Antineutrophil Cytoplasmic Antibody-Associated Vasculitides and Respiratory Disease

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Antineutrophil Cytoplasmic Antibody-Associated Vasculitides and Respiratory Disease

Jose A. Gómez-Puerta, MD, PhD; José Hernández-Rodríguez, MD; Alfonso López-Soto, MD, PhD; and Xavier Bosch, MD, PhD

Vasculitides associated with serum positivity for antineutrophil cytoplasmic antibodies (ANCAs) are a well-established subgroup affecting small- to medium-sized vessels that are commonly recognized as ANCA-associated vasculitis, which includes necrotizing granulomatous vasculitis (NGV) [formerly Wegener granulomatosis], microscopic polyangiitis (MPA), and Churg-Strauss syndrome. NGV usually starts as a granulomatous disease of the respiratory tract and progresses to systemic disease with proteinase 3 (PR3)-ANCA-associated vasculitis, suggesting an aberrant cell-mediated immune response to exogenous or endogenous antigens in the respiratory tract and resulting in granuloma formation. In NGV, granulomata may represent lymphoid structures ultimately responsible for PR3-ANCA production. In both NGV and MPA, necrotizing glomerulonephritis and necrotizing pulmonary capillaritis may well result from an injury orchestrated by ANCA. Untreated NGV and MPA normally are rapidly progressive and fatal. Pulmonary capillaritis with alveolar hemorrhage is a severe complication in patients with MPA and NGV. Because plasma exchange removes circulating ANCAs and other proteins from the blood, its use has been advocated in critical situations of severe renal and pulmonary involvement. However, no studies of plasma exchange in ANCA-associated vasculitis focused on pulmonary involvement have been reported. Dissecting the mechanisms of inflammation may identify molecular targets for future therapies in ANCA-associated vasculitis. Thus, biological agents are emerging as potential therapies in refractory cases. Notably, rituximab and infliximab have been trialed with apparent initial clinical success.

Abbreviations: AAV = antineutrophil cytoplasmic antibody-associated vasculitis; ANCA = antineutrophil cytoplasmic antibody; APACHE = acute physiology and chronic health evaluation; BVAS = Birmingham Vasculitis Activity Score; CSS = Churg-Strauss syndrome; LAMP = lysosomal membrane protein; MMF = mycophenolate mofetil; MPA = microscopic polyangiitis; MPO = antimyeloperoxidase antibody; NGV = necrotizing granulomatous vasculitis; PR3 = proteinase 3; TNF = tumor necrosis factor

Systemic vasculitides are uncommon life-threatening disorders in which vascular inflammation damages tissue through the occlusion or rupture of vessels. Vasculitides associated with serum positivity for antineutrophil cytoplasmic antibodies (ANCAs) affecting small- to medium-sized vessels are commonly recognized as ANCA-associated vasculitis (AAV). Although renal-limited vasculitis is closely associated with ANCAAs, Wegener granulomatosis (because of reported ethical concerns and editorial policies, we will use the term necrotizing granulomatous vasculitis [NGV] instead of Wegener granulomatosis throughout this article), microscopic poly-
The pathogenic role of ANCA.

**Pathogenesis of AAV**

**In Vitro and In Vivo Models Studying the Pathogenic Role of ANCA in Vasculitis**

The close clinical association between MPO-ANCA and PR3-ANCA and AAV, together with evidence from *in vitro* and animal models, suggests that they play a critical role in the pathogenesis of vascular damage in patients with AAV. ANCA antigens are mainly located within the cytoplasmic granules of resting neutrophils, "sheltered" from circulating ANCA. However, when neutrophils are primed by tumor necrosis factor (TNF)-α, other cytokines, or microbial products, MPO and PR3 traffic to the external leaflet of the neutrophil plasma membrane, facilitating ANCA binding. This preliminary low-grade inflammation may occur *in vivo* due to infection. *In vitro* studies show an orchestrating role for ANCA in neutrophil-mediated vascular injury models. Individual baseline levels of PR3 surface expression in resting neutrophils vary widely, and higher degrees of PR3 surface expression are reported in patients with NGV, possibly increasing the likelihood of PR3-ANCA binding.

ANCAs are believed to influence neutrophil-endothelial interactions. ANCAs induce changes in the neutrophil actin cytoskeleton, resulting in changes in shape and capillary sequestration and favoring adhesion to small-vessel endothelium. Only when adhering to endothelium can ANCA-activated neutrophils release reactive oxygen species and lytic enzymes, including MPO and PR3, damaging vessel walls. ANCA-activated neutrophils and monocytes also release proinflammatory cytokines, which activate and recruit more inflammatory cells, including monocytes and T cells, perpetuating deleterious immune responses.

**Granuloma Development in NGV: The Role of the Respiratory System**

NGV usually starts as a granulomatous disease of the respiratory tract and progresses to systemic disease with PR3-ANCA-associated vasculitis, suggesting an aberrant cell-mediated immune response to exogenous or endogenous antigens in the respiratory tract, resulting in granuloma formation. Cell types in NGV granulomas include PR3+ cell clusters (neutrophils and monocytes) surrounded by antigen-presenting cells and abundant T-helper type 1 CD4+CD28− effector memory T cells and maturing B and plasma cells, suggesting neoformation of lymphoid-like tissue. There are alterations in the differentiation of T cells, which display features of...
effectector memory T cells. As a major source of T-helper type 1 cytokines, CD4+CD28+ T cells are thought to be the driving force of granuloma formation. Abdulahad et al. found that patients with NGV in remission have an expanded number of regulatory T cells with a defective suppressor function, which may explain the development of NGV and its relapsing nature.

NGV granulomas may represent lymphoid structures the cellular components of which would ultimately be responsible for PR3-ANCA production. Voswinkel et al. found B lymphocyte-rich follicle-like aggregates in granulomatous NGV lesions. Exposure of the immune system to the complementary peptide of PR3 may produce antibodies to this peptide that generate anti-idiotype antibodies that cross-react with PR3. PR3-encoding gene complementary sequences have been identified in Staphylococcus aureus infections, the nasal carriage of which is associated with NGV, supporting the role of infectious agents as triggering factors of PR3 autoimmunity.

Uncertainties and Gaps: ANCA-Negative Vasculitis

Although the evidence for a pathogenic role for ANCs, mainly MPO-ANCs, is striking, various questions remain. For instance, some patients who are negative for ANCs fit the phenotype for MPO-ANCA-associated pauci-immune necrotizing glomerulonephritis. One study found that the histologic findings and prognosis in patients with ANCA-negative pauci-immune glomerulonephritis are comparable with those of patients with ANCA-positive disease. Neutrophil cell infiltration in tissues occurs independently of circulating ANCs in patients with ANCA-negative disease and, thus, may involve unidentified autoantibodies or T-cell-dependent mechanisms. In patients with NGV, patients remain more frequently negative for ANCs in the limited form (ie, upper airways) of the disease. However, ANCs are usually detected on the progression of disease to the systemic vasculitic stage. Another counterargument is that MPO-ANCs are not useful to monitor patients with MPO-AAV.

Kain et al. recently provided a novel molecular explanation for the origin and development of pauci-immune focal necrotizing glomerulonephritis, showing that infection by fimbriated bacteria can trigger cross-reactive autoimmunity to a previously characterized ANCA antigen, lysosomal membrane protein (LAMP)-2, resulting in the production of autoantibodies that activate neutrophils, damage human microvascular endothelium in vitro, and cause segmental necrotizing glomerulonephritis in rats. Together with reports that MPO-ANCs cause pauci-immune focal necrotizing glomerulonephritis in mice, it is possible that MPOs-ANCs act synergically with anti-LAMP-2 antibodies to cause injury. Alternatively, anti-LAMP-2 antibodies might alter the role of LAMP-2 in the presentation of cytoplasmic antigens, such as MPO and PR3, leading to the synthesis of antibodies against these proteins. Of 84 patients with biopsy-proven active pauci-immune necrotizing glomerulonephritis, 70 patients (83%) had positive enzyme-linked immunosorbent assay results for classic ANCA, 38 for MPO-ANCA, 39 for PR3-ANCA, and 7 for both antigens. However, 78 patients (93%) had antibodies to human LAMP-2, which may explain the negativity for PR3-ANCs and MPO-ANCs in some patients with typical AAV.

Clinical Forms of Lung Disease in AAV

Table 2 shows the spectrum of respiratory abnormalities found in patients with AAV. The recent European League Against Rheumatism recommendations for the management of primary small- and medium-vessel vasculitis classified AAV in different disease patterns, according to the extension and severity of the disease. These patterns were localized, (upper respiratory tract disease, lower respiratory tract disease, or both with no other systemic involvement or constitutional symptoms), early systemic (no organ-threatening or life-threatening disease), generalized (renal or other organ-threatening disease, with serum creatinine < 500 μmol/L [5.6 mg/dL]), severe (renal

<table>
<thead>
<tr>
<th>Condition</th>
<th>Abnormality</th>
</tr>
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<tbody>
<tr>
<td>NGV</td>
<td>Endobronchial granulomatous inflammation; Granulomatous nasal or paranasal inflammation; and Subglottic stenosis</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>Symptomatic and asymptomatic pulmonary nodules and infiltrates; Pleuritis and pleural effusion; Pulmonary arterial hypertension; and Pulmonary fibrosis</td>
</tr>
<tr>
<td>MPA</td>
<td>Symptomatic and asymptomatic pulmonary infiltrates; Pleuritis and pleural effusion; Pulmonary hemorrhage and alveolitis; Pulmonary fibrosis; and Pulmonary arterial hypertension</td>
</tr>
<tr>
<td>CSS</td>
<td>Allergic rhinitis; Nasal polyposis and obstruction; and Recurrent sinusitis</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>Asthma; and Infiltrates and nodules</td>
</tr>
</tbody>
</table>
or other vital organ failure, with serum creatinine levels > 500 μmol/L [5.6 mg/dL], and refractory (progressive disease not responsive to glucocorticoids and cyclophosphamide).

Classic forms of NGV primarily involve the upper and lower respiratory tracts and kidneys. However, NGV is limited to the upper respiratory tract or lungs in 25% of cases, with necrotizing granulomatous inflammation developing in patients that leads to chronic sinusitis, subglottic stenosis, orbital pseudotumor, and pulmonary nodules or infiltrates. Tracheobronchial disease is almost exclusive to patients with NGV and usually is associated with involvement of the supraglottic territories, pulmonary parenchyma, and other structures. Common symptoms include hoarseness, cough, dyspnea, stridor, wheezing, and hemoptysis due to cavitated pulmonary parenchymal lesions, alveolar hemorrhage, bronchiectasis, and blood from supraglottic airways. Lung nodules or infiltrates are apparent in 85% of patients with NGV, whereas transient and patchy pulmonary infiltrates have been reported in 38 to 77% of patients with CSS. However, asthma is the predominant symptom in CSS, occurring in > 95% of patients and usually preceding vasculitis by a mean time of 3 to 4 years. Other common forms of airflow involvement in patients with CSS include nasal obstruction, recurrent sinusitis, and nasal polyposis. As other vasculitic elements appear (eg, neuropathic or systemic involvement), asthma severity as well as bronchial, nasal, and sinus exacerbations may increase. Prolonged glucocorticoid treatment of asthma may partially or totally mask the clinical signs of untreated CSS.

Pulmonary involvement manifested as alveolar capillaritis-induced diffuse alveolar hemorrhage is reported in 25 to 55% of patients with MPA. Alveolar hemorrhage is increasingly recognized as a prominent pulmonary manifestation of NGV, occurring in around 5% of cases and occasionally as the initial finding. When accompanied by glomerulonephritis, it is considered to be a form of pulmonary-renal syndrome. Lung biopsy specimens reveal intra-alveolar and, frequently, interstitial RBCs (Fig 1). Often, there is pauci-immune hemorrhagic necrotizing alveolar capillaritis without evidence of granulomatous inflammation or prominent large-vessel lesions. Clinical features in patients with both MPA and NGV range from asymptomatic pulmonary infiltrates to hemoptysis, pleural effusion, and alveolar hemorrhage. A few cases present with interstitial lung involvement mimicking idiopathic pulmonary fibrosis, which may result from repeated alveolar hemorrhage due to pulmonary capillaritis.

Pulmonary functional alterations described in AAV include restrictive and obstructive patterns. The most frequent functional abnormality is a reduced lung carbon monoxide diffusing capacity, which may increase markedly when an active alveolar hemorrhage is present. In cases of diffuse interstitial involvement, a clear restrictive pattern is observed. Airflow obstruction is typical in asthma due to CSS. An altered flow-volume loop may be useful in the diagnosis of lesions causing obstruction of the large airways, such as subglottic or main bronchial stenosis in patients with NGV.

**Figure 1.** A: chest roentgenogram with posteroanterior view of a patient with NGV who was admitted to the hospital ICU with diffuse pulmonary hemorrhage and respiratory failure. B: lung biopsy specimen showing severe alveolar capillaritis with alveolar hemorrhage. Observe the thickened interalveolar septum with infiltrates of mononuclear cells (long arrow) and neutrophils (short arrow) [hematoxylin-eosin, original ×60].

**Prognosis of Pulmonary Complications of AAV**

AAV is potentially life threatening. Although outcomes differ, untreated NGV and MPA are normally
rapidly progressive and fatal. MPA mortality is highest in the first year after diagnosis, whereas NGV mortality increases progressively, perhaps reflecting the nature of the underlying disease. When glucocorticoids and other immunosuppressants are administered, patient survival improves dramatically, and > 90% of patients achieve remission at 6 months. However, relapse rates remain at around 50%, and severe vital organ-threatening damage and treatment-related adverse effects develop in approximately 25% of patients. About 10% of patients with AAV are refractory to standard immunosuppressant combination therapies and are at high risk for death. Features associated with high AAV mortality include age > 60 years, renal and pulmonary involvement (for NGV and MPA), cardiac involvement (for CSS), and a high disease activity index, as assessed by the Birmingham Vasculitis Activity Score (BVAS). A recent study comparing two large cohorts of French and American patients with AAV found that age was a predictor of treatment resistance, whereas PR3-ANCA positivity and lung involvement were predictors of relapse in both groups. Age and pulmonary infections were independent predictors of death in a study of 234 patients with AAV (MPA, 147 patients; NGV, 69 patients; CSS, 3 patients; and renal-limited vasculitis, 15 patients), in which 99 patients (42%) were > 65 years of age (mean ± SD age, 72 ± 5.6 years). Older patients had more severe pulmonary involvement, including pulmonary infiltration, interstitial fibrosis, and mechanical ventilation at presentation, and a higher risk of secondary pulmonary infection during follow-up, which was indeed more frequent in patients with pulmonary interstitial fibrosis.

Alveolar hemorrhage is the main cause of hospitalization and hospital ICU admission in cases of AAV with pulmonary complications. A study that analyzed clinical outcomes in 65 patients hospitalized for AAV found that respiratory failure, hemoptysis, smoking, and acute renal failure were strong predictors of hospital ICU admission, and 28-day mortality was increased in patients requiring ICU transfer, mechanical ventilation, or blood transfusions. Similarly, alveolar hemorrhage was the main reason for hospital ICU admission in another study of 38 patients with severe small-vessel vasculitis (NGV, 19 patients; MPA, 16 patients; CSS, 1 patient; and CNS vasculitis, 2 patients), and the 28-day mortality rate was 11% due mainly to septic shock. Patients who died had higher initial severity and multiorgan system failure scores, including acute physiology score and acute physiology and chronic health evaluation [APACHE] III score.

Patients with CSS seem to have a better prognosis, although severe complications, such as myocardial vasculitis and renal and CNS involvement, occur in a considerable number of patients. The French Vasculitis Study Group proposed the “five factor score,” a prognosis index for CSS that includes the following items: severe GI tract disease (bleeding, perforation, infarction, or pancreatitis); renal involvement (serum creatinine level ≥ 1.58 mg/dL); proteinuria (≥ 1 g/d); heart disease (infarction or heart failure); and CNS involvement. Having any factor adversely affects outcomes.

**TREATMENT**

**Treating Pulmonary Complications**

Table 3 shows the therapeutic options for AAV and indications according to the results of clinical trials. Therapy with glucocorticoids in combination with other immunosuppressants, such as cyclophosphamide or methotrexate, are the current mainstay of AAV treatment. Cotrimoxazole therapy has shown benefit when coadministered with the standard immunosuppressant therapy for remission maintenance of patients with NGV and upper respiratory tract disease.

The therapeutic options for pulmonary manifestations of AAV depend on the type of complication and the concomitant vasculitic features when pulmonary lesions are discovered. Pulmonary nodules or limited infiltrates may or may not be accompanied by constitutional symptoms or upper airway involvement, especially in patients with NGV and CSS, and patients should be treated with regimens for limited or early systemic disease, including glucocorticoids and methotrexate for induction remission, and azathioprine or methotrexate for remission maintenance (Tables 3, 4). In cases of pulmonary nodules with involvement of vital organs, such as the kidneys, intensive treatment, assessed by the renal function, should be administered. High doses of glucocorticoids and cyclophosphamide are recommended; plasma exchange also should be considered. Plasma exchange has been advocated in critical situations with severe renal and pulmonary involvement because it removes circulating ANCA and other proteins from the bloodstream (Table 4).

The treatment of pulmonary capillaritis and alveolar hemorrhage in patients with MPA and NGV remains empiric, and, apart from ventilatory support when indicated, patients should be treated according to the schema for severe renal involvement (Table 4). Despite early treatment with high-dose glucocorticoids, overall mortality remains high. Although reports have emphasized the utility of plasma exchange in NGV patients with alveolar hemorrhage (mainly with those with pulmonary-renal syndrome), no studies of plasma exchange in patients with AAV
have focused on pulmonary involvement. The best evidence has come from a randomized trial of plasma exchange as adjunct therapy in 137 patients with severe renal vasculitis who received high doses of IV methylprednisolone (n = 67) or plasma exchange (n = 70) [Methylprednisolone or Plasma Exchange for Severe Renal Vasculitis (or MEPEX) trial]. Plasma exchange was associated with increased renal recovery, a risk reduction for end-stage renal disease, and reduced dialysis dependency compared with methylprednisolone, supporting its use in patients with AAV and renal failure. Anecdotal reports have shown good results with the administration of recombinant coagulation factor VIIa in cases of alveolar hemorrhage in patients with CSS and MPA.

The management of subglottic disease remains challenging. For new-onset subglottic stenosis, medical treatment for localized disease is indicated. However, in cases with severe tracheobronchial disease, some authors have recommended therapy with systemic glucocorticoids and cyclophosphamide.

### Table 3—Therapeutic Agents for AAV

<table>
<thead>
<tr>
<th>Agent*</th>
<th>Type of Study†</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azathioprine</td>
<td>RCT</td>
<td>Standard agent used to maintain remission</td>
</tr>
<tr>
<td>Cotrimoxazole</td>
<td>RCT</td>
<td>Reduce risk of respiratory tract relapses in limited forms given concomitantly with glucocorticoids</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>RCT</td>
<td>Standard agent used to induce remission in generalized and severe disease</td>
</tr>
<tr>
<td>15-Deoxyspergualin</td>
<td>Prospective uncontrolled</td>
<td>Good alternative for treatment of refractory NGV; high rate of adverse side effects (mainly leukopenia)</td>
</tr>
<tr>
<td>IV Ig 52</td>
<td>RCT</td>
<td>Only one RCT in AAV; good response in patients with refractory NGV and MPA during first 3 months</td>
</tr>
<tr>
<td>Infliximab</td>
<td>Open-label trials</td>
<td>Useful alternative therapy for refractory AAV</td>
</tr>
<tr>
<td>Leflunomide</td>
<td>RCT</td>
<td>Good alternative as maintenance therapy</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>RCT</td>
<td>Good alternative to cyclophosphamide in patients with NGV and MPA with localized forms or non-life-threatening disease; limited efficacy as induction therapy</td>
</tr>
<tr>
<td>MMF 52</td>
<td>Prospective uncontrolled</td>
<td>Good alternative as maintenance treatment; little information as induction therapy</td>
</tr>
<tr>
<td>Plasma exchange</td>
<td>RCT for renal vasculitis</td>
<td>Good results in renal vasculitis and life-threatening disease situations, such as alveolar hemorrhage</td>
</tr>
<tr>
<td>Rituximab</td>
<td>Prospective long term</td>
<td>Good response mainly for vasculitis-related symptoms; partial or unsatisfactory response for granulomatous lesions</td>
</tr>
</tbody>
</table>

**RCT = randomized controlled trial.**

*Presented in alphabetical order.

†The best evidence available is collected.

‡15-Deoxyspergualin has not been approved by the US Food and Drug Administration or the European Medicines Agency.

### Table 4—Treatment of AAV According to Disease Extension and Severity

<table>
<thead>
<tr>
<th>Disease State</th>
<th>Treatment</th>
<th>NGV and MPA Remission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Localized disease</td>
<td>Steroids ± cotrimoxazole</td>
<td>2b/B Steroids ± cotrimoxazole</td>
</tr>
<tr>
<td>Generalized non-organ-threatening disease</td>
<td>Methotrexate + steroids</td>
<td>1b/A Methotrexate + steroids</td>
</tr>
<tr>
<td>Generalized organ-threatening disease</td>
<td>Pulse cyclophosphamide + steroids</td>
<td>1a/A Azathioprine + steroids</td>
</tr>
<tr>
<td>Diffuse pulmonary hemorrhage</td>
<td>High-dose of cyclophosphamide + pulse methylprednisolone</td>
<td>5/D Azathioprine + steroids</td>
</tr>
<tr>
<td></td>
<td>Cyclophosphamide + steroids + plasma exchange</td>
<td>4/C Azathioprine + steroids</td>
</tr>
<tr>
<td>CSS</td>
<td>Five-factor score ≥ 1 Cyclophosphamide + steroids</td>
<td>1a/A</td>
</tr>
<tr>
<td></td>
<td>Five-factor score = 0 Steroids</td>
<td>1a/A</td>
</tr>
</tbody>
</table>

Adapted from Bosch et al. 52

*Level of evidence and grade of recommendation according to Oxford Centre for Evidence-Based Medicine definitions.

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mide, regardless of the severity of other organ manifestations. On the other hand, Hoffman et al\(^5^4\) showed that the efficacy of local procedures, such as intralesional methylprednisolone injections and mechanical or balloon dilations, eliminate the need for new tracheotomies in almost all patients with NGV and subglottic stenosis. Silicone-coated stent implantation can be used as a good alternative,\(^5^3\) and in cases of fixed subglottic stenosis, intraluminal dilation, laser resection, or laryngotracheoplasty may be required.\(^3^0\) Finally, in patients with critical airway stenosis who are unresponsive to medical measures and dilation therapies, tracheostomy provides long-term relief.\(^3^0\) Therapy with inhaled glucocorticoids has shown benefits when the dosage of oral glucocorticoids is tapered to < 30 mg/d.\(^3^0\)

New Medications for AAV

Selective targeting of the immune mechanisms involved in vascular inflammation has the potential to effectively treat AAV while leaving host defense mechanisms relatively intact. More pathogenesis-oriented therapies could overcome current therapeutic defects by ablating key immune pathways with less toxicity.\(^5^0\) Although not exclusive to pulmonary involvement, currently used and experimental biological agents and new therapies are described in the following section.

Biological Agents

Anti-TNF-α Blockers: In vitro and in vivo evidence shows a central role of anti-TNF-α in AAV pathogenesis. TNF-α mediates granuloma formation in patients with NGV, and is increased in serum and vasculitic foci in those with active disease, with a return to normal levels during remission.\(^5^7\) TNF-α inhibition may be beneficial in patients with AAV, as animal models\(^1^3,5^8\) have shown that anti-TNF-α antibodies prevent and even strongly attenuate ANCA-induced focal necrotizing glomerulonephritis. However, clinical trials with anti-TNF-α agents (adalimumab, etanercept, and infliximab) in patients with AAV have not consistently shown a benefit. Etanercept showed disappointing results in maintaining remission in a randomized, placebo-controlled trial\(^5^8\) of 180 patients with NGV. In the same trial,\(^5^9\) etanercept administered with cyclophosphamide increased the risk of cancer beyond that observed with cyclophosphamide therapy alone. Therapy with infliximab has shown satisfactory remission rates (around 80%) and low relapse rates (around 15%) in several open-label trials\(^4^0,6^0–6^2\) in patients with refractory AAV. Josselin et al\(^6^3\) evaluated long-term outcomes in 15 patients with refractory systemic necrotizing vasculitides (NGV, 10 patients; MPA, 1 patient; rheumatoid arthritis vasculitis, 3 patients; and cryoglobulinemia, 1 patient) treated with infliximab (mean duration, 8 months). By day 45, 11 patients were in remission (BVAS, 0), and BVAS scores were reduced by > 50% in the remaining 4 patients. During follow-up, 5 patients achieved sustained remission; however, 10 patients relapsed at a median of 13 months, 3 of whom were still receiving infliximab. Adalimumab has been successfully tested\(^6^4–6^6\) in patients with several vasculitides, but there are no reports on its efficacy in patients with AAV. Randomized studies with infliximab and adalimumab in patients with refractory AAV are required.

Rituximab: Rituximab, a chimeric human and mouse monoclonal antibody that specifically depletes CD20+ B cells, has demonstrated potential for the treatment of B-cell-mediated autoimmune diseases, such as rheumatoid arthritis and systemic lupus erythematosus. The rationale for using rituximab in the treatment of AAV is based on its effective depletion of CD20-expressing precursors of ANCA-producing plasma cells.

Rituximab was first successfully used in a patient with chronic, relapsing NGV.\(^6^7\) Prospective open-label studies\(^6^8–7^0\) and retrospective studies\(^7^1,7^2\) have investigated rituximab as remission-induction therapy in patients with refractory or relapsing NGV (and MPA and CSS\(^6^9\)) in combination with glucocorticoids\(^6^8,7^1,7^2\) or cyclophosphamide.\(^6^9,7^0\) Overall, at a dose of 375 mg/m² in 4 weekly courses, rituximab has shown promising results in refractory cases.\(^5^9,6^9,7^1,7^2\) However, contradictory results were observed in patients with granulomatous lesions (eg, pulmonary nodules and retro-orbital masses). Rituximab was effective in eight cases\(^7^2\) of limited NGV unresponsive to three immunosuppressive agents but showed no benefit in other small series.\(^7^0,7^1\)

In these preliminary studies, rituximab-induced total depletion of circulating B cells at 1 month and ANCA titers generally decreased or became negative. Some patients experienced complete remission with no correlation with ANCA titers.\(^6^9,7^0,7^3\) Relapse rates ranged from 10 and 64%\(^6^8,6^9\) and frequently were preceded by a rise in ANCA titers and circulating B-cell recovery within 6 to 12 months.\(^7^1,7^3\)

More conclusive data depend on the final results of two large, ongoing, multicenter randomized trials of AAV. The Rituximab for the Treatment of NGV and MPA (or RAVE) trial (ClinicalTrials.gov identifier NCT00104299) is a prospective, multicenter, double-blind, placebo-controlled trial designed to establish the capacity of rituximab (compared to cyclophosphamide) to induce complete remission during the first 6 months after randomization.
ing the remission maintenance phase, all participants received therapy with oral azathioprine until month 18. The Rituximab for ANCA-Associated Renal Vasculitis (or RITUXVAS) trial is a phase II/III randomized clinical trial (EudraCT No. 2005–003610-15) that compared a rituximab-based regimen to standard care (combined regimen with cyclophosphamide and azathioprine for remission maintenance) in 44 patients with ANCA and renal involvement due to active NGV, MPA, or renal-limited vasculitis. Long-term B-lymphocyte depletion seems to be a promising approach to remission maintenance therapy in patients with refractory AAV (especially for vasculitis-related features) and is associated with a few adverse events.

**Abatacept:** With regard to AAV, there are no published reports on abatacept, which is a recombinant fusion protein with activity as a selective costimulation modulator that interferes with the interaction between antigen-presenting cells and T lymphocytes, and inhibits the activity of T lymphocytes. The Abatacept in AAV (or ABAVAS) trial (ClinicalTrials.gov identifier: NCT00482066) is an ongoing, prospective, double-blind, placebo-controlled trial assessing relapse rates of > 24 months in 112 patients with acute AAV presenting at first diagnosis or relapse. Patients will receive standard therapy with methotrexate and glucocorticoids and 12 months of therapy with abatacept or placebo.

**Other Therapies**

Leflunomide, a prodrug of the active metabolite of which inhibits a mitochondrial enzyme, has shown good results as remission maintenance therapy in patients with NGV. However, its use should be contemplated carefully because of its safety profile. Uncontrolled studies have suggested that mycophenolate mofetil (MMF) may be useful as induction therapy in AAV, even in patients who do not tolerate cyclophosphamide. A nonblinded clinical trial compared MMF therapy with intermittent cyclophosphamide pulses as induction treatment in 35 patients with AAV and moderate renal involvement. At month 6, BVAS scores were much lower in the MMF group, with more patients achieving complete remission and recovery of renal function. MMF also has been used for remission maintenance in patients with NGV after inducing remission with cyclophosphamide and glucocorticoids, with conflicting results. The results of the ongoing MMF vs Cyclophosphamide (or MYCYC) randomized clinical trial (EudraCT No. 2006–001663-33) and the completed MMF vs Azathioprine for Maintenance Therapy in AAV (or IMPROVE) trial (ClinicalTrials.gov identifier: NCT00307645), which was designed to define the optimal induction and maintenance therapy for AAV in patients with MMF, are awaited.

Because activated CD4 T cells producing T helper type 1 cytokines seem to play a crucial role in AAV, there is a rationale for the use of T-lymphocyte-blocking therapies, such as antithymocyte globulin. In a prospective, uncontrolled trial, a 10-day regimen of antithymocyte globulin induced remission in 13 of 15 patients with NGV.

15-Deoxyspergualin is an antiproliferative drug with effects on lymphocyte and macrophage function and neutrophil production. In an open-label study of 44 patients with refractory NGV, 45% of patients achieved complete remission after a median duration of 78 days, and around 40% of patients relapsed. Severe treatment-related side effects, which rarely led to treatment discontinuation, developed in one-half of the patients. The authors concluded that 15-deoxyspergualin may be a good alternative therapy for patients with refractory NGV, although it is not approved by the US Food and Drug Administration or the European Medicines Agency.

Patients with CSS have been treated with interferon-α since the 1990s because of its capacity to suppress the immune responses of overreactive T helper type 2 cells and their inhibitory effect on eosinophil effector functions. There have been no systematic studies of the effectiveness of therapy with interferon-α. Long-term use has been associated with leukoencephalopathy, which might limit its use in patients with CSS.

IV Igs have demonstrated clear benefits in Kawasaki disease. Uncontrolled series have suggested some beneficial effects in AAV patients. The only randomized controlled trial of IV Ig therapy showed a significant decrease in clinical and laboratory vasculitic activity in most patients (82%) in the IV Ig group during the first 3 months, but there were no subsequent differences between therapy with IV Ig and placebo.

**Conclusions**

Pulmonary involvement in patients with AAV is frequent. Depending on the nature of the lesions (nodules, infiltrates, or alveolar hemorrhage), patients may require different therapeutic approaches. In addition to glucocorticoids and other immunosuppressive agents, biological agents are emerging as potential therapies in refractory cases, although only rituximab and infliximab have been trialed with apparent initial clinical success. The results of ongoing and concluded trials are eagerly awaited. Dissect-
ing inflammatory mechanisms may identify molecular targets for future therapies in AAV. If safety concerns are overcome, a pathogenesis-based strategy might involve the combined use of agents directed to specific complications or situations in patients with AAV.

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Antineutrophil Cytoplasmic Antibody-Associated Vasculitides and Respiratory Disease

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