Steroid Added to Interferon-β Cuts MS Relapses

The relapse rate in patients receiving the combination was about a third of that seen in placebo patients.

BY MITCHEL L. ZOLER
Philadelphia Bureau

Intermittent, add-on treatment with an oral corticosteroid led to a significant drop in relapses among patients with multiple sclerosis who were previously relapsing on monotherapy with interferon-β in a controlled study with 130 patients.

If the efficacy of this cyclic regimen with methylprednisolone is confirmed in a second study now in progress, add-on, cyclic treatment with methylprednisolone "would be justified as routine therapy," said Dr. Per Soelberg Sørensen, who reported his finding at the World Congress on Treatment and Research in Multiple Sclerosis in Montreal.

Cyclic treatment with methylprednisolone as an add-on to interferon, mitoxantrone, or cyclophosphamide already is used off label at many multiple sclerosis (MS) clinics, said Dr. Sørensen, a professor in the department of clinical neuroscience and psychiatry at Rigshospitalet, Copenhagen.

The Nordic trial of methylprednisolone as add-on therapy to interferon-β (IFN-β) for the treatment of relapsing-remitting multiple sclerosis (NORMIMS), run by Dr. Sørensen and his associates at seven centers in Scandinavia, enrolled MS patients on long-term, subcutaneous treatment with interferon beta-1a who had at least one relapse during their previous year on treatment. In general, about 35% of MS patients on long-term treatment with IFN-β have relapses. The average relapse rate for all MS patients on a steady interferon regimen is 0.4 relapse events per year, Dr. Sørensen said in an interview.

The patients were randomized to receive either placebo or 200 mg of oral methylprednisolone daily for 5 days at 4 week intervals (a total monthly dose of 1 g). During the study, the interferon beta-1a regimen was maintained at a dosage of 44 mcg administered subcutaneously three times a week.

During 96 weeks of treatment, the annualized relapse rate of the 66 patients on methylprednisolone was 22%, compared with a 59% relapse rate among the 64 control patients on placebo, a statistically significant difference, said Dr. Sørensen.

During the study, 8 patients on methylprednisolone and 14 patients on placebo had a sustained increased in their disability based on at least a 1-point rise in their expanded disability status score. The average time it took for patients to have a sustained increase in their disability was 626 days for the patients on methylprednisolone and 376 days among those in the placebo group. The average number of active MS lesions seen with MRI in each patient during 1 year was 4.8 in those on the oral steroid and 5.4 in the control patients, a difference that just reached statistical significance. Methylprednisolone therapy was also well tolerated.

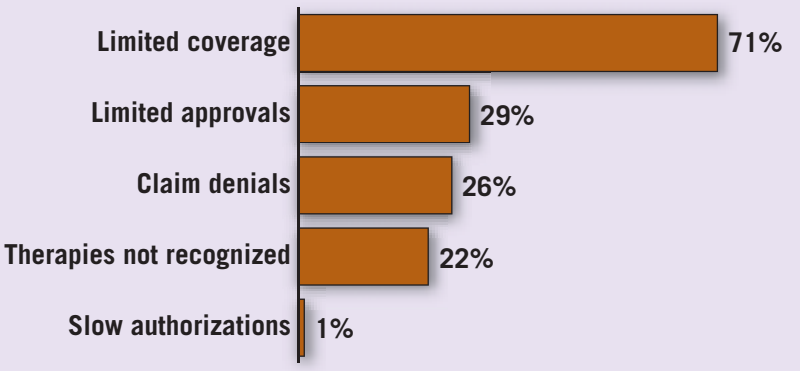
If methylprednisolone was used as cyclic, add-on therapy with IFN-β in routine practice, patients who failed to respond satisfactorily to the combination should be switched to other agents. Natalizumab and mitoxantrone are both approved as second-line drugs for MS and would be alternatives to consider, Dr. Sørensen said.

The second study of methylprednisolone added to interferon beta-1a in relapsing MS patients has treated more than 150 patients with the combination for 3 years. The methylprednisolone dosage used was higher, 500 mg/day for 3 days every 4 weeks (1.5 g/month), the maximum tolerable dose for this steroid, Dr. Sørensen said.

Results from this second study should be reported soon, according to Dr. Sørensen, who is also a coinvestigator for the second study. ■

DATA WATCH

Obstacles to Insurance Coverage of Specific Therapies for Multiple Sclerosis



Notes: Based on a 2006 survey of 143 neurologists currently managing MS patients. Respondents reported on physical, occupational, and speech therapy.
Sources: Teva Neurosciences Inc. and National Multiple Sclerosis Society

37% Case Reduction

MS Therapy *from page 1*

start injected treatment; not every patient will want that. But I would tell patients that the data suggest they could have several more episodes" of MS symptoms in the year after their initial event, Dr. Freedman, professor of neurology at the University of Ottawa and director of the MS Research Clinic at Ottawa General Hospital, said in an interview.

Patients enrolled in the study were aged between 18 and 45 years when they had a first neurologic event suggestive of MS that lasted for at least 24 hours and at least two clinically silent lesions that were 3 mm or larger on a T2-weighted brain MRI scan.

Common first neurologic events that are suggestive of MS include optic neuritis or acute partial transverse myelitis. Patients with such presentations who have not had a recent stroke or show no other identifiable cause are diagnosed with clinically isolated syndrome.

The Betaferon/Betaseron in Newly Emerging Multiple Sclerosis for Initial Treatment (BENEFIT) study randomized 468 patients with a first event suggestive of MS to treatment with 250 mcg interferon beta-1b subcutaneously every other day or placebo. The study was sponsored by Bayer Schering Pharma, which markets interferon beta-1b (Betaseron in the United States and Canada; Betaferon elsewhere). Dr. Freedman is a consultant to and advisory board member for Bayer Schering as well as for other drug companies.

Initial findings from this study, published in 2006, showed that after 2 years of treatment, 45% of the 176 patients in the placebo group and 28% of the 292 patients in the interferon group developed clinically definite MS (according to the Poser criteria)—an absolute reduction in cases of 17% and a relative risk reduction of 50%, a statistically significant difference (Neurology 2006;67:1242-9).

According to the McDonald MS criteria that were introduced in 2001, the rate of progression to MS after 2 years was 85% in the placebo arm and 69% in the interferon arm, a 16% absolute reduction in conversion rate and a 46% relative risk reduction, also statistically significant.

The rate of serious adverse effects was similar in the interferon and placebo arms, and the safety results with this formulation of interferon were consistent with results from previous studies. Based on these findings, the Food and Drug Administration expanded the indication for Betaseron in 2006 to include treatment for a first clinical event suggestive of MS.

'We now have evidence for long-term benefits in the cognitive test. There is no explanation for the better cognitive scores other than early treatment.'

Patients in the placebo arm were switched to interferon treatment after they developed clinically definite MS (based on Poser criteria) or after the end of 2 years of blinded treatment.

The 5-year outcome data in the new report by Dr. Freedman are from 358 of the original 468 patients (76%), including about 80% of the patients who began the study on interferon treatment and remained on interferon for 5 years, and about 70% of the patients who began the study on placebo and then crossed over to interferon treatment and received interferon for at least 3 years.

The 5-year results showed that over time and with crossover of the placebo patients, those who began interferon early continued to have a lower overall rate of progression to definite MS, although the difference between the placebo and active treatment groups fell to a 37% relative reduction, still a significant difference.

The relative rate of progression to MS by the McDonald criteria was reduced 45% in the patients who began interferon at their first clinical event.

The long-term follow-up phase also introduced a measure of disability linked to MS development, the expanded disability status score (EDSS). Three-year follow-up data reported last year showed that confirmed EDSS progression occurred in 24% of placebo patients and in 16% of patients treated with interferon up front, an 8% absolute difference and a 40% relative risk reduction that was statistically significant (Lancet 2007;370:389-97).

After 5 years, the relative risk reduction of the EDSS from early interferon treatment dropped to 24%, a difference that was not statistically significant. That reduction was not unexpected, because "all the disability was driven in the placebo group by the first year of disease," said Dr. Freedman.

A better indicator of the long-term impact of early interferon treatment was the Paced Auditory Serial Addition Test (PASAT) score, a measure of intellectual function and cognitive ability. A new finding in the 5-year follow-up was that patients who received interferon early on had significantly better average PASAT scores than did the patients who started interferon later.

"Early treatment is critical for patients, and we now have evidence for long-term benefits in the cognitive test," Dr. Freedman said. "There is no explanation for the better cognitive scores other than early treatment." He added that this benefit alone is a compelling reason for patients to start on interferon early.

Other benefits from early interferon treatment seen in the 5-year follow-up and reported by Dr. Freeman were a significantly better reduction in the relapse rate and a significantly reduced development of newly active brain lesions.

Dr. Freeman estimated that about two-thirds of patients in the United States are now choosing to begin treatment after the first clinical event suggestive of MS. ■