ABOUT THE AUTHORS

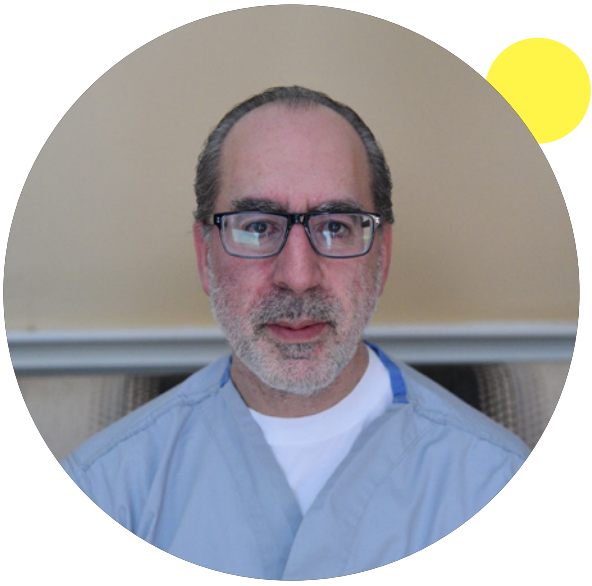
doi.org/10.58931/cait.2023.3251

Mats Junek, MD, MSc, FRCPC

Dr. Mats Junek is a Canadian-Australian Rheumatologist, Vasculitis fellow at McMaster University in Hamilton, Canada, and the Vasculitis Clinical Research Consortium/Vasculitis Foundation Vasculitis Fellow. He is concurrently completing the Clinician Investigator Program and a PhD in health research methods at McMaster. The focus of his research is on improving diagnostic methods, evolving improved treatment strategies, and improving our understanding of relapse across small vessel and large vessel vasculitis.

Affiliations:
Division of Rheumatology, McMaster University, Hamilton, ON
St. Joseph's Healthcare, Hamilton, ON

Nader Khalidi, MD, FRCPC



Dr. Nader Khalidi is currently Professor of Medicine, Division Director, Rheumatology, and the AbbVie Chair in Education in Rheumatology at McMaster University. He has been successfully involved as an investigator in vasculitis clinical research which includes the Diagnostic and Classification in Vasculitis, Oxford (DCVAS) as well as the Plasma Exchange and Glucocorticoids for treatment of ANCA vasculitis (PEXIVAS), and Mepolizumab in the treatment of eGPA (MIRRA).

Affiliations:
Division of Rheumatology, McMaster University, Hamilton, ON
St. Joseph's Healthcare, Hamilton, ON

ANCA-ASSOCIATED VASCULITIS FOR THE ALLERGIST AND IMMUNOLOGIST: A CLINICAL UPDATE

Introduction

The anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides are a group of multisystemic, relapsing, autoimmune diseases that include eosinophilic granulomatosis with polyangiitis (EGPA), granulomatosis with polyangiitis (GPA), and microscopic polyangiitis (MPA). While rare, with incidences between 1 and 25 per 100,000 individuals/year, these are diagnoses that should not be missed, as unrecognized, they are associated with significant morbidity and mortality.[1] Despite their infrequency, international collaborative research has resulted in multiple new therapeutic strategies across all three diseases.

Sinusitis in ANCA-associated Vasculitis

Sixty to sixty-five percent of patients with EGPA or GPA initially present with sinus symptoms.[2,3] EGPA typically presents with years of difficult-to-control, eosinophilic, polypotic rhinosinusitis with nasal polyposis and asthma, often requiring regular oral glucocorticoids in addition to conventional therapy to maintain disease control. Over time, blood eosinophilia becomes apparent, extra-sinopulmonary manifestations (e.g., eosinophilic pneumonia) often occur, and the disease evolves into EGPA with the emergence of vasculitic features that can include cardiomyopathy, gastrointestinal (GI) involvement, vasculitic skin lesions, and/or neuropathy.[1] Given that symptoms can be common to severe eosinophilic sinopulmonary disease, hypereosinophilic syndromes, and EGPA, it can be difficult to confirm the diagnosis if there are no overt vasculitic findings.[4] The 2022 classification criteria for ANCA-associated vasculitides (AAVs) have assisted in this process but require a vasculitis syndrome to first be diagnosed *before* considering EGPA-specific manifestations, and thus only provides limited inroads to this dilemma.[5] In addition to vasculitic manifestations, profound blood eosinophilia and serum ANCAs (typically to myeloperoxidase) can help differentiate EGPA from other diseases.[6] Recently, sputum ANCAs have demonstrated potential in detecting severe airway disease that is evolving into EGPA.[7]

GPA tends to present more acutely over weeks to months. It can initially manifest as rhinosinusitis (with episcleritis/conjunctivitis that mimics allergic disease in 10% of patients), but is often associated with bloody or purulent discharge suggesting infection that is refractory to antibiotics. As the disease progresses, up to 60% of patients will show tell-tale sinus bony destruction, septal perforation, and neo-osteogenesis on imaging.[8] Systemic manifestations that indicate a diagnosis of GPA includes diffuse alveolar hemorrhage and/or nodular lung disease; hematuria and glomerulonephritis; leukocytoclastic vasculitis; and mononeuritis multiplex.[1] ANCAs are seen in 90% of cases of GPA and are typically reactive to serine protease 3 (PR3). In addition to GPA, several other rheumatic diagnoses to consider based on the presence of erosive sinus disease are drug-induced vasculitis, cocaine-induced midline destructive lesions, IgG4-related disease, and relapsing polychondritis.

Updates in the Treatment of GPA and EGPA

The recent publication of the 2021 American College of Rheumatology guidelines for the management of AAV has consolidated treatment approaches.[9]

EGPA

As a disease with overlap of eosinophilic, allergic and vasculitic pathologies, the treatment for EGPA is varied and influenced by the underlying manifestations. Treatment for vasculitic manifestations of EGPA is often stratified by the five-factor score.[10] Patients with a score of zero, including those with refractory sinus symptoms but relatively mild vasculitis, can be treated with azathioprine or methotrexate; those with a score of one or greater can be treated with cyclophosphamide (followed by azathioprine) or, as suggested by forthcoming data from the REOVAS trial, potentially rituximab as well.[9,11] Vasculitic manifestations of EGPA are often responsive to therapy; the eosinophilic and sinopulmonary components have been more difficult to control with these agents and may require chronic, high-dose oral glucocorticoids.[12]This has changed, however, since the realization of the utility of anti-interleukin-5 (IL-5) agents in treating refractory sinopulmonary EGPA. The MIRRA trial demonstrated the efficacy of high- dose mepolizumab (300 mg subcutaneously every four weeks) to control disease and minimize glucocorticoid use in patients with EGPA; 28% of patients on mepolizumab achieved remission on 4 mg of prednisone per day or less at 52 weeks vs 3% of those taking placebo.[13] There were, however, few patients with true vasculitic manifestations; therefore, the use of mepolizumab for manifestations including cardiomyopathy and glomerulonephritis is not clear. Due to access issues, the conventional dose of 100 mg every four weeks has also been tried with some success, however, many patients do not achieve sufficient control with this dose and require either a switch to another anti-IL-5 agent or dose escalation of mepolizumab, with ongoing trials of alternative dosing strategies and agents.[14]

Despite this success, there continues to be a population of patients who have refractory sinopulmonary disease. This is a large driver of patient frustration and morbidity; assessments of health-related quality of life (HRQOL) indicate that sinus symptoms are the most frustrating for patients with EGPA.[12] Dupilumab, effective in managing other asthma and sinus disease, has similarly been found to be effective as either alternative or adjunctive therapy to anti-IL5 agents. The drug itself, however, may be associated with an increased risk of EGPA in patients with isolated sinopulmonary disease and may unmask it in vulnerable patients.[15] It is also important to note that while these drugs lower chronic oral glucocorticoid requirements for refractory EGPA patients, ongoing inhaled and/or intranasal therapy is often needed to achieve adequate disease

control. These parallel vasculitic and eosinophilic treatment strategies for EGPA, and the persistence of sinopulmonary disease, reinforce the heterogeneity of EGPA and the need to better understand both the disease pathogenesis and treatment options.[4]

GPA & MPA

The CYCLOPS, RITUXVAS and RAVE trials have ushered in the modern era of cyclophosphamide and rituximab as induction therapies for severe GPA and MPA. These agents achieve remission in over 90% of patients with these diseases.[16] The MAINRITSAN series, and RITAZAREM and PEXIVAS trials for maintenance therapy have demonstrated that continued treatment with rituximab can also provide durable remission with relapse rates as low as 5% per year, and that we can treat patients with lower doses of glucocorticoids than previously used.[16] Plasma exchange, long heralded as beneficial for diffuse alveolar hemorrhage, renal disease and mortality in AAV was found to have only some efficacy in acute, severe renal disease within the PEXIVAS trial and has shifted practice away from this intervention. Finally, the introduction of avacopan during the ADVOCATE trial has also helped realize the possibility of glucocorticoid-free treatments for AAV; however, its place in the therapeutic regimen is still being established.

In patients with non-severe disease including sinus involvement, methotrexate continues to be recommended. Sinus disease is, however, a source of impaired QOL; the disease is often refractory, requiring rituximab for effective treatment.[17,18] These findings indicate that our current disease construct of severe or non-severe GPA or MPA is limited. Future treatment regimens explore the possibility of shifting from crude indices of severity to a risk-based approach that allows for optimal strategies based on the patient and their disease. Furthermore, fatigue and sinus disease are identified as the largest drivers of ongoing morbidity and represent an area of unmet need that also requires close follow up.

Immune Consequences of Long-term B-cell Depletion in AAV

The diminished humoral response induced by rituximab is important for disease control in AAV, but it is also associated with increased risk of infection and poor vaccine response. While this was a significant concern during the COVID-19 pandemic, it spurred research that quantified that rituximab is associated with a 65% decrease in the capacity to mount an effective COVID vaccine response, and that B-cell recovery takes more than a year to achieve for 60% of patients.[19] As such, vaccinations should ideally be timed to two-to-three weeks prior to re-administration of rituximab. Furthermore, vaccines should be delayed to at least one year (if safely possible) following completion of rituximab therapy.

A second consideration of long-term rituximab administration is irreversible humoral suppression causing hypogammaglobulinemia. This has been found to occur in approximately 15% of patients, and individuals who demonstrate hypogammaglobulinemia following their first dose of rituximab are at higher risk for it at a later point.[20] While this predisposes a patient to recurrent infections, antibodies may have variable functionality, and antibody replacement with intravenous (IV) or subcutaneous immunoglobulins is indicated only for those with multiple infections, who often have IgG levels below 3 g/L.[9]

Conclusion

Multiple advances have been made in the treatment of AAV that have significantly improved outcomes for patients with these rare but potentially devastating diagnoses, although EGPA treatment continues to be a challenge for many patients. As the disease landscape evolves, research has shifted its focus to finding the optimal balance between disease control and therapeutic toxicity, as well as addressing patient-important outcomes such as sinonasal disease and fatigue. As new therapies are adapted from multiple disciplines, ongoing collaboration will be required to continue to improve the standard of care in AAV.

Corresponding Author:
Dr. M. Junek
Email: junekm@mcmaster.ca

Financial Disclosures:
M.J.: None declared
N.K.: Roche, BMS, AbbVie, Otsuka, GSK, Astra Zeneca and Mallincrkordt and Sanofi

References

1. *Kitching AR, Anders HJ, Basu N, Brouwer E, Gordon J, Jayne DR, Kullman J, Lyons PA, Merkel PA, Savage CO, Specks U. ANCA-associated vasculitis. Nature Reviews Disease Primers. 2020 Aug 27;6(1):71.*
2. *Doubelt I, Cuthbertson D, Carette S, Chung SA, Forbess LJ, Khalidi NA, Koening CL, Langford C, McAlear CA, Moreland LW, Monach PA. Clinical manifestations and long-term outcomes of eosinophilic granulomatosis with polyangiitis in North America. ACR Open Rheumatology. 2021 Jun;3(6):404-12.*
3. *Srouji IA, Andrews P, Edwards C, Lund VJ. Patterns of presentation and diagnosis of patients with Wegener's granulomatosis: ENT aspects. The Journal of Laryngology & Otology. 2007 Jul;121(7):653-8.*
4. *Furuta S, Iwamoto T, Nakajima H. Update on eosinophilic granulomatosis with polyangiitis. Allergology International. 2019;68(4):430-6.*
5. *Grayson PC, Ponte C, Suppiah R, Robson JC, Craven A, Judge A, et al. 2022 American College of Rheumatology/European Alliance of Associations for Rheumatology Classification Criteria for Eosinophilic Granulomatosis with Polyangiitis. Ann Rheum Dis. 2022;81(3):309-14.*
6. *Suzuki M, Nakazono A, Morita S, Fukuda A, Honma A, Suzuki T, Kimura S, Nakamaru Y, Homma A. Comparison of clinical characteristics of the nasal manifestations of eosinophilic granulomatosis with polyangiitis (EGPA) and eosinophilic chronic rhinosinusitis (ECRS). Allergology International. 2021;70(1):143-4.*
7. *Mukherjee M, Thomas SR, Radford K, Dvorkin-Gheva A, Davydchenko S, Kjarsgaard M, Svenningsen S, Almas S, Felix LC, Stearns J, Li QZ. Sputum antineutrophil cytoplasmic antibodies in serum antineutrophil cytoplasmic antibody-negative eosinophilic granulomatosis with polyangiitis. American Journal of Respiratory and Critical Care Medicine. 2019 Jan 15;199(2):158-70.*
8. *D'Anza B, Langford CA, Sindwani R. Sinonasal imaging findings in granulomatosis with polyangiitis (Wegener granulomatosis): A systematic review. American Journal of Rhinology & Allergy. 2017 Jan;31(1):16-21.*
9. *Chung SA, Langford CA, Maz M, Abril A, Gorelik M, Guyatt G, et al. 2021 American College of Rheumatology/Vasculitis Foundation Guideline for the Management of Antineutrophil Cytoplasmic Antibody-Associated Vasculitis. Arthritis Rheumatol. 2021;73(8):1366-83.*
10. *Guillevin L, Lhote F, Gayraud M, Cohen P, Jarrousse B, Lortholary O, Thibult N, Casassus P. Prognostic factors in polyarteritis nodosa and Churg-Strauss syndrome a prospective study in 342 patients. Medicine. 1996 Jan 1;75(1):17-28.*
11. *Dutertre M, Pugnet G, De Moreuil C, Bonnotte B, Benhamou Y, Chauveau D, Diot E, Duffau P, Limal N, Néel A, Urbansky G. Efficacité à long terme des schémas d'induction de la rémission au cours de la granulomatose éosinophilique avec polyangéite: résultats de l'essai REOVAS. La Revue de Médecine Interne. 2022 Dec 1;43:A375-6.*
12. *Latorre M, Baldini C, Seccia V, Pepe P, Novelli F, Celi A, Bacci E, Cianchetti S, Dente FL, Bombardieri S, Paggiaro P. Asthma control and airway inflammation in patients with eosinophilic granulomatosis with polyangiitis. The Journal of Allergy and Clinical Immunology: In Practice. 2016 May 1;4(3):512-9.*
13. *Wechsler ME, Akuthota P, Jayne D, Khoury P, Klion A, Langford CA, et al. Mepolizumab or Placebo for Eosinophilic Granulomatosis with Polyangiitis. N Engl J Med. 2017;376(20):1921-32.*
14. *Detoraki A, Tremante E, Poto R, Morelli E, Quaremba G, Granata F, et al. Real-life evidence of low-dose mepolizumab efficacy in EGPA: a case series. Respir Res. 2021;22(1):185.*
15. *Anai M, Yoshida C, Ozono K, Furukawa H, Ishimaru Y, Sakata S, Saruwatari K, Muramoto K, Tomita Y, Saeki S, Ichiyasu H. Successful concomitant therapy with mepolizumab and dupilumab for atypical eosinophilic granulomatosis with polyangiitis. Allergology International. 2022;71(2):259-61.*
16. *Krishnan A, Walsh M, Collister D. Management of antineutrophil cytoplasmic antibody-associated vasculitis: a changing tide. Current Opinion in Nephrology and Hypertension. 2023 May 1;32(3):278-83.*
17. *Lally L, Lebovics RS, Huang WT, Spiera RF. Effectiveness of rituximab for the otolaryngologic manifestations of granulomatosis with polyangiitis (Wegener's). Arthritis Care & Research. 2014 Sep;66(9):1403-9.*
18. *Cazzador D, Padoan R, Colangeli R, Pendolino AL, Felicetti M, Zanoletti E, Emanuelli E, Martini A, Doria A, Nicolai P, Schiavon F. Health-related quality of life in patients with anca-associated vasculitis and sinonasal involvement: a single-center cross-sectional study. JCR: Journal of Clinical Rheumatology. 2022 Jan 1;28(1):e89-94.*
19. *Moor MB, Suter-Riniker F, Horn MP, Aeberli D, Amsler J, Möller B, Njue LM, Medri C, Angelillo-Scherrer A, Borradori L, Radonjic-Hoesli S. Humoral and cellular responses to mRNA vaccines against SARS-CoV-2 in patients with a history of CD20 B-cell-depleting therapy (RituxiVac): an investigator-initiated, single-centre, open-label study. The Lancet Rheumatology. 2021 Nov 1;3(11):e789-97.*
20. *Roberts DM, Jones RB, Smith RM, Alberici F, Kumaratne DS, Burns S, Jayne DR. Immunoglobulin G replacement for the treatment of infective complications of rituximab-associated hypogammaglobulinemia in autoimmune disease: a case series. Journal of Autoimmunity. 2015 Feb 1;57:24-9.*

Clinical use not mentioned elsewhere in the piece

RINVOQ should not be used in combination with other Janus kinase (JAK) inhibitors, immunomodulating biologics (e.g., biologic DMARDs), or with potent immunosuppressants such as azathioprine and cyclosporine.

Pediatrics: The safety and efficacy of RINVOQ in adolescents weighing <40 kg and in children aged 0 to less than 12 years with atopic dermatitis have not yet been established. No data are available; therefore, RINVOQ should not be used in this pediatric patient population.

Geriatrics (≥65 years of age): Caution should be used when treating geriatric patients with RINVOQ.

Most serious warnings and precautions

Serious infections: Patients treated with RINVOQ are at increased risk for developing serious infections that may lead to hospitalization or death. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids. If a serious infection develops, interrupt RINVOQ until the infection is controlled. Reported infections include active tuberculosis (TB), which may present with pulmonary or extrapulmonary disease; invasive fungal infections, including cryptococcosis and pneumocystosis; and bacterial, viral (including herpes zoster), and other infections due to opportunistic pathogens. Test patients for latent TB before RINVOQ use and during therapy. Consider treatment for latent infection prior to RINVOQ use. Do not initiate treatment in patients with active infections including chronic or localized infections. Carefully consider the risks and benefits of treatment prior to initiating therapy in patients with chronic or recurrent infections. Closely monitor patients for signs and symptoms of infection during and after treatment, including the possible development of TB in patients who tested negative for latent infection prior to initiating therapy.

Malignancies: Lymphoma and other malignancies have been observed in patients treated with RINVOQ. An increase in malignancies, including lung cancer, were observed in RA patients ≥50 years with at least one additional cardiovascular (CV) risk factor who were taking a different JAK inhibitor, compared with tumour necrosis factor (TNF) inhibitors. Caution should be applied when using RINVOQ in geriatric patients, patients who are current or past smokers, and patients with other malignancy risk factors.

Thrombosis: Thrombosis, including deep venous thrombosis, pulmonary embolism, and arterial thrombosis, have occurred in patients treated with JAK inhibitors, including RINVOQ, for inflammatory conditions. Many of these adverse events were serious and some resulted in death. RA patients ≥50 years with ≥1 additional CV risk factor had a higher rate of all-cause mortality and thrombosis, including pulmonary embolism, deep venous thrombosis, and arterial thrombosis in a clinical trial with a different JAK inhibitor compared to TNF inhibitors. Consider the risks and benefits prior to treating patients who may be at increased risk for thrombosis. Discontinue RINVOQ and promptly evaluate patients with symptoms of thrombosis.

Major adverse cardiovascular events: Major adverse CV events, including non-fatal myocardial infarction, were observed more frequently in RA patients ≥50 years with ≥1 additional CV risk factor in a clinical trial with a different JAK inhibitor compared to TNF inhibitors. Caution should be applied when using RINVOQ in geriatric patients, patients who are current or past smokers, and patients with other CV risk factors.

Other relevant warnings and precautions

- Increases in lipid parameters, including total, low-density lipoprotein, and high-density lipoprotein cholesterol
- Gastrointestinal perforations
- Hematologic events
- Liver enzyme elevation
- Patients with severe hepatic impairment
- Concomitant use with other potent immunosuppressants, biologic DMARDs, or other JAK inhibitors
- Immunizations
- Viral reactivation, including herpes (e.g., herpes zoster) and hepatitis B
- Malignancies, including dose-related NMSC
- Increases in creatine phosphokinase
- Monitoring and laboratory tests
- Pregnant women
- Reproductive health
- Breast-feeding
- Geriatrics (≥65 years of age)
- Pediatrics (<12 years of age)
- Asian patients

For more information

Please consult the Product Monograph at rinvoq.ca/pm for important information relating to adverse reactions, drug interactions, and dosing information which have not been discussed in this piece. The Product Monograph is also available by calling us at 1-888-704-8271.

RINVOQ® upadacitinib