

Part 1: The need for novel treatment regimens for ANCA-associated vasculitis

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The last 30 years has seen remarkable progress in the treatment of Wegener's granulomatosis and microscopic polyangiitis [hereafter also referred to collectively as ANCA-Associated Vasculitis (AAV)]. Untreated, these diseases lead to markedly increased morbidity and mortality. Modern treatments have substantially changed the clinical outcome for many patients with AAV (1, 2). Nonetheless, death still occurs from disease manifestations such as alveolar hemorrhage and from infectious complications of therapy. Furthermore, the long-term cumulative damage from AAV can be substantial, including end-stage renal disease, upper airway destruction, permanent neuropathy, relapsing or persisting disease, low quality of life, and many other problems.

The major advance in therapy for AAV came with the introduction of treatment with cyclophosphamide in combination with high-dose glucocorticoids (1, 3, 4). The concept of treating vasculitis with "chemotherapy" was novel and so clearly more effective than prior treatment with glucocorticoids alone that demonstration of the efficacy of the cyclophosphamide-based regimen did not require a randomized trial or even a contemporary control group. Similarly, the initial studies of methotrexate as an alternative to cyclophosphamide for induction of remission for selected patients with Wegener's granulomatosis were uncontrolled cohort studies (5). These studies were followed by the introduction of other cyclophosphamide-sparing treatment regimens that include azathioprine or mycophenolate (6-9). Cyclophosphamide, methotrexate, azathioprine, and glucocorticoids are now all considered to have well-proven and effective roles in the treatment of AAV.

More recent progress in the development and adoption of new treatment regimens for AAV has resulted from several important factors occurring over the same 10-year period, including: i) development of validated outcome tools and design methods for clinical trials in AAV (10-12); ii) standardized disease classifications (13-15) for use in clinical research and incorporation of ANCA testing to aid in diagnosis; iii) formation of networks of

vasculitis centers that combine efforts on clinical trials (16, 17); iv) successful conduct of major, multi-center, randomized, controlled trials (6, 17, 18); v) availability of a wide variety of newly introduced immunosuppressive agents, including so-called "biologic" drugs; and vi) vastly expanded funding opportunities for clinical trials in vasculitis from multiple sources including the US National Institutes of Health (NIH), the European Union, international professional Rheumatology societies, and both traditional pharmaceutical and biotechnology companies. These factors have not arisen independently and have been synergistically beneficial to the field of vasculitis clinical research. Despite the great advances in the treatment of AAV and progress in the design and implementation of clinical trials in AAV, there remain many unmet needs that only new research and novel therapies will be able to adequately address. These unmet needs are often overlapping and include:

- *Less toxic treatment regimens.* The acute and cumulative toxicities of drugs currently used prescribed for AAV are substantial, especially the marrow suppressive and carcinogenic effects of cyclophosphamide and the many side effects of glucocorticoids (19, 20). Furthermore, many of these drugs are teratogenic, cause gonadal failure, or cause gestational complications; the need for safe treatment regimens for women during their childbearing years is urgent.
- *Prevention of relapse.* Relapse remains the norm for AAV, even after achievement of full clinical remission (1, 2, 20, 21). There is a need to find additional alternative drugs and/or dosing regimens for maintenance of remission in AAV.
- *Treatment of chronic, mild-moderate level disease.* Patients in such states are often referred to as having chronic active, persistent, or grumbling disease. Although such disease activity is not immediately life or organ-threatening, it can result in significant reduction in a patient's quality of life and result in cumulative disease and treatment-related damage, especially from chronic use of moderate doses of glucocorti-

coids. Clinical trials in AAV to date have not particularly focused on this segment of the patient population; however, as safer agents are introduced for AAV, then perhaps effective chronic treatment regimens will be better defined.

- *Treatment of exceptionally "resistant" cases.* Some patients are intolerant of, or unresponsive to, all currently available treatment agents for AAV or require unacceptably prolonged courses of cyclophosphamide and/or glucocorticoids. Such patients are in dire need of alternative therapies to avoid death from their vasculitis or from toxicities of therapy. Novel therapies are frequently given to such subjects in small early-phase trials (22-24); however the lack of efficacy of a treatment among such cases may not necessarily indicate the drug has no role in the treatment of AAV.

- *Further advances in non-drug therapy.* Patients with AAV require treatment of both disease-related active disease and disease-related damage through non-drug treatments. Although progress has been made in these areas of treatment, much still needs to be done. For example, sub-glottic disease is an often devastating problem in Wegener's granulomatosis; a treatment protocol involving tracheal/sub-glottic local dilation and local administration of glucocorticoids is successful in improving and retaining a good airway in many, but not all patients (25). Similarly, destructive sinonasal and retroorbital disease can be approached surgically but much better preventive therapy and post-damage options are urgently needed. Patients with AAV and end-stage renal disease are routinely considered for renal transplantation but may face logistic hurdles; better understanding of management of transplantation in patients with AAV is needed.

This Symposium report outlines the current status of the development of novel therapies for AAV. There is great excitement about the potential for B-cell depletion to treat a wide variety of autoimmune diseases and Part 2 of this report describes the theoretical, labora-

tory, and clinical evidence supporting the testing of B-cell depleting therapy for AAV. Similarly, the potential to alter the immune response in AAV by newer types of anti-proliferative drugs, other powerful immunosuppressive agents, and biologics other than B-cell depleting drugs are discussed in Part 3.

The outcome of studies of these novel agents will have importance not only for the treatment of Wegener's granulomatosis and microscopic polyangiitis, but also for the insight they will provide into the pathophysiology of these diseases. Furthermore, the impact of the study of new therapies for AAV will influence the treatment of other forms of vasculitis and, quite possibly, other autoimmune diseases. Patients, researchers and clinicians eagerly await results of studies using these novel treatments.

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