Early Treatment Slowed Progression of MS

BY SHARON WORCESTER

FROM THE ANNUAL CONGRESS OF THE EUROPEAN COMMITTEE FOR TREATMENT AND RESEARCH IN MULTIPLE SCLEROSIS (ECTRIMS)

Patients with clinically isolated syndrome who receive early treatment with glatiramer acetate have more than a 40% reduction in the risk of developing multiple sclerosis, compared with those whose treatment is delayed, according to findings from a prospectively planned 5-year follow-up of patient in the phase III PreCISe study.

After a 2-year extension phase of the 3-year double-blind, placebo-controlled study, 33% of 80 patients who had received early treatment with glatiramer acetate (GA) developed clinically definite multiple sclerosis (CDMS), compared with 50% of 118 patients who began treatment at the end of the initial 3-year double-blind phase. Each patient received 20 mg of GA daily by subcutaneous injection.

GA is marketed as Copaxone by Teva Pharmaceutical Industries. It is approved in 51 countries, including the United States, and is indicated for reducing the frequency of relapses in relapsing-remitting MS, including those who have experienced a first clinical episode and who have MS features on MRI.

In the Teva-sponsored study, disability progression, as measured by the Expanded Disability Status Scale, occurred in only 21% of patients over 5 years. No differences in progression were noted between the early and delayed treatment groups, according to the principal investigator, Dr. Giancarlo Comi, director of the department of neurology and Institute of Experimental Neurology at the University Vite Salute, San Raffaele, Italy.

"The long-term study results support the benefit of early GA treatment in delaying conversion to CDMS and in reducing MRI burden, including less accumulation of irreversible brain damage," Dr. Comi said in an interview.

Patients in this 2-year extension phase were initially enrolled in the double-blind phase of PreCISe, and were randomized to receive active early treatment with GA or placebo. Findings from a planned interim analysis showed that treatment reduced the risk of CDMS by 44% versus placebo, and delayed disease progression by 722 days vs. 336 days. That phase was stopped after a mean exposure of 2.32 years, and patients were offered the opportunity to enter the open-label extension phase, during which all patients received treatment.

Early treatment reduced the risk of CDMS and delayed its onset compared with placebo in the randomized phase of the trial, but also was associated in the open-label extension with a delay of nearly 3 years in the time to conversion to CDMS compared with delayed treatment.

MRI findings from the PreCISe study, which were presented in a separate session at ECTRIMS, also confirmed the importance of early treatment, according to the principal investigator for that portion of the study, Dr. Massimo Filippi, director of the Neuroimaging Research Unit and professor of clinical neurology at the Scientific Institute and University Ospedale San Raffaele, Milan, and his colleagues.

Early initiation of treatment with GA reduced disease activity and slowed the accumulation of brain atrophy over 5 years as demonstrated by MRI. The early treatment group had significantly fewer new T2 lesions – an indicator of disease activity – and lower T2 lesion volume – a predictor of disease progression – than did the delayed treatment group, the investigators found.

Percent change in brain volume was also significantly lower over the entire study period in patients who received early treatment with GA (–0.99% vs. –1.27%), they said.

The drop-out rate in the 5 years of the PreCISe study was 33% among treated patients, which attests to the established long-term safety profile in patients with relapsing-remitting disease, Dr. Comi said.

"It is very difficult to compare Copaxone to other interferons studied in CIS due to the differences in the type of patients included in each study, but basically the results are comparable, although only Copaxone showed an effect on brain atrophy after 5 years," Dr. Comi said. He added that the efficacy and safety results of this study establish the importance of early treatment with this drug in CIS patients presenting with positive brain MRI.

Chander Raman, Ph.D., an MS researcher and associate professor of clinical immunology and rheumatology at the University of Alabama at Birmingham, said the PreCISe findings confirm what neurologists have started to believe about managing CIS in adults – that treatment at the first clinical diagnosis of CIS is preferable to delay full conversion. ■

VITALS

Major Finding: CDMS occurred in a significantly smaller percentage of patients who underwent early treatment with glatiramer acetate than in those who delayed treatment until 3 years later with the drug (33% vs. 50%).

Data Source: A 2-year extension of the 3-year double-blind, placebo-controlled PreCISe study of 198 patients

Disclosures: Teva Pharmaceutical Industries funded the trial. Dr. Comi reported that he has received honoraria for speaking activities and personal compensation for advisory board and consulting activities from Teva Pharmaceuticals and other MS drug manufacturers. Dr. Filippi also reported financial relationship with Teva and other MS drug manufacturers. Dr. Raman has received grants from the National Multiple Sclerosis Society and the National Institutes of Health.

Teriflunomide Lowers Annualized Relapse Rate 30% in MS

BY SHARON WORCESTER

FROM THE ANNUAL CONGRESS OF THE EUROPEAN COMMITTEE FOR TREATMENT AND RESEARCH IN MULTIPLE SCLEROSIS (ECTRIMS)

Teriflunomide, a novel oral disease-modifying drug, significantly reduced the annualized relapse rate and the risk of disability progression in relapsing multiple sclerosis by about 30% in a 2-year, phase III trial.

The study of Teriflunomide in Reducing the Frequency of Relapses and Accumulation of Disability in Patients with Multiple Sclerosis (TEMSO), which was sponsored by Sanofi-Aventis, randomized 1,088 patients to receive a single daily dose of 7 mg or 14 mg of teriflunomide or placebo.

VITALS

Major Finding: Patients taking 7 mg/day or 14 mg/day of teriflunomide experienced a statistically significant 31% reduction in the annualized relapse rate.

Data Source: A randomized, placebo-controlled phase III study (TEMSO) involving 1,088 patients with relapsing MS.

Disclosures: Sanofi-Aventis sponsored the trial. The investigators disclosed financial relationships with many companies that manufacture drugs for MS, including Sanofi-Aventis.

The primary end point – the annualized relapse rate – was significantly lower among the 7-mg and 14-mg groups (0.370 and 0.369, respectively) than it was in placebo-treated patients (0.539). These rates represented a significant reduction of 31% compared with placebo. The 14-mg group also showed a significant 30% reduction in the risk of disability progression, Dr. Paul O'Connor reported at the congress.

Teriflunomide is the active metabolite of leflunomide, a synthetic, low-molecular-weight drug that was approved by the Food and Drug Administration in 1998 for the treatment of rheumatoid arthritis. The metabolite is a reversible inhibitor of the mitochondrial enzyme dihydro-orotate dehydrogenase (DHODH) that exerts anti-inflammatory, antiproliferative, and immunosuppressive effects, but the mechanisms by which it does so are not yet completely understood. Inhibition of pyrimidine biosynthesis (via suppression of DHODH) and interference with tyrosine kinase activity both appear to be involved.

The treatment groups also experienced a significant reduction in brain disease activity as measured by magnetic resonance imaging (MRI). The burden of disease as determined by total lesion volume, for example, was reduced by 39% and 67% in the 7-mg and 14-mg dose groups, respectively, compared with placebo, said Dr. O'Connor of St. Michael's Hospital, Toronto. He is the principal investigator for TEMSO.

"In my view, teriflunomide is a safe and effective new monotherapy, and it represents a potential first-line treatment for patients with relapsing MS," he said during a press briefing on the TEMSO findings.

The safety profile of teriflunomide in this study was a particularly strong, positive point, he added. The overall adverse event rates were the same in the placebo and treatment groups, as were the rates of adverse events leading to permanent discontinuation of treatment. The teriflunomide group had more nausea, diarrhea, increases in alanine transferase, and hair thinning than did those in the placebo group, but these effects were mild. Treatment was generally very well tolerated, and no opportunistic infections occurred, he said.

TEMSO participants were adults aged 18-55 years with relapsing MS and a score of 5.5 or lower on the Expanded Disability Status Scale, and had experienced at least one relapse in the year prior to enrollment, or two relapses in the prior 2 years.

The availability of an oral agent for the treatment of this complex and progressively disabling disease is very good news for MS patients, Dr. Giancarlo Comi said during the press briefing.

"Of course it is central in the management of these patients to have available drugs to modify the disease course … we are literally entering a period where we can provide patients with much better support than ever before," said Dr. Comi of Clinica Neurologica, Ospedale San Raffaele, Milan, Italy.

Indeed, other ongoing research is also demonstrating the safety and efficacy of teriflunomide, both as monotherapy and in combination with other treatments, said Dr. Mark Freedman of the Multiple Sclerosis Research Clinic at Ottawa Hospital. Dr. Freedman and Dr. Comi are investigators in the TEMSO trial.

For example, an open-label extension of a phase II trial of teriflunomide showed that teriflunomide was well tolerated during 8 years of continuous use following a 36-week double-blind portion of the study.

Dr. Freedman said that the results from a second phase III study of teriflunomide are expected to be reported in 2012. ■