Systemic Vasculitis Treatment and Monitoring Update, 2008

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Abstract
Vasculitic syndromes are among the most complicated diseases for primary care physicians and rheumatologists to diagnose and treat. There are a myriad of symptoms that can be mimicked by other conditions, and choice of medications can be complex. Some agents are toxic and determining which to prescribe and for how long can be a multifaceted, complex decision process. Developing new treatments and new ways of using already available therapies, while minimizing potential side effects, are of paramount importance. This review will focus on recently published data that could have an impact on the way we treat systemic vasculitis patients.

Vasculitic syndromes are among the most complicated diseases for primary care physicians and rheumatologists to diagnose and treat, not only because of a myriad of symptoms that can be mimicked by other conditions, but also because of the decision process that needs to take place to determine which medication (sometimes toxic) to use and for how long. Developing new treatments and new ways of using already available therapies, while minimizing potential side effects, are of paramount importance. The British Society for Rheumatology has recently published new guidelines that incorporate currently available data regarding diagnosis and treatment of patients with ANCA (anti-neutrophil cytoplasmic antibodies)-associated vasculitis, or AAV. The main objective is to provide guidance on when and how to use cyclophosphamide (CYC) as well as the other therapeutic options, and in which stages of the disease.1

The guidelines assume a definite diagnosis of AAV has been made, first, by the presence of symptoms and signs characteristic of systemic vasculitis, second, with demonstration of at least one of the following events: a. histological evidence of vasculitis or granuloma formation, or both, b. positive serology for ANCA, or c. specific, indirect evidence of vasculitis, and, finally, ascertaining that no other diagnosis accounts for the presenting symptoms and signs. In addition, it is noted that other causes of systemic illness, such as malignancy, infection, and drugs, are ruled out.

AAV treatment can be envisioned in two stages: induction of remission and maintenance. At each stage, the severity and extent of disease can be assessed by subdividing patients into three groups: 1. localized and early, or either; 2. generalized disease, with threatened organ involvement; and 3. severe or life-threatening disease. Once these determinations are made, the treatment algorithm can be used to guide therapy. For patients with localized and early disease, the guidelines recommend treatment with CYC or methotrexate (MTX), keeping in mind that some data suggest there may be more relapses with MTX.2 If there is progression or relapse, then CYC should be used. If localized disease causes significant destruction, CYC is the agent of choice. Generalized disease or threatened organ involvement would be treated with CYC and steroids, at the start. CYC can be used as an IV infusion, initially, every two weeks, and, later, every 3 weeks, or if given orally, daily. There does not appear to be a difference between IV and oral regimens for achieving remission and for relapse rates. Continuous oral CYC, however, leads to a higher total dose and can be associated with increased adverse events. Switching to maintenance therapy with other agents is recommended if remission has been achieved after 3 months of oral CYC or after 3 to 6 months of IV CYC. Patients presenting with severe renal disease should receive...
CYC and steroids, along with adjuvant plasma exchange. Plasma exchange can also be considered with pulmonary hemorrhage.

Steroids should be prescribed in the form of a daily oral dose, 1 mg/kg up to 60 mg daily. IV steroids as a pulse can be given at times, along with IV CYC. For maintenance following successful remission, CYC can be stopped, and patients can be treated with MTX or azathioprine. Patients should continue maintenance treatment for a minimum of 24 months. The guidelines also recommend continuing maintenance treatment for up to 5 years in patients who remain ANCA-positive. Relapsing disease can be managed with an increase in prednisone dose or optimization of the current immunosuppression in the case of a minor flare; however, when a major relapse occurs, CYC with increased steroids is the treatment of choice.

Infliximab, IV immunoglobulins, rituximab, CAMPATH-1H, and other options currently under investigation can be tried in refractory disease. A careful assessment of underlying factors, such as an infection or malignancy that may possibly lead to persistent or refractory disease, should be carried out.

As for monitoring patient response, the guidelines recommend using a validated tool. Unfortunately, the most commonly studied tools that are frequently used in randomized clinical trials (RCT) are not designed for routine care and would be difficult to implement. An easier tool to apply, such as an MDHAQ (multi-dimensional health assessment questionnaire), may find more use among practicing rheumatologists, as it has been shown to work with many different rheumatologic conditions. As will be discussed later, ANCA antibody levels do not seem to be reliable laboratory tests to monitor response or adjust treatment for possible relapse.

As many of the immunosuppressive medications used for the treatment of systemic vasculitides can cause serious adverse effects, recommendations regarding detecting and preventing these adverse events are given. These include use of mesna for protection against urothelial toxicity, antifungal prophylaxis, and prophylaxis against Pneumocystis jiroveci, consideration for Staphylococcus aureus treatment, screening for cervical malignancy, counseling about infertility with CYC, screening for tuberculosis, and vaccination and assessment for osteoporosis, along with cardiovascular and thromboembolic risk assessment.

The role of ANCA in the assessment of disease activity and prediction of remission and relapse has been debated. As a diagnostic tool, p-ANCA and c-ANCA have been very useful and over time have led to the renaming of Wegener’s granulomatosis (WG), Churg-Strauss syndrome, and microscopic polyangiitis as “ANCA-associated vasculitis,” as they all are associated with different degrees to p- or c-ANCA positivity.

Serial measurements of ANCA during follow-up and their usefulness in guiding therapy have been more controversial. The Wegener’s Granulomatosis Etanercept Trial (WGET) examined whether the addition of etanercept would have an effect on maintaining remission in WG patients treated with CYC (severe disease) or MTX (limited disease) to induce an initial remission. After remission, patients on CYC were switched to MTX. These patients were randomly assigned to etanercept or placebo, in addition to their current medications. Brief, sustained remission was achieved in 62/89 of patients in the etanercept group and 64/85 of patients in the control group. There were no differences in numbers of flares between the groups.

WGET, in addition to showing that there probably is a limited role for etanercept in WG treatment, has yielded further subgroup analysis reports that have contributed greatly to our understanding of WG and its treatment. For example, a subgroup analysis of the MTX-treated patients in the WGET study provides good information for the possible role of MTX in WG treatment. Fifty-two patients with limited WG were treated with MTX. Of these, 46/52 (88.5%) achieved remission and at 6 months 35/52 (67.3%) were still in remission. These data suggest that, for patients with limited WG, MTX may be as good a choice as CYC for remission induction therapy.

Recently, WGET data were analyzed to assess the utility of ANCA. Patients were evaluated from their first sustained remission (defined as BVAS [Birmingham Vasculitis Activity Score]/WG = 0 for 6 months) to their first relapse (defined as a BVAS/WG increase of at least 1 point). For patients who relapsed within 1 year, the increase in ANCA was 40%. There were no differences in ANCA levels among patients who relapsed versus those who did not. ANCA levels were only weakly associated with disease activity. Decreased ANCA levels were not associated with a shorter time to remission, and increased levels did not predict relapse. A cross-sectional analysis of ANCA levels was not significant, which suggests that ANCA cannot be compared between patients. In addition, less than 10% of longitudinal variation in disease activity was explained by ANCA levels. The conclusion was that preemptive treatment secondary to increased ANCA levels cannot be recommended at this time.

In another study, etanercept was used in patients who had been refractory to treatment for polymyalgia rheumatica (PMR) with a relapsing course, and who had not been able to decrease their prednisone doses. Only six patients were studied, yet the information from this study is useful for this problem, which has some frequency in clinical care. All patients treated with etanercept had a sustained remission, as defined by EULAR (European League Against Rheumatism) response criteria, with at least 70% improvement in four patients and 50% in two patients. As well, all patients were able to significantly decrease their median prednisone daily dosage. There was no significant adverse event noted in this small study. Even though this investigation was a small study, it does provide some data that can be directly applied to clini-
cal care and may provide another option for PMR patients who are not able to be weaned off steroids, secondary to recurrent flares of disease. Longer and larger trials may better define the role of etanercept in PMR treatment.

Martinez and colleagues of the French Vasculitis Study Group examined the role of intravenous immunoglobulin (IVIG) for the treatment of relapsing vasculitides associated with ANCA. They enrolled 19 WG and three microscopic polyangiitis patients who had relapsed after their initial treatment. Patients were maintained on the same regimen with which they experienced the relapse, and IVIG as added. Those with severe renal involvement were excluded. Patients received 0.5 mg/kg/day of IVIG for 4 days every month, for a total of 6 months. Patients were followed for 24 months. At the end of the study period, 13 of 22 patients were in complete remission, as determined by BVAS, and one patient was in partial remission. Seven patients relapsed, and one had a treatment failure. Of the 14 patients who were in remission at 9 months, eight were still in remission at 24 months. There were no serious adverse events noted.

As the investigators also state, IVIG can be a good option for patients failing on their current treatments to induce remission, as this agent was successful for a majority of the patients with minimal serious side effects. As this was an open label study, caution is needed before this therapy can be universally accepted. Larger and longer studies would provide further useful information about the exact role of IVIG in the treatment of ANCA-associated vasculitides.

Mahr and coworkers examined the role of MTX in the treatment of giant cell arteritis (GCA). Several previous studies had looked at the same question, but the use of MTX in addition to steroids had yielded mixed results. The investigators conducted a meta-analysis of individual patient data from three placebo-controlled randomized clinical trials of MTX in GCA. They identified four studies that provided data; three were analyzed, as the fourth trial’s data were no longer available. This was different from previous meta-analysis in that individual patient level data were pooled.

A total of 161 were treated for 48 weeks: 84 were treated with MTX and 77 by placebo. Over half of the patients, 61% (98/161), had a first relapse and 29% (46/161) had a second relapse, number needed to treat was 4 for the first relapse and 5 for the second relapse. There was also increased probability of sustained discontinuation of corticosteroids and decreased cumulative corticosteroid dose in the MTX arm. There were differences between the MTX arm and placebo arm with regard to adverse events. This meta-analysis seems to suggest that MTX can be considered a useful adjunct therapy to usual care in GCA, which improved outcomes and had no increase in adverse events.

Conclusion
Several studies over the last 12 months have provided information related to new uses for etanercept, IVIG, and MTX. Treatment of vasculitis, where data are limited because of lack of large randomized clinical trials, has to, in part, depend on smaller, but, at the same time, innovative studies. The studies reviewed above may present new options for treatment of patients with systemic vasculitides. In addition, the new treatment guidelines from the British Society for Rheumatology will likely be helpful to clinicians who care for these patients who are commonly difficult to treat and manage.

Disclosure Statement
Yusuf Yazici, M.D., serves as a consultant to Roche Laboratories, Celgene, Bristol-Myers Squibb Co., and Centocor, and serves on the speakers’ bureau of Pfizer, Inc. and Bristol-Myers Squibb Co.

References