

Ranirestat Improved Sensory Nerve Function

Findings from a 48-week extension study support the polyol pathway as being a major pathophysiological mechanism underlying diabetic sensorimotor polyneuropathy.

BY CONNI BERGMANN KOURY, EDITOR-IN-CHIEF

Treatment with the aldose reductase inhibitor ranirestat improved nerve function in patients with diabetic sensorimotor polyneuropathy (DSP).

According to results published in *Diabetes Care*, treatment with 20 mg/day improved both nerve conduction velocity and vibration detection threshold following 60 weeks of therapy. "The improved sensory nerve function observed after 12 weeks was maintained at 60 weeks, and improved motor nerve function was observed at 60 weeks," wrote lead author Vera Brill, MD, FRCPC, and colleagues. Dr. Brill is from the department of medicine at the University of Toronto.

DSP is a frequent and potentially serious complication that can lead to foot ulceration and diabetes, the researchers said. "A fundamental pathophysiological mechanism in DSP is aberrant activity of the polyol pathway, in which hyperglycemia increases aldose reductase enzyme activity," investigators wrote. Glucose is converted to sorbitol in increased amounts, resulting in accumulations of sorbitol and fructose in the nerves. It is hypothesized that if a pharmacological agent could inhibit the aldose reductase enzyme system, nerve sorbitol and fructose would decrease and nerve damage could be prevented and possibly reversed.

In the phase 2 trial, patients with mild to moderate DSP were randomized in double-blind fashion to one of three groups: placebo, 5 mg/day or 20 mg/day ranirestat (AS-3201; Dainippon Pharmaceuticals, Teaneck, NJ) for 12 weeks. Dr. Brill and colleagues wrote that the placebo-assigned patients had a mean nerve sorbitol concentration of 3.14×10^{-2} nmol/mg wet nerve. For patients who received 5 mg/day ranirestat this was reduced by 65.2% and for the 20/mg day group, it was reduced by 83.5%.

Patients receiving treatment also had improved sensory nerve conduction velocities, particularly those receiving the higher dose, Dr. Brill said. Following the 12-week sural nerve biopsy study, patients were offered the opportunity to participate in a 48-week extension phase of the trial and

receive either treatment dose of ranirestat. "We aimed to determine whether the improved nerve function observed in the biopsy study was maintained after 60 weeks of treatment with ranirestat," Dr. Brill and colleagues wrote.

Patients in the trial had electrophysiological tests, the Toronto Clinical Neuropathy Score and vibration detection thresholds performed at entry, 12 weeks and at 60 weeks. Ninety-two of 94 eligible patients entered the extension phase of the trial. The treatment groups were demographically comparable. Most of the patients had type 2 diabetes for about 14 years and DSP for about 5 years at study entry.

After 60 weeks of treatment, peroneal motor nerve conduction velocity improved in the 20 mg/day group. Sural and median nerve conduction velocity improved after both 12 and 60 weeks with 20 mg/day treatment and vibration detection threshold improved after 60 weeks of 20 mg/day treatment with ranirestat. The agent was well tolerated and there were no differences in adverse events between the 5-mg/day and the 20-mg/day groups.

"The unexpected improvements in nerve function and clinical features of DSP after 12 weeks of treatment with 20 mg/day ranirestat were not lost but became even more evident after 60 weeks of therapy," Dr. Brill wrote. "The magnitude of nerve conduction velocity improvement after ranirestat therapy for 60 weeks is an indicator of the strong efficacy of this [aldose reductase inhibitor] in polyol pathway inhibition."

While the extension trial results need to be confirmed in a placebo controlled trial, the investigators say the current findings support the polyol pathway as being a major pathophysiological mechanism underlying DSP. ■

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Brill V, Buchanan RA, for the Ranirestat Study Group. Long-term effects of ranirestat (AS-3201) on peripheral nerve function in patients with diabetic sensorimotor polyneuropathy. *Diabetes Care*. 2006;29:68-72.