Antineutrophil Cytoplasmic Antibody-associated Vasculitis Management 2020: Where Are We Now?

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The management of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) has come a long way from the first postmortem descriptions of the diseases in the 1930s and 1950s1. Pivotal phases have been the introduction of glucocorticoids (GC) and cyclophosphamide (CYC), the association with ANCA in the 1980s, and consensus classification and nomenclature systems from 1990 onwards2. These advances laid the foundations for larger-scale clinical investigations that have informed both the development of recommendations statements in the 2000s and the evaluation of newer therapies3. In parallel with these activities have been improvements in physician training and healthcare delivery, which have shortened diagnostic delay, and improved mortality and endstage renal disease risks4. Statements to guide AAV management have now been produced at national and international levels, and an update of the Canadian Vasculitis Society (CanVasc) 2015 statement is published in this edition of The Journal of Rheumatology5.

This is an extensive piece of work with 39 recommendation statements, 15 of them new for this update covering diagnosis, drug therapies, eosinophilic granulomatosis with polyangiitis (EGPA), children, monitoring, and prophylaxis. So what is new? Solid-phase assays for proteinase 3–ANCA and myeloperoxidase (MPO)-ANCA are the preferred initial serologic tests reflecting superior performance when compared to indirect immunofluorescence (cytoplasmic or perinuclear ANCA). There is more discussion on GC dosing as better data have emerged and momentum builds to limit doses. The place of rituximab (RTX) in induction has been extended to relapse prevention; plasma exchange use for refractory vasculitis has decreased; and mycophenolate mofetil (MMF) is an alternative induction option. The use of biomarkers to guide drug dosing during remission maintenance, and the duration of maintenance treatment is reviewed. Areas that have received less attention, and have fewer data, include the delivery of healthcare to patients with vasculitis, patient education and its role in decision making, and the tailoring of drug therapy in older patients.

The key themes influencing the design of induction regimens are the opposing aims of wanting to further reduce steroid exposure while achieving faster and more complete remission. Although the safety profile and 6-month efficacy of RTX is attractive, the slow effect for aggressive presentations demands higher steroid dosing until its therapeutic effect is manifest. This has encouraged combinations of RTX with CYC, which have been shown to require less CYC and, in an observational cohort, to permit GC removal after two weeks6. Both methotrexate and MMF appear in the recommendations as alternative induction agents on the basis of relatively small trials with noninferiority hypotheses and in the presence of conventionally dosed GC. What is less clear from the initial reports is that both are associated with high early relapse rates and subsequent requirement for RTX or CYC.

Despite a histologic classification as a “pauci-immune” vasculitis, in comparison to immune complex disorders such as systemic lupus erythematosus, complement dysregulation occurs in the pathogenesis of AAV8. Lower circulating complement C3 component levels associate with worse outcomes and complement factors, including factor B, C3d, and C5b-9, are present in renal biopsies from patients with AAV9. Attention has focused on complement C5a due to its known role as an anaphylatoxin, its ability to prime neutrophils for ANCA activation, and the abrogation of experimental AAV by C5a receptor blockade10,11. A specific oral inhibitor of the C5a receptor, avacopan, was shown in the phase II CLEAR study to be an alternative induction agent to GC and in the phase III ADVOCATE study to lead to more sustained remissions at 52 weeks, when avacopan with placebo prednisone was compared to a prednisone-tapering regimen12,13. In addition to concom-

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See CanVasc AAV recommendations, page 555
Depleting B cells with RTX is not sufficient to normalize T cell dysregulation and when B cells return, the disease takes off. The therapeutic options being considered include combined treatment with the anti-B cell activating factor monoclonal belimumab, use of more potent anti-CD20, or targeting T cells directly.

Patients with EGPA are more likely to follow a refractory course than those with GPA and microscopic polyangiitis (MPA), and more likely to suffer higher cumulative GC exposure, driven in part by chronic asthma and nasosinus disease. They were excluded from clinical trials of RTX and recommendations have relied on quite old studies from the French Vasculitis Study group (FVSG). The successful testing of the anti-interleukin (IL) 5 monoclonal antibody mepolizumab is directly of benefit to patients and is encouraging development of other anti-IL-5 agents, such as benralizumab (ClinicalTrials.gov: NCT04157348). At the same time, genomic studies have shown that MPO-ANCA is a key biomarker with immunogenetics, the same as that for MPO-ANCA-positive MPA/GPA, whereas polymorphisms of other genes including those relating to eosinophil activation are found in the ANCA-negative subgroup. There appear to be differences in response to RTX between ANCA-positive and -negative EGPA, and possibly better response to anti-IL-5 therapy in the ANCA-negative group. These developments will drive a new classification of EGPA and help guide drug selection for individual patients.

Many older goals of research into AAV are being met: reductions in GC and CYC exposure, managing relapse risk, and better understanding of the immunopathology of vasculitis, particularly, that mediated by ANCA autoantibodies. The disease frequency and phenotypic heterogeneity has been a challenge for clinical investigators and has inspired the development of collaborative networks, such as the FVSG, European Vasculitis Society (EUVAS), Vasculitis Clinical Research Consortium (VCRC), Japan Research Committee for Intractable Vasculitis, and CanVasc; global participation across these networks has supported a sequence of recent studies. The increasing pace of clinical research accelerated by more pharmaceutical company involvement underlines the priority of translating advances to routine practice. Hopefully, this guidelines group will be busy again in another five years.

### Table 1. Factors increasing relapse risk in ANCA-associated vasculitis (GPA and MPA).

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<tr>
<th>Baseline Factors</th>
<th>Factors During Follow-up</th>
<th>Treatment-related Factors</th>
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<tr>
<td>Diagnosis of GPA</td>
<td>History of previous relapse</td>
<td>Lower cumulative cyclophosphamide exposure</td>
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<td>PR3-ANCA</td>
<td>Persisting ANCA-positive after induction</td>
<td>Oral immunosuppressive and/or glucocorticoid withdrawal</td>
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<td>Ear, nose, and throat involvement</td>
<td>Conversion from ANCA-negative to positive or rise in ANCA (especially after RTX)</td>
<td>RTX withdrawal</td>
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<td>Lower serum creatinine</td>
<td>Shorter time to B cell return after RTX</td>
<td>MTX or MMF induction (PR3-ANCA)</td>
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ANCA: antineutrophil cytoplasmic antibody; GPA: granulomatosis with polyangiitis; MMF: mycophenolate mofetil; MPA: microscopic polyangiitis; MTX: methotrexate; PR3: proteinase 3; RTX: rituximab.
REFERENCES