Pulse Cyclophosphamide Beats Daily for Vasculitis

BY DAMIAN McNAMARA
Miami Bureau

BIRMINGHAM, ENGLAND — Pulsed cyclophosphamide is as effective as daily oral administration for patients with systemic vasculitis and is associated with fewer side effects, according to initial results of a study presented at the annual meeting of the British Society for Rheumatology.

Six previous randomized, controlled trials demonstrate the efficacy of cyclophosphamide for induction and maintenance of remission of generalized vasculitis in a majority of patients up to 6 months, Dr. David Carruthers said. However, the optimal dosing regimen remains unknown.

"A common question is: Does the route of cyclophosphamide administration make a difference?" said Dr. Carruthers, a consultant rheumatologist at City Hospital, Birmingham (England).

In unpublished data from the completed CYCLOPS (Daily Oral Versus Pulsed Cyclophosphamide for Renal Vasculitis) study, researchers compared remission rates at 3 and 6 months for 160 patients randomized to intermittent pulse therapy or daily oral therapy.

The rate of remission at 3 months was 70% in the pulse regimen group and 65% in the conventional daily oral regimen group. At 6 months, 92% of the pulse therapy group achieved remission, compared with 86% of the daily oral group.

"This seems to indicate pulse is as effective," Dr. Carruthers explained. "There was no difference in patient survival either."

The researchers found a higher rate of infection—including severe and life-threatening leukopenia—with continuous oral therapy, compared with pulse cyclophosphamide, Dr. Carruthers said. Pulse therapy has a potential for higher long-term remission rates, compared with daily therapy, "but that remains to be seen," he said.

Cyclophosphamide appears to cause equal rates of induction of remission compared with methotrexate in other studies, Dr. Carruthers said, however, methotrexate remission takes longer to achieve.

In addition, there was a 70% relapse rate at 1 year with methotrexate, compared with 45% with continuous oral cyclophosphamide, among 100 participants in the NORAM (Methotrexate Versus Cyclophosphamide for "Early Systemic" Disease) study (Arthritis Rheum. 2005;52:2461-9). "Most relapses occurred when patients were off all therapy, including steroids," Dr. Carruthers said.

Mean time to relapse was 13.5 months in the NORAM study. Dr. Carruthers said, "It does seem that prolonged therapy is necessary beyond 12 months."

In response to a question from an audience member on the use of azathioprine for induction of remission, Dr. Carruthers said: "Cyclophosphamide use in a targeted manner is more predictable than use of azathioprine for induction of remission."

Although Dr. Carruthers recommended cyclophosphamide as initial therapy, he said it might not be necessary for the maintenance phase. "It appears unnecessary to keep patients on cyclophosphamide once remission is achieved. They can be given azathioprine for up to 18 months." For example, findings from the CYCAZERAM (Cyclophosphamide Versus Azathioprine as Remission Maintenance Therapy for ANCA [antineutrophil cytoplasmic antibody]–associated Vasculitis) study demonstrated no increase in relapse when azathioprine was substituted for cyclophosphamide after remission was achieved (N. Engl. J. Med. 2003;349:36-44).

"Tapering the dose of oral steroids is probably needed for all," Dr. Carruthers said. "But it is not clear if steroid maintenance is needed after 18 months or not." A meeting attendee asked if any randomized, controlled trial compared prednisone and cyclophosphamide for remission induction. "No," Dr. Carruthers said. "The early studies were retrospective reviews. I don't think now we can ethically do studies where we put patients on steroids only versus cyclophosphamide."

The British Society for Rheumatology, in conjunction with the British Health Professionals in Rheumatology, expects to release guidelines for the management of adults with ANCA-associated vasculitis soon, Dr. Carruthers said. The recommendations will be available on their Web site (www.rheumatology.org.uk). The European Vasculitis Study Group, which updates its study findings at www.vasculitis.org, is another source of clinical information. ■

Thorough Patient History Can Pinpoint Raynaud of the Nipples

BY SHERRY BOSCHERT
San Francisco Bureau

SAN FRANCISCO — With only a handful of case reports in the medical literature, Raynaud phenomenon of the nipples isn't often a physician's first thought when a breastfeeding mother describes nipple pain.

However, if there are no signs of infection and no cracks or fissures on the nipples, consider this rare cause of nipple pain, especially if the woman has a history of Raynaud syndrome, Sharon R. Wiener said at a meeting on antepartum and intrapartum management sponsored by the University of California, San Francisco.

Patients diagnosed with Raynaud phenomenon of the nipples should avoid exposure to cold, vasoconstricting drugs, nicotine, and caffeine.

The pain from this vasospasm of the nipples while breast-feeding usually is bilateral, severe, and a spasm-like throb. The nipple usually turns very white but may be blue, purple, or red, said Ms. Wiener, a certified nurse-midwife at the university.

This problem has been misdiagnosed as a candidal infection. Among 12 women in a 2004 case report who ultimately were diagnosed with Raynaud phenomenon of the nipples, 8 had been treated for candidiasis of the breast. Following them for 4 months and diligently taking detailed histories led to the correct diagnosis and treatment, she said.

A recent patient seen by Ms. Wiener said she had been diagnosed with Raynaud syndrome about 5 years before her pregnancy. She complained of episodes in which her nipples would become cold and then go into spasms for many hours.

"She was very concerned, appropriately, that she was going to have difficulty breastfeeding," Ms. Wiener said.

Sending patients in whom you suspect this problem to a lactation consultant to identify poor latch can support the diagnosis. Alternatively, try applying a cold compress or ice to the nipple to see if it triggers the phenomenon.

It's important to prepare the woman for the effect this may have. "I've done this twice. In one case, I got a dramatic response," she said. "I know this sounds horrible," but it's preferable to prescribing treatment without a firm diagnosis.

The treatment of choice is the calcium channel blocker nifedipine, 5 mg b.i.d. for 2 weeks. "It's very quick acting" and a vasodilator, she said. "The handful that I have treated have responded very well and didn't need a repeat of the prescription. Why that is, I can't tell you."

Raynaud phenomenon of the nipples has been associated with factors that restrict the blood vessels, including rheumatologic diseases, endocrine diseases, autoimmune diseases, cigarettes, and caffeine.

Advise the patient to avoid exposure to cold, vasoconstricting medications, nicotine, and caffeine. In mild cases, warm compresses or warm showers may suffice as treatment. Topical nitroglycerine appears to be effective treatment in half of cases. ■

B-Cell Depleting Rituximab Shows Promise in Myopathies

BY NANCY WALSH
New York Bureau

BARCELONA — Clinical improvement in a small series of patients with inflammatory myopathies treated with rituximab suggests that B-cell depletion may prove useful in these disorders, according to Dr. Marlies Blom of the department of rheumatology, Radboud University Nijmegen Medical Centre (the Netherlands).

Among seven patients who had either dermatomyositis, polymyositis, or antisynthetase syndrome, two infusions of 1,000 mg rituximab 2 weeks apart resulted in a mean 30% increase in muscle strength at 3 months, Dr. Blom reported in a poster session at the annual European Congress of Rheumatology.

The patients' subjective reports of improvement in muscle strength were later confirmed by using handheld dynamometry.

The patients ranged in age from 38 to 58 years, and the duration of their disease ranged from 3 to 16 years. Four of the seven were female.

Previous treatments included oral and intravenous prednisone, methotrexate, azathioprine, cyclophosphamide, interferon, etanercept, and intravenous immunoglobulin.

A mean 13% improvement was reported on Health Assessment Questionnaire (HAQ) scores, and improvements also were also seen in levels of creatine phosphokinase, a marker of disease activity.

In one patient, a muscle biopsy taken 4 months after treatment showed a total absence of CD20+ B cells. This patient's Disease Activity Score–28 (DAS28) score fell from 6.83 to 4.46 after 3 months, according to Dr. Blom.

After initial good response, three patients required retreatment for exacerbations of myositis at about 6 months.

No serious adverse events were observed and immunoglobulin levels remained within normal ranges.

These results suggest that B cells play an important role in the pathogenesis of inflammatory myopathies, Dr. Blom noted.

Another recent report suggested that a possible rationale for considering B-cell depletion as a therapeutic strategy in dermatomyositis was that treatment with rituximab had previously been shown to result in improvements in muscle strength in humorally mediated autoimmune peripheral neuropathies (Arthritis Rheum. 2005;52:601-7).

The importance of humoral immunity in dermatomyositis also is suggested by the observation that perifascicular endothelial immunoglobulin and complement deposition are thought to result in the muscle ischemia and atrophy (J. Rheumatol. 2006;33:1021-6).

Furthermore, the observation that there are antibodies specific for myositis also supports the concept of B-cell–mediated humoral abnormality in dermatomyositis (Medicine [Baltimore]. 1991;70:360-74). ■