B-Cell Depletion May Benefit Sjögren's Patients

BY NANCY WALSH
New York Bureau

San Antonio — The lengthening list of potential uses for rituximab may soon include the treatment of early and active Sjögren's syndrome—but with a caution.

In Sjögren's syndrome, high levels of B-cell autoreactivity are associated with high disease activity, systemic complications, and a markedly elevated risk for the development of B-cell lymphoma, Justin Pijpe, M.D., said at the annual meeting of the American College of Rheumatology.

Current treatment approaches for the autoimmune disease, including corticosteroids and hydroxychloroquine, have been largely unsuccessful in alleviating symptoms and have no impact on the course of disease.

Rituximab (Rituxan) is a monoclonal antibody that binds to the CD20 receptor on B cells, leading to B-cell depletion. The drug is now being investigated in a phase I/II study to determine if B-cell depletion may be a beneficial approach in Sjögren's syndrome, Dr. Pijpe reported in a poster session.

To date, six patients, all female and whose mean age is 50 years, have been treated with four infusions of rituximab, 375 mg/m^2, given weekly.

All had early disease that was characterized by B-cell hyperactivity, with IgG levels exceeding 15 g/L and had the autoantibodies IgM-Rf and anti-SSA/B. Patients with early disease—4 years' duration or less—typically still have substantial residual exocrine gland function, he explained.

Preliminary data on clinical efficacy suggest marked subjective improvement of fatigue, sicca complaints, and health status, as well as an increase in salivary gland function, said Dr. Pijpe of University Hospital Groningen (the Netherlands).

Analysis of saliva showed a decrease in inflammatory activity, and lacrimal gland function was unchanged or showed slight improvement.

Serologic analysis revealed a decrease in erythrocyte sedimentation rate and rheumatoid factor level, and levels of IgG remained stable or decreased.

Repeat biopsies of the parotid glands showed an increase in IgA:IgG plasma cell ratio, suggesting a specific decrease in IgG-producing B cells in the affected tissue.

Rituximab seems to be very effective in the treatment of early Sjögren's syndrome, Dr. Pijpe said.

But further investigation is needed, given that two patients developed a serum sickness–like clinical picture, necessitating treatment cessation.

"I was very surprised, because this type of adverse event is very rare," he said. "Our patients showed a clinical presentation compatible with serum sickness, but serologic analysis was not fully characteristic for a type III hypersensitivity reaction," he told this newspaper.

For example, there was no proteinuria, and the one patient who was tested for human antichimeric antibodies was negative.

On the other hand, there was an acute phase response and a slight increase of C3d in both patients, findings that are indicative of complement consumption, he said.

This type of reaction has not been reported in recent studies of rituximab in systemic lupus erythematosus and rheumatoid arthritis.

Only three cases of serum sickness after rituximab treatment have been reported previously, he said. ■

Safety of HCQ in Pregnancy Backed By Small Studies

BY JEFF EVANS
Senior Writer

Düsseldorf, Germany — The anti-inflammatory compound hydroxychloroquine appears to be relatively safe during pregnancy, according to a small number of studies totaling about 250 patients.

But these studies have not provided overwhelming evidence proving the safety of hydroxychloroquine, Jean-Charles Piette, M.D., said at an international conference on cutaneous lupus erythematosus.

Until 1995, nearly all physicians stopped hydroxychloroquine (Plaquenil) when a patient with lupus erythematosus (LE) became pregnant because there were no data on whether the drug was safe during pregnancy, said Dr. Piette of Hôpital Pitié-Salpétrière, Paris.

Now, many physicians who treat about four to five pregnant women with connective tissue disorder each year regularly prescribe antimalarials to such patients despite a lack of evidence officially establishing the safety of the drugs during pregnancy. In fact, 69% of 52 physicians who responded to a survey about the use of antimalarials during pregnancy said they continued antimalarials in pregnancy sometimes, often, or always (J. Rheumatol. 2002;29:700-6).

Hydroxychloroquine (HCQ) is known to cross the placenta and is present in similar concentrations in blood from the umbilical cord and the mother (Arthritis Rheum. 2002;46:1123-4).

In one study, 33 women with LE who were exposed to HCQ during 36 pregnancies had similar obstetric outcomes and levels of lupus activity, compared with 53 unexposed pregnant women with LE from the same lupus pregnancy center (Ann. Rheum. Dis. 1996;55:486-8). The investigators in the trial concluded that the continuation of HCQ "is probably safe during pregnancy," Dr. Piette noted.

In a separate study, HCQ did not cause any disease flares in a group of eight women with systemic LE and two with discoid LE, whereas three patients had flare-ups in a placebo group of nine patients with systemic LE and one with discoid LE. None of the infants born to women taking HCQ had congenital abnormalities, and all of them had normal auditory and neuroophthalmologic evaluations at 1.5-3 years of age (Lupus 2001;10:401-4).

No unusual side effects occurred in another series of 53 pregnancies in women with LE that resulted in live births.

A study conducted by Dr. Piette and his colleagues compared 133 consecutive pregnancies in 90 women with connective tissue disease who took HCQ with 70 consecutive pregnancies in 53 control women with similar disorders who did not take HCQ. Of the pregnancies in women who received HCQ, 122 were exposed to 400 mg/day, and the remaining 11 received 200 mg/day.

Three malformations occurred in exposed infants, while four developed in the infants of control women. One child died as a result of prematurity in each group.

After the last follow-up of children at a mean age of 26 months (age ranging from 12 to 108 months), none of the children exposed to HCQ had visual, hearing, growth, or developmental abnormalities (Arthritis Rheum. 2003;48:3207-11).

Despite data that show no teratogenicity with HCQ, the Physicians' Desk Reference Web site for patients advises pregnant patients to avoid HCQ except in the suppression or treatment of malaria when the benefit outweighs any possible hazards.

HCQ exists at low levels in breast milk—344 ng/mL and 1,424 ng/mL in a report on two mothers—and is delivered in extremely low levels to breast-feeding children. ■

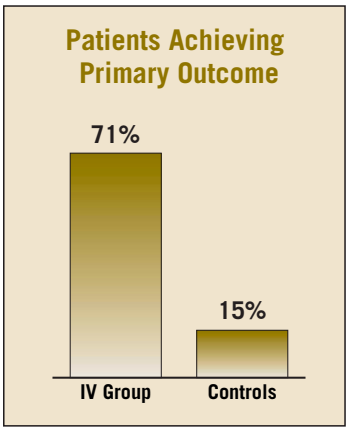
High-Dose IV Steroid Allows Prednisone Tapering in Giant Cell Arteritis

BY NANCY WALSH
New York Bureau

San Antonio — The use of high-dose pulsed intravenous glucocorticoid infusions may provide a means of effectively inducing remission in patients with giant cell arteritis, Mehrdad Mazlumzadeh, M.D., said at the annual meeting of the American College of Rheumatology.

First-line treatment for this condition, in which the arteries of the head and neck become inflamed, is with oral prednisone. This approach leads to rapid suppression of the inflammatory processes and resulting symptoms, which can include headache, fatigue, and even blindness. Inflammatory infiltrates persist in the temporal arteries, however, and many patients relapse.

And because extended courses of oral therapy typically are needed, patients are at risk for the many adverse effects associated with long-term steroid exposure, said Dr. Mazlumzadeh, a rheumatologist at the Mayo Clinic, Rochester, Minn.



In a study that included 27 patients with biopsy-proven giant cell arteritis, all participants received oral prednisone in a dose of 40 mg/day. They also were randomized to receive either pulse IV methylprednisolone, 15 mg/kg per day for 3 days, or intravenous saline.

The goal was to determine if high-dose pulse methylprednisolone as the initial treatment of giant cell arteritis would allow for more rapid tapering of oral prednisone without increasing the number of relapses. The primary outcome was reduction in the oral prednisone dose to no more than 5 mg/day after 34 weeks of therapy. "The results were impressive," Dr. Mazlumzadeh said.

Of the 14 patients in the intravenous treatment group, 10 achieved the primary outcome vs. 2 of 13 in the control group—71% vs. 15%, a statistically significant difference.

Remission was defined as being off prednisone altogether with no recurrences for at least 2 months. Six of the active treatment patients were in remission at 18 months. None of the control patients achieved remission, he said.

There were 21 disease flares in the active treatment group and 34 in the control group. The rate of relapses per 100 person-months of treatment in the control group was 14.5, compared with 8.3 in the active treatment group.

The median cumulative dose of prednisone in the active treatment group was 4,853 mg, compared with 7,215 mg in the control group.

There were no differences between the groups in terms of the development of steroid-associated complications including osteoporosis, hypertension, hyperlipidemia, and diabetes.

No life-threatening disease-associated complications or vision loss occurred. One patient in the intravenous treatment group developed pyelonephritis 11 days after starting therapy. ■