Vasculitis Relapse Management Requires Vigilance

BY NANCY WALSH
New York Bureau

Boston — Although 3 decades have passed since the introduction of a regimen combining daily oral cyclophosphamide with prednisone transformed antineutrophil cytoplasmic antibody–associated vasculitis from a uniformly fatal disease to one with an 80% survival rate, the management of relapse in this and other small-vessel vasculitides remains a vexatious challenge with no approved treatments, Dr. Carol A. Langford said at the annual meeting of the American College of Rheumatology.

Antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis and microscopic polyangiitis are by nature relapsing diseases, and currently no treatment can reliably prevent recurrence.

“Let me think of an image: we cannot prevent relapse, our approach must be based first on correctly identifying relapse—which sounds straightforward but frequently is not—and then selecting the treatment option that best addresses the patient’s treatment history, disease severity, and that takes into account the risks and benefits of the regimen,” said Dr. Langford of the Cleveland Clinic Foundation, department of rheumatic and immunologic diseases, and currently no treatment can reliably prevent recurrence.

It’s also important to differentiate new disease activity from a relapse in the same way each time, but the suggestion of disease activity in one site should alert the clinician to the possibility of new activity in another site.

“Often you have gone through this careful thought process and have determined that your patient is relapsing, the question becomes what approach to use, and whether treatment of relapse is any different from initial treatment. The answer is yes and no,” she said. Overall, the treatment options remain the same; there are no regimens used solely for initial treatment or maintenance therapy. Aside from cyclophosphamide and prednisone, the most commonly used agents today are azathioprine and methotrexate.

In a recent review of patients treated at Dr. Langford’s center, 57 of the 150 patients with severe disease were initially treated with cyclophosphamide, and 25 with mild to moderate disease were treated with methotrexate. Following initial improvements, all patients continued on methotrexate, with sustained remission being seen in 78%. Although 49% relapsed within 1 year and 60% relapsed within 2 years, 82% of relapsed patients were able to achieve subsequent remission with additional treatment (Medicine [Baltimore] 2005;84:194-200).

Treatment after relapse must consider drug toxicities that might have occurred with past treatment, organ damage, and any new medical conditions. Other considerations include whether the dosages of medications and duration of therapy have been adequate in the past, whether the method and timing of administration have been optimal, and if the patient has been compliant.

A patient who has been doing well for several years on methotrexate and has a mild relapse does not necessarily need to receive the very expensive—but very toxic—cyclophosphamide.

“I would look for ways to optimize the methotrexate, keeping in mind that, whenever possible, cyclophosphamide should be reserved for instances when its lifesaving capacity may be needed,” said Dr. Langford.

The site and severity of relapse also are important. “We rarely would consider cyclophosphamide for isolated sinonasal relapse,” Dr. Langford said.

An additional difficult question relates to the optimal duration of maintenance therapy to prevent relapse. “The clinician knows, ‘the answer unfortunately is, we don’t know,'” she said. Some patients are able to stop treatment and remain in remission, but studies have shown that relapse rates are higher when patients are no longer on treatment. If a patient has done well for a minimum of 2 years, consideration can be given to tapering treatment depending on risks and benefits, but this must be done on an individual basis. “However, if someone has a residual creatinine of 4 mg/dl and is fighting for every last glomerulus, I wouldn’t want to stop to maintain therapy if toxicity is not an issue,” Dr. Langford said.

Finally, new agents are becoming available to treat ANCA-associated vasculitis. “Some patients elect to use these new agents to modify or replace the standard treatments, unproved therapies should not be used except in the context of clinical trials. ANCA-associated vasculitis and microscopic polyangiitis are potentially life-threatening diseases. “If the agent is not effective, the disease could worsen or unexpected toxicities could be seen,” Dr. Langford said.

For example, a trial that evaluated adding etanercept or placebo to standard therapy with cyclophosphamide or methotrexate, there were no differences between the groups in the rates of sustained remission or severe adverse events, but six patients in the etanercept group developed solid tumors, compared with no patients in the placebo group (N. Engl. J. Med. 2005;352:352-361).

Interferon-Regulated Chemokine Levels Predict Lupus Flare

BY NANCY WALSH
New York Bureau

Boston — Elevated levels of the three interferon-regulated chemokines that correlate with disease activity in systemic lupus erythematosus might prove useful for the prediction of disease flares. Findings from research sponsored by the National Institute of Arthritis and Musculoskeletal and Skin Diseases and the Lupus Research Institute “strongly suggest” monitoring interferon-regulated chemokines in lupus will be useful as a clinical tool to aid physicians in decision making, according to one of the investigators.

“Valid biomarkers of disease activity in systemic lupus erythematosus would have the potential to improve the management of this heterogeneous, multisystem autoimmune disease that is characterized by relapsing and remitting disease activity,” Jason W. Bauer, Ph.D., said during his presentation at the annual meeting of the American College of Rheumatology.

The interferon pathway has arisen as one of the more promising sources of biomarkers, with several interferon-regulated chemokines having been found at elevated levels in the serum of patients with systemic lupus erythematosus (SLE), he said.

Now under the auspices of the Autoimmune Biomarkers Collaborative Network, researchers have analyzed serum samples from 288 patients from the Hopkins Lupus Cohort over the course of 1 year.

Patients were seen quarterly or whenever a flare occurred, for a total of 1,310 visits. Detailed laboratory and clinical assessments including physician’s global and SLE disease activity index (SLEDAI) scores were obtained at each visit. Levels of the chemokines CXCL10, CC22, and CCL19 were measured using chemiluminescent multiplex enzyme-linked immunosorbent assays, and a normalized chemokine score was created to reflect the combined levels of all three.

“Before evidence that interferon-regulated chemokines are biomarkers of SLE activity, we first used a cross-sectional approach to determine whether active lupus cases have higher levels of chemokines than inactive cases,” said Dr. Bauer of the University of Minnesota, Minneapolis.

Patients were classified as active if they had an SLEDAI score of 6 or greater, and inactive if the SLEDAI score was 2 or below and the physician’s global assessment was 0.

Comparison of the chemokines from single visits of active patients with those of inactive patients found significant upregulation, particularly for CXCL10 and CCL19, in the active patients.

A cross-sectional approach also was used to compare chemokine scores according to SLEDAI scores. Patients with low chemokine scores were more likely to have SLEDAI scores of 0. Those with scores higher than 6 were more likely to have high levels of the three chemokines.

“We believe that these two cross-sectional approaches show these [chemokines] to be very robust markers of SLE disease activity,” said Dr. Bauer.

Similar findings were seen with serum chemokine levels over time, with elevated levels being associated with periods of flare and lower levels seen with remission. Moreover, levels of the three chemokines were much more closely with flare than did classical laboratory variables such as sedimentation rate, complement levels, or anti-dsDNA antibody titers, he said.

“Finally, we found that patients who had high baseline chemokine scores were more likely to experience a flare during the following year than were those with low baseline scores,” he said. This approach also could provide a reliable measure of disease activity for use in clinical trials, but must be validated using samples from independent SLE cohorts, he added.

In an earlier study, Dr. Bauer and his colleagues wrote, “We hypothesize that high levels of systemic chemokines in active SLE, driven by type 1 interferon, lead to a state of ‘chemokine confusion’ that alters the normal trafficking and chemotaxis of leukocytes in the body, setting the stage for widespread, systemic autoimmunity.” High-level production of chemokines may also contribute to human SLE by recruiting immune and inflammatory cells into target tissues.” (PLoS Med. 2006; 3(12):e491.)