# Celebrating progress in the vasculitides, old and new

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For more on the **International Vasculitis Workshop** see https://vasculitis-barcelona2024.com

For more on the **Fifth International Symposium on IgG4-related Disease** see https://igg4rdmilan2024.com

Ahead of the 21st International Vasculitis Workshop and the Fifth International Symposium on IgG4-related Disease, *The Lancet Rheumatology* celebrates progress in research on the vasculitides by publishing a Series of detailed reviews on three major forms: antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis, giant cell arteritis, and IgG4-related disease. We mark the occasion with two complementary Series reviews on each of these conditions. All three forms of vasculitis have witnessed substantial steps forward over the past twenty years in treatment, diagnosis, or both. Indeed, IgG4-related disease was recognised as a unique autoimmune disease barely twenty years ago and not classified properly as a variable-vessel vasculitis until last year.[1]

We split each form of vasculitis into two papers for the following reasons. First, all three diseases can be regarded as pathophysiological spectra that are polarised. Thus, anti-proteinase 3 (PR3) ANCA-associated vasculitis resides at one end of the disease spectrum and anti-myeloperoxidase (MPO) ANCA-associated vasculitis at the other.[2,3] Similarly, cranial giant cell arteritis and large-vessel giant cell arteritis occupy the two ends of the giant cell arteritis spectrum,[4,5] and proliferative as opposed to fibrotic IgG4-related disease claim comparable spaces in IgG4-related disease.[6,7]

It is important to acknowledge that for all three diseases, the spectra are marked by substantial overlap in the middle. For example, both PR3-ANCA-associated vasculitis and MPO-ANCA-associated vasculitis involve the alveolar capillaries, renal glomeruli, the skin, and peripheral nerves in ways that are essentially identical. Furthermore, a high proportion of patients with cranial giant cell arteritis could be shown to have large-vessel disease if appropriate imaging studies are done. In addition, evidence of fibrosis is present in all forms of IgG4-related disease by the time the disease is recognised, regardless of whether a patient is identified as belonging to the proliferative subset or the fibrotic subset.

Second, knowledge of these diseases has expanded so much over the past two decades that it is challenging to address the topics of ANCA-associated vasculitis, giant cell arteritis, or IgG4-related disease within a single monograph without omitting important disease aspects, including some of the subtleties that make these diseases so challenging and fascinating.

It is controversial and therefore interesting to consider whether the polar ends of these disease spectra will be regarded over time as separate diseases altogether. Currently, the strongest case for separate diseases is in ANCA-associated vasculitis. Detailed studies of potential genetic risk factors and cytokine profiles in PR3-ANCA-associated vasculitis as opposed to MPO-ANCA-associated vasculitis have identified important differences between these diagnoses.[2] In addition, outcome studies have consistently reported greater likelihoods for disease flares among patients with PR3-ANCA-associated vasculitis and documented the greater risk of advanced renal dysfunction at the time of presentation in patients with MPO-ANCA-associated vasculitis.[8] Yet, the understanding of ANCA-associated vasculitis is still not sufficiently nuanced to suggest different therapeutic approaches for these two conditions. Only time will tell if future scientific discoveries and emerging treatment options will favour such treatment strategies in ANCA-associated vasculitis.

With regard to giant cell arteritis, the revolution in cross-sectional and vascular imaging techniques has led to substantial growth in the awareness of large-vessel disease, even in patients whose symptom complexes suggest only cranial involvement.[9] Conversely, temporal artery biopsies or detailed ultrasound studies in patients who present with large-vessel disease manifestations alone frequently confirm the simultaneous presence of disease within cranial vessels—despite the absence of symptoms anticipated to accompany cranial disease.[10] It remains unclear whether patients with large-vessel giant cell arteritis have disease that is more refractory to therapy than cranial giant cell arteritis, partly because the classification of patients as having one form or another is generally suboptimal—ie, it is not inclusive of either sufficient vascular imaging or biopsy sampling to classify patients accurately into one giant cell arteritis subset or the other (or to confirm unequivocal overlap). More comprehensive imaging studies that permit even greater resolution could ultimately shed important light on this question. In the meantime, however, it is useful to discuss the two ends of this disease spectrum

separately to address the nuances that characterise each subset, even while acknowledging that considerable overlap and clinical variability exist regarding the vascular distributions of giant cell arteritis.

Finally, it has become clear that, regarding the spectrum of blood vessels affected, IgG4-related disease is among the most diverse forms of recognised vasculitis. At the microscopic level, IgG4-related disease has long been known to cause obliterative phlebitis, a manifestation of a small-vessel vasculitis. At the macroscopic level, IgG4-related disease is an important cause of aortitis, the classic example of a large-vessel vasculitis. Indeed, IgG4-related disease can affect blood vessels of essentially any size on either the venous or the arterial side of the circulation, including the frequently dramatic yet underappreciated involvement of the coronary arteries, a manifestation of medium-vessel vasculitis.[1] IgG4-related disease is therefore classified most precisely within the Chapel Hill Consensus Nomenclature as a variable-vessel vasculitis,[11] joining Behçet's disease and Cogan's disease in this category. IgG4-related disease also involves a substantial degree of parenchymal disease that is clearly not vasculitic in nature—another striking way in which IgG4-related disease resembles granulomatosis with polyangiitis.

Two polar ends of IgG4-related disease have also become apparent.[12] In the proliferative subset, patients typically present with multi-organ disease and high serological biomarkers of disease activity. Moreover, such patients typically show impressive (if unsustained) responses to therapies such as glucocorticoids and B-cell depletion. In contrast, patients with the fibrotic subset of IgG4-related disease (typified by retroperitoneal fibrosis) are more likely to present with less extensive disease, to have lower degrees of serological activity, and to show less obvious responses to current therapies. Nevertheless, overlap of these two perceived ends of the disease spectrum is commonly observed. Patients with proliferative IgG4-related disease might be discovered to have retroperitoneal fibrosis even while manifesting certain classic proliferative disease features such as the so-called Mikulicz disease—the simultaneous involvement of the lacrimal, submandibular, and parotid glands[6]—or type 2 IgG4-related autoimmune pancreatitis. Future studies that strive to detail the pathophysiology of IgG4-related disease in a comprehensive manner will need to offer explanations for the evolution of these subsets.

These three disease spectra share two additional features: namely, the potential for causing enormous damage, and the ongoing search for treatments that lead to more than just temporary remissions. All three of these vasculitides are associated with major disease-related morbidity. In many cases, the prevention of disease-related damage depends more upon clinical acumen and swift diagnosis than the availability of effective therapies. Patients with ANCA-associated-vasculitis are still far too likely to incur irreversible renal damage before diagnosis.[8] Most vision loss in giant cell arteritis occurs not after the start of treatment but before the diagnosis is even established. Vision loss is frequently the event that brings the patient to medical attention.[4] And in IgG4-related disease, there remains a disturbingly high proportion of patients who have permanent pancreatic injury even before the diagnosis has been given a name, leading to diabetes, exocrine pancreatic failure, or both.[6]

Finally, none of these diseases are cured by the treatment approaches available now. If begun early enough, current therapies can drive these diseases into remission with a reasonably high degree of certainty. Yet no treatment yields reliably sustained disease remission without ongoing remission maintenance therapy, and glucocorticoids still play a far too prominent role in the treatment of all three. The achievement of both elusive aims—disease recognition before the occurrence of irreversible organ injury and the establishment of permanent remissions (also known as cures)—will require collaborations between astute clinicians and creative scientists who work together with a razor-like focus. It is precisely those types of clinicians and scientists that these Series papers are intended to inspire.

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