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Review

# B-cell depleting agents for ANCA vasculitides: A new therapeutic approach

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ABSTRACT

Vasculitides associated with anti-neutrophil cytoplasmic antibody (ANCA) serum positivity affecting small and medium-sized vessels are defined as ANCA-associated vasculitis (AAV). Glomerulonephritis in AAV is characterized by focal necrosis, crescent formation, and few or no immunoglobulin deposits. In vitro and animal evidence suggests that ANCA play a pathogenic role in AAV. Specific gene expression signatures are reported to predict long-term prognosis in AAV, suggesting the possibility of individualizing therapy and identifying new therapeutic targets. Although immunosuppressants and glucocorticoids are the cornerstone of AAV therapy, results from two recent randomized controlled trials have shown the non-inferiority of rituximab, compared with cyclophosphamide, for the induction of remission in patients with severe AAV. In fact, in April 2011, the US Food and Drug Administration (FDA) approved rituximab, combined with glucocorticoids, as a front-line therapy for adult patients with granulomatosis with polyangiitis (GPA; Wegener's granulomatosis) or microscopic polyangiitis. This new indication for rituximab provided the first ever FDA-approved therapy for these two diseases and the first alternative to cyclophosphamide for the treatment of severe disease in almost 40 years. However, issues regarding the use of maintenance therapy after rituximab, the concurrent use of cyclophosphamide and the toxicity of rituximab remain unanswered and should be clarified in ongoing and future randomized controlled trials.


**Contents**



*Abbreviations:* AAV, ANCA-associated vasculitis; ANCA, anti-neutrophil cytoplasmic antibodies; Breg, regulatory B cells; CRP, C-reactive protein; cPR3, PR3 complementary peptide; CSS, Churg–Strauss syndrome; CYC, cyclophosphamide; ESR, erythrocyte sedimentation rate; FNGN, focal necrotizing glomerulonephritis; GBM, glomerular basement membrane; GFR, glomerular filtration rate; GPA, granulomatosis with polyangiitis; IL-7R, interleukin-7 receptor; ICAM, intercellular adhesion molecule; IFN, interferon; LAMP-2, lysosomal membrane protein-2; MPA, microscopic polyangiitis; MPO, myeloperoxidase; NET, neutrophil extracellular traps; PBO, placebo; PR3, Proteinase 3; RCT, randomized controlled trial; RPGN, rapidly progressive glomerulonephritis; RTX, rituximab; SLE, systemic lupus erythematosus; TCR, T cell receptor; TLRs, toll like receptors; TNF, tumor necrosis factor.

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## 1. Introduction

Vasculitides associated with serum positivity for anti-neutrophil cytoplasmic antibodies (ANCA) affecting small and medium-sized vessels, known collectively as the ANCA-associated vasculitides (AAV), include granulomatosis with polyangiitis (GPA; formerly Wegener's granulomatosis) [1], microscopic polyangiitis (MPA), and Churg–Strauss syndrome (CSS). Glomerulonephritis in AAV patients is characterized by focal necrosis, crescent formation, and few or no immunoglobulin deposits (Fig. 1). The new classification of ANCA-associated glomerulonephritis is shown in Table 1. Lung involvement varies from transient focal infiltrates or interstitial disease to massive pulmonary hemorrhagic alveolar capillaritis, the most life-threatening presentation of small-vessel vasculitis. ANCA directed against proteinase 3 (PR3-ANCA) are detected primarily in GPA, and anti-myeloperoxidase antibodies (MPO-ANCA) tend to occur in MPA and CSS [2]. However, significant overlap to this rule exists, with substantial subsets of GPA patients being MPO-ANCA positive and significant subsets of MPA or CSS patients having ANCA directed against MPO. Further, a minority of patients with "AAV" do not have detectable ANCA in their sera [3]. In vitro and animal evidence suggests that ANCA themselves play a role in the pathogenesis of AAV and are not merely bystanders or epiphenomena. In 2002, in vivo studies found that murine MPO-ANCA resulted in intrinsic pauci-immune renal vasculitis [4]. Although there is accumulating evidence for the pathogenic role of ANCA, especially MPO-ANCA, some questions remain unclear, and no convincing animal model has been postulated for PR3-ANCA glomerulonephritis or vasculitis.

Immunosuppressants of varying toxicity, together with glucocorticoids, are the cornerstone of AAV therapy [5]. Recent data confirm that rituximab (RTX) is a valid alternative to cyclophosphamide (CYC) for the induction of remission in severe AAV, and that RTX-based regimens are preferable in patients with relapsing disease. In this review, we focus on the latest data from clinical trials testing B-cell depleting agents in ANCA vasculitides, a new therapeutic approach that can change the therapeutic schedules of clinicians in charge of patients with GPA and MPA.

## 2. Understanding the pathophysiology of AAV

Better knowledge of the main pathogenic mechanisms of AAV could result in safer therapies that target the principal immune pathways mediating the disease. However, the knowledge about the pathogenesis of AAV remains incomplete but a significant body of literature now explains many of the processes involved in the development of autoimmunity, the action of ANCA on neutrophils, the role of T and B cells and the development of tissue injury in these disorders [6]. Recently, Lepse et al. performed a comprehensive review of the immunopathogenesis of AAV [6]. Fig. 2 illustrates the various processes involved.

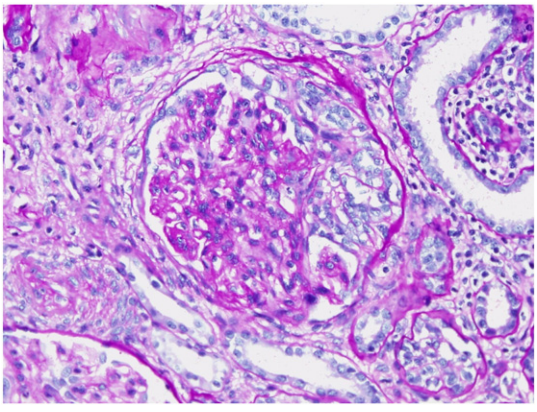

**Fig. 1.** Light microscopy shows a glomerulus with a partial cellular crescent. Periodic acid–Schiff staining (×200).

### 2.1. Role of ANCA

The pathogenic role of ANCA has been suspected since 1990, when Falk et al. demonstrated that ANCA stimulate respiratory bursts in neutrophils and trigger the release of primary granule constituents [7]. In vitro studies show that ANCA incite vascular damage by inducing neutrophil effector functions, including cytokine and chemokine release, and produce lysis through adhesion to cultured endothelial cells [2]. A pathogenic role for ANCA in a mouse model was shown in 2002 by Xiao et al. [4], who passively administered murine anti-myeloperoxidase (MPO) IgG to $Rag2^{-/-}$ mice that lacked functioning T and B cells. The result was a focal necrotizing glomerulonephritis (FNGN) with no immune deposits, with damage to ~15% of glomeruli. In contrast, the pathogenic potential of PR3-ANCA has not been similarly confirmed. Analogous experiments with PR3 in animal models have not demonstrated the induction of granulomatous inflammation typical of GPA or even provided the model for the development of vasculitis [8].

Some possible explanations for the differences in experimental evidence relating to the effects of MPO- and PR3-ANCA have been proffered. GPA is suggested to be initiated by aberrant cell-mediated immune responses to exogenous or endogenous respiratory tract antigens, resulting in the granuloma formation and the subsequent development of humoral autoimmunity to PR3 [9]. The autoantigen complementarity hypothesis of PR3-directed autoimmunity implicates the PR3 complementary peptide, which is encoded by the PR3 gene antisense strand [10]. The theory proposes that the inciting immunogen that elicits a cascade of immunological events is not the self-antigen (the autoantigen) or its mimic, but rather a protein that is complementary in surface structure to the autoantigen; that is, a protein homologous or identical to the amino acid sequence of translated antisense RNA from the noncoding strand of the autoantigen gene. The cascade begins when this complementary protein initiates the production of antibodies, which in turn elicit an anti-antibody or anti-idiotypic response. These anti-idiotypic antibodies can now react with the autoantigen. The search for complementary proteins has yielded microbial and fungal proteins, consistent with concept that invading micro-organisms can deliver the inciting immunogen [11]. The complementary protein might be derived endogenously by aberrant antisense transcription or exogenously by a microbe such as *Staphylococcus aureus* using a complementary, antisense, mimicking protein that binds to (and might inhibit) the antimicrobial properties of PR3 or MPO [12,13]. PR3 anti-complementary specificity has been demonstrated in human antibodies and T cells. The protein complementary to the middle portion of PR3 might be the endogenous protein plasminogen and there is reported dual specificity of antibodies to plasminogen and complementary PR3, hence supporting this hypothesis [14]. Plasminogen antibodies, which are found in ANCA disease, inhibit fibrinolysis and are associated with a greater risk of thrombosis.

### 2.2. Novel autoantibodies

Kain et al. [15] recently suggested that molecular mimicry is the basic mechanism involved in pauci-immune FNGN in patients with ANCA-associated vasculitis, although the antigen involved is LAMP-2 rather than PR3 or MPO. In neutrophils, LAMP-2 is located on the membranes of intracellular vesicles containing MPO and PR3, and is abundant on the surface of endothelial cells. LAMP-2 plays a role in antigen presentation and adhesion of peripheral blood mononuclear cells to vascular endothelium. The authors proposed a different rationalization for the source and development of pauci-immune FNGN, with possible clinical repercussions [15]. They discovered that infection by fimbriated bacteria might generate cross-reactive autoimmunity to LAMP-2, resulting in the production of autoantibodies that