Don't Use ANCA Levels to Guide Treatment

BY BRUCE JANCIN
Denver Bureau

SNOWMASS, COLO. — Rheumatology would be well served if the term "ANCA-associated vasculitis" was banished from the medical lexicon, Dr. Gary S. Hoffman asserted at a symposium sponsored by the American College of Rheumatology.

"Practitioners who accept this nomenclature may be misled and apply the concept of [antineutrophil cytoplasmic antibody–associated] vasculitis or—the greatest disservice of all, but one well embedded in the literature now—'ANCA disease,' in a fashion that's detrimental to patient care. They mistakenly assume [antineutrophil cytoplasmic antibodies] are required for disease, correlate with disease activity, and can be used as a guide to treatment," said Dr. Hoffman, professor of medicine at the Cleveland Clinic Foundation/Lerner College of Medicine.

In fact, the rheumatologist continued, none of that's true.

"This is not an academic argument," he added. "I see ANCA being misused on almost a weekly basis in patients sent to me."

The resultant patient harm can take the form of delayed diagnosis and treatment of small-vessel vasculitis because of excessive reliance upon a negative ANCA test, or, conversely, inappropriate use of powerful immunosuppressive agents in ANCA-positive patients with sinusitis but no small-vessel sinusitis, Dr. Hoffman continued.

Dr. Hoffman readily conceded his position is controversial. ANCA's proponents use the term ANCA-associated vasculitis to refer to four diseases in which ANCA is present to a variable extent.

Patients can be harmed if diagnosis and treatment of small-vessel vasculitis are delayed because of excessive reliance upon a negative ANCA test.

These include Wegener's granulomatosis, microscopic polyangiitis, Churg-Strauss syndrome, and immune complex–negative rapidly progressing glomerular nephritis.

He argued that these conditions are actually strikingly different both clinically and pathologically.

And ANCA can't serve as a true unifying principle, since it's not universally present in these diseases.

Indeed, in the two best studies to date in Churg-Strauss syndrome, one from France and the other Italy, only 38% of patients with the disorder were ANCA positive at diagnosis, indicating the disease is not driven by ANCA.

"My concern is that the terms ANCA-associated vasculitis and ANCA-disease dumb down the complexity of these diseases to the clinician," Dr. Hoffman explained.

ANCA testing is unequivocally of value in the diagnosis of small-vessel vasculitides in patients with a moderate to high pretest probability.

Under those circumstances, a positive result may eliminate the need for biopsy.

When the pretest probability is low, however, ANCA testing will have substantial false-positive and -negative rates, according to Dr. Hoffman.

He cited a landmark study of the diagnostic value of ANCA in idiopathic systemic vasculitis which concluded the test is negative in 15%-20% of affected patients (Kidney Int. 1998;53:743-53).

Serial ANCA testing should definitely not be used to guide immunosuppressive therapy or try to predict relapse, in Dr. Hoffman's view.

"Don't ever base your treatment decision making primarily on the ANCA test," he stressed. "That is a surefire formula for getting your patient in trouble."

He cited a recent rigorously conducted study by the Wegener's Granulomatosis Etanercept Group involving 156 patients followed with serial ANCA testing over nearly 3 years.

The investigators concluded ANCA titers bore little relationship to disease activity. Increases in pro–proteinase 3-ANCA or mature PR3-ANCA weren't significantly associated with relapse, and decreases weren't associated with remission (Ann. Intern. Med. 2007;147:611-9).

Audience member Dr. Ulrich Specks of the Mayo Clinic, Rochester, Minn., observed that ANCA testing "has many pitfalls and can be misleading." But he is firmly convinced ANCA influences disease phenotype.

Dr. Hoffman concurred.

"People who are high-titer ANCA positive tend to have more severe disease. ANCA may enhance the pathogenic process that is already established. I think it may well be much like anti–double-stranded DNA in lupus and rheumatoid factor in rheumatoid arthritis," Dr. Hoffman commented. ■

Dexamethasone Pulse Rivals High-Dose Tx in Myopathies

BY PATRICE WENDLING
Chicago Bureau

CHICAGO — High-dose dexamethasone pulse therapy is a good alternative to daily prednisone as first-line treatment of subacute inflammatory myopathies, Dr. Janneke van de Vlekkert reported at the annual meeting of the American Academy of Neurology.

In a prospective, multicenter, double-blind trial of 62 newly diagnosed adults with dermatomyositis or nonspecific myositis, significant difference was seen at 18 months in the composite score of six clinical outcome measures among patients receiving prednisone 70 or 90 mg/day versus those who received six cycles of oral dexamethasone 40 mg/day for 4 consecutive days at 28-day intervals.

No significant differences were seen among patients taking dexamethasone and those given prednisone on the study's outcomes, which included remission.

The mean composite score was 2.8 (median 2.0) in both treatment groups, Dr. van de Vlekkert and associates reported.

No significant differences were observed among the 30 patients treated with dexamethasone and the 32 treated with prednisone for the six outcomes that comprised the composite score. These included remission (5 vs. 9 patients, respectively), remission less than 3 months (2 vs. 3 patients), no relapse (16 vs. 20 patients), Medical Research Council sum score at least 138 out of 140 (16 vs. 16 patients), visual analog scale score of 0-2 for muscle pain (18 vs. 13 patients), and no cushingoid appearance (18 vs. 13 patients).

The mean time until remission was 58 weeks in both groups, while the median time until relapse was 44 weeks in the dexamethasone group and 60 weeks in the prednisone group.

Based on these findings, the study was halted prematurely after inclusion of 62 patients instead of the planned 80 patients.

Side effects occurred in significantly fewer patients treated with dexamethasone than in patients with prednisone, including any side effect (22 vs. 29, respectively), diabetes mellitus (1 vs. 10), and mood changes (8 vs. 20), Dr. van de Vlekkert of the Academic Medical Center, Amsterdam, and associates reported.

The improved side effect profile is notable, as daily high-dose prednisone is the standard treatment of subacute inflammatory myopathies, and major drawbacks of long-term therapy with prednisone are its side effects, the investigators noted.

Dr. van de Vlekkert disclosed no conflict of interest related to the study, which was supported by the Princess Beatrix Fund, the Hague, the Netherlands. ■

Topical, Systemic Therapies Are on the Horizon for Lupus

BY BRUCE JANCIN
Denver Bureau

WAIKOLOA, HAWAII — Keep an eye out for two promising novel therapies for cutaneous lupus—one topical, the other systemic—as they currently work their way through the drug developmental pipeline, Dr. David Fiorentino advised.

The topical agent is 0.5% R-salbutamol cream. Salbutamol, a β_2-agonist, is widely prescribed in an inhaled powdered formulation for the treatment of asthma and chronic obstructive pulmonary disease, Dr. Fiorentino said at the annual Hawaii dermatology seminar sponsored by the Skin Disease Education Foundation.

Dermatologists at Copenhagen University Hospital and Astion Pharma believed the drug had therapeutic potential in cutaneous lupus based on its anti-inflammatory effects, its ability to inhibit superoxide generation from stimulated granulocytes, and its inhibition of interleukin-2 and interferon-gamma release by stimulated T cells.

They found that twice-daily topical therapy showed greater efficacy in subcutaneous lupus erythematosus than in treatment-resistant discoid lupus erythematosus in their nine-patient open-label pilot study (Arch. Dermatol. 2007;143:1589-90).

Inhaled salbutamol is associated with mucosal irritation, tachycardia, and tremor.

Two lupus patients developed dermatitis after topical therapy, but there was no tachycardia or tremor despite twice-daily treatment of up to 2,000 cm^2.

Topical salbutamol is slated for a phase III clinical trial this year, according to Dr. Fiorentino, a dermatologist at Stanford (Calif.) University.

"It would be really nice to have another topical therapy besides corticosteroids," he said.

The systemic therapy is efalizumab (Raptiva), which is approved for the treatment of psoriasis.

Efalizumab is a humanized monoclonal antibody directed against the CD11a chain of leukocyte-functioning antigen. It blocks T-cell activation.

A growing body of anecdotal evidence suggests that this biologic is effective for treating discoid and subcutaneous lupus erythematosus refractory to conventional therapies.

Dermatologists at Leeds (England) General Infirmary reported that 12 of 13 patients with discoid lupus showed responses ranging from good to excellent after a mean of less than 6 weeks on efalizumab (Arch. Dermatol. 2007;143:873-7).

Dr. Fiorentino added that he, too, has used efalizumab off label and has found it "incredibly effective" in patients with subacute or discoid lupus.

He disclosed having interests in Genentech Inc.

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