Oral Laquinimod Reduced MS Relapses by 23% in Phase III Study

BY SHERRY BOSCHERT

FROM THE ANNUAL MEETING OF THE AMERICAN ACADEMY OF NEUROLOGY

HONOLULU – Two years of taking the investigational oral drug laquinimod reduced multiple sclerosis relapses and slowed progression toward disability and brain atrophy, compared with placebo, in a phase III study of 1,106 patients with relapsing-remitting multiple sclerosis.

The annualized relapse rate declined by 23% among patients who took laquinimod 0.6 mg daily in the randomized trial, which involved 139 centers in 24 countries, Dr. Giancarlo Comi and his associates reported at the meeting. The annualized relapse rates were 0.304 on laquinimod and 0.395 on placebo.

The laquinimod group also showed a 36% reduction in disability progression, which "is quite a big thing, more than what has been reported" in previous drug studies, said Dr. Comi, director of the department of neurology and the institute of experimental neurology at the Scientific Institute and University of Vita-Salute San Raffaele, Milan.

Most importantly, he said in an interview, the laquinimod group showed 33% less brain atrophy over the course of the study. "That's interesting because most drugs fail to have an effect on this," he said.

A parallel trial is underway to confirm the findings, and results from the trial are expected in the fall of 2011.

DR. COMI

These multiple benefits may be tied to laquinimod's novel mechanism of action, which addresses both the disease's acute inflammatory activity and the accumulation of irreversible tissue damage, he said.

The results suggest that laquinimod is a "very promising" treatment, Dr. Comi said. "In the end, what matters is how much damage there is to the patient and how much the drug was able to prevent that."

Baseline characteristics of the two groups were similar, including demographics, clinical factors and MRI findings. At the start of the study, 46% of the laquinimod group and 40% of the placebo group had active disease. Patients in both groups had had MS for an average of 9 years.

Patients underwent clinical evaluations every 3 months and yearly MRI exams. By the end of the study, the mean number of gadolinium-enhanced lesions on MRI was 37% lower in the laquinimod group and the mean number of new T2 lesions was 30% lower, compared with placebo. The mean number of new T1 lesions, which are characterized by more severe tissue damage, was 27% lower with the drug, compared with placebo.

Laquinimod appeared to be well tolerated. Seventy-nine percent of patients who were randomized to laquinimod and 77% of patients who were randomized to placebo finished the double-blind study.

Elevations of liver enzymes were more common in the laquinimod group (7%) than in the placebo group (3%), but these were transient and reversible and did not lead to signs of liver problems, Dr. Comi said. Liver enzyme elevations greater than three times the upper limit of normal occurred in 2% of the placebo group and 5% of the laquinimod group.

The overall rates of adverse events were low (22% on laquinimod and 16% on placebo) and did not differ significantly between the drug and placebo groups. Two patients on placebo died from unrelated causes, with no deaths in the laquinimod group. The laquinimod group reported higher rates of abdominal pain (5%) and back pain (16%), compared with placebo (3% and 9%, respectively).

In 2010, the oral medication fingolimod (Gilenya) was approved as adjunctive therapy for relapsing-remitting MS. Concerns about increased risks for cardiac problems, immune suppression, and cancer with fingolimod were not a problem in the laquinimod study, Dr. Comi said.

One patient in the placebo group developed pericarditis. There was no evidence of decreased immune function on laquinimod. For example, 17% on placebo on 20% on laquinimod developed herpes infection. There were six cases of cancer in the placebo group and eight in the laquinimod group, for rates of 1.1% and 1.5%, respectively.

A parallel trial is underway to confirm the findings, and results from that trial are expected in the fall of 2011, he said.

Teva Pharmaceuticals, which is developing laquinimod, funded the study. Dr. Comi has received compensation from Teva, Novartis, Sanofi-Aventis, Merck Serono, and Bayer Schering Pharma. Some of his associates in the study reported relationships with Teva and other companies manufacturing drugs for MS. ■

VIEW ON THE NEWS

Drug Will Easily Find a Niche

The results were very positive on disease and on relapse rate reduction. These were both very good signs. In addition, laquinimod was a relatively or maybe very safe medication for people to take.

In contrast, some of the newer agents are having difficulty going through the phase III testing for approval. For example, one of the other agents has been held up in the Food and Drug Administration review because of safety concerns.

Another one that was just approved has risks for immune suppression. Laquinimod does not appear to have a risk for immune suppression, yet it has efficacy in relapsing-remitting MS.

Many patients who will tolerate one drug will not tolerate another drug, so it will be very easy to find a niche for this particular drug.

Most patients don't want an injectable therapy. On the other hand, we have to recognize that even an oral medication can pose some risks. Laquinimod does not seem to have any of those risks, but it causes immune modulation, so it may fit in early MS where it may show its greater efficacy.

What we've learned in the last 10 years – and most important of all – is not which drug to use, but when to treat, and to treat early, because treating early seems to be where we can see the best and most effect.

Laquinimod has a different mechanism of action. It seems to involve the signaling pathways that are in the innate immune system. We're learning about that now. There is going to be much more to be learned about this drug after it's approved in terms of its mechanisms of action.

SCOTT S. ZAMVIL, M.D., *is professor of neurology at the University of California, San Francisco. He was not associated with the laquinimod study. He has been a consultant for Teva Pharmaceuticals, Biogen Idec, and Serono. In addition, Dr. Zamvil has received grant support or served on data safety monitoring boards for multiple drug companies.*

New MS Criteria Aim to Simplify Diagnosis

BY KERRI WACHTER

FROM ANNALS OF NEUROLOGY

An international panel has revised the McDonald criteria for the diagnosis of multiple sclerosis to simplify the use of imaging in determining the dissemination of central nervous system lesions both in space and time, while preserving sensitivity and specificity.

The new revisions also address the applicability of the criteria in non-Western Caucasian populations – specifically Asian and Latin American populations – and children and adolescents.

The changes update the 2005 version of the criteria based on new evidence and consensus, which "pointed to the need for their simplification to improve their comprehension and utility and for evaluating their appropriateness in populations that differ from the largely Western Caucasian adult population from which the criteria were derived," wrote lead author Dr. Chris H. Polman and his coauthors (Ann. Neurol. 2011;69:292-302).

In an accompanying editorial, Dr. Richard A. Rudick agreed (Ann. Neurol. 2011;69:234-6). "The McDonald criteria were not just for clinical trials, but for neurologists in practice. However, some neurologists found the McDonald criteria complex and difficult to use in the clinic, and even experienced MS specialists were uncertain about some aspects of the criteria." Dr. Rudick is the director of the Mellen Center for Multiple Sclerosis Treatment and Research at the Cleveland Clinic.

The 2010 revisions to the McDonald criteria are intended to allow a more rapid diagnosis of MS in some instances, with equivalent or improved specificity or sensitivity, and will clarify and simplify the diagnostic process with fewer required MRI examinations, according to Dr. Polman of the neurology department at the Free University in Amsterdam, and his coauthors.

The International Panel on Diagnosis of MS reviewed published research related to the diagnosis of MS and to the original and revised McDonald criteria, gathered from literature searches of English-language publications.

The panel stressed that the updated criteria should be applied only to patients who present with a typical clinically isolated syndrome (CIS) suggestive of MS or symptoms consistent with a central nervous system (CNS) inflammatory demyelinating disease, because the development and validation of the criteria have been limited to patients with such presentations. It also remains imperative that alternative diagnoses be considered and excluded.

Neuromyelitis Optica and Spectrum Disorders

The panel focused on the differential diagnosis for MS of neuromyelitis optica (NMO) and NMO spectrum disorders, because "there is increasing evidence of relapsing CNS demyelinating disease characterized by involvement of optic nerves (unilateral or bilateral optic neuritis), often severe myelopathy with MRI evidence of longitudinally extensive spinal cord lesions, often normal brain MRI (or with abnormalities atypical for MS), and serum aquaporin-4 (AQP4) autoantibodies."

The panel agreed that this phenotype should

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