Vasculitis: Again, Changing the Standard of Care

> If you do not know history . . . you are a leaf that does not know it is part of a tree.
>
> –Michael Crichton

The history of medicine was first marked by descriptive accounts of illness–without meaningful therapeutic interventions–followed by empiric treatment, prospective observational studies, and finally controlled trials. Rare diseases have had a painfully slower progression through these stages. For noninfectious systemic vasculitides, the last stage of this journey was not achieved until the 1990s. Before 1970, we had little understanding of vasculitis etiology or why certain vasculitides favored particular organs and spared others, why some damaged only a single site, why some targeted parenchyma in addition to vessels, and why others were associated with autoimmune diseases. We since have learned that vessels are not merely conduits; they are uniquely specialized to serve each organ (1). Vessels also have territorially unique immunologic characteristics (2). These observations emphasize that characterization of vasculitides on the basis of vessel size and features of inflammatory infiltrates, although diagnostically useful, is also superficial. Still, our understanding of organ targeting remains deficient.

The early period of therapeutics was similarly uninformed. The anti-inflammatory and immunosuppressive actions of corticosteroids led to their use in vasculitis. Relapsing disease came to be an expected outcome with corticosteroid tapering, made necessary by profound morbidity accompanying long-term therapy. Corticosteroids had variable initial benefit in granulomatosis with polyangiitis (GPA), extending mean survival from only around 5 months to 12.5 months. The stage was set for new interventions. Anecdotal reports of improvement of GPA with use of cytotoxic agents encouraged Fauci and Wolff (3) to undertake observational trials of daily cyclophosphamide plus corticosteroids. The results exceeded expectations; among 15 patients who received adequate courses of treatment, 13 achieved remission. Long-term studies of larger cohorts that used cyclophosphamide for at least 1 year after induction of remission confirmed efficacy, even in immediately life-threatening circumstances. However, also noted were high relapse rates (50%) as well as severe disease–induced and irreversible cyclophosphamide-induced morbidity (such as cancer, myelodysplasia, and infertility) (4).

The 1990s brought general acceptance of the diagnosis of microscopic polyangiitis (MPA), previously lumped together with polyarteritis nodosa. This disorder was recognized as vasculitis affecting small and, less often, medium-sized vessels; glomerulonephritis was common and often associated with pulmonary capillaritis. Microscopic polyangiitis was noted to be clinically distinct from GPA, because it is not associated with granuloma formation, upper airway destruction, tubular airway injury, or mass lesions. Like untreated GPA, MPA often was rapidly fatal in the setting of pulmonary–renal syndrome (5). Cyclophosphamide–corticosteroid treatment in patients with MPA was usually life saving. In time, both GPA and MPA were found to be associated with antineutrophil cytoplasmic antibodies (ANCAs); patients with MPA mostly have antibodies to myeloperoxidase, whereas those with GPA usually have antibodies to proteinase-3. Thus, although MPA and GPA are similar in their production of life-threatening vasculitic injury, their ANCA associations, and their response to cyclophosphamide–corticosteroid therapy, they differ in phenotype and ANCA antigen target. Distinct genetic associations (6) also raised questions about whether patients with GPA and those with MPA should be combined in clinical trials without subset analyses.

Long-term data revealed dangers of treating any form of vasculitis with long-term cyclophosphamide. An unmet need to discover safer therapies required larger patient cohorts, which could be accomplished only by collaborative networks. Indeed, network formation has been among the most important breakthroughs in this field. Extensive collaborations emerged in the United States, France, Italy, and throughout Europe (**Supplement Table**, available at Annals.org). The resulting opportunities led to enhanced funding; investigation of surrogate markers of disease activity, pathogenesis, outcomes, genetic associations, and socioeconomic impact; collaborations with patient support groups; and fellowship programs. Network development was an iterative process that required up to 10 years from inception to produce controlled trials.

Network studies taught us that short courses of cyclophosphamide, followed by methotrexate, azathioprine, or mycophenolate mofetil, to induce and maintain remission were all variably effective. Long-term use of cyclophosphamide, with its many side effects and sometimes life-threatening complications, could be avoided. However, within each protocol, relapses became more frequent with drug tapering or discontinuation.

Elimination of cytotoxic therapies was made possible by the emergence of rituximab, a B-cell–depleting, anti-CD20 monoclonal antibody with demonstrated effectiveness in rheumatoid arthritis and non-Hodgkin lymphoma. Although many facets of the immune response are engaged in ANCA-associated vasculitis, it was hoped that dramatically reducing B cells would be efficacious. Perhaps because rituximab-mediated B-cell depletion also affects pathways beyond the primary target, rituximab demonstrated effectiveness similar to that of cyclophosphamide (7–9). However, as with other protocols, relapses occurred after rituximab discontinuation.

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As reported in *Annals*, the French Vasculitis Study Group has extended earlier trials of MAINRITSAN (Maintenance of Remission Using Rituximab in Systemic ANCA-Associated Vasculitis) for a total of 36 months (10). Ninety-seven patients who had already completed MAINRITSAN2 and were in remission were randomly assigned again, this time to receive infusions with either rituximab or placebo every 6 months. Relapse-free survival was clearly superior with rituximab (96%) versus placebo (74%). In addition, 6 patients in the placebo group had major relapses, which did not occur in the rituximab group. Major relapses were treated with high-dose corticosteroids and rituximab, and all 6 patients achieved remission. As the authors note, results must be viewed in the context of patient status at enrollment: Patients were in remission, did not require high-dose corticosteroids, and had tolerated rituximab well in MAINRITSAN2.

The authors make a convincing argument that long-term rituximab should be the standard of care for ANCA-associated vasculitis. However, an unanswered question is, how long should long-term treatment continue in any patient? Even in this relatively well population, rituximab therapy was not without some serious adverse events. Certainly, for patients in whom relapses are likely to cause profound disability or death, extreme caution is advised before discontinuing any form of successful, well-tolerated therapy. However, for lower-risk patients, what are the risk–benefit properties of preemptive rituximab treatment versus cautious monitoring for and treatment of early signs of relapse? What distinguishes patients who enjoy extended periods of remission after stopping rituximab treatment (74% of the MAINRITSAN3 control group) versus those who have a relapse within 6 to 12 months of stopping rituximab therapy? Given that ANCA metrics and B-cell reconstitution are not reliable predictors of imminent relapse, what other surrogate markers might guide preemptive treatment?

This has been an extraordinary era for vasculitis. Networks have made studies like MAINRITSAN possible and have brought us closer to answering these and many other questions.

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