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REVIEWS

Systemic Vasculitis: Still a Challenging Disease

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• The efficacy of current therapeutic regimens in patients with systemic vasculitis is high, at the expense of considerable treatment toxicity. Optimal therapy for patients with these potentially life-threatening diseases is still debated. Our increased understanding of the pathogenetic mechanisms of systemic vasculitis has led to the development of new therapeutic alternatives, with better potential specificity for both the inflammation and immunologic causes of vasculitis: new immunosuppressive drugs (mycophenolate), monoclonal antibody modulators of lymphocyte function (rituximab), and cytokine-directed therapies (infliximab and etanercept). The safety and efficacy of such agents increasingly are being investigated in patients with systemic vasculitis. Additionally, many randomized prospective clinical trials have been completed to determine the precise roles for more conventional treatments (cyclophosphamide, azathioprine, and plasma exchange), providing an expanding evidence base to guide therapy in these challenging diseases. There now is clear evidence that duration of cyclophosphamide therapy can be relatively short (3 months), long-term maintenance therapy is needed to avoid relapse (often azathioprine), and patients at relatively greater risk for relapse can be identified. We review the most recent data on the current management of systemic antineutrophil cytoplasmic antibody-associated vasculitis, with emphasis on strategies to improve long-term outcome and reduce treatment toxicity while minimizing the risk for relapse. *Am J Kidney Dis* 46:173-185.

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INDEX WORDS: Antineutrophil cytoplasmic antibodies (ANCA); systemic vasculitis; immunosuppression.

ANTINEUTROPHIL CYTOPLASMIC antibody (ANCA)-associated vasculitides (AAVs) were, in most cases, until quite recently, life-threatening diseases with a fatal outcome caused by vital organ failure. Recent basic and clinical research has enormously improved our understanding of the pathogenesis and treatment of these diseases and improved both patient and renal survival. Although these diseases remain potentially life threatening, a fatal outcome now is less common. In view of this achieved improved survival, major aims of treatment include minimizing treatment toxicity and preventing longer term organ damage.

WE NOW HAVE SOLID EVIDENCE

The standard treatment regimen (a combination of oral corticosteroids and oral cyclophosphamide) is effective in reversing or controlling disease in up to 90% of patients.^{1,2} A complete or partial remis-

sion can be induced in most patients with AAVs, even those most severely affected. However, 1-year mortality and need for dialysis therapy are close to 25% for patients presenting with severe renal disease (creatinine level at presentation > 5.7 mg/dL [$>500 \mu\text{mol/L}$]) treated conventionally.

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Long-term prognosis has improved because responding patients, mainly those who are dialysis independent, have a 5-year survival rate of more than 70%.³ Most of these improvements in outcome have been achieved on the basis of observational cohort studies, rather than randomized controlled trials.

During the last 2 years, a number of high-quality trials have been completed that enable us to be more confident about therapy for AAV. The Methylprednisolone or Plasma Exchange for Severe Disease (MEPEX) and Cyclophosphamide or Azathioprine for Remission Therapy (CYCAZAREM) trials, for example, which examined the role of plasma exchange (PE) in induction therapy and choice of agent for maintenance of remission (discussed later), will have a major impact on treatment strategies for AAVs, respectively. Trials also have been completed using newer anticytokine therapies (etanercept and infliximab). **Table 1** lists most trial data in patients with systemic vasculitis.

The pathogenesis of the diseases also is becoming clearer, particularly the pathogenic role of ANCA. ANCAs activate primed neutrophils, enhance neutrophil cytotoxicity to endothelial cells, and interfere with normal neutrophil apoptosis. In animal models of myeloperoxidase (MPO)–ANCA disease, ANCAs themselves are capable of inducing pauci-immune glomerular necrosis and crescent formation when transferred into naïve mice.⁴ ANCAs modulate clinical features in patients according to pattern and specificity, and to some extent, ANCA titer predicts disease activity. Experimental evidence also supports a pivotal role for tumor necrosis factor α (TNF- α) in both endothelial damage and renal pathological states in patients with AAV. TNF- α is produced in situ (in glomeruli) in human disease by activated infiltrating mononuclear cells and resident renal cells. There is a clear correlation between TNF- α production and histological signs of activity in patients with systemic vasculitis⁴ and between serum levels of TNF- α receptor and disease activity.⁵

EVALUATING STRATEGIES TO IMPROVE REMISSION WITH LESS TOXICITY

PE and Methylprednisolone for Severe Acute Disease

One of the current challenges lies in tailoring immunosuppression to reduce treatment-associated morbidity and mortality without compromis-

ing organ function, remission rates, or relapse frequencies. For patients with the most severe renal disease, recovery of renal function is of paramount importance. Patients historically have been treated with either PE or intravenous methylprednisolone, the former having less toxicity despite being more invasive. A definitive role for PE now is emerging after much debate. The MEPEX trial randomly assigned more than 150 patients with the most severe renal disease and AAV (creatinine level > 5.7 mg/dL [> 500 μ mol/L]; most patients required dialysis) to receive either 7 sessions of PE performed at least 3 times weekly or intravenous methylprednisolone (3 g during 3 days), in addition to oral steroids and cyclophosphamide. Preliminary results showed that renal recovery from dialysis in patients with AAV was approximately 70% when PE was used compared with only 50% with intravenous methylprednisolone. Full results and longer term follow-up are awaited. Previous observational studies also showed that PE was of benefit in this situation and also for other severe clinical features, such as lung hemorrhage.⁶

We now would use PE in all patients presenting with severe renal failure, providing at least 7 exchanges during the first 2 weeks, in combination with oral steroids and cyclophosphamide. We additionally would use it for all patients with pulmonary hemorrhage regardless of level of renal function.

Oral or Intravenous Cyclophosphamide

Cyclophosphamide is a drug with a narrow therapeutic index, and treatment-related morbidity and mortality can exceed that caused by the vasculitic disease itself. This is particularly true in elderly persons, for whom these diseases are more common. Use of intermittent intravenous pulses of cyclophosphamide has been investigated as a possible therapeutic alternative to daily oral cyclophosphamide to reduce total cyclophosphamide exposure. de Groot et al⁷ found in their meta-analysis that the lower cumulative dose of cyclophosphamide when administered as intravenous pulses (375 mg to 1,000 mg/m² every 2 to 4 weeks) was associated with fewer infections and hematologic complications (leukopenia), but was equally effective in induction of remission compared with oral treatment (2 mg/kg/d). Unfortunately, pulsed dosing also carried a

Table 1. Recent Prospective Clinical Trials in Systemic Vasculitis

Study	Study Aims	Method/Population	Follow-Up	End Points	Results	Conclusion
MEPEX	MP vs PE for severe renal disease in AAV	Randomized prospective: 73 PE, 76 MP	Data available for 3 mo	Renal recovery from dialysis	70% off dialysis with PE vs 50% with intravenous MP	PE should be first choice of therapy to provide maximal chance of renal recovery (preliminary data) in AAV with severe renal disease
CYCAZAREM	C vs AZA during remission in AAV	Randomized prospective: 73 C; 71 AZA	18 mo	Relapse (primary end point) and adverse effect rates (secondary end point)	Switching from C to AZA after 3 mo (after induction of remission) induced no significant difference at 18 mo in relapse rate (15.5% vs 13.7%, $P = 0.65$) or adverse effects between the 2 groups	Withdrawal of C and substitution of AZA after remission is safe and can reduce long-term exposure to C
WGET	Etanercept for maintenance of remission in WG	Randomized placebo controlled: 174 patients with WG	27 mo	Sustained remission, adverse effects	No difference in rates of sustained remission (69.7% vs 75.3%, $P = 0.39$), significantly higher rate of neoplastic diseases in the etanercept group ($P = 0.01$) vs standard therapy	Etanercept is not effective in maintenance of remission in WG and is associated with a high rate of treatment-related complications
ACTIVE	Infliximab in the treatment of AAV, either acute or persistent	Prospective: 16 with acute AAV; 16 with persistent AAV	17 mo	Induction of remission, adverse effects, rate of relapses	Induction of remission in 88% of patients treated with infliximab, 88% sustained improvements in patients with chronic persistent AAV, 21% severe infections	Infliximab may be effective in induction of remission in AAV; however, with possible increased risk for infection, results need confirmation in larger randomized trials

Abbreviations: MP, methyl prednisolone; C, cyclophosphamide; AZA, azathioprine; ACTIVE, anti-cytokine therapy in vasculitis.

greater risk for relapses, which, of course, exposes patients to additional organ damage and additional treatment with immunosuppressive agents. Several smaller studies of patients with less severe vasculitis found no difference in mortality, relapse rate, or efficacy of these 2 forms of therapy, but more adverse effects in patients administered cyclophosphamide orally.^{8,9} A European prospective, multicenter, randomized study (Cyclophosphamide Orally or Pulsed in Systemic Vasculitis) is in progress to compare these 2 forms of therapy for efficacy of induction, maintenance of remission, and relative adverse effects in patients with renal vasculitis. It also will answer questions about the relative benefits in proteinase 3 (PR3)- and MPO-ANCA-associated vasculitis.

In our view, the current evidence does not allow a major distinction to be drawn between the 2 forms of therapy with cyclophosphamide, and we favor individual units being completely familiar with one or other method in general, reducing the dose for severe renal impairment and increasing age of patients and watching carefully for bone marrow suppression (weekly complete blood counts, at least initially).

Azathioprine for Maintenance Therapy

Although the addition of cyclophosphamide induces remission better than steroids alone, especially in patients with Wegener granulomatosis (WG), it clearly would be beneficial if the course could be as short as possible to minimize its potential toxicity. There now is excellent evidence that azathioprine may be substituted for cyclophosphamide approximately 3 months after initiating induction therapy for maintenance therapy in patients with AAV without an increase in relapse rate during the initial 18 months. The CYCAZAREM study was the first European Vasculitis Study Group (EUVAS) trial completed and fully reported.¹⁰ Patients with AAVs were either administered 1 year of oral cyclophosphamide or switched to azathioprine therapy after 3 months' induction with cyclophosphamide. Remission was induced in 93% of 155 patients. There was no significant difference at 18 months in relapse rates between the 2 groups. Short-term adverse effects of the 2 immunosuppressive regimens were similar. This study therefore clearly showed the utility of only 3 months of cyclophos-

phamide therapy followed by azathioprine in induction and minimizing early relapse.

We now would treat all patients with AAVs and renal disease with 3 months of cyclophosphamide therapy before switching to azathioprine if the patient is in remission. We would keep all patients on azathioprine therapy for at least 12 months if in remission, and usually longer.

Methotrexate

Methotrexate also has been investigated as a less toxic alternative to cyclophosphamide in patients with mild to moderate forms of systemic vasculitis (without such life-threatening complications as pulmonary hemorrhage or renal insufficiency), either as primary induction treatment in patients developing severe adverse effects to cyclophosphamide or for patients with chronically persistent disease (eg, arthralgia, neuropathy, sinus disease) while on cyclophosphamide therapy. Early data showed acceptable remission rates (79%), but frequent relapses (58%), in the majority of patients after the reduction or discontinuation of methotrexate.¹¹ An additional study of 42 patients with not immediately life-threatening WG found that remission was obtained in 71% of patients within a median of 4.2 months.¹² Preliminary results of the EUVAS prospective, randomized, controlled Nonrenal Wegener's Treated Alternatively With Methotrexate Trial showed no difference in the (good) remission rate between the 2 groups at 6 months (83% versus 84%), but a greater relapse rate in methotrexate-treated patients (69% versus 42%; $P = 0.02$).¹³ Immunosuppression was stopped after 1 year in this study, leading to high relapse rates thereafter in both groups, reinforcing the importance of longer term treatment. None of these patients had renal disease.

We would use methotrexate for patients with nonrenal AAV for whom we are keen to avoid cyclophosphamide or disease is clinically thought to be only mild. However, we would continue therapy for at least 18 months, and usually longer.

Other Agents

Limited experience exists with the use of other agents as induction therapy in patients with systemic vasculitis, but cyclosporin A,¹⁴ intravenous immunoglobulin,^{15,16} and mycophenolate mofetil (MMF) have been used, with some lim-

ited success. Therefore, these agents should be considered only in patients with a contraindication to cyclophosphamide, PE, or methotrexate. Finally, infliximab (a monoclonal anti-TNF antibody) has been used in a pilot study in addition to conventional immunosuppression for induction of remission in patients with AAV. Remission rates greater than 80% were obtained with a possible reduction in steroid dose (discussed later).

STRATEGIES TO REDUCE RELAPSES AND IMPROVE QUALITY OF LIFE

Primary systemic vasculitides often are chronic relapsing diseases, potentially requiring prolonged immunosuppression. Therefore, their long-term management must address not only the induction of remission, but also the potential need for repeated courses of treatment and cumulative risk for toxic effects of therapy. Preliminary findings suggest (not surprisingly) that vasculitis has an impact on patients' lives similar to that of other chronic illnesses and is associated with decreased quality of life and increased distress.¹⁷ The level of incapacitation depends on disease activity, but also is strongly influenced by its treatment and the associated side effects. During recent years, it has become evident that medical management of patients with AAVs should focus on improving not only survival, but also quality of life; decreasing side effects of treatment; and reducing the incidence of relapse.

The CYCAZAREM trial clearly showed that switching from cyclophosphamide to azathioprine therapy after 3 months had no deleterious impact on relapses (equal in both groups) during the next 18 months, but reduced total exposure to the substantially more toxic agent. This is likely to be beneficial for patients surviving longer. However, there is some concern (discussed later) that, for a minority of patients, 3 months of cyclophosphamide therapy may be too brief a time.

Mycophenolate Mofetil

MMF should, at least theoretically, be as effective as azathioprine in the maintenance of remission in patients with systemic vasculitis. However, data currently are conflicting. In a pilot study of 11 patients with WG or microscopic polyangiitis, MMF after standard induction

therapy was effective in maintenance of remission.¹⁸ Conversely, another recent trial (of 14 patients with WG treated with daily cyclophosphamide and glucocorticoids to induce remission) showed that MMF was well tolerated, but relapses occurred in 43% of patients.¹⁹ The International Mycophenolate Mofetil Protocol to Reduce Outbreaks of Vasculitis study (a prospective, randomized, multicenter trial launched by EUVAS) is still actively recruiting patients and will establish the exact role of MMF (compared with azathioprine) in maintenance therapy for patients with renal vasculitis. MMF is substantially more expensive than azathioprine and sometimes difficult to titrate to a therapeutic dose because of gastrointestinal toxicity.

We generally reserve MMF therapy for patients with mild relapses while being administered azathioprine for whom we do not want to re-introduce cyclophosphamide therapy.

Methotrexate

Methotrexate also may be used effectively to maintain remission in patients with nonrenal disease initially treated with corticosteroids and cyclophosphamide. This immunosuppressive protocol is attractive because it combines the efficacy of cyclophosphamide (used with minimal risk for a limited period) with methotrexate, a drug with a more favorable toxicity profile. In a report by Langford et al²⁰ of 31 patients treated in this way, the relapse rate at 2 years was only 16%.

Trimethoprim-Sulfamethoxazole

Use of trimethoprim-sulfamethoxazole has been investigated for its beneficial role in preventing relapses in patients with WG, probably by reducing the nasal carriage of staphylococci, but potentially also as an immunomodulatory agent. Recurrence of upper-airway disease is reduced by long-term use, but not relapses in other organs.²¹ However, trimethoprim-sulfamethoxazole has an important role when administered in a low dose to patients treated with aggressive immunosuppressive regimens as prophylaxis for opportunistic infections caused by *Pneumocystis* and *Nocardia* species.

We use trimethoprim-sulfamethoxazole in all patients during induction therapy as prophylaxis for infection caused by *Pneumocystis* species

and subsequently continue it long term in those with WG and head and neck disease.

Cyclosporine and Leflunomide

Cyclosporine has limited efficacy in patients with vasculitis: the switch from cyclophosphamide to cyclosporine was followed by an unacceptably high relapse rate in 1 study of patients with WG.²² Leflunomide is an inhibitor of de novo pyrimidine synthesis (with consecutive inhibition of T-cell proliferation) and has anti-inflammatory effects (through inhibition of production of the pro-inflammatory cytokines TNF- α and interleukin 1 β).²³ Already used with encouraging results in patients with rheumatoid arthritis,²⁴ this drug presently is being evaluated in an open-label study of patients with WG as a remission maintenance agent.²⁵

Infliximab and Etanercept

Experimental and pathological data showed that TNF has a major role in sustaining the ongoing inflammation in patients with AAV and in the activation of endothelial cells, making TNF blockade an attractive therapeutic strategy in patients with vasculitis. TNF blockade has at least 3 potential roles in patients with AAV: as a component of induction therapy to achieve rapid remission and salvage of vital organ function, as a steroid-sparing agent, and as rescue therapy for patients with refractory vasculitis. Two anti-TNF treatments currently are approved for clinical use: etanercept (Enbrel; Immunex Corp, Seattle, WA) is a soluble TNF receptor and infliximab (Remicade; Schering-Plough Corporation World Headquarters, Kenilworth, NJ) is a chimeric monoclonal anti-TNF antibody. The WG Etanercept Trial (WGET) examined the potential use of the anti-TNF agent etanercept in reducing relapses in patients with WG.²⁶ One hundred eighty-one patients were randomly assigned to the administration of etanercept in addition to either cyclophosphamide or methotrexate and steroids. Seventy percent of patients achieved remission, but relapse rates were very high (>50%) regardless of the use of etanercept. Unfortunately, patients in this study had doses of their baseline immunosuppression (steroids) reduced rapidly, and in most, immunosuppressive drugs were discontinued completely during the first year despite being at high risk for relapse.

This result differs from that shown with an alternative anti-TNF agent, infliximab, in a smaller study (discussed next) in which patients showed clinical benefit from treatment, whether with acute disease or persistently active vasculitis.

Monitoring ANCA

Data from several centers and cohort studies and also the CYCAZAREM trial suggested that disease in patients with PR3-ANCA and MPO-ANCA may behave differently and hence require a different approach to treatment. Most recently, this was confirmed in a large single-center cohort of patients (N = 80) with AAV followed up for a median of 46.7 months. Patients with PR3-ANCA had more aggressive disease and poorer outcome compared with MPO-ANCA-positive patients.²⁷ Several other studies also suggested there are differences, especially in relapse rates, with greater rates for patients with PR3-ANCA or disease classified as WG.⁷ One therefore could argue that MPO-ANCA-positive patients could be treated with a less toxic lower dose treatment, such as intravenous cyclophosphamide, whereas patients with potentially more aggressive disease may require oral cyclophosphamide as induction treatment.²⁸ Longer term maintenance immunosuppression also may need to be adjusted according to disease subtype so that patients with increased relapse risks are offered longer term treatment, for example.

We routinely increase the duration of maintenance immunosuppression therapy (usually low-dose prednisolone and azathioprine) in patients in remission with PR3-ANCA or persistent ANCA titers to at least 3 and usually 5 years (no evidence for the duration of therapy).

HOW TO TREAT PATIENTS WITH RESISTANT OR PERSISTENT DISEASE

Standard induction therapy with cyclophosphamide and corticosteroids fails to induce remission in approximately 10% of patients.²⁹ What are alternative therapies for this category of patients?

Deoxyspergualin

Deoxyspergualin is an immunosuppressive agent with multiple actions, including suppression of humoral immune responses by blocking

the transcriptional activation of κ L chain expression during B lymphocyte development, and the development of cytotoxic T cells. Deoxyspergualin was effective for the induction of remission in 19 patients with active refractory WG in 1 multicenter pilot study.³⁰ It also was used successfully in 5 patients with proliferative glomerulonephritis.³¹ A prospective, multicenter, controlled trial of patients with WG currently is underway for those with chronic persistent disease despite conventional immunosuppression. Deoxyspergualin is administered as a subcutaneous injection daily and induces reversible neutropenia in recipients. Careful monitoring therefore is required during its use.

Antithymocyte Globulin

Successful use of polyclonal antibodies in the form of antithymocyte globulin directed against activated lymphocytes has been reported in a small number of patients with intractable WG, with induction of partial or complete remission in 4 of 5 patients during a follow-up of 5 to 12 months.³² Another EUVAS study (SOLUTION [Antithymocyte Globulin for Refractory Vasculitis]) recently described a favorable outcome (complete or partial remission) with antithymocyte globulin therapy in 13 of 15 patients with histologically proven active refractory WG unresponsive or intolerant to cyclophosphamide.³³

Monoclonal Antibodies

Several other monoclonal antibodies directed against key molecules involved in the systemic and vascular inflammatory process have been used. Alemtuzumab (Campath-1H; Millennium and ILEX Partners, LP, Cambridge, MA) is an anti-CD52 monoclonal antibody targeted to lymphocytes, used initially in the treatment of patients with resistant B-cell chronic lymphoid leukemia.³⁴ It has been used for a small number of patients with intractable vasculitis.^{35,36} Some patients showed significant benefit; however, there are concerns about the mortality risk associated with its use in this setting (patients with previous exposure to potent immunosuppressive agents). Rituximab is an anti-CD20 chimeric monoclonal antibody developed initially for treatment of patients with lymphoma lymphocytes, but now also used in patients with systemic lupus erythematosus and systemic vasculitis. In a case

report of a single patient with chronic relapsing WG, Specks et al³⁷ presented the successful use of rituximab, inducing complete remission with the disappearance of circulating B lymphocytes and reduction in cytoplasmic ANCA (c-ANCA) titers. Preliminary data from other centers (as yet unpublished) has confirmed these findings in small numbers of patients. The US National Institute of Allergy and Infectious Diseases currently is assessing a protocol based on administration of daclizumab, a monoclonal antibody directed against the α subunit of the interleukin 2 receptor, as a remission agent in patients with WG.

Infliximab and Etanercept

Selective antagonists of cytokines (especially TNF) recently were developed and shown to be of major benefit in patients with rheumatoid arthritis, for example. In an open-label trial, Stone et al³⁸ evaluated the safety and efficacy of etanercept in patients receiving conventional treatment for WG and concluded that treatment with etanercept in combination with cyclophosphamide improved markers of disease activity while being very well tolerated. However, intermittently active WG (occasionally severe) was common (75% of cases). A much larger prospective, randomized, controlled trial was just reported to assess the efficacy of etanercept in patients with WG (WGET). Patients had acute active disease and, although most entered remission, more than 50% subsequently experienced a relapse. However, baseline immunosuppression also was reduced rapidly. Etanercept therefore has no role in managing patients with active WG with such a protocol.

Infliximab also has been used in the treatment of patients with vasculitis. Alone or in combination with standard treatment, the TNF blockade induced by infliximab results in clinical remission, reduced inflammation, and improved endothelium-dependent vasomotor responses.³⁹ An open-label, multicenter, prospective, clinical trial of patients with AAV showed that infliximab was effective at inducing remission in 88% of patients and permitted reduction in steroid doses. Even more exciting were results in patients with chronic persistent disease in this study, for whom the addition of infliximab to their current treatment resulted in sustained improvements in 88%.

However, infections were common, occurred in 21% of patients, and occasionally were severe, and 20% of patients experienced a relapse during the first year.⁴⁰

Finally, another promising alternative to cyclophosphamide is etoposide, an inhibitor of mitosis successfully administered to patients with WG who were either resistant to or intolerant of cyclophosphamide therapy.⁴¹⁻⁴³

We currently use infliximab as first-line therapy for patients with persistently active disease despite 2 to 3 months of cyclophosphamide and steroid therapy, but would consider deoxyspergualin or rituximab. Ideally, such therapies should be used in the context of a clinical trial.

HOW TO PREDICT RELAPSES

The utility of ANCA testing in predicting relapse in patients with AAV has been investigated in several studies and remains controversial. Persistence or reappearance of ANCAs after initial treatment has been shown to be a risk factor for relapse. In patients with WG, a positive c-ANCA titer after 12 months of treatment was associated with an increased risk for relapse (relative risk, 4.37) during a median follow-up of 53 months.⁴⁴ Jayne et al⁴⁵ also found that persistence of ANCA in patients with WG or microscopic polyangiitis was associated with a greater relative risk for relapse as opposed to patients achieving ANCA negativity. A recent clinical study retrospectively analyzed the evolution of AAVs for patients treated with cyclophosphamide only or those switched to azathioprine therapy after induction of remission (at 3 months). Ten of 13 patients who were c-ANCA positive at the time of treatment switch experienced a relapse. The study concluded that patients who are still ANCA positive at the time of treatment switch have a high risk for relapse.⁴⁶ However, it should be remembered that patients can experience relapse even if ANCA test results are negative. There are few data to suggest whether persistent ANCAs beyond 1 year continue to increase the risk for relapse.

We do not alter therapy specifically in relation to persistence of ANCAs, but increase the frequency of monitoring, warn patients to report new symptoms, and continue maintenance immunosuppression for a longer period in patients with persistent ANCAs or PR3-ANCA.

Aside from the absolute presence or absence of ANCAs in serum, increase in ANCA titers also has been associated with the occurrence of relapse: increases in ANCA titer (c-ANCA) preceded all 17 observed relapses in patients with WG included in the prospective study of Cohen Tervaert et al⁴⁷ and were noted in 82% of cases studied by Chan et al.⁴⁸ In the prospective study of Boomsma et al,⁴⁹ relapse of WG was observed in 71% of patients who showed an increase in PR3-ANCA titers, which also implies that in almost 30% of patients with an increase in ANCA titers, no clinical relapse occurred. Other observational studies support this lack of association in a substantial minority of patients.⁵⁰ Schmitt and van der Woude⁵¹ recently reviewed several studies, most of them retrospective, that looked at the relationship between increase in ANCA titer and relapse in patients with AAV. They found that an increase in ANCA titers was followed by relapse in 210 of 365 patients (58%) when ANCAs were detected by means of indirect immunofluorescence and 220 of 295 patients (75%) when ANCAs were detected by means of enzyme-linked immunosorbent assay.⁵¹ The investigators also noted significant differences between studies concerning the definition of relapse, evaluation of disease activity, intervals of ANCA detection, and so on, making it difficult to assess the real value of ANCA measurements in the follow-up of patients with AAV.

Given the association of increasing ANCA titers with subsequent relapse in many patients, can ANCA titers be used to prevent relapse through preemptive treatment? A single prospective, randomized, controlled study was reported that used preemptive therapy in patients with WG who experienced a significant increase in ANCA titers without clinical signs of relapse. Patients with a 4-fold (or greater) increase in ANCA titers had their immunosuppression increased (either dose increased [eg, steroids] or change to more potent agent). The observed relapse rate was 55% in the untreated group (with an increase in ANCA titer that was not treated) as opposed to 0% in the preemptively treated group. Moreover, patients without preemptive therapy required more aggressive treatment for the subsequent clinical relapse than those treated preemptively.⁵² Finally, a retrospective observational study from Han et al⁵³ also

showed that preemptive treatment based on monitoring serial ANCA titers was useful for the prevention of relapses in patients with AAV: the cumulative incidence of relapses was reduced by 82% ($P = 0.0002$) during 1 year between patients who did and did not receive preemptive increased immunosuppression when ANCA titers increased.⁵³

Although the outcome of these studies is encouraging, it remains difficult to justify the initiation or intensification of immunosuppressive therapy based solely on an increase in ANCA titers in a stable asymptomatic patient, because a significant number of these patients (25% to 30%) would receive an unnecessary increase in immunosuppression because they would not subsequently experience a relapse. The data certainly justify regular monitoring of ANCA titers and increased awareness of the risk for relapse in patients with persistent or increasing ANCA titers. Outstanding questions include the effects of a preemptive approach on long-term outcome, survival, toxicity from immunosuppression, and duration of preemptive treatment.⁵⁴

We do not routinely increase immunosuppression based solely on increasing ANCA titers, but make this decision based on clinical review in addition to serological data. We warn patients to be more wary and often increase the frequency of clinical review if ANCA titers increase.

HOW TO REDUCE THE HAZARDS OF IMMUNOSUPPRESSIVE DRUGS

The therapeutic strategies described have markedly decreased mortality in patients with AAV. With patients surviving for longer periods, long-term hazards of prolonged treatment with cyclophosphamide and corticosteroids have emerged, with the toxicity of treatment contributing significantly to the chronic morbidity and mortality of vasculitis. However, just as important are risks from disease relapses contributing to end-organ damage. The National Institutes of Health experience with WG reported a contribution of treatment toxicity to permanent damage in more than 50% of patients,⁵⁵ including steroid-induced diabetes, bladder and lymphoproliferative malignancy, and infertility.⁵⁶

Infectious complications are the most common cause of death or severe morbidity in patients with systemic vasculitis, and their fre-

quency is associated with age and concomitant steroid dosage.⁵⁷ The most common infections reported in recent studies are pneumonia, urinary sepsis, and soft-tissue infections caused by conventional organisms (*Escherichia coli*, streptococci, and staphylococci), and, less commonly, viruses (varicella zoster and cytomegalovirus) and opportunistic organisms (*Pneumocystis* species, fungal pneumonia, tuberculosis). Pneumonia remains the most common infectious clinical complication. Implementation of results of the CYCAZAREM trial (described previously) should reduce these long-term risks by allowing use of the less toxic azathioprine for long-term disease control without increasing the risk for early relapses.⁸ The leukopenia induced by cyclophosphamide also is a dangerous risk factor for infection, and avoiding this is of crucial importance. Granulocyte colony-stimulating factor can be useful for patients with myelosuppression to minimize the risk for infections associated with leukopenia.⁵⁸ Cyclophosphamide doses should be decreased in elderly patients, and white blood cell counts should be monitored closely. Opportunistic infections can be reduced by the use of prophylactic cotrimoxazole (*Pneumocystis* and *Nocardia* species) and avoiding cyclophosphamide in patients with hepatitis B-associated vasculitis.⁵⁹ Cyclophosphamide metabolites also can cause hemorrhagic cystitis and long-term bladder damage and malignant change. With intravenous dosing, this can be minimized by the use of oral mesna at the time of treatment. For long-term oral dosing, it is sensible (but no evidence) to use cyclophosphamide in the morning so that potentially toxic metabolites do not remain in the bladder overnight.

Use of an alternate-day glucocorticoid tapering regimen after remission of vasculitis disease also is an important strategy to minimize the serious side effects of these drugs. This was illustrated by a multicenter trial⁶⁰ in which overall mortality was decreased from 43% to 26%, and the rate of infectious complications, from 20% to 3% by means of alternate-day steroid use. All patients should receive prophylaxis for osteopenia, the precise treatment depending on the baseline risk (calcium and vitamin D, alfacalcidol, or bisphosphonates [but caution in patients with renal failure]). There are published guidelines in the United States and United Kingdom

Table 2. Prognostic Markers in Systemic Vasculitis

Prognostic Marker	Effect
Persistence or increasing ANCA titers ⁴⁵	Possible increased risk for relapse; effects of preemptive treatments questionable
PR3-ANCA vs MPO-ANCA ^{27,66}	Increased risk for relapse and more aggressive disease with PR3-ANCA
Increased age and creatinine level at presentation ^{57,67,68}	Both associated with worse outcome for renal recovery and death
Intercurrent infection, especially nasal <i>Staphylococcus aureus</i> in WG ⁶⁹	Associated with relapse and chronic persistent disease
Chronic lesions on renal biopsy ^{54,70}	Associated with worse renal outcome after induction therapy
Treatment with prednisolone alone vs prednisolone + cyclophosphamide ⁵⁴	Use of steroids alone increases risk for relapse
Treatment with pulse vs continuous cyclophosphamide ⁴	Increased relapse rate possible with pulsed therapy
Early reduction in immunosuppression ⁵⁸	Associated with relapse

for the prevention of steroid-induced osteoporosis. Patients also should receive gastric acid suppression for ulcer prophylaxis.

WHAT ARE PROGNOSTIC MARKERS FOR LONG-TERM OUTCOME?

The outcome of vasculitis has moved from simple measures of death and organ failure to more complex assessments of the acquisition of irreversible organ damage.⁶¹ This will be important in the assessment of new treatments. Numerous clinical studies have investigated the prognosis for patients with vasculitis and found several prognostic markers consistently associated with long-term outcome (Table 2). Many of these have been discussed. Identification of patients at greater risk for poor outcome is important when considering the risks versus benefits of potent immunosuppression, but there is no simple method of identifying patients who will uniformly respond poorly to treatment. Furthermore, because vasculitis causes life-threatening disease in multiple organs, the ongoing morbidity can be significant in the absence of treatment. If patients have renal-limited disease only, it is easier to decide that recovery is so unlikely that the risks of immunosuppression are not warranted, and patients should accept renal failure. We generally treat all patients presenting acutely as described previously, but then use these prognostic markers when deciding on the extent of initial immunosuppression in patients not initially responding. Patients with a better pre-

dicted outcome, but who have not responded initially, would be offered a second-line induction agent (infliximab, rituximab, or MMF). Prognostic markers also are useful in deciding on risks and benefits of lengthy long-term maintenance immunosuppression and on educating the patient about the likely long-term outcome.

TREATING ELDERLY PATIENTS

The incidence of vasculitis is increasing in the elderly population; the proportion of patients with vasculitis and rapidly progressive glomerulonephritis who are 70 years or older has increased from approximately 10% in the 1980s to more than 30% in series reported in the 1990s.⁶² Elderly patients with AAV have more acute renal failure, more associated renal disease, and worse creatinine levels, but fewer extrarenal clinical manifestations than younger patients at the time of presentation of vasculitis.^{50,63} Older patients also may respond less well to treatment and have more severe treatment complications (septicemia, bone fractures) and worse survival than younger subjects.⁶³⁻⁶⁵ It therefore will be very important to identify the best treatments for elderly patients.

CONCLUSION

Although current treatments of patients with AAVs can produce a high response rate in induction of remission, treatment toxicity remains a major problem. Long-term management of chronic disease also is a challenge. Recent

progress in understanding the pathogenic mechanism of inflammation in this challenging disease has allowed the development of new therapies with better specificity for both the inflammation and immunologic cause of vasculitis. Unresolved issues still remain, including how best to combine these novel therapies for maximum benefit. Randomized controlled clinical trials sufficiently powered to answer important and specific questions in patients with vasculitis have now been reported, and it is crucial that these are continued to establish the proper role for these new agents.

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