Don't Discount Severity of Small-Vessel Vasculitis

BY DIANA MAHONEY
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BOSTON — Despite the availability of "pretty good therapies" for Wegener's granulomatosis and microscopic polyangiitis, "these forms of small-vessel vasculitis still regularly kill people, so do not underestimate the misery associated with them," said Dr. Peter Merkel at a meeting on rheumatology sponsored by Harvard Medical School.

"These are bad diseases that cause major, permanent damage to multiple organ systems," said Dr. Merkel of Boston University. "While the available treatments can effectively induce remission in some patients, many other patients die. Some die early from hemorrhage or other problems; some die later from concurrent disease or treatment toxicity. The important thing to remember is that these diseases kill."

The first line of defense against such an outcome is the accurate diagnosis of acute disease, and early, aggressive therapy. Unfortunately, a number of obstacles can get in the way of both, Dr. Merkel said.

Because these conditions are relatively rare, "many rheumatologists don't see a lot of these patients and thus do not have a good sense of the spectrum of the disease and its presentations," he noted.

When a patient presents with symptoms suggestive of acute vasculitis, "the first thing to do is look for trouble," said Dr. Merkel. "There's always more to acute vasculitis than you think. If you look for trouble, you will almost certainly find it, and this is important because you want to find and treat the worst part of the disease first." A good evaluation for potential small-vessel vasculitis should include a full medical history and physical. "This is not a 20-minute visit. It requires a long, comprehensive examination with a full set of labs," Dr. Merkel stressed. "Certainly, one of the first things is to get a urine specimen to assess possible kidney involvement, and, for dipstick positive specimens, you have to be willing and able to do a microscopic examination of the urinary sediment right then and there," he said. "Early changes in urine are critical to evaluating these patients, and in order to identify such changes, the specimen for microscopic examination has to be as fresh as possible. If you send the specimen to the lab, the red cells and formed solids will have disintegrated."

In the case of acute disease, 'jump right in with glucocorticoids, especially if you suspect acute glomerulonephritis or pulmonary hemorrhage.'

Unfortunately, microscopic examination of urine sediment is a "lost art," said Dr. Merkel. "It requires a degree of skill acquired through practice. It's hard to get used to doing if you're not seeing hundreds of patients with these diseases, and most rheumatologists are not seeing hundreds of these patients," he said.

"However, if you're not comfortable doing this, you cannot take care of these patients on your own."

Testing for antineutrophil cytoplasmic antibodies (ANCA) is also necessary. "Although there is a subset of patients who test negative for ANCA, a positive test is a useful diagnostic and prognostic marker for Wegener's granulomatosis and microscopic polyangiitis," Dr. Merkel stressed.

Chest x-rays are also considered an essential diagnostic tool, "but they often miss things," said Dr. Merkel. "Anyone being evaluated for possible Wegener's should have a CT scan of the chest—and often even the head and neck—to look for subparotid disease or tracheal narrowing." Because upper-airway and lung involvement are devastating, "it's important to have a low threshold when looking for neck disease, so you can get it early," he said.

Pulmonary function testing and an ophthalmological examination to identify inflammatory eye disease should be conducted, as should audiograms, said Dr. Merkel. "Hearing loss, in particular, is an underappreciated problem in small-vessel vasculitis. Audiograms are noninvasive and cheap, and should be standard practice in these patients."

Although electromyography and nerve conduction studies may be useful for identifying and localizing neurologic involvement in these diseases, "they are painful, annoying, and expensive tests and generally unnecessary if you do a proper examination," said Dr. Merkel.

Before making a diagnosis, "rule everything else out, particularly infections," Dr. Merkel stressed. "Infections are the great mimicker and cotraveler of vasculitis, so be sure to look for them."

As the diagnostic criteria for these conditions are fulfilled, get a good team together to address the multiple organ system assaults, said Dr. Merkel. And, in the case of acute disease, "jump right in with glucocorticoids, especially if you suspect acute glomerulonephritis or pulmonary hemorrhage. These are among the few true rheumatoid emergencies, and nothing works faster for acute ANCA-associated vasculitis than steroids." Immunosuppressive therapy, which is the mainstay of treatment for these conditions, "can usually wait until the patient is more stable or the diagnosis has been confirmed, but you don't want to miss treating acute renal or pulmonary disease, or even bad eye disease, because the consequences can be devastating," he said. ■

To Optimize Cyclophosphamide Tx, Order Frequent Labs, Educate Patients

BY DIANA MAHONEY
New England Bureau

BOSTON — The current standard of care for initial treatment of severe Wegener's granulomatosis and microscopic polyangiitis—glucocorticoids plus daily oral or pulse intravenous cyclophosphamide—is far from perfect, according to Dr. Peter A. Merkel of Boston University Medical Center.

"In randomized controlled trials, the remission rate with severe disease associated with this treatment is less than 90%, and sometimes less than 80%, so there are still a substantial number of patients who never reach remission," Dr. Merkel said at a meeting on rheumatology sponsored by Harvard Medical School. Even when initial treatment induces remission, the risk of relapse and retreatment is high. Moreover, prolonged cyclophosphamide use has been tied to ovarian/testicular failure, bladder carcinoma and hemorrhage, cystitis, infections, and myelodysplasia.

"Because most rheumatologists don't have a high volume of patients with these diseases, most don't have a lot of personal, anecdotal experience with cyclophosphamide treatment, which can lead to problems," said Dr. Merkel.

"One of the biggest problems I see is undertreatment," Dr. Merkel noted. "All of the studies and trials use 2 mg/kg per day as the treatment goal, adjusting for renal disease as necessary," while in practice patients are often receiving less. "It's better to give the right dose up front and adjust down if need be. Many patients require dose reductions. That's fine. It doesn't mean the therapy is wrong."

Overdosage is also common. "Often, adjustments for renal disease are not being made, and they must be," said Dr. Merkel. "The goal is not neutropenia, although sustained lymphopenia is associated with prolonged remission."

Another roadblock to optimal therapy is inadequate lab testing. "There should be labs done on these patients every week initially, certainly no less frequently than every 2 weeks," said Dr. Merkel. "White count values can drop pretty quickly, which is typically what happens in those patients who end up with neutropenia and sepsis. Often those outcomes could have been prevented with proper monitoring." Unfortunately, clinicians' tendency to become lax over the course of cyclophosphamide therapy coincides with a patient's most vulnerable period. "This is when steroids are being tapered and the risk of cumulative cyclophosphamide toxicity is greatest."

With frequent lab testing, "you can anticipate white count drops, and when you see a trend, you can start adjusting, rather than waiting until the count has dropped so low that treatment has to be stopped entirely," said Dr. Merkel.

Other tips include avoiding twice-daily or evening dosing, "because the cyclophosphamide can accumulate in the bladder overnight." Encourage hyperhydration to prevent cyclophosphamide-induced cystitis, Dr. Merkel stated.

One of the most prevalent treatment inadequacies "is failing to spend enough time talking to patients about cyclophosphamide," said Dr. Merkel. "This is a toxic drug and patients need to be educated about it. For example, they need not only to know that they have to drink water, but also why they must drink water and why they should take the drug early in the day. This should be a long conversation, not just an aside." ■

Variation in CTGF Gene Is Linked to Systemic Sclerosis

A variation in the promoter region of the gene that encodes connective-tissue growth factor (CTGF) appears to confer susceptibility to systemic sclerosis, reported Dr. Carmen Fonseca of Royal Free and University College Medical School, London, and associates.

The researchers genotyped 500 white patients with systemic sclerosis and 500 healthy, white, unrelated control subjects, screening for a specific polymorphism (G-945C) in the region of the CTGF promoter. Significantly more of the patient group (30%) than the control group (19%) carried the polymorphism, they said in the Sept. 20 issue of the New England Journal of Medicine.

There was a strong association between G-allele homozygotes and the presence of specific antibodies—antitopoisomerase 1 and anticentromere—associated with the disease as well as with interstitial lung fibrosis. Positivity for anticentromere antibody previously has been linked to vascular complications such as isolated pulmonary arterial hypertension, which suggests that "a second mechanism involving CTGF overexpression is playing a role" in systemic sclerosis, they said.

"The effects of CTGF on cell proliferation or extracellular matrix production, if induced within certain vessels, could be plausible explanation for this association," Dr. Fonseca wrote (N. Engl. J. Med. 2207;357:1210-20).

"Our data clearly show an association between the G-945C polymorphism in CTGF and systemic sclerosis, which renders CTGF a susceptibility gene for this complex disease," they added.

"These data provide new insight into the pathogenesis of systemic sclerosis, including clues to the mechanisms leading to specific disease subtypes. Moreover, they may also be relevant to mechanisms underlying a wide range of other human disorders with a fibrotic component," Dr. Fonseca and her associates said.

—Mary Ann Moon