

## **CanVasc Consensus Recommendations for the Management of Antineutrophil Cytoplasm Antibody-associated Vasculitis: 2020 Update**

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My name is Arielle Mendel and I'm an Assistant Professor of Medicine in the Division of Rheumatology at McGill University Health Center. And on behalf of my co-authors today, I'll be taking you through an overview of some important aspects of our recent publication, the 2020 update of the CanVasc consensus recommendations for the management of antineutrophil cytoplasm antibody (ANCA)-associated vasculitis. This was published online in September of 2020 and is in the April 2021 print issue of The Journal.

No funding was received for the making of these recommendations, and I do not have any disclosures. Disclosures from all CanVasc Working Group members are contained within the data supplement 3 of the publication.

So, the Canadian Vasculitis Research Network comprises adult and pediatric rheumatologists, nephrologists, and other specialists from across Canada with expertise in ANCA-associated vasculitis, otherwise known as AAV. And in 2015 CanVasc created recommendations for the management of ANCA-associated vasculitis.

Now the body of literature guiding the management of AAV has grown substantially since then and continues to grow, so we aim to revise and develop new recommendations based on the most current available evidence.

Why is this important to the medical community? Well, ANCA vasculitis is relatively rare but potentially life threatening, and it's a chronic rheumatic disease. And many community physicians including specialists may not have had much clinical exposure to patients with these conditions to feel comfortable with management. So, these recommendations are intended as a resource for all physicians caring for patients with ANCA vasculitis.

We started our work by performing a needs assessment among CANVASC core and associate members where members voted on the most important questions to address in this update.

We then performed an updated literature review directed at these questions and our search strategy is available in data supplement 3.

Based on review and critical appraisal of the literature, we revised existing recommendations and created new draft recommendations.

The draft was subjected to a 2-step modified Delphi consensus procedure whereby the CanVasc Working Group voted on the inclusion and wording of each recommendation in 2 stages.

The draft recommendations were revised at each stage and patients provided suggestions and feedback as well.

In the end, we kept 12 original 2015 recommendations, we created 16 revised recommendations, and 11 new recommendations.

And we used the European Alliance of Associations for Rheumatology (EULAR) criteria to categorize the level of evidence associated with each statement, which was the same grading system used for the 2015 publication.

So now I'll take you through a few of the new and revised recommendations.

We discuss each of the new or revised recommendations in significantly more detail in the full-length version of the recommendations, which is contained within data supplement 1.

And we also discuss items which the working group felt were important forthcoming aspects of ANCA vasculitis management for which formal recommendations could not be made at this stage.

So, this is the very first recommendation and it relates to ANCA testing and we recommend that immunoassays detecting MPO and PR3 ANCA, such as ELISA tests, to be the preferred testing method over indirect immunofluorescence, for example, recording of cANCA and pANCA, and this is due to their superior discriminatory performance in several studies that you can see here.

There is now evidence to allow us to recommend that a reduced dose glucocorticoid tapering protocol can be considered in patients with severe ANCA vasculitis receiving induction with cyclophosphamide (CYC) or rituximab (RTX).

The most important point here is that some tapering regimen should be followed to avoid patients being left on high-dose steroids for an extended period of time unnecessarily, so patients should start to taper within 2 weeks of receiving their first dose of induction treatment.

In the data supplement 2, we actually suggest 2 possible tapering regimens, one closely following the taper used in the RAVE trial in 2010, and the other the reduced dose taper from the PEXIVAS trial.

This is because certain clinical subgroups were underpowered in PEXIVAS to be able to assess the safety and efficacy of this reduce dose taper, for example, those receiving RTX induction. A clinician could choose either one of these regimens, but the importance is to follow one, and you can see that by 4 months, in both cases patients are taking less than 10 mg of prednisone daily.

In terms of choice of induction therapy for organ-threatening disease, there appears to be no difference between RTX and CYC for remission at 6 months, relapse at 12 months, death, or serious adverse events, including infections.

There may be reasons to favor RTX including avoiding the risks of female or male infertility, or premature ovarian failure, and there may be reasons to favor CYC in certain circumstances as well.

In the largest clinical trial ever conducted in ANCA vasculitis, there was no difference in the primary outcome of end-stage renal disease or death between patients receiving or not receiving plasma exchange for severe ANCA vasculitis.

And a Cochrane Metaanalysis found no difference and sustained remission, total adverse events, or death at any time point.

Of note, it found that a 26% increase in the relative risk of serious infections with plasma exchange. Thus, we do not recommend that it be used first-line in patients presenting with severe ANCA vasculitis.

Based on 2 major randomized control trials, it is clear that in both CYC- and RTX-treated patients, relapsing and with new disease, RTX is a superior maintenance agent compared to azathioprine, and thus we recommend it as first-line maintenance. Of note, we recognize RTX is not available for maintenance everywhere in Canada, which will hopefully change soon.

Our recommendations have a section dedicated to eosinophilic granulomatosis with polyangiitis or EGPA.

One of our statements is that mepolizumab add can be a treatment option in nonsevere, steroid-dependent, and relapsing EGPA. Of note, patients with newly diagnosed and or severe EGPA were not included in this main trial for which the recommendation is based.

The working group felt that more data was needed before recommending it as a first-line therapy for newly diagnosed EGPA.

Of note, mepolizumab at this dose is not available to most patients in Canada.

The last recommendation I'll mention is from the monitoring and prevention section of those recommendations, which I encourage readers to review.

We recommend that trimethoprim sulfamethoxazole or Septra prophylaxis be continued in all patients receiving RTX or CYC induction therapy to continue for 3 months after

finishing CYC, and to continue until 6 months has passed since the last RTX dose was received.

Aside from preventing pneumocystis pneumonia, there is data that trimethoprim sulfamethoxazole specifically may reduce all-cause infections and patients receiving RTX maintenance, which is one of the reasons we made this recommendation.

There are of course other indications for specifically PJP prophylaxis, including the use of high-dose corticosteroids.

In summary, we hope our new and revised recommendations will continue to help physicians make therapeutic choices for optimal treatment of patients with ANCA vasculitis, which will minimize relapses, infections, glucocorticoid toxicity, and ultimately, we hope, reducing damage.

Since the initial publication of these recommendations in September 2020, there are already new high impact publications which further promise to change the therapeutic landscape in AAV. We anticipate updating these recommendations, therefore, in the next few years.

As I mentioned, we discussed some of these anticipated changes in the text, especially in the full-length article, which is contained in data supplement 1.

An important next step in Canada will be to evaluate the real-world safety and effectiveness of ANCA vasculitis treatments, including RTX biosimilars as they compare to the originator.

And I'd like to acknowledge all the CanVasc contributors to this publication and recommendations, and a special mention to Dr. Daniel Ennis, Dr. Ellen Go, and Dr. Christian Pagnoux.

I'd also like to thank the Canadian Rheumatology Association Guidelines Committee for their review of our manuscript as well as the patients who are involved in the recommendation development.

Thank you.