.74; 2.51, 95% CI: 1.24–5.08; 3.57, 95% CI: 1.70–7.46).

However, long-term immunosuppressive treatments and corticosteroids increase toxicity, resulting in adverse events such as secondary immunodeficiency [13], which may increase mortality [14]. In clinical practice, a common question often arises from patients regarding when all immunosuppressive therapy can be discontinued. While there is substantial evidence from two RCTs suggesting that extending maintenance therapy for longer than 24 months reduces the risk of relapse,

* Corresponding author at: Rheumatology Unit, Department of Medicine DIMED, University of Padova, Via Giustiniani 2, 35128 Padova, Italy.
E-mail address: roberto.padoan@unipd.it (R. Padoan).

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there is a lack of consistent high-quality evidence to inform decisions regarding the discontinuation of maintenance therapy.

Therefore, the optimal risk assessment strategy to guide maintenance therapy decisions in AAVs is still an unmet need. In the present review we will discuss differing perspectives on this unsolved problem: "Biomarker-guided personalised approach on top of generic maintenance strategy guidelines" supported by Mark Little, or "ANCA specificity-related personalised maintenance treatment after intensive B-cell depletion" supported by Dario Roccatello.

2. Biomarker-guided personalised approach on top of generic maintenance strategy guidelines

Several lines of evidence underline the relapsing nature of AAV, and the requirement for maintenance immunosuppression, with clinical trial data from the pre-RTX era indicating an approximately 40% probability of relapse within the first five years post diagnosis [15]. For example, when therapy is stopped at 12 months after diagnosis in cyclophosphamide-treated patients, 46% relapsed within 18 months [16] and, in the REMAIN trial, withdrawal of AZA therapy by 24 months, as opposed to continuing for four years, resulted in almost three times as many relapses with a clear end-stage kidney disease signal in the withdrawal group [17]. Thus, relapse of AAV is frequent (particularly in the pre-antiCD20 era), often recurrent [18] and preventable with maintenance therapy. Additionally, after the first year following diagnosis, nearly 10% of subsequent deaths were due to active AAV [19] and, when studying the risk factors for developing ESKD in AAV, the strongest independent factor is the occurrence of a renal relapse, conferring a nine-fold increased risk [20,21]. Thus, as well as exposing the patient to additional induction immunosuppression, relapse of AAV has severe clinical consequences.

As RTX use as an induction agent for AAV increases around the world, relapse profiles have changed. It appears that four doses of RTX at induction without subsequent maintenance therapy is associated with a similar 18-month relapse risk to a combination of cyclophosphamide induction and AZA maintenance [22]. However, relapses still occur after RTX induction: in the AZA maintenance arm of the RITAZAREM study (all of whom received RTX induction), the two-year relapse probability was 39%, one third of these relapses being major [23]. Therefore, the current EULAR guidelines [11] recommend maintenance treatment with six-monthly programmed RTX for a period of up to 48 months, with similar approaches in other regional guideline documents. Tailoring treatment to a return in ANCA, B-cells or clinical symptoms was associated with a higher relapse risk [24] and is not recommended for general use.

However, there are clearly individuals who successfully remain off treatment for many years without relapse [25] and, conversely, those whose immune systems remain activated and primed to cause injury shortly after withdrawal of immunosuppression. In such heterogeneity lies opportunity for a personalised approach. We have known for some time that broad stratification using ANCA status (PR3-ANCA, persistent positive, switch from negative to positive), peripheral (CD5+ low) B-cell return post RTX, induction therapy intensity (pulsed intravenous as opposed to daily oral cyclophosphamide), pattern of organ involvement (respiratory tract versus renal-limited), helps to assign patients to a higher relapse risk category. Unbiased cluster analysis has identified certain clinical phenotypes as being associated with relapse [26]. However, these clinical factors, along with putative biomarkers, have generally been studied in isolation and the concept of varying risk over time has rarely been incorporated into analyses. The latter point is critical as the individual patient's relapse risk at a point in time is heavily influenced by the integral of both inherent time-invariant factors (such as ANCA specificity) and, more importantly, the cumulative effect of events occurring up to that time (e.g., relapse, time-varying immunosuppression exposure, infections, end-stage kidney disease). Advanced modelling techniques that combine these factors will be more likely to generate precise estimates of future relapse risk.

Many lines of evidence indicate that, although the immune system may return to a normal state in some patients, in others the immune system remains either primed and activated, or "exhausted" and incapable of responding, leading to a high and low risk of relapses respectively. For example, in the adaptive immune system, pro-inflammatory T helper 17 (Th17) lymphocytes [27], CD95+ activated B cells and autoantibody-producing plasmablasts may remain expanded [28] and regulatory lymphocytes [29,30] are suppressed. In some, the innate immune system remains activated, reflected in, for example, elevated calprotectin levels [31] and affected organs show persistent subclinical inflammation [32]. HLA DPB*0401 and PRTN3 genotype [33,34] may also influence relapse probability. Recent evidence also supports the concept that the presence of biomarkers of an "exhausted" immune system is characterised by low risk of autoimmune re-activation, but increased risk of infection [35,36].

Thus, as advised by international guidelines, maintenance therapy is required in AAV for a period. However, there are likely possibilities to tailor this therapy, or even discontinue it, in selected individuals. Such an approach will require development of readily assayed biomarkers that reflect the underlying state of immune activation and careful development of multi-modal artificial intelligence algorithms validated in a wide range of population settings.

3. ANCA specificity-related personalised maintenance treatment after intensive B-cell depletion

Anti-CD20 treatment has been demonstrated to be successful in inducing remission in patients with newly diagnosed and recurrent disease in randomized controlled studies [37–39]. More recently retrospective and prospective studies have investigated the effectiveness of repeat dose RTX as maintenance therapy [40,41]. Frequency and dosage of repeat infusions of RTX, as well as length of maintenance therapy, are still open questions [42]. Similarly, it is still unknown if dosing should be administered at a set interval or be triggered by symptoms, i.e., rise in ANCA titre and B cell count, or both. Additionally, the long-term results following the cessation of RTX treatment are still unknown.

In previous studies, we demonstrated a successful outcome of patients with refractory AAV treated with either the so-called "improved protocol" (4 + 2 infusions) of RTX or a RTX- cyclophosphamide combined regimen [43,44]. More recently, efficacy and safety of an intensive B-cell depletion treatment (IBCDT) were compared to a traditional cyclophosphamide-AZA regimen in a control case study on a cohort of AAV patients, specifically selected due to their severe renal impairment (defined as <15 ml/min eGFR per 1.73 m^2). The IBCDT protocol, consisting of a combination of the RTX improved protocol (4 + 2), cyclophosphamide, and methylprednisolone pulses, had been already used in several severe immune-mediated disorders [45–49]. In critically ill patients with AAV a single cycle of IBCDT without any maintenance regimen has been proven to be equivalent to a standard scheme of cyclophosphamide for remission induction and AZA for maintenance. Despite the absence of any maintenance regimen, IBCDT was associated with a long-lasting remission (with a median relapse-free survival of 44 months) particularly in patients with MPO-AAV. A "watchful waiting" strategy that involves regular monitoring of the ANCA titres and CD19+ cells count seems to be appropriate [50] in these circumstances.

The Efficacy Study of Two Treatments in the Remission of Vasculitis (MAINRITSAN) trial [51], in which patients received cyclophosphamide as induction therapy followed by either a low-dose RTX maintenance regimen (2 doses of 500 mg at 6 months and then 500 mg every 6 months) or AZA maintenance therapy, provided evidence for the superiority of RTX. Indeed, patients in the RTX group experienced fewer relapses than patients in the AZA group (5% versus 29%; $P = 0.002$ at 28 months). The long-term follow-up data from the MAINRITSAN study confirmed the superiority of RTX for maintaining remission at 5 years. The relapse-free survival rate under RTX was 57.9% compared to 37.2%

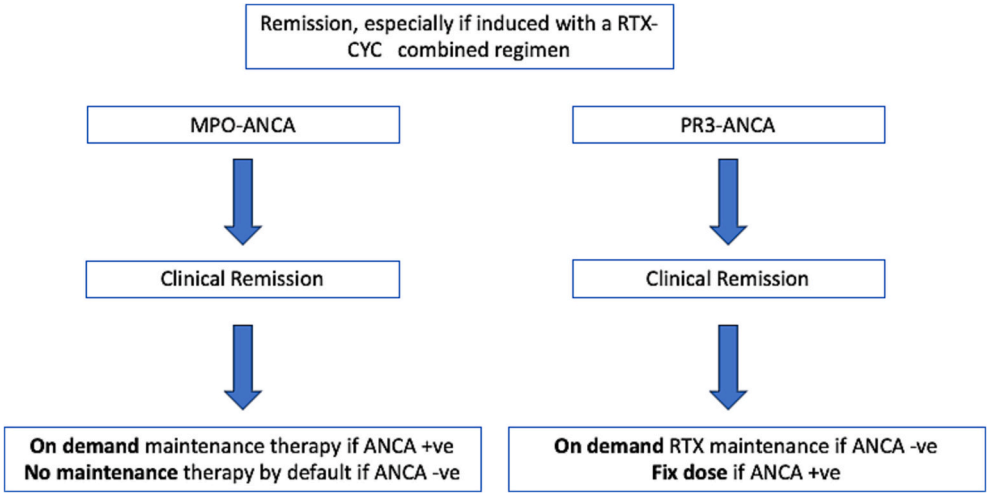

Fig. 1. The San G. Bosco Hub Hospital (Turin) algorithm proposal based on ANCA specificity and ANCA status. Similar to Mayo Clinic experience [53] in Turin cohort persistently negative ANCA test (especially MPO specificity) resulted in a highly negative predictive value for relapse. Evaluating of histological activity by repeat renal biopsy is considered in case of re-appearance or worsening of urinary abnormalities.

with AZA ($P = 0.012$) [52].

The MAINRITSAN 2 trial [24], which aimed to further define the ideal interval of RTX administration for maintenance treatment, showed that the biomarker-based group had a lower RTX exposure rate (17.3% versus 9.9%; $P = 0.22$) compared to the group receiving RTX at a fixed-interval (every 6 months).

In a retrospective study on patients with MPO-AAV with renal involvement followed at the Mayo Clinic between 1996 and 2015 (#159 eligible), relapse rate, MPO-ANCA status, and remission-maintenance therapies were reviewed. In this survey, 46% of the patients who had MPO-ANCA reappearance had a relapse. Frequency was higher in patients who were persistently MPO-ANCA-positive (39% and 30%), while patients who remained MPO-ANCA–negative did not relapse. In the Mayo Clinic cohort, persistently negative MPO-ANCA test had a 100% negative predictive value for relapse [53].

Out of 427 patients followed in North Carolina, 277 (65%) discontinued therapy, with a median discontinuation time of 20 months from initial induction. Among these, 14% stopped for two or more separate periods, and 23% stopped for periods of five years or longer. The likelihood of discontinuing therapy was higher in MPO-ANCA positive cases, as well as in patients with only glomerulonephritis. Interestingly, 194 patients never experienced a relapse, and the characteristics of those who did stop treatment and those who never stopped were comparable [25]. According to this study, considering time off therapy as a time-dependent covariate is associated with approximately half as many relapses as continuous therapy.

In over 20-years of experience with a large cohort of prospectively enrolled patients (the G. Bosco Hospital Turin experience), 127 out of 164 patients were eligible for evaluation. This included 33 GPA-AAV (all of whom were PR3-ANCA-positive) and 94 MPA-AAV patients (90% of whom were MPO-positive). Of this cohort, 30% had severe renal impairment. Forty-three per cent of patients with MPA-AAV did not experience relapse despite the absence of maintenance treatment. Notably, compared to other regimens, IBCDT assured a significant lower rate of flare. At remission, 73% of patients were ANCA negative and 17% positive. Half of those who were ANCA-negative, remained persistently negative without maintenance therapy. This was especially the case of MPO/pANCA vasculitis (56%), though a consistent proportion of PR3/cANCA vasculitis patients (41%) showed a similar feature.

These data underline the importance of achieving ANCA negative status following induction therapy. These data also provide evidence that, at least in MPO-associated ANCA vasculitis, a maintenance therapy after an intense B cell depletion regimen may not be required.

The G. Bosco Hospital Turin experience indicates that, at the very least, an intensive B cell depleting protocol for remission induction, with no maintenance immunosuppression by default, may be preferable to the practice of delivering fixed doses of RTX regardless of the clinical assessment, due to the delayed onset of relapse.

4. Conclusions

In conclusion, AAV is prone to relapse, sometimes for many years, where early discontinuation of treatment results in a significant surge in relapse rates and unfavourable outcomes. Following the introduction of RTX to the treatment arsenal, the relapse profiles have improved significantly. Even if therapy discontinuation immediately following induction of remission has traditionally been considered unachievable, recent studies indicate a growing interest from both patients and healthcare providers to explore this possibility.

While there are individuals who can successfully remain off treatment for several years without relapse, in others the immune system remains primed and ready to induce damage upon withdrawal of immunosuppression. Recognizing this heterogeneity offers the opportunity for a personalised approach, utilizing broad stratification using factors like ANCA status, B-cell repopulation post-RTX, intensity of induction therapy, pattern of organ involvement and novel biomarkers of sub-clinical immune system activation. The goal is to identify patients at low or high risk of relapse, while acknowledging that this risk fluctuates over time due to inherent factors and cumulative events.

Accordingly, after induction therapy, particularly with RTX or RTX/cyclophosphamide -based regimens, approximately 75% of patients with AAV become ANCA negative. Over half of these patients maintain their negative status without a maintenance regimen if they have MPO-ANCA. This percentage is lower in PR3-ANCA patients, but it's still substantial. The strategy at San G. Bosco Hub Hospital – Turin (Fig. 1) involves monitoring the re-occurrence of ANCA and CD19 (i.e., $>$ 3 CD19 cells) if RTX has been used. When peripheral B-cells repopulate, ANCA titres become crucial in management decisions.

Finally, there is growing interest in exploring additional biomarkers and examining the prognostic implications of histologic findings in repeated renal biopsies. It's time to shift our perspective, considering individual risk factors for relapse and damage, as well as patient preferences when deciding on the duration of maintenance treatment. We advise this with a degree of caution, emphasizing that patient participation is crucial as they are often the first and most accurate predictors of onset of disease activity.

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DR: Advisory boards: Novartis, Vifor; teaching honoraria: GSK, BMS, Roche, Novartis; UpToDate contributor.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Dario Roccatello reports a relationship with Novartis Pharma AG that includes: consulting or advisory. Dario Roccatello reports a relationship with Vifor Pharma Ltd. that includes: consulting or advisory. Dario Roccatello reports a relationship with GlaxoSmithKline Inc. that includes: speaking and lecture fees. Dario Roccatello reports a relationship with Bristol Myers Squibb Co that includes: speaking and lecture fees. Dario Roccatello reports a relationship with Roche that includes: speaking and lecture fees. Dario Roccatello reports a relationship with Novartis Pharma SAS that includes: speaking and lecture fees. Dario Roccatello reports a relationship with UptoDate Inc. that includes: paid expert testimony. Mark A Little reports a relationship with AnaptysBio Inc. that includes: consulting or advisory. Mark A Little reports a relationship with Lightstone that includes: consulting or advisory. Mark A Little reports a relationship with Vifor Pharma Ltd. that includes: funding grants. Mark A Little reports a relationship with Euroimmun Medical Laboratory Diagnostics AG Institute for Experimental Immunology that includes: funding grants.

Data availability

Data will be made available on request.

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