Side Effects With Fingolimod Called Transient

BY SHERRY BOSCHERT

FROM THE ANNUAL MEETING OF THE AMERICAN ACADEMY OF NEUROLOGY

VITALS

Major Finding: Transient reductions in heart rate on fingolimod hit a nadir at 4-5 hours after starting therapy and then increased to baseline over time, whereas reductions in atrioventricular conduction that began within the first 6 hours after starting therapy became attenuated and reached baseline levels by 1 month; increases in blood pressure of 1-3 mm Hg starting 2-6 months into treatment were sustained.

Data Source: Analysis of pooled data on 2,552 patients in two phase III clinical trials of fingolimod for relapsing-remitting multiple sclerosis.

Disclosures: The analysis was funded by Novartis, which markets fingolimod. Dr. DiMarco disclosed financial relationships with Novartis and other pharmaceutical companies. His associates in the study have been employees of Novartis, have held stock in the company, or disclosed other financial relationships with Novartis and other pharmaceutical companies.

HONOLULU – The first approved oral medication for multiple sclerosis causes transient reductions in heart rate and atrioventricular conduction and a sustained increase in blood pressure, according to investigators who analyzed pooled data from two phase III trials.

The cohorts from the two phase III clinical trials of fingolimod (Gilenya) for relapsing-remitting muscular sclerosis involved 854 patients treated with the currently approved dosage of fingolimod (0.5 mg/day), 849 patients on a higher dosage (1.25 mg/day), 418 patients on placebo, and 431 patients treated with weekly intramuscular injections of 30 mcg interferon beta-1a (Avonex) for 1-2 years.

The investigators measured vital signs hourly for 6 hours after starting treatment and at quarterly follow-up visits. Patients underwent an ECG before the first dose, 6 hours after treatment initiation, and if they developed symptoms during those 6 hours, as well as at selected follow-up visits. The studies did not use continuous ECG monitoring because they were designed to mimic treatment initiation in a neurologist's office.

Heart rates hit a nadir approximately 4-5 hours after starting fingolimod, and then began to increase, Dr. John DiMarco reported at the meeting. By 2 weeks after starting therapy, heart rates in the fingolimod groups were almost back to baseline, and thereafter were similar to baseline heart rates in the placebo group. As expected, inteferon therapy caused some tachycardia.

In the first 6 hours of treatment, the lowest measured heart rate was below 35 beats per minute (bpm) in one patient on fingolimod 1.25 mg/day and one patient on interferon. Heart rates fell to as low as 35-39 bpm in six patients on fingolimod 1.25 mg/day, reported Dr. DiMarco, a cardiologist and professor of medicine at the University of Virginia, Charlottesville.

A heart rate nadir of 40-44 bpm was seen in approximately 1% of the low-dose fingolimod group, 3% of the high-dose fingolimod group, 0.2% of the placebo group, and no patients on interferon. A nadir of 45-54 bpm was measured in 18% on low-dose fingolimod, 29% on high-dose fingolimod, 6% on placebo, and 3% on interferon.

The lowest heart rate was 55-64 bpm in 49% on low-dose fingolimod, 50% on high-dose fingolimod, 37% on placebo, and 33% on interferon. Heart rates never fell below 65 bpm in 32% on low-dose fingolimod, 18% on high-dose fingolimod, 56% on placebo, and 64% on interferon.

Patients could be discharged at the 6-hour follow-up if any slowing in heart rate had started to return toward baseline, the heart rate was at least 55 bpm or greater than 80% of the baseline rate, and the patient had no symptoms related to bradycardia and no new, clinically relevant abnormality on ECG.

Observation beyond the 6-hour period was required in 12% on low-dose fingolimod, 18% on high-dose fingolimod, 3% on placebo, and 1% on interferon. Clinicians chose to hospitalize 2% of patients on fingolimod 0.5 mg/day, 3% of patients on 1.25 mg/day, 0.5% of patients on interferon, and none on placebo.

Symptoms of bradycardia were seen in 0.5% of patients on 0.5 mg/day fingolimod, 1% of patients on 1.25 mg/day, and no patients in other groups. All were described as mildly or moderately severe.

Conduction abnormalities also were more common within 6 hours of taking low-dose fingolimod (7%) or high-dose fingolimod (13%), compared with placebo or interferon (4% each). First-degree atrioventricular (AV) block was seen in 5% on low-dose fingolimod, 10% on high-dose fingolimod, 2% on placebo, and 3% on interferon. A Wenckebach second-degree AV block was seen in 0.2% on low-dose fingolimod, 0.7% on high-dose fingolimod, and no patients in the other groups. Two patients (0.2%) in the high-dose fingolimod group developed 2:1 second-degree AV block.

One patient in the low-dose fingolimod group and three in the high-dose fingolimod group were treated for heart rate or conduction abnormalities, although two of these patients were asymptomatic. Fingolimod was discontinued after the first dose in 1% of the high-dose group. In the others, the AV conduction changes attenuated with continued therapy and returned to baseline levels by 1 month.

The rise in blood pressure on fingolimod was small, but sustained and statistically significant, starting within 2-6 months of treatment initiation. Systolic and diastolic blood pressure increases averaged 1-2 mm Hg on 0.5 mg/day fingolimod and 1-3 mm Hg on 1.25 mg/day fingolimod, compared with placebo.

Rates of hypertension adverse events were higher in the fingolimod groups – 4% on the lower dose and 5% on the higher dose – compared with the placebo group (3%) or the interferon group (2%). The proportions of patients who needed antihypertensive therapy, however, were similar between groups: 5% on low-dose fingolimod, 6% on high-dose fingolimod, 6% on placebo, and 4% on interferon.

Patients who were treated responded to standard antihypertensive therapy.

Data for the analysis came from the Efficacy and Safety of Fingolimod in Patients With Relapsing-Remitting Multiple Sclerosis (FREEDOMS) trial and from the Trial Assessing Injectable Interferon vs. FTY720 Oral in Relapsing-Remitting Multiple Sclerosis (TRANSFORMS). Both were international, multicenter, randomized double-blind trials. ■

Natalizumab Has Minimal Effect on Response to Vaccines

BY SHERRY BOSCHERT

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Major Finding: Immune responses to tetanus toxoid immunization occurred by 28 days in 15 of 16 patients taking natalizumab and in all 24 control patients.

Data Source: Open-label, multicenter, randomized study of 60 patients with relapsing-remitting multiple sclerosis.

Disclosures: Biogen Idec and Elan Pharmaceuticals, which comarket Tysabri, funded the study. Dr. Pardo disclosed financial relationships with Biogen Idec, Acorda, Bayer, EMD Serono, Novartis, Pfizer, and Teva Neuroscience. A coinvestigator disclosed relationships with these and other companies, and two other coinvestigators were employees of Biogen Idec.

HONOLULU – Patients taking natalizumab showed similar or only slightly delayed humoral immune responses following vaccinations, compared with patients not taking the drug for relapsing-remitting multiple sclerosis in a multicenter, randomized, open-label study.

Natalizumab (Tysabri) acts as an immunomodulator, which raised questions about its potential effects on patients' responses to neoantigens and recall antigens. Previous studies have shown that some other biologic immunomodulatory drugs reduce antibody responses in patients, said Dr. Gabriel Pardo, director of the Oklahoma Medical Research Foundation's Multiple Sclerosis Center of Excellence, Oklahoma City.

Antitetanus toxoid antibody levels measured before and after immunization were similar between groups.

DR. PARDO

Dr. Pardo and his associates studied 30 patients who had been taking natalizumab (Tysabri) for 6 months to treat their multiple sclerosis and 30 others with the disease who had never taken the drug. All 60 patients received a single tetanus toxoid vaccination in order to assess memory antibody responses to a recall antigen. At least 2 weeks later, they also received three keyhole limpet hemocyanin (KLH) vaccinations in order to assess de novo antibody responses.

Overall, 27 patients in the control group and 24 in the natalizumab group completed the study. None stopped the drug or dropped out of the study because of drug-related side effects.

A similar proportion of both groups responded to the tetanus immunization within 28 days – 15 of 16 patients in the natalizumab group (94%) and all of 24 control patients. The difference between groups was not statistically significant, Dr. Pardo and his associates reported at the meeting.

The one patient in the natalizumab group who did not respond within 28 days had a clinical response at 56 days after immunization.

Responses were defined as at least a twofold increase in specific serum immunoglobulin G (IgG) by 28 days after immunization, compared with baseline levels.

Median antitetanus toxoid antibody levels measured before and after immunization were similar between groups.

Antibody responses to the KLH vaccines also were similar between groups at 14, 28, and 56 days after immunizations. Anti-KLH antibody levels were similar between groups at all time points.

In the natalizumab group, the numbers of various lymphocytes increased over time, including CD3-positive, CD4-positive, and CD8-positive lymphocytes and B cells and natural killer (NK) cells. The investigators did not analyze humoral responses to live vaccines.

Adverse events were seen in 26 of 30 patients on natalizumab, which were most commonly disease relapse (5 patients) and influenza, paresthesia, or injection site reaction, each of which occurred in 4 patients. ■