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VASCULITIS (LR ESPINOZA, SECTION EDITOR)

Advances in Therapy for ANCA-Associated Vasculitis

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Abstract The anti-neutrophil cytoplasmic antibody-associated vasculitides include granulomatosis with polyangiitis (Wegener's granulomatosis) and microscopic polyangiitis. The introduction of therapy with cytotoxic agents such as cyclophosphamide transformed these diseases from fatal diagnoses to chronic conditions characterized by cycles of relapse and remission. Modern treatment strategies have focused on minimizing cyclophosphamide exposure or eliminating its use altogether. Two randomized clinical trials have shown that rituximab is not inferior to cyclophosphamide for induction of remission in patients with severe granulomatosis with polyangiitis (Wegener's) or microscopic polyangiitis. For patients with non-life threatening disease, methotrexate may be used to induce and maintain remission, although some patients may have a higher long-term risk of relapse as a result. For patients with life-threatening disease, plasma exchange may be an effective adjuvant therapy. This article reviews seminal studies from the past decade that have contributed to the current standard of care.

Keywords Microscopic polyangiitis · Wegener's granulomatosis · Granulomatosis with polyangiitis · ANCA · Cyclophosphamide · Therapy · ANCA-associated vasculitis · Plasma exchange · Remission · Treatment · Biological therapy

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Introduction

Granulomatosis with polyangiitis (Wegener's) and microscopic polyangiitis are idiopathic forms of vasculitis that affect the small and medium-caliber blood vessels, and are associated with the presence of circulating anti-neutrophil cytoplasmic antibodies (ANCA) [1]. Microscopic polyangiitis is the most common of the pulmonary-renal syndromes, a disparate group of diseases characterized by pulmonary hemorrhage and glomerulonephritis [2]. In addition to vascular inflammation, granulomatosis with polyangiitis (Wegener's) is characterized by the presence of necrotizing granulomatous lesions, which can lead to diverse manifestations, including cavitary lung lesions, subglottic stenosis, and chronic sinusitis [3]. Although the necrotizing granulomatous manifestations of granulomatosis with polyangiitis (Wegener's) are most commonly found in the respiratory tract, they may also appear in other organ systems, and may lead to a diverse set of disease manifestations that can include orbital pseudotumor, Eustachian tube dysfunction, and mucocutaneous disease.

When first described, granulomatosis with polyangiitis (Wegener's) and microscopic polyangiitis were almost uniformly fatal. In the absence of immunosuppressive therapy, the one-year mortality associated with the systemic form of granulomatosis with polyangiitis (Wegener's) was 82 %, with a mean survival of only 5 months [4]. Similarly, the first case reports of microscopic polyangiitis were autopsy studies, further attesting to the substantial mortality associated with these diseases in the absence of effective therapy [5]. Glucocorticoids alone had only a small effect on the severity of these diseases; the use of glucocorticoids for treatment of patients with granulomatosis with polyangiitis (Wegener's), for example, increased the mean survival time from 5 months to 12.5 months, but did not affect the long-term outcomes associated with this disease [6].

In 1973, Anthony Fauci and Sheldon Wolff reported their experience at the National Institutes of Health using cytotoxic

agents such as cyclophosphamide for treatment of granulomatosis with polyangiitis (Wegener's) [7]. Of the 17 patients treated, many of whom were refractory to high-dose glucocorticoid therapy, a clinical response was observed in 14. From this experience evolved a protocol that combined the use of high-dose glucocorticoids and oral cyclophosphamide; this protocol continues to form the basis of the modern standard of care for the ANCA-associated vasculitides. Patients treated using this protocol received glucocorticoids for a median of 12 months, but continued to receive cyclophosphamide until a year after remission had been achieved, which could mean five years or longer of continuous exposure.

Prolonged courses of cyclophosphamide are clearly effective for the treatment of this disease; when treated in this fashion, 91 % of patients will have some clinical response, and 75 % will enter remission for some period of time. The cost of remission is substantial, however; 46 % of patients will develop a serious infection, 57 % will become infertile, and 43 % will develop hemorrhagic cystitis. Prolonged therapy with cyclophosphamide is also associated with a 33-fold increased risk of bladder carcinoma and an 11-fold increased risk of lymphoma [8]. Overall, 42 % of patients develop some form of serious morbidity directly attributable to therapy.

Clinical research on the treatment of the ANCA-associated vasculitides over the last decade has focused on determining strategies to reduce our reliance on cytotoxic agents such as cyclophosphamide. This article reviews several recent, seminal studies, and discusses how they have affected the current standard-of-care for treatment of these diseases.

How Long Do Patients Need to Be Treated with Cyclophosphamide?

The substantial toxicity associated with prolonged courses of cyclophosphamide necessitated a new approach to the treatment of granulomatosis with polyangiitis (Wegener's) and microscopic polyangiitis. Instead of using a single agent for treatment of the ANCA-associated vasculitides, investigators began to speak of a staged treatment approach involving two treatment phases: remission induction and remission maintenance [9]. Induction of remission was achieved by use of a short course (e.g., three to six months) of cyclophosphamide, and remission was maintained by using a less toxic immunosuppressive agent, such as methotrexate or azathioprine.

The benefits of a two-step approach were immediately clear: a shorter course of cyclophosphamide would substantially reduce the risks associated with prolonged exposure to this drug. Several case series supported this approach, but it was not until 2003 that the efficacy of this staged protocol was demonstrated in a randomized clinical trial. The CYCAZAREM (cyclophosphamide versus azathioprine for remission in generalized vasculitis) trial enrolled 155 subjects with granulomatosis with polyangiitis (Wegener's) or microscopic polyangiitis, all of whom were treated with daily oral cyclophosphamide (2 mg/kg) until remission was achieved [10]. Of these subjects, 143 (92 %) achieved remission, at which point, subjects were randomized to one of two different treatment strategies: half of the subjects continued to receive cyclophosphamide at a slightly reduced dose (1.5 mg/kg), similar to that called for by the Fauci–Wolff protocol. Half of the subjects, however, received treatment with daily oral azathioprine (2 mg/kg). The primary endpoint of this study was relapse frequency, which was identical between the two groups (13.5 % versus 15.9 %, $P=0.65$). It therefore seemed clear that a short course of cyclophosphamide followed by a longer course of azathioprine was as effective as the longer courses of cyclophosphamide that used to be standard.

At that point, however, it was not clear whether this protocol could be generalized to other steroid-sparing agents. Around this time, the French Vasculitis Study Group hypothesized that methotrexate might be a safer alternative to azathioprine, and would be associated with fewer adverse events. The WEGENT trial was designed to test this hypothesis [11]. All subjects received intravenous cyclophosphamide (0.6 g/m^2 i.v. every two weeks for the first month, followed by 0.7 g/m^2 every three weeks) to induce remission over a period of six to twelve months. When remission was achieved, patients were randomized to receive maintenance therapy with either methotrexate (0.3 mg/kg weekly) or azathioprine (2 mg/kg daily) for an additional twelve months, after which all patients received trimethoprim/sulfamethoxazole alone for remission maintenance. This study revealed no difference in the number of adverse events between the two treatment arms. Interestingly, this study also revealed no difference in relapse-free survival, either at 18 months (90.5 % versus 88.9 %) or at 36 months (69 % versus 64.1 %), indicating that methotrexate and azathioprine are equally effective at maintaining remission, after remission has been induced with cyclophosphamide.

The WEGENT trial demonstrated that multiple agents could be equally effective as remission-maintenance agents. It was, however, not clear from the study whether the choice of steroid-sparing agent affects outcome. The IMPROVE (international mycophenolate mofetil protocol to reduce outbreaks of vasculitis) trial examined this question by enrolling 159 patients with ANCA-associated vasculitis who were treated with cyclophosphamide (either oral or intravenous) for three to six months until remission was achieved [12]. Of the 159 subjects enrolled, 126 entered remission, and were randomized to receive either azathioprine (2 mg/kg daily) or mycophenolate mofetil (2 g/day) for six months. Doses of both agents were tapered over time; at the end of six months, the dose of the remission maintenance agent was reduced by 25 %, and at the end of nine months, subjects in both arms were receiving only half of their initial dose of the remission-maintenance agent (i.e., azathioprine

1.0 mg/kg versus mycophenolate mofetil 1 g daily). The primary endpoint of this study was time to first relapse.

The incidence of flare among subjects receiving mycophenolate mofetil was 0.22 per person-year, almost double the incidence observed among subjects maintained on azathioprine (0.13, P=0.04 for the comparison). The hazard ratio for flare associated with the use of mycophenolate mofetil was 1.7 (9.5 % CI: 1.06–2.71, P=0.03); the hazard ratio did not change when using a model that was adjusted for age, gender, diagnosis, renal function at entry, and route of cyclophosphamide administration (i.e., intravenous versus oral). Because this was not a dose-ranging study, it is impossible to know whether mycophenolate mofetil might have been more effective if a more aggressive treatment protocol had been used [13]. This study does demonstrate, however, that a short course of cyclophosphamide by itself is not enough; both the remission-induction and remission-maintenance phases are important to determining outcome, and the choice of remission maintenance agent affects the incidence of relapse.

How Much Cyclophosphamide Is Needed to Induce Remission?

One important strategy to reduce cyclophosphamide toxicity is to reduce the duration of exposure. Another important strategy, however, is to simply use less drug. Administering pulses of cyclophosphamide intravenously has long been standard for the treatment of patients with systemic lupus erythematosus, and is associated with substantially less cumulative exposure to this drug.

In 1997, a study by Guillevin et al. of 50 subjects with granulomatosis with polyangiitis suggested that both intravenous and oral cyclophosphamide were equally effective at inducing disease remission, but that use of intravenous cyclophosphamide was associated with a substantially higher risk of relapse (60 % versus 13 %, P=0.02) [14].

A subsequent meta-analysis of 11 studies encompassing 202 subjects with ANCA-associated vasculitis also demonstrated a trend toward more relapses among subjects receiving treatment with intravenous cyclophosphamide, but the difference was not statistically significant (OR 1.79, 95 % CI: 0.85–3.75) [15]. This meta-analysis did reveal, however, that subjects who received treatment with intravenous cyclophosphamide did not experience an increase in mortality or progression to end-stage renal disease, despite receiving substantially less drug (17 g versus 35 g).

The CYCLOPS (daily oral versus pulse cyclophosphamide during induction phase for generalized vasculitis) trial was an attempt to address this question definitively [16]. Subjects with newly diagnosed ANCA-associated vasculitis who had glomerulonephritis (with serum creatinine between 1.7 and 5.7 mg/dL) received cyclophosphamide for three to six months, until remission was achieved. Half the patients were randomized to receive therapy with daily oral cyclophosphamide (2 mg/kg) whereas half received intravenous cyclophosphamide (15 mg/kg every 2 weeks for the first month, then every three weeks thereafter). All subjects received azathioprine (2 mg/kg) as a remission maintenance agent, for a cumulative total of 18 months of therapy.

At the end of the remission induction phase, the proportion of subjects who achieved disease remission was equal in both groups (82.2 % versus 84.2 %). The time to remission was also equivalent, with a hazard ratio of 0.96 (95 % CI: 0.71–1.29). The number of subjects reaching the primary endpoint, which was the proportion of subjects with disease-free survival at 9 months, was also equivalent (74 % versus 68 %, P=0.06). The use of intravenous cyclophosphamide was associated with an increased risk of relapse over the 18 months of observation, but the difference was not statistically significant (hazard ratio 1.98, 95 % CI: 0.75–5.20). Again, subjects who received intravenous cyclophosphamide received substantially less drug (8.2 g versus 15.9 g, P<0.001).

Long-term follow-up of subjects enrolled in CYCLOPS indicates that the risk of relapse continues to increase among the subjects initially treated with intravenous cyclophosphamide. After a median follow-up of 4.3 years, the risk of relapse was lower among patients who had received oral cyclophosphamide (HR 0.50, 95 % CI 0.26–0.93, P=0.029), although there was no difference in renal survival or overall survival [17]. The long-term follow-up of subjects enrolled in CYCLOPS implies that the risk of flare may be inversely proportional to cyclophosphamide exposure, with higher cumulative doses leaving subjects at lower risk for disease flare. Because the excess flare risk does not seem to threaten life or renal function, this trade-off may be beneficial for many patients, but the long-term data make this less clear.

Do All Patients Require Treatment with Cyclophosphamide?

Standard therapy of subjects with ANCA-associated vasculitis generally entails use of cyclophosphamide. However, patients with these diseases often present with relatively mild manifestations, raising the question of whether some patients could forgo treatment with cyclophosphamide altogether.

Multiple case series have demonstrated the efficacy of this approach for subjects with mild forms of granulomatosis with polyangiitis (Wegener's) [18–20]. In 2005, deGroot et al. published the results of NORAM (non-renal Wegener's alternatively treated with methotrexate), a randomized clinical trial that compared the efficacy of methotrexate versus cyclophosphamide for treatment of patients with granulomatosis with polyangiitis (Wegener's) with early

systemic disease (which is defined as disease that is neither organ-threatening nor life-threatening) [16].

One hundred subjects were enrolled, and were randomized to receive therapy either with daily oral cyclophosphamide (2 mg/kg) or weekly methotrexate (20–25 mg) for 12 months, after which all therapy was withdrawn. Subjects were tapered to prednisolone 7.5 mg/day by the sixth month after randomization; glucocorticoids were discontinued by the twelfth month after randomization, and subjects were followed for a total of 18 months.

At 6 months, an equivalent number of subjects in both groups had reached disease remission (93 versus 90, P= 0.78). There were several signals, however, that subjects who received methotrexate might not fare as well. Subjects who received treatment with cyclophosphamide achieved remission more rapidly, and required less glucocorticoids to do so (6.2 g versus 8.8 g, P=0.001). At 18 months, subjects who received cyclophosphamide were also substantially less likely to have relapsed (46.5 % versus 70 %, P= 0.02).

With long-term follow-up of subjects enrolled in the NORAM trial, however, it becomes even more clear that subjects who initially received methotrexate continue to be more likely to relapse [21]. After a median of 6.0 years of follow-up, cumulative relapse-free survival was lower among subjects who had originally received methotrexate (P=0.056). Moreover, these subjects were more likely to require subsequent treatment with cyclophosphamide (P= 0.037), which must dampen our enthusiasm for this strategy as a method of avoiding cyclophosphamide exposure.

This, by no means, negates the value of strategies that eschew cyclophosphamide altogether, particularly for subjects who do not have glomerulonephritis. One-third of subjects enrolled in the NORAM trial had hematuria, and it seems possible that these subjects were largely responsible for the poor long-term response to methotrexate. For subjects with limited flares of vasculitis, characterized by organ involvement that is unlikely to evolve into life-threatening manifestations (for example, chronic sinusitis or arthralgias) methotrexate is a valuable alternative to cyclophosphamide for remission induction [22].

What Is the Role of Plasma Exchange in the Treatment of ANCA-Associated Vasculitis?

Plasmapheresis has long been used to manage multiple conditions driven by autoimmunity such as anti-glomerular basement membrane disease. The theoretical advantages of plasmapheresis are clear: it provides the opportunity to remove the offending antibody rapidly without subjecting the patient to additional immunosuppression. Plasma exchange has been used for the treatment of patients with ANCA-associated vasculitis at least since the 1980s [23], and is particularly tempting given the link between ANCA and the pathogenesis of these diseases [24]. Current EULAR guidelines recommend the use of plasmapheresis of patients with rapidly progressive glomerulonephritis to promote renal survival [25].

The best evidence supporting the use of plasma exchange for patients with granulomatosis with polyangiitis (Wegener's) and microscopic polyangiitis comes from MEPEX (methylprednisolone or plasma exchange for severe renal vasculitis), a randomized controlled trial in which 137 patients with ANCA-associated glomerulonephritis and serum creatinine >5.8 mg/dL were randomized to receive either seven sessions of plasmapheresis over a 14-day period or intravenous methylprednisolone (1 g daily for 3 days) [26]. All patients received standard-of-care therapy, which included three months of oral cyclophosphamide (2.5 mg/kg/day) followed by azathioprine for remission maintenance. the MEPEX study demonstrated that plasma exchange was associated with an improvement in both mortality and renal function at three months, which persisted through 1 year.

In 2011, Walsh et al. conducted a meta-analysis of nine randomized clinical trials (including MEPEX) which examined the effect of plasma exchange for 387 patients with either renal vasculitis or idiopathic rapidly progressive glomerulonephritis [27]. The relative risk of the combined endpoint of end-stage renal disease or death was 0.80 (95 % CI 0.65-0.99, P=0.04), but the effect of plasma exchange on each endpoint individually was not statistically significant. The results of this meta-analysis imply that the major benefit of plasma exchange comes from prolonging renal survival, but the sample size of this study was too small to yield a definitive analysis. This benefit must be weighed against the risks associated with plasma exchange, which removes clotting factors and protein-bound drugs, and therefore is not an entirely benign intervention.

How Effective Is Biologic Therapy for Treatment of ANCA-Associated Vasculitis?

The first major foray into the use of biologic agents for treatment of systemic vasculitis was the Wegener's granulomatosis etanercept trial (WGET), a double-blind, controlled trial of 180 subjects with granulomatosis with polyangiitis (Wegener's) who were randomized to receive adjunctive therapy with etanercept (or placebo) , in addition to standard-of-care therapy [28]. All subjects received remission induction therapy with either methotrexate (for limited disease) or cyclophosphamide (for severe disease); in addition, subjects were randomized to receive etanercept 25 mg twice weekly or placebo. Etanercept had no effect on the frequency of achieving sustained remission, which was

the primary endpoint of the trial (69 % for etanercept versus 75 % for placebo, P=NS). There was also no difference in the time to remission, duration of remission, or in the frequency of remission, flares, or adverse events.

Although the WGET dampened enthusiasm for an anti-cytokine approach to the treatment of ANCA-associated vasculitis, it is important to note that it did not answer all the relevant questions. There is substantial evidence from case series, for example, that other anti-TNF inhibitors (such as, infliximab) may be effective for treatment of granulomatosis with polyangiitis (Wegener's) when used in combination with conventional therapy [29]. This is not necessarily surprising; there are numerous examples of inflammatory disorders that fail to respond to etanercept, but do respond to other anti-TNF agents, and it would not be conceptually difficult to add granulomatosis with polyangiitis (Wegener's) to this list. It should be noted, however, that even if effective, anti-TNF strategies seem to be associated with a substantial increase in the risk of infection, which must be taken into consideration before embarking upon this strategy [30].

Enthusiasm for anti-TNF strategies waned further with the advent of B-cell strategies. Although we had long assumed that granulomatosis with polyangiitis (Wegener's) is a T-cell-mediated disease, multiple case reports and observational studies revealed that rituximab, a monoclonal antibody against CD20 that leads to prolonged depletion of B-cells, was effective for the treatment of subjects who were unable to tolerate, or had failed to respond to, standard immunosuppressive therapy [31].

In 2011, the United States Food and Drug Administration approved rituximab for treatment of patients with granulomatosis with polyangiitis (Wegener's) and microscopic polyangiitis, in large part on the basis of two randomized clinical trials that were published simultaneously in 2010.

RITUXIVAS (rituximab versus cyclophosphamide in ANCA-associated vasculitis) was an open-label study that randomized 44 patients with newly-diagnosed ANCA-associated glomerulonephritis to receive treatment with rituximab (375 mg/m^2 weekly for four weeks) or three to six months of intravenous cyclophosphamide, followed by azathioprine for remission maintenance [32]. Because the efficacy of rituximab for treatment of ANCA-associated glomerulonephritis was unknown at that time, patients randomized to receive rituximab were also treated with two to three pulses of cyclophosphamide, depending on their clinical response. The co-primary endpoints were sustained remission and the incidence of adverse events at 12 months.

In RITUXIVAS, rituximab was not superior to cyclophosphamide for achieving sustained remission, which was defined as the absence of disease activity for at least six months (76 % versus 82 %, P=0.68). Interestingly, subjects who received rituximab experienced as many serious adverse events as subjects who were treated with cyclophosphamide (42 % versus 36 %, P=0.77). This may indicate that these events were largely driven by the use of glucocorticoids in accordance with the protocol, rather than the study drug.

RAVE (rituximab for ANCA-associated vasculitis) examined a broader cross-section of patients with ANCA-associated vasculitis, with more sanguine results. RAVE was a multicenter, double-blind, double-placebo-controlled trial that randomized patients with severe granulomatosis with polyangiitis (Wegener's) or microscopic polyangiitis to receive treatment with rituximab (375 mg/m^2 IV weekly for four weeks) or conventional immunosuppression, which consisted of three to six months of daily oral cyclophosphamide (2 mg/kg) followed by 12 to 15 months of daily oral azathioprine (2 mg/kg) [33]. Unlike RITUXIVAS, only half of the patients enrolled in RAVE had glomerulonephritis; furthermore, patients were excluded from this trial if their serum creatinine was greater than 4 mg/dL. The primary endpoint of this study was achievement of glucocorticoid-free remission at six months.

RAVE revealed that rituximab was non-inferior to cyclophosphamide for achieving remission in the absence of glucocorticoids at six months (64 % versus 53 %, P=0.09), and that rituximab was equally effective for patients who entered the trial with either pulmonary hemorrhage or glomerulonephritis. When the definition of remission was expanded to include patients who remained on low dose glucocorticoids (as was permitted in the RITUXIVAS trial), the incidence of remission increased, but the difference between the two groups was not statistically significant (71 % versus 62 %, P=0.10). Subgroup analysis indicated that for patients with a history of relapsing disease, rituximab was superior to cyclophosphamide for achieving remission at six months (67 % versus 42 %, P=0.01). As in RITUXIVAS, however, the incidence of adverse events was comparable in both groups, probably owing to the predetermined glucocorticoid tapering regimen.

Although it is tempting to consider rituximab for remission induction for all patients with ANCA-associated vasculitis, it is important to remember that we best understand how to use rituximab for patients who are similar to the subjects who were enrolled in these two trials. Whether rituximab is adequate to induce remission in patients with renal or respiratory failure due to ANCA-associated vasculitis is not yet clear. Furthermore, the vasculitic manifestations of granulomatosis with polyangiitis (Wegener's) respond more readily to rituximab than do the necrotizing granulomatous manifestations (such as orbital pseudotumor and pachymeningiits) [34], indicating that some patients may be better candidates for this drug than others.

Moreover, although rituximab has a clear role for remission induction, its role for remission maintenance is somewhat less clear. One open-label study revealed that routine retreatment with 1 g rituximab every 6 months resulted in 12 % relapse over 2 years, compared with relapse of 73 % in the absence of maintenance therapy [35]. This incidence of relapse is, unfortunately, similar to that observed among patients receiving

remission maintenance therapy with conventional agents. Therefore, this retreatment strategy would presumably best serve patients who had already failed conventional immunosuppressive therapy.

Conclusions

For several decades, treatment of granulomatosis with polyangiitis (Wegener's) and microscopic polyangiitis has relied heavily on the use of cytotoxic agents such as cyclophosphamide. Clinical trials over the past decade have focused on identifying methods of minimizing exposure to cyclophosphamide, or avoiding cyclophosphamide altogether for a subset of patients. These efforts have largely been successful, validating the modern treatment strategy, which uses a short course of cyclophosphamide for remission induction, followed by a longer course with an antimetabolite for remission maintenance. Patients with mild disease may respond to remission induction with methotrexate and forgo treatment with cyclophosphamide entirely, possibly in exchange for a higher risk of disease relapse. Patients with critical disease manifestations, such as renal or (possibly) respiratory failure may benefit from plasma exchange, although the benefit may not be long-lived. Finally, a broad range of patients with ANCA-associated vasculitis may respond to treatment with rituximab. This is an appealing treatment for patients at the extremes of age—either young patients who are concerned about maintaining fertility or elderly patients who may not tolerate cytotoxic agents. Rituximab may also be a tempting strategy for patients with "grumbling" disease that has responded incompletely to antimetabolites and chronic low-dose glucocorticoid therapy. As rituximab answers some questions, however, it raises others: how to use rituximab as a remission maintenance agent, and the risks of chronic retreatment are not yet clear. What is clear, however, is that patients in this decade are better off than patients in the preceding decade, and progress in this decade raises the hope that outcomes for patients with these diseases will continue to improve.

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References

Papers of particular interest, published recently, have been highlighted as:
•• Of major importance

1. Seo P, Stone JH. The antineutrophil cytoplasmic antibody-associated vasculitides. Am J Med. 2004;117(1):39–50.
2. Chung SA, Seo P. Microscopic polyangiitis. Rheum Dis Clin North Am. 2010;36(3):545–58.
3. Gadola SD, Gross WL. Vasculitis in 2011: The renaissance of granulomatous inflammation in AAV. Nat Rev Rheumatol. 2012;8(2):74–6.
4. Wolff S, Fauci A, Horn R, Dale D. Wegener's granulomatosis. Ann Intern Med. 1974;81:513–25.
5. Wohlwill F. Ueber die nur mikroskopisch erkenbarre form der periarteritis nodosa. Arch Pathol Anat. 1923;246:377–411.
6. Fauci A, Doppman J, Wolff S. Cyclophosphamide-induced remissions in advanced polyarteritis nodosa. Am J Med. 1978;64:890–4.
7. Fauci A, Wolff S. Wegener's granulomatosis: Studies in eighteen patients and a review of the literature. Medicine. 1973;52:53–61.
8. Hoffman GS, Kerr GS, Leavitt RY, et al. Wegener's granulomatosis: An analysis of 158 patients. Ann Intern Med. 1992;116:488–98.
9. Langford C, Talar-Williams C, Barron K, Sneller M. A staged approach to the treatment of Wegener's granulomatosis: Induction of remission with glucocorticoids and daily cyclophosphamide switching to methotrexate for remission maintenance. Arthritis Rheum. 1999;42(12):2666–73.
10. Jayne D. Randomised trial of cyclophosphamide versus azathioprine during remission in ANCA-associated systemic vasculitis (CYCAZAREM). J Am Soc Nephrol. 1999;10:105A.
11. Pagnoux C, Mahr A, Hamidou MA, et al. Azathioprine or methotrexate maintenance for ANCA-associated vasculitis. N Engl J Med. 2008;359(26):2790–803.
12. Hiemstra TF, Walsh M, Mahr A, et al. Mycophenolate mofetil vs azathioprine for remission maintenance in antineutrophil cytoplasmic antibody-associated vasculitis: A randomized controlled trial. JAMA. 2010;304(21):2381–8.
13. Zahr N, Arnaud L, Marquet P, et al. Mycophenolic acid area under the curve correlates with disease activity in lupus patients treated with mycophenolate mofetil. Arthritis Rheum. 2010;62(7):2047–54.
14. Guillevin L, Cordier J, Lhote F, et al. A prospective, multicenter, randomized trial comparing steroids and pulse cyclophosphamide versus steroids and oral cyclophosphamide in the treatment of generalized Wegener's granulomatosis. Arthritis Rheum. 1997;40(12):2187–98.
15. de Groot K, Adu D, Savage CO. The value of pulse cyclophosphamide in ANCA-associated vasculitis: Meta-analysis and critical review. Nephrol Dial Transplant. 2001;16(10):2018–27.
16. De Groot K, Rasmussen N, Bacon PA, et al. Randomized trial of cyclophosphamide versus methotrexate for induction of remission in early systemic antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheum. 2005;52(8):2461–9.
17. Harper L, Morgan MD, Walsh M, et al. Pulse versus daily oral cyclophosphamide for induction of remission in ANCA-associated vasculitis: Long-term follow-up. Ann Rheum Dis. 2012;71(6):955–60.
18. de Groot K, Muhler M, Reinhold-Keller E, Paulsen J, Gross W. Induction of remission in Wegener's granulomatosis with low dose methotrexate. J Rheumatol. 1998;25:492–5.
19. Hoffman GS, Langford CA. Can methotrexate replace cyclophosphamide in the treatment of a subset of Wegener's granulomatosis and microscopic polyangiitis? Nat Clin Pract Rheumatol. 2006;2(2):70–1.
20. Langford C, Fauci A, Talar-Williams C, Sneller M. Treatment of Wegener's granulomatosis with methotrexate and glucocorticoids: Update on rate of relapse. Arthritis Rheum. 1996;39:S211.
21. •• Faurschou M, Westman K, Rasmussen N, et al. Long-term outcome of a clinical trial comparing methotrexate to cyclophosphamide for remission induction of early systemic ANCA-associated vasculitis. *Arthritis Rheum*. 2012. *It is sobering to realize that a strategy that initially seemed to spare patients from exposure to cyclophosphamide may not work as well as we had hoped. Presumably, in cases where equipoise seems to exist, cyclophosphamide should be chosen over methotrexate as an initial*

remission induction strategy until the implications of this study are clearer.

22. Villa-Forte A, Clark TM, Gomes M, et al. Substitution of methotrexate for cyclophosphamide in Wegener granulomatosis: A 12-year single-practice experience. Medicine (Baltimore). 2007;86 (5):269–77.
23. Pinching A, Rees A, Pussell B, Lockwood C, Mitchison R, Peters D. Relapses in Wegener's granulomatosis: The role of infection. BMJ. 1980;281:836–8.
24. Jennette JC, Falk RJ, Gasim AH. Pathogenesis of antineutrophil cytoplasmic autoantibody vasculitis. Curr Opin Nephrol Hypertens. 2011;20(3):263–70.
25. Mukhtyar C, Guillevin L, Cid MC, et al. EULAR recommendations for the management of primary small and medium vessel vasculitis. Ann Rheum Dis. 2009;68(3):310–7.
26. Jayne DR, Gaskin G, Rasmussen N, et al. Randomized trial of plasma exchange or high-dosage methylprednisolone as adjunctive therapy for severe renal vasculitis. J Am Soc Nephrol. 2007;18 (7):2180–8.
27. •• Walsh M, Catapano F, Szpirt W, et al. Plasma exchange for renal vasculitis and idiopathic rapidly progressive glomerulonephritis: A meta-analysis. *Am J Kidney Dis*. 2011;57(4):566–574. *This meta-analysis is the closest we have to a definitive statement regarding the utility of plasma exchange for patients with ANCA-associated glomerulonephritis.*
28. Wegener's Granulomatosis Etanercept Trial (WGET) Research Group. Etanercept plus standard therapy for Wegener's granulomatosis. N Engl J Med. 2005;352(4):351–61.
29. de Menthon M, Cohen P, Pagnoux C, et al. Infliximab or rituximab for refractory Wegener's granulomatosis: Long-term follow up A prospective randomised multicentre study on 17 patients. Clin Exp Rheumatol. 2011;29(1 Suppl 64):S63–71.
30. Booth A, Harper L, Hammad T, et al. Prospective study of TNFalpha blockade with infliximab in anti-neutrophil cytoplasmic antibody-associated systemic vasculitis. J Am Soc Nephrol. 2004;15(3):717–21.
31. Zouboulis C, et al. Adamantiades-behcet's disease: Interleukin-8 is increased in serum of patients with active oral and neurological manifestations and is secreted by small vessel endothelial cells. Arch Dermatol Res. 2000;292:279–84.
32. •• Jones RB, Tervaert JW, Hauser T, et al. Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. *N Engl J Med*. 2010;363(3):211–220. *This article, and the subsequent reference, let to the first drug approved by the United States Food and Drug Administration for the treatment of systemic vasculitis. Reviewing both articles carefully will give you a better sense of the limits of our understanding regarding the use of rituximab for patients with ANCA-associated vasculitis.*
33. Stone JH, Merkel PA, Spiera R, et al. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. N Engl J Med. 2010;363 (3):221–32.
34. Holle JU, Dubrau C, Herlyn K, et al. Rituximab for refractory granulomatosis with polyangiitis (Wegener's granulomatosis): Comparison of efficacy in granulomatous versus vasculitic manifestations. Ann Rheum Dis. 2012;71(3):327–33.
35. •• Smith RM, Jones RB, Guerry MJ, et al. Rituximab for remission maintenance in relapsing ANCA-associated vasculitis. *Arthritis Rheum*. 2012. *Epub ahead of print. The key unanswered question regarding rituximab is how to use the drug for remission maintenance. This study describes the outcomes associated with one possible re-treatment strategy.*