Treatment of ANCA-associated Systemic Vasculitis

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Abstract
The antineutrophil cytoplasmic antibodies (ANCA)-associated small vessel vasculitides include Wegener’s granulomatosis, Churg-Strauss syndrome, microscopic polyangiitis (MPA), and the renal limited form of MPA, also known as pauci-immune or idiopathic crescentic glomerulonephritis. ANCA are probably necessary but not sufficient for disease pathogenicity. Classical induction and maintenance therapy of these conditions with corticosteroids and long-term cyclophosphamide is associated with occasional relapse and major toxicities. Therefore, treatment regimens being investigated include induction with methotrexate or, especially for patients with more aggressive disease accompanied by renal insufficiency, therapies that include either pulses of methylprednisolone or plasma exchanges. Nontraditional options for maintenance therapy may include step-down treatment with azathioprine or mycophenolate mofetil. For patients with Wegener’s granulomatosis, studies have shown a reduced occurrence of flares with the use of co-trimoxazole. Finally, although a carefully randomized controlled trial with etanercept demonstrated that this tumor necrosis factor (TNF)-blocking agent was not superior to conventional maintenance therapy, a biologic agent with a different mechanism of action, rituximab, may prove a satisfactory alternative.

The systemic vasculitides were traditionally classified according to the size of blood vessel most prominently involved. 1,2 For example, the large vessel vasculitides include giant cell or temporal arteritis and Takayasu arteritis; medium-sized vessel vasculitic syndromes include polyarteritis nodosa, Kawasaki’s disease, and isolated angiitis of the CNS. Vasculitis involving the small vasculature includes Henoch-Schönlein purpura, essential cryoglobulinemia, hypersensitivity vasculitis, vasculitis secondary to an autoimmune connective tissue disease, vasculitis secondary to viral infection, and vasculitis associated with antineutrophil cytoplasmic antibodies (ANCA), including Wegener’s granulomatosis, 3,4 Churg-Strauss granulomatosis, 2,5,6 microscopic polyangiitis (MPA), 7,8 and the renal limited form of MPA sometimes known as pauci-immune glomerulonephritis or idiopathic crescentic glomerulonephritis. An alternative classification system for vasculitis is based on the presence or absence of immune complex deposition. The types of vasculitis associated with the local presence of antigen and antibody complexes include Henoch-Schönlein purpura, cryoglobulinemia, systemic lupus erythematosus, and rheumatoid arthritis. In contrast, the vasculitic syndromes that accompany Wegener’s granulomatosis, Churg-Strauss granulomatosis, MPA, and the limited form of MPA involving only the glomeruli tend to be pauci-immune and occur in the absence of antigen and antibody deposition.

The focus of this article will be the treatment of pauci-immune small vessel vasculitis associated with the presence of ANCA. Specifically, following a brief summary of the major clinical features of Wegener’s granulomatosis, Churg-Strauss granulomatosis, MPA, and the limited form of MPA involving only the glomeruli, there is a discussion of the pathogenicity of ANCA and an update on the current management of these conditions.

Wegener’s Granulomatosis
In 90% of Wegener’s granulomatosis patients, 9 typical features include upper and lower respiratory tract disease, such as nasal septal perforation, deformity, ulceration, or epistaxis, recurrent sinus disease, and more rarely trachea involvement. Eighty-five percent of patients have pulmonary...
features with infiltrates or cavitary nodules often manifested as cough, hemoptysis, and dyspnea, although patients with pulmonary stigmata can be asymptomatic. Seventy-five percent of Wegener’s granulomatosis patients have glomerulonephritis, which usually presents with microscopic hematuria, proteinuria, and casts. Additionally, many of the patients have arthralgia, myalgia, sometimes frank arthritis, purpuric rash because of the presence of co-occurring cutaneous small vessel hypersensitivity vasculitis, peripheral neuropathy most characteristically meeting criteria for mononeuritis multiplex, and occasionally various types of eye and ear involvement. Most patients with Wegener’s granulomatosis have anemia, thrombocytosis, and elevated acute-phase reactants such as slow elevated erythrocyte sedimentation rate and high C-reactive protein. The majority of Wegener’s granulomatosis patients are positive for C-ANCA and for antibodies to proteinase 3 (PR-3).

Diagnosis of Wegener’s granulomatosis in the past often required biopsy of tissue from the lung, kidney, skin, nerve, sinus, or nose. However, currently diagnosis is often made simply by the presence of the typical clinical features, consistent imaging studies such as CT scans, and positive serology. When tissue is available, the characteristic pathologic features include the triad of granulomas, neutrophilic vasculitis, and necrosis.

Churg-Strauss Granulomatosis

Churg-Strauss granulomatosis is sometimes known as allergic granulomatosis and angiitis. Atopy with allergic rhinitis and asthma often precede the diagnosis. Both peripheral blood and tissue eosinophilia, the latter in the presence of granulomas, often accompanies the disorder. Fleeting pulmonary infiltrates typify this condition. Serology with positive P-ANCA with specificity for myeloperoxidase is often seen in Churg-Strauss granulomatosis. Extra-pulmonary features include skin involvement, mesenteric ischemia, peripheral neuropathy, myocarditis, and rarely coronary arteritis.

Microscopic Polyangiitis

Microscopic polyangiitis (MPA) is characterized by glomerulonephritis in 90% of patients; pulmonary capillaritis in 50%; gastrointestinal involvement in 50%; skin involvement in 60%; ear, nose, and throat involvement in 35%; and musculoskeletal features in 60%. MPA is the most common cause of acute pulmonary-renal syndrome, although the differential diagnosis includes Wegener’s granulomatosis, Churg-Strauss granulomatosis, lupus erythematosus, Goodpasture’s disease (antiglomerular basement membrane disease), and cryoglobulinemia.

MPA has many similarities to Wegener’s granulomatosis. Both are often accompanied by generalized, systemic constitutional complaints such as fever, malaise, weight loss, arthralgia, myalgia, and mucositis. Glomerulonephritis is present in nearly 90% of patients with MPA but is somewhat less likely in patients with Wegener’s granulomatosis, with a 70% frequency. On the other hand, pulmonary features are present in 80% of patients with Wegener’s granulomatosis compared to approximately 30% to 40% of patients with MPA.

Role of ANCA in Pathogenicity

The consistent demonstration of ANCA in patients with these forms of small vessel vasculitis raises the issue of their pathogenicity. ANCA are a heterogeneous group of circulating antibodies directed against antigens in the primary granules of neutrophils and the peroxidase-positive lysosomes of monocytes. ANCA are measured by direct immunofluorescence. However, the antigenic specificities of ANCA as determined by ELISA may include serine PR-3, myeloperoxidase, or atypical antigens. Cytoplasmic ANCA (C-ANCA) are most commonly directed against PR-3, which is strongly associated with Wegener’s granulomatosis and less commonly with Churg-Strauss granulomatosis or MPA. Perinuclear ANCA (P-ANCA) often have more heterogeneous specificities. These antibodies may be directed against myeloperoxidase but also against other antigens. Sometimes ANCA have atypical patterns; these have been designated X-ANCA. The atypical specificities may include elastase, cathepsin G, or lactoferrin. Therefore, patients with immunofluorescence positive for ANCA should have confirmatory ELISA to determine the presence or absence of antibodies to PR 3 or myeloperoxidase (Table 1).

C-ANCA is seen in 85% of patients with Wegener’s granulomatosis, and evidence suggests that antibody titers correlate with disease activity and severity. C-ANCA can also be seen in 45% to 50% of patients with MPA, 25% of patients with the renal-limited form of MPA, 10% of patients with Churg-Strauss granulomatosis, and even 5% of the patients with polyarteritis nodosa. P-ANCA with specificity for myeloperoxidase are seen in 45% to 80% of patients with microscopic polyangiitis, 65% of patients with renal-limited microscopic polyangiitis, 60% of patients with Churg-Strauss granulomatosis, and 15% of patients with polyarteritis nodosa. Interestingly, several medications have been associated with the induction of antibodies to myeloperoxidase (anti-MPO), including propylthiouracil, hydralazine, minocycline, and D-penicillamine. Atypical ANCA are sometimes reported in patients with inflammatory bowel disease, chronic liver disease, and occasionally in patients with rheumatoid arthritis or lupus erythematosus.

Table 1 Prevalence of ANCA Positivity in Rheumatic Diseases

<table>
<thead>
<tr>
<th>Disease</th>
<th>C-ANCA (%)</th>
<th>P-ANCA (%)</th>
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<tr>
<td>Wegener’s granulomatosis</td>
<td>85</td>
<td>10</td>
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<tr>
<td>Microscopic polyangiitis (MPA)</td>
<td>15-45</td>
<td>45-80</td>
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<tr>
<td>Renal-limited MPA</td>
<td>25</td>
<td>65</td>
</tr>
<tr>
<td>Churg-Strauss granulomatosis</td>
<td>10</td>
<td>60</td>
</tr>
<tr>
<td>Polyarteritis nodosa</td>
<td>5</td>
<td>15</td>
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The evidence for pathogenicity includes the positive correlation between ANCA titers and disease activity, the induction of oxygen radical release and cell degranulation as well as inhibition of microbicidal function induced by ANCA binding to neutrophils and monocytes, and the finding that increased surface exacerbation of PR-3 on neutrophils correlates with disease activity.\textsuperscript{13,14} Additionally, experimental data demonstrate that ANCA binding to endothelial cells induces injury and that increased circulating endothelial cell concentration correlates with disease activity.\textsuperscript{15} Using confocal microscopy, researchers have demonstrated the binding of ANCA to neutrophils that have been primed with cytokines such as TNF.\textsuperscript{14,15} Further evidence for the pathogenicity of ANCA is derived from animal models including mice that are deficient in T and B lymphocytes (Rag2\textsuperscript{-/-}). When these mice were induced to generate ANCA with myeloperoxidase specificity,\textsuperscript{16} they developed histologically demonstrable glomerulonephritis and vasculitis.

Some evidence mitigates against the pathogenicity of ANCA. Such evidence includes the absence of disease in fetuses or newborns of pregnant women with circulating ANCA and clinical ANCA-associated small vessel vasculitis (AASV). To our knowledge, there have been no reports of a syndrome of neonatal AASV. Additionally, the passive transfer of ANCA to experimental animals does not consistently induce vasculitis. Furthermore, in one model, rats immunized with human myeloperoxidase developed antihuman MPO, which cross-reacts with rat myeloperoxidase, but did not develop clinical or histologic signs of vasculitis. Finally, high titers of ANCA can be found in patients without active vasculitis.\textsuperscript{17}

Summarizing the evidence regarding a pathogenic role for ANCA in AASV, it is likely that these antibodies are necessary but not sufficient for the development of the clinical syndromes. For example, TNF activation is required to induce neutrophils to express PR-3 on their surface before ANCA can bind to the neutrophils. Although speculative, these data are consistent with a scenario in which specific preparatory signals must reach adequate threshold levels to allow high-titer ANCA to induce the full expression of these clinical syndromes.

**Treatment Approaches**

The goals of treatment in AASV are initially induction of response and then maintenance of remission. To assess treatment success, a disease severity scale can be useful. Many informative studies regarding the current standard of care for the treatment of AASV are provided by the European Vasculitis Study Group (EUVAS). The EUVAS disease intensity scale classifies AASV into forms such as localized, early systemic, generalized, severe, and refractory disease.

Traditionally, AASV, such as Wegener’s granulomatosis, had mortality rates in excess of 80\% within 3 years without adequate treatment. The standard treatment of choice for induction of a response is the use of prednisone 1 mg/kg/day in combination with cyclophosphamide 1 to 2 mg/kg/day via the oral route. This standard induction protocol achieves remission in 70\% to 93\% of patients. The main concern about this management approach is twofold. First, serious side effects may accompany treatment chronically with an alkylating agent and second, late relapses may occur. Therapeutic approaches or strategies to minimize the use of cyclophosphamide include the use of less toxic agents for induction or maintenance of remission, the administration of cyclophosphamide in a potentially less noxious route (eg, intravenous pulses as opposed to daily oral administration), and the use of step-down therapy.\textsuperscript{18}

This article will review three alternatives for induction of response in patients with AASV, two nontraditional management approaches for the maintenance of disease, the positive results associated with the use of co-trimoxazole for patients with Wegener’s granulomatosis, and the negative experience with the use of the biologic agent etanercept.

A novel approach that will be briefly discussed is based on an open-label experience with a B-cell depleting therapy, rituximab (Table 2).

**Table 2 Clinical Trials**

<table>
<thead>
<tr>
<th>Induction Maintenance</th>
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<tr>
<td>CYCLOPS\textsuperscript{a}</td>
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<tr>
<td>NORAM\textsuperscript{b}</td>
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<tr>
<td>MEPEX\textsuperscript{c}</td>
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<tr>
<td>RITUXIMAB\textsuperscript{d}</td>
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\textsuperscript{a}Cyclophosphamide (CYT) Oral vs Intravenous Pulses.
\textsuperscript{b}MTX vs CYT for AASV without renal involvement.
\textsuperscript{c}Methylnitrosourea vs Plasma Exchange for Severe AASV.
\textsuperscript{d}Rituximab vs placebo for refractory AASV.
\textsuperscript{e}Azathioprine vs CYT for remission maintenance.
\textsuperscript{f}Mycophenolate mofetil vs CYT for remission maintenance.
\textsuperscript{g}Etanercept vs CYT for remission maintenance.
\textsuperscript{h}Co-trimoxazole vs placebo for remission maintenance.

**Cyclophosphamide**

The efficacy of oral cyclophosphamide and prednisone is well established for management of AASV. However, the efficacy of treatment and reduction of side effects in diseases such as lupus nephritis using intravenous cyclophosphamide rather than oral cyclophosphamide has led to a trial studying the relative benefits of these two routes of administration. The expectation is that intravenous pulse cyclophosphamide as compared to oral cyclophosphamide will be associated with a lower prevalence of bladder toxicities (eg, hemorrhagic cystitis, bladder fibrosis, and transitional cell carcinoma of the bladder) and a lower prevalence of a permanent gonadal dysfunction. A trial in 2001 found that the intravenous route was as effective at inducing remission of AASV and was associated with fewer infectious complications and leukopenia, as compared to the oral route, but the intravenous route was associated with the risk of more relapses.\textsuperscript{19} Therefore, the EUVAS designed CYCLOPS, a randomized controlled trial comparing the efficacy of
daily oral cyclophosphamide to pulse intravenous cyclophosphamide in 160 patients with renal vasculitis. The results have not yet been published but should clarify the role of pulse cyclophosphamide in the management of AASV.20

**Methotrexate**

EUVAS also formally studied the role of methotrexate in the treatment of AASV via the NORAM trial (Non-Renal Alternative with methotrexate), which directly compared oral methotrexate (20 to 25 mg/week) plus prednisone to oral cyclophosphamide (2 mg/kg/day) plus prednisone in the management of AASV.21 This trial was designed to determine whether methotrexate is as effective as cyclophosphamide for the induction of remission in patients who have Wegener’s granulomatosis or MPA without significant impairment of renal function. Methotrexate plus prednisone has shown similar remission rates to the standard oral cyclophosphamide plus prednisone regimen, but preliminary data indicated that the rate of relapses is higher with the methotrexate plus prednisone regimen. Therefore, this approach may be most appropriate for patients with milder forms of AASV, such as head- and neck-limited Wegener’s granulomatosis.

**Plasma exchange vs methylprednisolone**

Studies have been designed to look at the best management of patients with more severe forms of systemic small vessel vasculitis. In the MEPEX trial, also sponsored by EUVAS, intravenous methylprednisolone as compared to plasma exchange was studied in patients with severe vasculitis.22 A total of 151 patients with renal vasculitis (mostly patients with MPA) with a serum creatinine in excess of 5.6 mg/dL were randomized to receive either cyclophosphamide 2.5 mg/kg oral daily plus methylprednisolone 50 mg/kg as three daily pulses or cyclophosphamide plus plasma exchanges occurring as seven 4-liter exchanges over 14 days. Interim analysis revealed that after 3 months, 69% of the plasma exchange group was alive and dialysis independent compared to 49% of those treated with intravenous methylprednisolone (P=.02). This benefit was sustained in the 1-year follow-up. The interim 3-month results in 124 of the 151 patients enrolled revealed that end-stage renal disease occurred in 23 of the 61 patients that received methylprednisolone (37%), compared to 9 of 63 patients (15%) that received plasma exchange. In conclusion, plasma exchanges are preferred over pulse steroids in the initial management of severe AASV with renal insufficiency.

**Maintenance**

Management approaches for the maintenance of disease remission were investigated in the Wegener’s granulomatosis trial with etanercept and in the CYCAZAREM and IMPROVE trials, as well as in a study that explored the benefits of co-trimoxazole to prevent relapses of Wegener’s granulomatosis (Table 2).

In the Wegener’s Granulomatosis Etanercept Trial (WGET), eight centers in the United States enrolled 180 patients in a randomized controlled trial to determine the benefits of maintenance treatment with etanercept in Wegener’s granulomatosis patients who had achieved remission.23 The primary outcome was predefined as a sustained remission and required a Birmingham vasculitis activity score of 0. Of the 174 patients who could be evaluated, 126 (72%) had a sustained remission, but only 86 (49%) remained in remission for the duration of the trial. There were no significant differences between the etanercept and control (placebo-injection) group in the rates of sustained remission (70% vs 75%, P=.39), sustained periods of low-level disease activity (87% vs 91%, P=.32), or time required to achieve those measures. Disease flares were prominent in both the etanercept and placebo-treated groups, with 118 flares in the etanercept group (23 severe and 95 limited) and 134 in the control group (25 severe and 109 limited). Solid cancers developed in 6 patients in the etanercept group as compared with none in the control group (P=.01). In conclusion, etanercept is not effective for the maintenance of remission in patients with Wegener’s granulomatosis, durable remissions were achieved in only a minority of the patients, and there was a high rate of treatment-related complications, such as the aforementioned malignancies.

The EUVAS CYCAZAREM trial, a randomized study of maintenance therapy for vasculitis associated with ANCA, was published in 2003. It compared the continuation of cyclophosphamide after disease remission to “step-down” to an antimetabolite with fewer side effects, azathioprine.24 Therefore, this study investigated whether exposure to cyclophosphamide could be reduced by substitution of azathioprine at remission without an increase in disease flare. The patients studied had a new diagnosis of generalized vasculitis, Wegener’s granulomatosis, or MPA. All patients received at least 3 months of therapy with oral cyclophosphamide and prednisolone to achieve a remission. After remission, patients were randomly assigned to continue cyclophosphamide therapy (1.5 mg/kg of body weight per day) or substitute regimen of azathioprine (2 mg/kg/day). Both groups continued to receive prednisolone and were followed for 18 months from study entry. The primary endpoint was disease relapse. A total of 155 patients were enrolled, 144 (93%) entered remission and were randomly assigned to either azathioprine (71 patients) or continued cyclophosphamide (73 patients). Eleven relapses occurred in the azathioprine group (16%), and 10 occurred in the cyclophosphamide group (14%, P=.65, NS). Severe adverse events occurred in 15 patients during the induction phase (10%), in 8 patients in the azathioprine group during the remission phase (11%), and in 7 patients in the cyclophosphamide...
group during the remission phase (10%, \( P=0.94 \), NS, for the comparison between groups during the remission phase). In conclusion, for patients with generalized vasculitis, the withdrawal of cyclophosphamide and the substitution of azathioprine after remission did not increase the rate of relapse. Thus, the duration or exposure to cyclophosphamide may be safely reduced.

**Mycophenolate Mofetil**

There has been recent interest in the purine antimetabolite mycophenolate mofetil as a disease-modifying agent in autoimmune diseases. In an open-label investigation of the use of mycophenolate mofetil for maintenance therapy of patients with Wegener’s granulomatosis or MPA and renal involvement, treatment was associated with an absence of relapse in 10 of the 11 studied patients (91% efficacy).25 A subsequent NIH trial conducted in 2004 assessed mycophenolate mofetil for remission maintenance after induction with cyclophosphamide; results indicated that this agent was well tolerated, but the relapse rate was 43% (6 of 14 patients).26 In light of these conflicting results, the EUVAS IMPROVE trial is accruing large numbers of patients to compare the efficacy of mycophenolate mofetil to azathioprine for remission maintenance.

**Co-trimoxazole**

Respiratory tract infections appear to trigger relapses in patients with Wegener’s granulomatosis who are in remission. Uncontrolled data have suggested that treatment with trimethoprim sulfamethoxazole (co-trimoxazole) might be beneficial. A 1996 publication described a prospective randomized, placebo-controlled study of the efficacy of co-trimoxazole (800 mg sulfamethoxazole and 160 mg trimethoprim) given twice daily for 24 months for the prevention of relapses in patients with Wegener’s granulomatosis in remission during or after treatment with cyclophosphamide and prednisolone.27 Relapses and infection were assessed with predefined criteria based on clinical, laboratory, and histopathologic findings. Patients were evaluated at least once every 3 months for signs of disease-activity, compliance with the treatment regimen, side effects, and evidence of infections. Titers of ANCA were measured serially. Forty-one patients were assigned to receive co-trimoxazole and 40 patients to receive placebo. Eighty-two percent of the patients on co-trimoxazole remained in remission at 24 months compared with 60% of the patients in the placebo group. There were fewer respiratory tract infections (\( P=0.005 \)) and nonrespiratory infections (\( P=0.05 \)) in the co-trimoxazole group compared to the placebo group. There were no significant differences in antineutrophil cytoplasmic antibody titers at any time. Statistical analysis identified treatment with co-trimoxazole as an independent factor associated with prolonged disease-free survival and a positive ANCA test at the start of treatment as a risk factor for relapse. In conclusion, treatment with co-trimoxazole reduces the incidence of relapses in patients with Wegener’s granulomatosis.

**Novel Approaches**

For patients with refractory disease or intolerance to treatment with more standard cytotoxic agents, novel approaches may be of utility. Specifically, rituximab has been studied in patients with refractory antineutrophil cytoplasmic antibody-associated vasculitis.28-30 Rituximab is a novel genetically engineered anti-CD20 therapeutic monoclonal antibody that selectively depletes CD20 positive B cells. Rituximab was recently FDA-approved for the treatment of rheumatoid arthritis approximately 11 years after it was initially approved for the treatment of non-Hodgkin’s lymphoma. As reported in 2005, 11 consecutive patients with severe refractory ANCA-associated vasculitis treated at the Mayo Clinic between January 2000 and September 2002 were enrolled in an open-labeled trial to receive rituximab. The refractory nature of their AASV was defined as active disease not controlled by maximally tolerated cyclophosphamide and corticosteroids (\( N=8 \)) or a contraindication to cyclophosphamide manifested as drug-induced bladder toxicity (\( N=1 \)) or prolonged cytopenias (\( N=2 \)). The cohort had a mean age of 31 years (range 41-71 years); 6 were men and 5 were women; the mean disease duration was 6 years; 10 patients had Wegener’s granulomatosis and 1 MPA; 5 had active renal disease; all had active severe disease with Birmingham vasculitis activity scores ranging from 3 to 11. Treatment consisted of four weekly injections of rituximab at a dose of 375 mg/m² of body surface area. Additionally, these patients received prednisone up to 1 mg/kg daily, which was tapered once disease activity improved. Findings included that B cells were depleted in all patients, disease remission was induced in all patients within 6 months, remission persisted if B cells remained absent, and at 6 months acute-phase reactants such as C-reactive protein and sedimentation rate were reduced. ANCA titers fell in all 11 patients, 8 patients became ANCA negative, and in the 5 patients with renal disease, 2 were able to discontinue dialysis, 1 worsened then stabilized, and 2 remained stable. Of the original 11 patients, 9 experienced reconstitution of B cells. Of these 9, 2 remained ANCA negative and in remission at 5, 8, and 10 months posttreatment. Two relapsed at 7 and 12 months after steroid withdrawal and, when their ANCAs rose, were re-treated with rituximab and demonstrated a response. Three patients experienced an increase in their ANCA, prompting re-treatment with rituximab: their disease remained quiescent. One patient remained persistently ANCA positive but appeared to have persistent clinical remission; because of rising ANCA titers, this patient was re-treated and did not experience a disease flare. In this group of 11 patients, infusion reactions were infrequent, but 4 patients experienced infection (2 of whom had a
predisposition, as infections were diagnosed and treated before rituximab therapy). In conclusion, B cell depletion appears to be effective in refractory AASV, remission is maintained while B cells are absent, and re-treatment in the face of flare or rising ANCA titers re-established clinical remission.

Summary
The ANCA-associated vasculitic syndromes are a group of complex conditions unified by the presence of antibodies that target neutrophils and mononuclear cells. Although the precise pathogenic mechanisms associated with these types of antibodies need to be fully explored, evidence suggests that they contribute to the inflammatory processes that underlie these conditions. Classical induction treatment with prednisone and cyclophosphamide is often successful but remains imperfect because of toxicity, especially that associated with the prolonged use of an alkylating agent. Studies support the use of methotrexate with prednisone for induction in patients with milder disease at the cost perhaps of a slight increase in rate of relapse. The relative benefits of oral as compared to the better tolerated intravenous pulses of cyclophosphamide still need to be fully explored. For patients with the severest forms of AASV, especially with accompanying renal insufficiency, the use of plasma exchange appears to be associated with superior outcomes compared with the use of intravenous methylprednisolone. Maintenance therapy is often adequate with the use of azathioprine or mycophenolate mofetil. For patients without sulfonamide allergy, the rationale for the use of co-trimoxazole in Wegener’s granulomatosis appears justifiable, not only to reduce the likelihood of Pneumocystis pneumonia, but to reduce flare rate, presumably because the streptococcal nasal carrier state is reduced. Finally, although etanercept was not associated with fewer relapses when compared to conventional management, for patients with refractory AASV, biologics such as rituximab with a different mechanism of action may be appropriate. The future looks bright for patients with—and clinicians dedicated to the care of—AASV. The completion of ongoing studies, as well as future randomized controlled trials are likely to assist in establishing the best possible management of AASV with the goal of inducing and maintaining a response with the least possible toxicity in the majority of patients.

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