Systemic Vasculitis Often First Diagnosed in ICU

BY BRUCE JANCIN
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PARIS — Antineutrophil cytoplasmic antibodies (ANCA)–associated vasculitis is not uncommonly first diagnosed in the intensive care unit.

Cardiac, pulmonary, and intestinal manifestations of systemic necrotizing vasculitis were the most frequent reasons for admission to the intensive care unit (ICU) in his series of patients with previously undiagnosed ANCA-associated vasculitis, Dr. Roberto Caporali reported in a presentation at the annual European Congress of Rheumatology.

"It may be important for ICU physicians to include ANCA-associated vasculitis/systemic vasculitis in the differential diagnosis for patients admitted to the ICU with unexplained severe systemic manifestations," added Dr. Caporali of the University of Pavia (Italy).

The rheumatologist presented a retrospective study of 76 patients with ANCA-associated vasculitis—46 with Wegener's granulomatosis and 30 with Churg-Strauss syndrome—of whom 12 were admitted to the ICU. In 10 of the 12, the ICU was where the diagnosis of vasculitis was first made.

The two patients whose diagnosis was known prior to ICU admission had advanced disease, and both died in the hospital of multiorgan failure. In contrast, all 10 patients diagnosed in the ICU remained alive after a minimum follow-up of 24 months.

Five of the 10 patients diagnosed in the ICU were admitted because of cardiac involvement, 2 for intestinal manifestations of active systemic vasculitis, 2 because of alveolar hemorrhage, and 1 for laryngeal stenosis.

Patients with Wegener's granulomatosis had classic prodromal symptoms of ANCA-associated vasculitis—including asthma, sinusitis, nasal polyposis, and/or peripheral eosinophilia—for a median of 3 months prior to their ICU stay.

Patients with Churg-Strauss had prodromal symptoms longer, for more than 1 year on average, Dr. Caporali continued.

He said the rheumatic diseases most frequently encountered in the ICU are rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis, and vasculitis. Few studies have been published on systemic vasculitis in the setting of the ICU, and they are small in size because the diseases are so uncommon.

Dr. Caporali noted that last year intensivists at the Mayo Clinic reported on 38 consecutive patients with necrotizing small-vessel vasculitis admitted to the ICU. Nineteen of the patients had Wegener's granulomatosis, 16 had microscopic polyangiitis, 2 had CNS vasculitis, and 1 patient had Churg-Strauss. In contrast with the Italian experience, in only one-third of the Mayo Clinic cases was the diagnosis of vasculitis established during this hospitalization.

The reasons for ICU admission included diffuse pulmonary alveolar hemorrhage in 14 patients, sepsis in 5, seizures in 3, and pneumonia in 2. The median ICU length of stay was 4 days (Chest 2007;131:972-6).

The 28-day mortality rate was 11%, with a 1-year mortality of 29%. That was a markedly lower short-term mortality than predicted by Acute Physiology And Chronic Health Evaluation (APACHE III) scores.

A German audience member reported good success using plasmapheresis in patients with microscopic polyangiitis and pulmonary involvement, and she asked if Dr. Caporali has had a similarly favorable experience.

He replied that all patients in his study received the classic combination of high-dose steroids and cyclophosphamide, although plasmapheresis was added with good results in two patients in the ICU because of combined intestinal and renal involvement.

"I think plasmapheresis could also be a good option for patients with alveolar hemorrhage," he added. ■

TNF Blockers No Help in New-Onset Giant Cell Arteritis

BY NANCY WALSH
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NEW YORK — Tumor necrosis factor inhibitors, given in conjunction with corticosteroids for recent onset giant cell arteritis or polymyalgia rheumatica, do not appear to confer a substantial benefit over treatment with steroids alone, judging from findings from recent studies.

Systemic corticosteroids represent the cornerstone of treatment for both giant cell arteritis (GCA) and the forme fruste of this large vessel vasculitis, polymyalgia rheumatica (PMR).

However, in the 50-year-and-older age group susceptible to these conditions, steroid-related toxicities such as osteoporotic fractures represent significant hazards.

Therefore, various types of adjunctive cytotoxic and anti-inflammatory drugs—most notably methotrexate—have been tried for potential roles as steroid-sparing agents. Results thus far have been disappointing. (See related story.)

More recently, the tumor necrosis factor (TNF) blocking agents have been investigated for use both as monotherapy and in conjunction with corticosteroids, according to Dr. Nicolo Pipitone of the Arcispedale Santa Maria Nuova, Reggio Emilia, Italy.

The rationale for using TNF inhibitors lies in the fact that circulating levels of this cytokine are elevated in patients with GCA and PMR, and it is overexpressed in the temporal arteries of patients with GCA, Dr. Pipitone said at the Fourth International Conference on Giant Cell Arteritis and Polymyalgia Rheumatica.

Small early studies with infliximab initially seemed promising, with a few patients going into remission, so randomized trials were undertaken. For GCA, 44 patients with newly diagnosed disease were randomized to receive corticosteroids plus infliximab (5 mg/kg), or placebo at weeks 0, 2, 6, and every 8 weeks thereafter, with steroids being tapered within 6 months.

An interim analysis at week 22 found no difference between the groups in the proportions of patients who were relapse free, in time to first relapse, or in cumulative prednisone dose.

There was a trend for more infections in the infliximab group, with three serious infections, compared with one in the placebo group.

There also were six infusion reactions in the infliximab group and none in the control group. In the active treatment group, antibodies to infliximab developed in 27%, and antibodies to double-stranded DNA developed in 16% (Ann. Intern. Med. 2007;146:621-30). The study was discontinued prematurely, Dr. Pipitone said.

'The drug may represent an effective alternative to corticosteroids in patients with GCA who had corticosteroid dose-limiting comorbidities.'

A second trial included 51 patients with newly diagnosed PMR who were randomized to receive corticosteroids plus 3 mg/kg infliximab or placebo at weeks 0, 2, 6, 14, and 22, with steroids being tapered over 16 weeks.

In this trial, again, the proportions of patients who were relapse free at 52 weeks did not differ between the two groups, and the investigators concluded that the treatment "does not substantially affect the course of polymyalgia rheumatica" (Ann. Intern. Med. 2007;146:631-9).

In contrast to these studies of new onset disease, however, benefits have been seen with TNF blockade in patients with refractory, long-standing disease.

In six of seven reported cases of refractory GCA, patients had a positive response to infliximab. Disease duration in these patients ranged from 1 to 5 years, and steroid dosages ranged from 7.5 mg/day to 40 mg/day. Among four of these patients, reported as a single case series, three were steroid free and in remission following three infusions of infliximab at 3 mg/kg (Arthritis Rheum. 2001;44:2933-5).

More recently, 17 patients with longstanding biopsy-proven GCA who were in remission on stable dosages of prednisone (10 mg/day or more) were randomized to etanercept or placebo, 25 mg twice weekly for 12 months. Prednisone was tapered according to a prearranged schedule but adjusted if flares occurred, and the primary end point was the ability to withdraw steroids at 12 months.

The primary end point was met by 50% of the etanercept-treated patients but by only 22% of the placebo-treated patients, Dr. Pipitone said at the meeting, which was sponsored by the Hospital for Special Surgery. A total of 50% of the etanercept group experienced a flare, as did 78% of the placebo group.

Although the numbers in this study were small and statistical significance was not reached, the findings do suggest that there may be some benefits in subsets of patients with longstanding, steroid-resistant GCA, Dr. Pipitone said.

An additional role for TNF blockade may be for patients who cannot tolerate or are unwilling to take corticosteroids. In a separate poster presentation at the meeting, Dr. Carlotta Nannini of Misericordia e Dolce Hospital, Prato, Italy, described three elderly women with biopsy-confirmed GCA.

Erythrocyte sedimentation rates (ESR) in the three patients were 78 mm/hour, 96 mm/hour, and 84 mm/hour, whereas C-reactive protein (CRP) levels were 8.3 mg/dL, 13.4 mg/dL, and 7.6 mg/dL.

All three had poorly controlled diabetes despite insulin therapy, with a mean fasting glucose level of 210 mg/dL; hypertension, with mean systolic and diastolic blood pressures of 180 mm Hg and 100 mm Hg; and severe osteoporosis with multiple vertebral fractures.

Despite the need for treatment, these patients declined steroid therapy because of their comorbidities, according to Dr. Nannini.

They did, however, consent to treatment with adalimumab (40 mg) every 2 weeks.

After 1 month of therapy, all three were in remission, with ESRs less than 20 mm/hour, CRPs less than 0.5 mg/dL, and no remaining musculoskeletal, cranial, or systemic symptoms.

After 6 months, the adalimumab dosage was reduced to 40 mg once monthly; after 12 months of therapy, the drug was discontinued in two of the three patients. They remain in remission 4 and 5 months later, whereas the third patient is completing 1 year of treatment with good response.

"Comorbidities such as diabetes, hypertension, and osteoporosis are very common among patients with GCA, highlighting the need for corticosteroid-sparing agents. … Our limited experience with adalimumab suggests that the drug may represent an effective alternative to corticosteroids in patients with GCA who had corticosteroid dose-limiting comorbidities," she concluded.

Dr. Pipitone described these findings with adalimumab as "quite intriguing." He added, however, "I don't think we can make a case for the use of TNF blockers in clinical practice, at least not at this stage."

Neither Dr. Pipitone nor Dr. Nannini reported conflicts of interest. ■