L52. Vasculitis treatment: Is it time to change the standard of care for ANCA-associated vasculitis?

Introduction

In contrast to observational studies of the pre-1990 era, recent changes in the approach to treatment have been driven by multicenter, national and international controlled trials. The
medical community is indebted to large collaborative networks for improving our understanding of the burden of these diseases, treatment options and outcomes. Well-established vasculitis consortia include the European Vasculitis Study Group (EUVAS), the French Vasculitis Study Group (FVSG), Italian Vasculitis Study Group (IVSG), and the Vasculitis Clinical Research Consortium (VCRC). They have functioned as independent entities and have also joined to produce cross-collaborative ventures. Through their efforts, we have learned a great deal and together have trained a growing new generation of care providers, investigators and leaders in the field of autoimmune vascular injury.

The results of this effort include putting an end to the once only proven effective treatment for all forms of severe AAV, chronic cyclophosphamide (CYC) plus glucocorticosteroids (GCS). While CYC plus GCS converted life-threatening and often fatal diseases into chronic illnesses, it also carried an unacceptable burden of adverse events, which in themselves could cause severe morbidity or death. We first learned that alternatives to CYC [e.g. methotrexate (MTX)] could be effective for milder forms of AAV [1–3]; and for more severe disease, short-term CYC (3–6 months), followed by other less toxic therapies [e.g. MTX, azathioprine (AZA), or mycophenylate mofetil (MMF)] can be effective once CYC-induced improvement had occurred [4].

These strategies dramatically reduced adverse events (AE) and lead to long-term remissions in many, although not all patients [5–7]. Relapse rates have been noted to be particularly high when treatment has been tapered to below therapeutic thresholds or discontinued [3,6–8]. These observations raise the 1st question I will address in regard to suggestions for changing the standard of care and conduct of clinical trials.

Should a well-tolerated, effective therapy be discontinued after an arbitrary period of time in remission?

To date, most treatment trials have included follow-up for up to 18 months following remission, with patients then treated based on best medical judgment. One recent observational retrospective study of GPA sought to determine if remission maintenance outcomes differed in patients already in remission who were subsequently treated for either an additional period of less than 18 months vs. at least 18 months. From almost 800 patients screened, 157 with adequate follow-up (18 months to 16.8 years [mean 3.1 years]) were included. Treatment for greater than 36 months was associated with a 66% reduction in hazard ratio for relapse (HR 0.34 [95% CI 0.15, 0.76], P = 0.008) (figure 1).

In those who continued maintenance medications for at least 18 months, 90% of relapses occurred after stopping therapy. Among all patients who relapsed on therapy, 52% were receiving a median dose of 15 mg/week of MTX (range 5–22.5 mg/wk) and 67% were receiving a median dose of 50 mg/day (range 25–100 mg/d) of AZA. There were no differences between the two groups in overall adverse events or GPA-related morbidity [8]. These results have urged our group to advocate for long-term indefinite maintenance therapy in all patients with GPA, in whom treatment has been well tolerated, remission sustained and for whom there are no plans for pregnancy. For this data and our practice to be more widely endorsed requires confirmation.

**Figure 1**

Kaplan-Meier curves for relapse-free remission in granulomatosis with polyangiitis patients based on duration of maintenance therapy: ≤ 18 months, 18–36 months and ≥ 36 months

From: Springer et al. [8].
of these findings in a randomized prospective controlled study. A similar analysis would be required for MPA to determine risk–benefit relationships.

**Should there be a change in standard of care for monitoring CYC therapy?**

The genesis of this question is based on results of multiple EUVAS studies in which it has been noted that the leading cause of death in this modern era of therapy for AAV is severe infection [9]. Leukopenia (e.g. white blood counts (WBC) < 3000/mm³) continues to be linked to death from severe infection, especially if high doses of GCS are being used concurrently. Continued concerns about severe and fatal infections demands that future studies examine comparative effectiveness of monitoring protocols for SAEs, especially those related to bone marrow toxicity. This issue is most germane to CYC for which the effects on bone marrow progenitors are additive over time and greater than for other agents used to treat vasculitis. Such a study has never been conducted and is long overdue. Until cost-effective/risk–benefit data are available, our practice has been to monitor CBC and creatinine values on a weekly basis as long as patients receive CYC for induction of remission. Dose reductions of CYC occur to avoid WBC of less than 4000/mm³. If WBC counts of less than 3000/mm³ occur, daily CYC doses are held until the WBC normalizes and then CYC is restarted at a dose below that which caused leukopenia. In our experience, this approach has minimized severe infections (17%) and mortality (3.7%) over a median follow-up period of 4.5 years [6].

**Should AAV subsets be combined in future clinical studies?**

Since the 1980s, the discovery of an association between GPA (WG) and MPA with ANCA lead the vasculitis community to endorse the concept of ANCA-associated vasculitis (AAV). Whether limitations in test sensitivity explain the approximately 10% of patients with clinical and pathological features of GPA and MPA who are ANCA-negative remains unknown. The term AAV is usually also applied to Churg-Strauss syndrome (CSS) or eosinophilic granulomatosis with polyangiitis (EGPA), in which only about 40% of patients are ANCA positive. The association is more notable in patients with EGPA and glomerulonephritis wherein 50–80% of patients are ANCA positive [10,11].

This data is based on small numbers of patients. Other data that supports a unique place for EGPA within the spectrum of vasculitis is enhancement of the pathway for eosinophils developing from IL-5 stimulated hematopoietic (CD34+) progenitor cells. In vitro studies have provided evidence that ANCA is pro-inflammatory. Murine models in which T and B cell antigen receptor-deficient animals (e.g. Rag 2 knockout) are reconstituted with splenocytes producing anti-MPO or are given anti-MPO antibody will develop organ injury in which lesions include vasculitis and glomerulonephritis [12].

That ANCA titers correlate crudely at best with disease activity and risk of relapse raises questions about other factors that may play a role in pathogenesis. Clinical trials have often combined patients with GPA and MPA because of the belief that these diseases were more similar than different. In some instances, EGPA and renal-limited vasculitis have been included as well. Combining what had been considered distinct illnesses in the pre-ANCA era was defended based on a shared family of antibodies. However, these diseases are most often clinically distinct; patients with GPA usually often have mass lesions, ENT involvement and histopathological findings of granulomatous inflammation, features usually not seen in MPA. In EGPA, the clinical phenotype is similar to GPA, but differs in asthma and eosinophilia being part of the clinical profile. While the upper and lower airways are involved in both diseases, in GPA tubular airway stenoses may occur in over 1/5 of cases, a feature that would be very rare in EGPA. Recent studies have also revealed differences in prognosis and likelihood of relapse in GPA and more specifically in patients with PR3 vs. MPO ANCA, regardless of clinical phenotype. Again, these observations speak to a role of ANCA in pathogenesis and influencing disease expression [13].

**Should genetic differences be considered in disease distinctions and influence clinical trials in the future?**

In a genome-wide association study (GWAS), Lyons and colleagues [14] have recently demonstrated that GPA and MPA are associated with different SNPs in the HLA region. GPA is associated with a SNP in the HLA-DP gene whereas MPA is associated with a SNP in the HLA-DQ locus. These distinctions were even more striking when comparing patients based on ANCA serotype. Those who were anti-PR3 positive were far more likely to have the risk allele located at the HLA-DP region. The association of MPA and the risk allele in the HLA-DQ gene was less striking. The authors conclude that there is a significant genetic contribution to pathogenesis of GPA and MPA. How these observations may affect immunopathogenesis is uncertain. Many questions remain. We would also like to know:

- a. What genetic and/or environmental co-factors may be required to produce disease?
- b. What implications do these results have for ANCA-negative GPA and MPA?
- c. Are there gene/gene interactions (epistasis) that are important in AAV? This may be particularly relevant to genetic variants that alone may not show an effect but in the presence of another variant may become important.
- d. Do epigenetic factors, such as methylation of DNA or modification of histone proteins, influence pathogenesis? Are these factors also passed on from generation to generation?
e. Does this GWAS alone provide an additional reason to modify clinical trials that have combined all AAV under a single umbrella?

Barring cost limitations, whole genome sequencing in these diseases is likely to provide answers to these questions. While the last question (e) is debatable, this author believes that when one combines the often striking differences in clinical and histological phenotypes and influences of ANCA-serotype, the argument becomes much more compelling. No doubt it will be more difficult to recruit for separate studies of GPA, MPA and EGPA, but we should anticipate that results will add clarity beyond studies of “ANCA-disease(s)”.

**Do new data on biologic agents in AAV urge a change in standard of care?**

Two seminal randomized controlled studies (RAVE and RITUX-VAS), published in 2010, evaluated induction of remission using rituximab (RTX), a chimeric monoclonal antibody directed against the B cell specific antigen CD20. RTX plus GCS were compared to GCS and CYC, transitioned to AZA (CYC/AZA), for severe GPA and MPA [13,15]. Both reports demonstrated that RTX was as effective as CYC/AZA. For those persons with concerns about fertility and those who have had serious prior AEs from CYC that would increase their risks of further toxicity, RTX is an especially important option. For newly diagnosed patients with severe disease, who receive limited duration (3–4 months)-induction therapy with CYC, these issues are less of a concern.

These and other studies have also taught us that RTX does not guarantee complete and GCS-independent remissions. Over time relapses are common. New randomized trials are evaluating re-treatment on a planned schedule vs. treatment based on the earliest unequivocal indications of relapse. From these efforts, we will learn more about the short and long-term relative risks of maintenance therapy using every 4–6 months RTX vs. RTX followed by AZA vs. re-treatment based on early indications of relapse. In clinical practice, strategies for re-treatment based on detecting signs of disease recurrence include the need for formulae and care systems structured to respond immediately to patients’ new, hopefully modest, symptoms and surrogate markers of relapse. Unfortunately, sensitive and specific surrogate markers are not available. In addition, patients not having access to a care-provider system structured to provide a timely clinical response risks incremental permanent damage, disability and mortality.

Preliminary data on RTX re-treatment are now available from several centers (table I). The first reports of RTX efficacy in GPA were from the Specks’ group at the Mayo Clinic in 2001 [16]. That group has recently provided a retrospective evaluation of their 10-year experience with RTX in 53 patients with refractory GPA [17]. This cohort is independent of patients who were enrolled in the RAVE study. Most patients (64%) were treated prophylactically to prevent relapses while others were treated for clinical indications of relapse. In all patients treated preemptively with RTX, remission was maintained. Preemptive repeated RTX was effective and relatively safe. There was no evidence that patients developed resistance to RTX-induced B cell depletion over time.

Another retrospective cohort analysis included 39 patients with either GPA or MPA, who were in complete (#22) or partial remission (#17) and treated with RTX. Follow-up was for at least 1 year after the first RTX infusion. Twenty of the 39 were evaluated over 2 or more years post-RTX. The majority (35/39) received two 1-g doses given 2 weeks apart, and in 33/39 a single 1-g dose every 4 months. Only three patients experienced relapses; the percent of patients on cytotoxic agents decreased from 87% to 30% at 24 months. Among the 92% of patients taking prednisone at start of RTX, 55% were still on prednisone at 24 months follow-up [18]. While these results are encouraging, the number of patients still requiring glucocorticosteroids and other immunosuppressive agents plus RTX is noteworthy. The authors also recognized that for GPA and MPA, diseases that may be life-long, this period of follow-up is relatively short especially for assessment of long-term adverse effects RTX.

A 3rd single-centre retrospective study of 73 patients compared sequential subsets who received rituximab for refractory or relapsing GPA and MPA [19]. Patients had previously been treated with a median of four immunosuppressive agents apart from GCS. Ninety-three percent had previously received CYC therapy. In over 90%, those therapies had been in use at the time that RTX was added. The analysis included three subsets: A (n = 28) received RTX induction and further RTX at the time of subsequent relapse; B (n = 45) received routine RTX re-treatment every 6 months for 2 years (2 × 1 g induction, and 1 g every 6 months, 6 g total) and C, a rescue group (n = 19) consisted of group A patients who relapsed and were then started on every 6 months re-treatment over 2 years. Group A received treatment during the authors’ initial experience with RTX (2002–2006), whereas the re-treatment approach to therapy started in 2006. The authors found that complete plus partial remissions occurred in over 90% of all groups. However, as expected, at 2 years follow-up, relapses occurred in 73% of the group (A) that did not receive maintenance RTX therapy. Only 12% of patients given maintenance RTX (group B) relapsed (P < 0.001) and among patients in group A who subsequently received scheduled rituximab (group C), relapses occurred in only two of 18 cases (11%) (P < 0.001) at 24-month follow-up. From start to conclusion of RTX treatment, there was a significant reduction in use of other immunosuppressive agents, including prednisolone. Glucocorticoids were withdrawn in six of the 28 patients (21%) in group A, 17 of the
### Table I

**Overview: tituximab data regarding maintenance therapy for GPA and MPA**

<table>
<thead>
<tr>
<th>Author (ref)</th>
<th>Number of patients</th>
<th>Follow-up (F/U) (months)¹</th>
<th>Indication for RTX: Active (A) disease or Maintenance (M) of remission</th>
<th>RTX dose/interval</th>
<th>Efficacy CR or PR²</th>
<th>Relapse rates</th>
<th>Daily requirement for GCS at start RTX</th>
<th>Need for daily GCS at F/U</th>
<th>Serious adverse events³</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cartin-Ceba</td>
<td>53</td>
<td>Median = 53 (interquartile range = 32–74)</td>
<td>A and M</td>
<td>Variable dose and interval</td>
<td>CR among all treated prophylactically</td>
<td>60% after 1st RTX, re-treated achieved remission</td>
<td>Not reported All in remission stopped GCS</td>
<td>Not reported</td>
<td>30 infections⁴</td>
</tr>
<tr>
<td>Rhee</td>
<td>39</td>
<td>24</td>
<td>M 17 CR² 22 PR²</td>
<td>1000 mg q4 mos</td>
<td>12 months F/U: 22 PR, 64% achieved CR 17 CR remained in CR</td>
<td>8% after 20 months</td>
<td>92%</td>
<td>59% for all For 2 yr F/U 55%</td>
<td>4 (10%)</td>
</tr>
<tr>
<td>Smith (see text for subsets)</td>
<td>73</td>
<td>24–48</td>
<td>A and M</td>
<td>1000 mg q6 mos</td>
<td>&gt; 90%</td>
<td>73% (A); 11–12% (B and C) Increase after RTX stopped in B, C</td>
<td>Median/range A: 11 (0–45), B: 10 (0–40), C: 5 (0–20) Total on GCS not stated</td>
<td>Median/range at 24 months, A: 5 mg (0–25), B: 2.75 (0–40), C: 1 (0–10) Total – 59% GCS use</td>
<td>32–47% among all groups</td>
</tr>
<tr>
<td>Guillevin³</td>
<td>114</td>
<td>28</td>
<td>M</td>
<td>500 mg q6 mos</td>
<td>3.6% vs. 27% AZA group</td>
<td>27% RTX 31% AZA</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

¹ In some reports, follow-up is not precisely indicated for all patients. Approximations are provided based on available data.

² CR: complete remission; PR: partial remission.

³ Only prospective randomized controlled study. Interim analysis. Comparison to standard of care for maintenance (azathioprine) of remission. Included GPA (#86), MPA (#23) and renal-limited vasculitis (#5). Only listed study to include renal-limited subset.

⁴ Reported in table because not clear how many were treated with antibiotics or required hospitalization. There was one death from *Pneumocystis pneumonia* in a patient for whom PCP prophylaxis had been discontinued.

⁵ Immunoglobulin levels were not routinely assessed in these studies, but limited data indicates that repeated RTX therapy has a high likelihood of producing hypogammaglobulinemia [14,19,21].
45 patients (38%) in group B, and nine of the 19 patients (47%) in group C by 24-month follow-up. That a significant minority of patients in RTX re-treatment groups still required low to moderate doses of prednisolone (table I) after 2 years is of concern and a cautionary footnote in the evolving RTX story. The frequency of relapses was also noted to increase after RTX therapy was stopped at 24 months (figure 2).

The frequency of serious adverse events (32–47%), including infections, did not differ between treatment groups. The authors concluded that “in the absence of better biomarkers, routine re-treatment is the only strategy likely to be effective” (for maintaining long-term remission). They also advise that “...should improved biomarkers become available, closer adjustment of drug dosing to the individual patient’s needs will be achievable.”

Among all preliminary reports, the FVSG has performed the first and thus far only prospective randomized controlled study that compares repeated dosing of RTX to conventional treatment [20]. The study is entitled “maintenance of remission using rituximab in systemic ANCA-associated vasculitis.” The acronym for the study is MAINRITSAN. Patients were enrolled after remission was achieved with traditional agents. A total of 114 patients were included who had GPA (#86), MPA (#23) or renal-limited vasculitis (#5). The RTX group received maintenance re-treatment every 6 months (500 mg RTX, 5 infusions over 18 months) and was compared to the group receiving maintenance therapy with AZA (2 mg/kg/d) for 22 months. The primary endpoint was frequency of major relapses at 28 months. The reported interim analysis included 74% of patients who had completed 28 months follow-up. Major relapses occurred in 3.6% of the RTX group and 27% of the AZA group, which included three deaths. SAEs were observed among 18 of 59 patients in the AZA arm (31% of patients) and 15 of 55 (27%) in the RTX arm. Infectious complications were about the same in both arms. While an interim analysis, the authors concluded that RTX maintenance therapy was superior to AZA.

These studies share the goal of determining the value of chronic, repeated therapy with RTX. However, they differ in several respects. Similarities, differences and outcomes are summarized in table I.

How should we use this still evolving data to answer the questions posed in regard to patient care and design of future studies?

It is well known that a large majority of patients who discontinue maintenance therapies for GPA or MPA will relapse within 2 years. This has encouraged many authorities to recommend long-term maintenance therapy as long as it is well tolerated and not complicated by severe AEs. Should this guidance be applied to all patients with these diseases? If not all, which subsets and what agents should be utilized? To best answer these questions, it is important to revisit some of the strengths and weaknesses in the data:

- the RAVE and RITUXVAS studies demonstrated non-inferiority of RTX to CYC followed by step-down therapy with AZA for remission-induction in AAV. However, these studies did not demonstrate superiority of RTX in regards to efficacy or safety in the overall populations studied. The comparable AE profiles between RTX and CYC/AZA arms is likely related to limiting the duration of CYC exposure and thus toxicity, and shared AEs related to GCS therapy which continue to be considerable;
- in RITUXVAS, CYC was used for induction of remission along with RTX. We do not know how RTX would have performed in those patients if they were treated only with concurrent GCS;
- in RAVE, in the RTX group 2nd agents were not allowed and RAVE excluded patients with immediately life-threatening diseases, including those likely to require ventilator support or dialysis;
• many open-label observational studies and MAINRITSAN added RTX to ongoing therapies that included agents such as CYC, AZA, MTX or MMF;
• the RTX studies reviewed in this paper have not adequately informed us about optimal doses and treatment intervals for maintaining remission. However, they have demonstrated clinical effectiveness;
• all of the RTX studies reviewed have been cautious in warning that for AAV, diseases that may require prolonged, if not lifelong therapy, chronic repeated RTX use may be associated with as yet unrecognized adverse events. Nonetheless, available information about RTX use in other diseases, to date, has been encouraging in that many of the SAEs associated with cytotoxic agents are not apparent for RTX, e.g. bone marrow suppression, mutagenic effects that may lead to liquid and solid tumors, teratogenicity, and sterility. Additional information is needed in regards to repeated RTX therapy and hypogammaglobulinemia. Emerging data in the AAV-RTX literature suggests this is common and data in rheumatoid arthritis (RA) trials justifies that concern [21–24]. In spite of these findings, in RA serious infections are infrequent after repeated B cell depletion. However, RA patients rarely require high dose GCS concurrent therapy for life-threatening complications, a common circumstance in AAV;
• in RA rare cases of progressive multifocal leukoencephalopathy (PML) have been reported with RTX use. The incidence of PML in RA treated with RTX has been estimated to be approximately 1:25,000 [25,26]. Although to date, no cases of PML have been reported in RTX-treated AAV, the risk of PML in RTX-treated vasculitis is unknown.
Recognizing that in time new data will better inform us about how we can further improve patient care, for the present, I believe certain recommendations and cautions can be offered for readers’ consideration:
• RTX is a proven effective treatment for GPA and MPA. It should be considered the treatment of choice for induction of remission in:
  o patients of reproductive age for whom maintenance of fertility is an important concern,
  o RTX is the preferred therapy for patients in whom CYC has been utilized in the past and for which CYC would be considered for severe disease manifestations at the time of relapse;
• RTX maintenance therapy should be considered for patients who have experienced prior RTX-mediated complete remission of at least 6 months duration:
  o in patients who have already experienced severe critical organ damage and in whom further damage is judged likely to cause profound disability or death (e.g. renal replacement therapy, blindness, pulmonary crippling),
  o for patients who have had excellent responses to RTX, retreatment should be considered with the earliest convincing signs of relapse; not just for severe disease. This recommendation is based on data that has shown that early “mild” disease does not spontaneous regress, but instead always progresses to more severe disease and incremental damage;
• cautions when considering RTX:
  o the most effective dose and intervals for dosing are still under study. To date, every 6 months schedules have been very effective, utilizing doses of 500–1000 mg,
  o RTX with only GCS has not been adequately evaluated in patients with immediately life- or critical organ threatening diseases. In this setting CYC and high dose GCS has often been organ and life-saving,
  o long-term risks from many years of intermittent RTX use in AAV have not been adequately assessed. Sporadic cases of Pneumocystis pneumonia urge inclusion of PCP prophylaxis for these patients,
  o for patients who enjoy prolonged remissions, the best individualized duration of RTX therapy is unknown. Nonetheless, for patients in whom further damage is judged likely to cause profound disability or death, extreme caution is advised when successful maintenance therapy of any kind is discontinued.

Conclusions
Over a period of only 20 years, multicenter, national and international controlled trials have revolutionized the process of discovery in vasculitis and vastly improved patient care. Remissions are more safely achieved and toxicities have been drastically reduced. Chronic long-term CYC therapy is no longer justified. Better tolerated maintenance therapies have eliminated many of the feared side effects previously attributed to years of CYC treatment. Judicious, limited use of CYC continues to be life-saving, albeit not without significant risks. Infectious complications of all forms of treatment still cause greater mortality in the first year of therapy, than GPA and MPA themselves. Appropriate monitoring for infection-related risk factors and their prevention has not been and should be studied in the future. A dramatic example of risk recognition and reduction is prophylactic therapy for P. pneumonia.
Recent GWAS studies have supported the notion that GPA and MPA have different genetic foundations. This adds to knowledge that these are clinically and pathologically distinct diseases even though they both respond to broadly immunosuppressive-anti-inflammatory therapies. These observations strengthen the argument that GPA and MPA or, as some prefer “PR3- and MPO-polyangiitis”, should be studied separately in clinical treatment trials. If this was pursued based on serological classification, it would ignore 10% of patients who are ANCA-negative but have clear clinical and pathological evidence of these diseases.
Perhaps the most important discovery in clinical therapeutics for vasculitis in past 40 years is that RTX is as effective as CYC for induction of remission of GPA and MPA. Early data suggests RTX is also very effective for maintenance of remission. Many studies are now underway to examine optimal doses, intervals, risks and duration of RTX therapy. Whether all subsets of patients, regardless of disease severity or organs affected will equally benefit also needs to be addressed. No doubt, guidelines will change, as they should. In the interim, available data does allow for reasonable decision-making about how and when to use RTX for GPA and MPA.

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References