

New Therapeutic Approaches to Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitides: Looking at Tomorrow

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Almost 50 years have passed since the addition of cyclophosphamide to steroids, which became established as the main therapeutic regimen for patients with small vessels vasculitides. This derived mainly from the contribution of Fauci et al. who had amassed considerable clinical and therapeutic experience in the early 1970s [1,2]. This approach has represented the standard therapy for small vessels vasculitides for more than two decades, at least until the first randomized trial performed by the European Vasculitis Study Group in 2003 [3], when reducing the cumulative dosage of cyclophosphamide, via a switching therapy schedule with azathioprine or methotrexate, was proposed as maintenance therapy after the induction of disease remission. This option was then supported by further evidence over the years [4].

More recently, the introduction of B cell-targeted therapy has undoubtedly been one of the major breakthroughs in the management of these disorders, defined more precisely today as antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitides (AAV). A substantial equivalence between the anti-CD20 monoclonal antibody rituximab and the standard immunosuppressive therapy for the induction of complete remission was shown by the RAVE-ITN trial in 2010 [5]. Nonetheless, the rates of relapse have not been markedly improved by the use of rituximab induction [6], and

the maintenance of remission is still one of the most intriguing therapeutic challenges in the field of AAV.

The latest evidence dates back to last November, when Guillevin and team [7] reported the superiority of repeated doses of rituximab for AAV relapse prevention as compared with azathioprine during a total follow-up period of 28 months. However, as observed by Jayne in his editorial in the same issue of the *New England Journal of Medicine* [8], “the duration of the follow-up after the last dose of rituximab was short [...] thus, the problem of longer term relapse risk and the need for further observation and therapy remain,” as does the problem of the high incidence of rituximab-related severe adverse events [8].

Despite the expansion of the therapeutic armamentarium, the issue of severe side effects related to the above therapies indeed remains a pivotal point, together with the difficulty in restoring, or preserving in the long term, the renal function of affected patients [9]. In addition, the relapse rate within 5 years of the diagnosis of AAV is still very high, especially in patients with proteinase 3 (PR3)-AAV [9].

Therefore, the challenges in the approach to AAV are focused on identifying new therapeutic targets, which eventually will be better tolerated and more specific. Furthermore, new insight into AAV pathogenesis might be useful to identify additional disease markers in order to improve monitoring of the disease and prediction of relapse [9].

What about future research directions for AAV therapies? Although the role of B cells in AAV has not been completely elucidated, and given the evidence of the impressive efficacy of rituximab in AAV, it has been postulated that other B cell tar-

gets could be potential therapeutic alternatives in AAV management. Ofatumumab, a novel anti-CD20 monoclonal antibody, has shown a potent ability in binding CD20, leading to greater complement-dependent cytotoxicity [10]. Epratuzumab, the anti-CD22 monoclonal antibody that acts as an immunomodulatory agent by inducing B cell anergy, has been tested in systemic lupus erythematosus (SLE) and might be a potential option in some AAV cases [11]. Belimumab, the anti-BAFF monoclonal antibody approved for SLE, is currently under investigation as another option for preventing AAV relapse (ClinicalTrials.gov No NCT01663623).

Furthermore, the contribution of the alternative complement pathway in the pathogenesis of AAV has been investigated intensely in recent years, despite the fact that AAV are usually considered pauci-immune diseases in which immune complex and complement deposition are typically absent or scarce [12]. Alternative pathway activation has been related to different neutrophil-mediated diseases, including AAV, but the exact mechanisms through which this pathway and the neutrophils interact remain largely unstudied.

Xiao et al. [13] were the first to suggest a critical role for complement in the induction of necrotizing crescentic glomerulonephritis through their mouse model of ANCA disease. The authors transferred anti-MPO antibodies, induced in MPO-deficient mice, into wild-type mice, thus determining crescentic glomerulonephritis. When the recipient mice were deficient in complement C5 or factor B, they did not develop the disease; on the contrary, glomerulonephritis was detected in the same animal models when they were deficient in

C4, a factor of the classical and mannose-binding lectin pathways of complement. The same group also showed that pretreating mice with C5-inhibiting monoclonal antibody prevented the development of renal damage.

In 2009 Xing et al. [14] detected several components of the alternative pathway, such as factor B, factor P (properdin), C3d and the membrane attack complex in glomeruli and in small blood vessels of kidney biopsy specimens from AAV patients. The levels of C5a, a cleavage product of complement C5 with anaphylatoxic and chemotactic features, which is responsible for the amplification of the inflammatory response and represents the final event in the activation of that pathway, were then found by Yuan et al. [15] to be elevated in active AAV in patients' plasma and urine. The authors later demonstrated the alternative pathway activation in the circulation of a larger population of patients with active AAV and confirmed the strong increase in plasma levels of C5a, as compared with inactive AAV patients [16].

The rationale for inhibiting C5a underlies the ongoing phase 2 trial (CLEAR; ClinicalTrials.gov No NCT01363388), which is investigating the role of CCX168, a novel orally administered small molecule inhibitor of C5a receptor (C5aR), in patients with AAV [17].

In the present issue of this journal, Ballanti and colleagues [18] pointed their attention to the complement system as a potential target for novel therapeutic approaches to small-medium vessel vasculitides. The authors reviewed the contribution of complement system in the pathogenesis of such diseases and discussed the rationale of blocking the alternative complement pathway, which participates in several innate and adaptive immune functions. Intriguingly, it has been observed that ANCA-activated neutrophils themselves release factors that might contribute to the activation of complement system [13]. Myeloperoxidase (MPO) has been shown to mediate the alternative pathway-induced C3 deposition in some models [19]. There is evidence that properdin, present in secondary neutrophil

granules, is instrumental in determining this event because it can directly interact with neutrophil components, namely MPO, but also with proteinase 3 (PR3), elastase and cathepsin G. Properdin is the only known 'positive regulator' in the complement system that acts as initiator of the alternative complement pathway after neutrophil degranulation. Given its 'pattern recognition' capability, properdin might represent another potential target to be investigated in the near future [19]. However, given the role of the alternative pathway and particularly of properdin pivotal in maintaining health, there is concern about possible side effects related to this approach. Clearly, discovering further details of the pathophysiological mechanisms of AAV will set the basis for a wider spectrum of potential therapeutic targets.

The growing knowledge of innate immunity mechanisms coming from basic research – not least the release of neutrophil extracellular traps (NETs), a process referred to as 'NETosis' in the course of AAV – will certainly open new perspectives on these devastating diseases whose biological mechanisms still represent a fascinating and stimulating conundrum. Finally, due to the rarity of AAV conditions, they represent a prime example of a research area that might take advantage of international research cooperation programs, given the limited number of patients, the fragmentation of research itself, and the lack of widespread expertise in such a field. For all these reasons, multicenter studies and clinical trials are crucial to confirm the preliminary evidence and to orientate both basic and clinical research [20].

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