

# New insights into the immunopathogenesis and treatment of small vessel vasculitis of the kidney

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## Purpose of review

Glomerulonephritis is an important manifestation of small vessel vasculitides such as Wegener granulomatosis, microscopic polyangiitis, and Churg–Strauss syndrome. Renal involvement in these diseases is characterized by a pauci-immune segmental necrotizing and crescentic glomerulonephritis that is strongly associated with circulating antineutrophil cytoplasmic autoantibodies. We will review recent advances in understanding the pathogenesis of antineutrophil cytoplasmic autoantibody-related renal vasculitides and innovative approaches to their treatment.

## Recent findings

An experimental milestone in antineutrophil cytoplasmic autoantibody research has been reached in the past year. Using an innovative mouse model, investigators from the University of North Carolina in Chapel Hill have recently acquired robust data supporting the pathogenic role of antineutrophil cytoplasmic autoantibodies in the glomerulonephritis and small vessel vasculitis, analogous to those seen in microscopic polyangiitis and Wegener granulomatosis. Novel immunosuppressive approaches have been examined including preliminary studies using biologic agents, such as antagonists of tumor necrosis factor and monoclonal antibodies to B lymphocytes.

## Summary

Recent insights into the pathogenesis of antineutrophil cytoplasmic autoantibody-related vascular injury and the availability of new biologic, immune response modifiers to complement standard chemical immunosuppressive agents offer exciting new prospects for investigation in the management of patients with small vessel renal vasculitides.

## Keywords

vasculitis, glomerulonephritis, antineutrophil cytoplasmic autoantibodies (ANCA), Wegener granulomatosis, microscopic polyangiitis

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## Abbreviations

ANCA	antineutrophil cytoplasmic autoantibodies
MPA	microscopic polyangiitis
MMF	mycophenolate mofetil
MPO	myeloperoxidase
TNF	tumor necrosis factor

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## Introduction

Early detection and treatment of glomerular involvement are recognized to be critical determinants of renal survival in patients with small vessel renal vasculitis, such as Wegener granulomatosis, microscopic polyangiitis (MPA), and Churg–Strauss syndrome. In patients presenting with prominent extrarenal manifestations of these diseases, there is often opportunity to identify early and treatable forms of glomerulonephritis. Unfortunately, in patients with renal-limited vasculitis, there is often substantial renal damage prior to diagnosis of glomerular disease. Discovery of antineutrophil cytoplasmic autoantibodies (ANCA) led to studies suggesting common pathogenetic mechanisms in these entities, as well as providing tools to facilitate diagnosis [1\*]. Continued investigation of ANCA and other immunopathogenetic mechanisms has not only increased our understanding of small vessel renal vasculitis but may open avenues for new therapeutic approaches.

## Immunopathogenesis of small vessel renal vasculitis

The characteristic light microscopy lesions of small vessel renal vasculitis are segmental necrotizing and crescentic glomerulonephritis [2\*]. Despite high levels of circulating immune complexes in these diseases, early studies by immunofluorescence microscopy showed few if any immunoglobulin or complement component deposits. Early on, some argued unconvincingly that following their instigation of the nephritogenic process, immune complexes were simply evanescent.

Given the paucity of evidence for nephritogenic humoral immune mechanisms in tissue sites of disease activity, other investigators logically examined the alternative that cell-mediated immune mechanisms may be operant [3]. Indeed, some studies of renal biopsies from patients with ‘pauci-immune’ glomerulonephritis reported that T cells and macrophages are present within active, necrotizing glomerular tuft lesions, cellular crescents

and periglomerular infiltrates [4]. Unfortunately, it has been difficult to prove whether these infiltrating cells represent primary cell-mediated immune responses or secondary nonspecific chronic inflammatory processes. Several experimental models have produced only equivocal evidence in this regard; lymphoid cell transfers from affected to naïve animals generally have not produced segmental necrotizing or crescentic glomerular lesions akin to those of human small vessel renal vasculitis [5].

A recent study using a novel approach may represent a significant advance in dissecting the relative roles of humoral and cellular immunity in glomerular disease [6••]. Wu and colleagues isolated CD4<sup>+</sup> T cells from rats immunized to a recombinant form of glomerular basement membrane. Upon transfer of in-vitro activated T-cell lines (generated from immunized donors) to pertussis toxin-primed naïve syngeneic rats, the recipients developed severe proteinuria and cellular crescents, without evidence of antibody or complement deposition in glomerular lesions. These insights may foster studies examining the potential role of cell-mediated processes in relevant models of renal vasculitis.

### **Anti-neutrophil cytoplasmic autoantibodies: historical questions and recent answers emerging from experimental models**

The serendipitous discovery of ANCA by Davies and colleagues [7] when they incubated plasma samples from patients with necrotizing glomerulonephritis with normal human neutrophils (intending to measure circulating immune complexes) was a major milestone in the history of renal vasculitis. The clinical association of ANCA with Wegener granulomatosis was described in a seminal paper by van der Woude and colleagues in 1985 [8]. Standardization and development of the Chapel Hill nomenclature of small vessel vasculitis appeared in 1994 [9]. Multiple studies have subsequently shown the strong association of ANCA with small vessel vasculitis of the kidney, all of which led to the practice of grouping together the ANCA-associated glomerulonephritides in numerous clinical studies. While ANCA offered the prospect of new insights into the pathogenesis of renal vasculitis, it has been difficult to achieve consensus on several challenging issues (Table 1).

For more than a decade, experimental data were interpreted, at best, to offer a reasonable hypothesis for the pathogenic role of ANCA in systemic and renal vasculitis. The hypothesis proposed by Falk and colleagues [10] suggested that individuals developing ANCA (from an otherwise undefined autoimmune diathesis) were susceptible to vasculitic disease if the following sequence were to occur: an intercurrent event

**Table 1. Challenges in determining the pathogenetic role of ANCA in small vessel vasculitis**

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Some patients with high titers of ANCA do not have glomerulonephritis or small vessel vasculitis.
While some studies suggest that changes in ANCA titers presage vasculitic flares, there are generally weak correlations between ANCA titers and disease activity.
ANCA could represent a secondary phenomenon, resulting from immune responses to neutrophil antigens released by another primary vasculitic process.
Because antigen targets of ANCA reside in neutrophils and monocytes, it is difficult to explain the predilection of glomeruli and small vessels to vasculitic injury.
Given the lack of reactivity of ANCA with normal neutrophils, it is difficult to explain their role <i>in vivo</i> (which would seem to require yet another priming event leading to surface expression of neutrophil antigens in order to be accessible to ANCA).
Failure to produce vasculitic disease by active immunization with known ANCA-specific antigens and by passive transfer of ANCA-positive plasma are indirect evidence against a primary role of ANCA in small vessel vasculitis.

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(notably, infection) caused rearrangement and surface expression of neutrophilic lysosomal enzymes (which were then accessible to ANCA); such neutrophils were envisioned to be fully activated, or even 'supercharged' for releasing free radicals and lytic enzymes, thereby being poised to amplify inflammation at sites where the integrity of vascular endothelium might be compromised.

The nature of vascular perturbations that could evolve to vasculitic processes is unclear. However, a provocative study by Woywodt and colleagues [11••] has recently shown that the number of endothelial cells released into the circulation may provide a useful measure of vasculitic disease activity. The study is based on a novel technique of counting circulating endothelial cells which can be identified by their formation of rosettes of synthetic beads coated with specific anti-human endothelial cell antibody. These investigators found that patients with active ANCA-associated vasculitis had an approximate 10-fold increase in circulating endothelial cells compared to patients with inactive vasculitis and other controls. Interestingly, the endothelial cells displayed markers of necrosis rather than apoptosis. Additional studies of this methodology as a monitoring tool, supplementing ANCA titers and other clinical and laboratory parameters, are clearly warranted to assess their cost/benefit outside the research setting.

### **Pivotal mouse model demonstrating the pathogenicity of antineutrophil cytoplasmic antibodies**

During the past year, the Chapel Hill group of nephrologists and pathologists has presented compelling evidence in a mouse model of the pathogenic role of ANCA in glomerulonephritis and small vessel vasculitis [12•]. Xiao and colleagues have taken an innovative

experimental approach to circumvent many of the problems and to address some of the challenges to the pathogenicity of ANCA outlined above [13••]. These investigators used myeloperoxidase (MPO) knock-out mice, which mounted brisk ANCA-equivalent immune responses to repeated doses of native mouse MPO. Adoptive transfer of splenic lymphocytes and gamma globulin fraction of sera from MPO and control immunized animals was performed. Key recipients were Rag2 mice that expressed normal MPO but were incompetent for both humoral and cellular immune pathways. In splenocyte transfer, there was a dose-dependent induction of anti-MPO ANCA in recipients, peaking at approximately 10–13 days. Depressed renal function, as well as extensive glomerular necrosis and cellular crescents, occurred in the same time frame in experimental but not in control mice. Vasculitic lesions were also noted in extrarenal tissues, particularly the lung vasculature with resultant pulmonary hemorrhage.

In the second phase of the experiments, transfer of anti-MPO globulin fraction (without splenocytes) to both immunodeficient and genetically-related immunocompetent recipients produced segmental fibrinoid necrosis of glomeruli with cellular crescents within 6 days. In the discussion of this seminal paper, the investigators argue their proof of causality between ANCA and systemic vasculitis, based on the eight criteria proposed by Hill for concluding that an association is indicative of causation [14]. Although this study represents one of the most significant advances in recent decades in supporting the role of autoantibodies in the pathogenesis of small vessel vasculitis, important questions remain to be answered in completely addressing the challenges raised in Table 1. The alternative, or possibly complementary, roles of cell-mediated immune mechanisms warrant continued investigation in this disease. Finally, congruent with the goals for understanding most other autoimmune diseases, the pursuit of causes for the underlying loss of self-tolerance and emergence of autoreactivity via ANCA warrant continued investigation.

### **Advances in the treatment of small vessel vasculitis of the kidney**

In recent years, continued progress has been made in the treatment of small vessel renal vasculitis. The growth of knowledge regarding glomerular immunopathology together with the expansion of therapeutic agents capable of directly targeting immunologic pathways have increasingly raised the possibility of targeting specific effector mechanisms that may be involved in disease pathogenesis. However, until such time when data exist to support the safety and efficacy of such novel therapeutic approaches in the vasculitides, the use of regimens combining glucocorticoids and a

cytotoxic agent will continue to form the foundation of therapy.

The greatest body of prospective standardized therapeutic data has come from studies in Wegener granulomatosis. Information regarding the treatment of MPA or Churg–Strauss syndrome has, to date, largely come from combined series with other vasculitides [15,16]. These data, together with the uniformity of the glomerular histology, currently support the use of similar treatment approaches in these diseases when glomerulonephritis is present.

#### **Cyclophosphamide**

Prior to the availability of effective therapy, active Wegener granulomatosis affecting a major organ system was almost universally fatal. Patient outcome improved dramatically with the introduction of daily cyclophosphamide and glucocorticoids [17,18] and long-term studies have clearly established the efficacy of this regimen to induce remission and prolong survival [19,20]. Although combined therapy with cyclophosphamide and glucocorticoids remain the most effective initial treatment for active glomerulonephritis, this regimen is associated with toxicity. Extended observation has also confirmed the propensity for disease relapse in a high proportion of patients, bringing with it the potential for organ damage and the need for further immunosuppressive treatment. For this reason, current research has continued to pursue less toxic therapeutic options that reduce the risk of relapse.

#### **Methotrexate**

Several studies have demonstrated that methotrexate can effectively induce remission of active Wegener granulomatosis that is not immediately life threatening [21–24]. Although methotrexate cannot be given to patients with renal insufficiency, one study found the use of methotrexate and prednisone as initial therapy for patients with Wegener granulomatosis-related glomerulonephritis and a normal or near normal level of serum creatinine was not associated with a long-term decline in renal function [25].

The ability of methotrexate to maintain remission following induction with daily cyclophosphamide has also been examined. Langford *et al.* [26•] conducted a standardized prospective trial in which 31 patients with active Wegener granulomatosis.

In another study, Reinhold-Keller *et al.* [27•] treated 71 patients with methotrexate 0.3 mg/kg/week after remission was induced with glucocorticoids and daily cyclophosphamide given for 5–66 months. Twenty-six patients (37%) relapsed. Glomerulonephritis was a feature of 16 relapses, with 14 patients exhibiting a rise

in serum creatinine from normal values to 1.5–2.0 mg/dl. One patient relapsed with rapidly progressive glomerulonephritis and pulmonary hemorrhage that had a fatal outcome. Leukopenia prompted withdrawal of therapy in two patients and dosage reduction in an additional nine patients.

While both of these trials found methotrexate to be a well-tolerated therapy for the maintenance of remission in Wegener granulomatosis, they differed significantly in the severity of renal relapse. The reason for such divergent findings is unclear. Given the potential for glomerulonephritis to be asymptomatic and rapidly progressive, close surveillance for the detection of renal relapse is important. Such monitoring should be applied, not only during treatment with methotrexate, but in all clinical settings for patients with a primary small vessel vasculitis.

#### **Azathioprine**

Azathioprine is a purine antimetabolite with which there has been extensive experience in renal transplantation. Its immunosuppressive properties, comparative safety profile to cyclophosphamide, and its ability to be given to patients with renal insufficiency have made azathioprine an attractive agent for consideration in patients with Wegener granulomatosis. Data from open-label series suggested that while azathioprine was not effective for inducing remission of active Wegener granulomatosis, it might have a role in maintaining remission induced by cyclophosphamide [18]. Preliminary results from a randomized prospective multicenter trial suggest that after remission induction with cyclophosphamide, azathioprine was as effective as continued cyclophosphamide for the prevention of relapse [28].

#### **Mycophenolate mofetil**

Recent studies have begun to explore the use of mycophenolate mofetil (MMF) for the treatment of vasculitis. Interest in investigating this agent in the vasculitides was prompted by the comparative experience with azathioprine in solid organ transplantation as well as its mechanism of action.

Nowack and colleagues [29•] examined the use of MMF for maintenance therapy in nine patients with Wegener granulomatosis and two patients with MPA. In this study, patients were treated with MMF and glucocorticoids for maintenance of remission following induction with cyclophosphamide. Of the 11 patients, only one Wegener granulomatosis patient relapsed in the 14th month of maintenance therapy. Adverse events included abdominal pain, diarrhea, respiratory infection, leukopenia, and cytomegalovirus colitis. Encouraging experiences have also been found in small series and case reports [30–32].

While the toxicity of MMF is favorable compared with cyclophosphamide, recent publications highlight potential cautions in vasculitis patients. Gastrointestinal complaints and bone marrow toxicity led to dose reduction or MMF cessation in all of the five patients with Wegener granulomatosis or MPA and end-stage renal disease who were treated by Haubitz and colleagues [33]. Maes *et al.* [34] described an acute inflammatory syndrome characterized by fever, arthralgias, and muscle pain that developed in two Wegener granulomatosis patients receiving MMF. In another case report, cytomegalovirus colitis occurred in a patient with Wegener granulomatosis during treatment with MMF and low-dose prednisolone [35].

At the current time, assessment of the efficacy of MMF is limited by small sample sizes of the available data. Larger randomized trials are needed to better appreciate what role MMF may have in the vasculitic diseases.

#### **Biologic immunomodulators**

Monoclonal antibody and recombinant DNA technology has led to an expanding range of biologic therapies capable of directly targeting components of the immune response. The examination of these novel immunomodulatory agents in the vasculitides may provide both new treatment options and insights into disease pathogenesis.

Although reports on the use of biologic agents in the vasculitides have begun to appear in the literature, none of these allows any conclusions to be drawn regarding their efficacy. Experience in other settings has shown that these therapies can be associated with both unexpected effects on disease and toxicity. It is therefore critical that the use of biologic agents in the vasculitic diseases be examined in rigorous investigational studies prior to their use in clinical practice.

#### *Tumor necrosis factor modulatory agents*

Agents capable of modulating tumor necrosis factor (TNF) have been of interest in Wegener granulomatosis based on the presence of granulomatous inflammation and the potential role of T helper type 1 cytokines in this disease.

Etanercept is a dimeric fusion protein consisting of the extracellular ligand-binding portion of the human 75 kDa TNF receptor linked to the Fc portion of human IgG1. Stone and co-workers performed a 6-month open-label phase I study in which 20 patients received etanercept 25 mg twice a week in combination with standard therapies for Wegener granulomatosis [36•]. Etanercept was well tolerated with few adverse events. There are currently two ongoing randomized trials within the United States examining etanercept in Wegener granulomatosis.

Three reports have examined the use of infliximab, a chimeric IgG1 monoclonal antibody that binds specifically to TNF. Booth and colleagues [37] described their experience with infliximab in three patients with Wegener granulomatosis and three with MPA who had relapsing vasculitis involving the eyes or lung. Three intravenous doses of infliximab 200 mg were given at monthly intervals for 3 months. Five patients had remission of their disease, with treatment allowing glucocorticoid withdrawal in three patients and reduction by more than 50% in the other two patients. Although one patient experienced fatigue, myalgia, and blurred vision 24 h after the first infusion, infliximab was otherwise well tolerated.

Bartolucci and associates treated 10 patients with refractory vasculitis (seven Wegener granulomatosis, two rheumatoid vasculitis, and one hepatitis C associated cryoglobulinemic vasculitis) with infliximab 5 mg/kg days 1, 14, and 42 and then every 8 weeks for 6 months [38]. Immunosuppressive agents were held between days 0–42 in 8 patients while glucocorticoids were maintained or decreased in a dose range of 5–65 mg/day. Complete or partial remission occurred in all patients. Infliximab was well tolerated with two patients experiencing a transient cutaneous eruption, one of whom discontinued therapy.

Lamprecht *et al.* examined the use of infliximab in six patients with refractory Wegener granulomatosis manifested by retro-orbital disease, cavitating pulmonary nodules, or rapidly progressive glomerulonephritis [39]. Patients received infliximab (3 mg/kg in two patients and 5 mg/kg in four patients) with a 2-week interval after the first administration and 4-week intervals between infusions until remission, in addition to cyclophosphamide and glucocorticoids. Remission was induced in five patients and glucocorticoid doses were tapered. No serious side effects occurred, although one patient withdrew because of a suspected systemic infection.

#### Rituximab

Rituximab is a chimeric monoclonal antibody directed against the CD20 antigen found on the surface of normal and malignant B lymphocytes. Under the hypothesis that elimination of pathogenic ANCA would lead to the induction and maintenance of remission, Specks and colleagues used rituximab combined with prednisone to treat a patient with relapsing proteinase-3 ANCA-positive Wegener granulomatosis [40\*\*]. At the completion of the 4 weekly infusions of rituximab 375 mg/m<sup>2</sup>, ANCA became negative, which was followed by clinical improvement. Nine months after treatment, the ANCA titer started to rise and the patient was treated with a second course of rituximab. Following these infusions,

ANCA remained at high levels but the patient's disease remained in remission. The persistence of ANCA after the second course of rituximab along with continued clinical remission raises new questions regarding both the longevity of ANCA-producing plasma cells and the author's original hypothesis. Further investigation may provide insights not only on the effectiveness of rituximab in Wegener granulomatosis but also the role of ANCA in disease pathogenesis.

#### Conclusion

Renal involvement in small vessel vasculitis is characterized by a pauci-immune segmental necrotizing and crescentic glomerulonephritis that is strongly correlated with ANCA. Recent experimental evidence strongly suggests a pathogenic role of ANCA for the development of small vessel renal vasculitis in a mouse model. Advances in the understanding of disease pathophysiology together with the expanding development of novel immunomodulatory therapies will continue to provide potential new avenues of investigation for the treatment of these diseases.

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