Long-Term Effects of Ranirestat (AS-3201) on Peripheral Nerve Function in Patients With Diabetic Sensorimotor Polyneuropathy

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OBJECTIVES — We aimed to determine whether ranirestat, an aldose reductase inhibitor, maintains the improved nerve function observed in patients with diabetic sensorimotor polyneuropathy (DSP) after completing a 12-week nerve biopsy study.

RESEARCH DESIGN AND METHODS — Patients with mild to moderate DSP, as determined by the presence of sural nerve responses, were enrolled in a double-blind, placebo-controlled biopsy trial and randomized to placebo or 5 or 20 mg/day ranirestat for 12 weeks. Patients completing this biopsy study were offered a 48-week extension at the same ranirestat dose or at 5 mg/day ranirestat if they were originally treated with placebo. Electrophysiological tests, the Toronto Clinical Neuropathy Score, and vibration perception thresholds (VPTs) were performed at entry and at 12 (end of the biopsy study) and 60 (end of the 48-week extension) weeks.

RESULTS — Peroneal motor nerve conduction velocity (NCV) improved in the 20-mg/day group following 60 weeks of treatment. Sural and median sensory NCV improved after both 12 and 60 weeks of treatment with 20 mg/day. VPT improved after 60 weeks of treatment with 20 mg/day. Ranirestat was well tolerated with no difference in adverse events between the 5- and 20-mg/day groups.

CONCLUSIONS — Twenty milligrams ranirestat per day improves NCV and VPT following 60 weeks of administration. The improved sensory nerve function observed after 12 weeks of therapy was maintained at 60 weeks, and improved motor nerve function was observed at 60 weeks.

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In spite of advances in the management of diabetes, diabetic sensorimotor polyneuropathy (DSP) continues to be a frequent and potentially serious complication, leading to foot ulceration and amputation (1). A fundamental pathophysiological mechanism in DSP is aberrant activity of the polyol pathway, in which hyperglycemia increases aldose reductase enzyme activity (2). This activation then results in an increased conversion of glucose to sorbitol, leading to accumulation of sorbitol and fructose in nerves. If the aldose reductase enzyme system could be pharmacologically inhibited by an aldose reductase inhibitor (ARI) with decreases in nerve sorbitol and fructose, nerve damage might be prevented and possibly reversed.

Ranirestat (AS-3201), a novel ARI developed by Dainippon Pharmaceutical (Osaka, Japan) demonstrated potent inhibition of the polyol pathway after 12 weeks of treatment (3). In this phase 2 trial, patients were randomized to one of three groups: placebo or 5 or 20 mg/day ranirestat in a double-blind fashion for 12 weeks. The placebo-treated patients had a mean nerve sorbitol concentration of \(3.14 \times 10^{-2}\) nmol/mg wet nerve, similar to other reports from studies (4). This was reduced by 65.2% in those patients who received 5 mg/day ranirestat and by 83.5% in those who received 20 mg/day ranirestat. Concomitant with inhibition of the polyol pathway, patients had improved sensory nerve conduction velocities (NCVs), particularly those receiving the higher dose. On completion of the 12-week sural nerve biopsy study, patients were offered a 48-week extension phase and treated with either 5 or 20 mg/day ranirestat. We aimed to determine whether the improved nerve function observed in the biopsy study was maintained after 60 weeks of treatment with ranirestat.

RESEARCH DESIGN AND METHODS — The extension study was a multicenter, double-blind, randomized, efficacy study in which patients previously randomized to placebo in the original 12-week phase 2 biopsy study received 5 mg/day ranirestat. Those previously randomized to either 5 or 20 mg/day ranirestat continued their same dose. The double blind was maintained for all patients, investigators, technicians, and research staff. The efficacy procedures including nerve conduction studies (NCS), vibration perception threshold (VPT), and the Toronto Clinical Neuropathy Score (TCNS) were performed as previously described at entry into the 12-week
biopsy study, at the end of the biopsy study, which was entry into the 48-week extension for each patient, and at the end of the extension, i.e., 60 weeks of treatment (3). Those patients who switched from placebo to 5 mg daily were not included in the efficacy analyses due to the different duration of treatment with ranirestat. The TCNS evaluates the signs and symptoms of DSP (5). The maximum TCNS has a value of 19 points by which the severity of DSP is categorized, i.e., 0–5: no neuropathy, 6–8: mild neuropathy, 9–11: moderate neuropathy, and 12: severe neuropathy.

The study inclusion criteria for the biopsy study have been previously described (3). Only patients completing the 12-week biopsy study were offered the 48-week extension study. The central core laboratory (University of Toronto) continued to review all NCS, VPT, and TCNS results for each patient to ensure the consistency of study procedures and high quality data (6). The extension study was approved by the institutional review boards at each of the six participating centers. All study patients provided separate written informed consent for the extension study.

### Study end points

Baseline values for NCS, VPT, and TCNS were taken from the entry values into the 12-week biopsy study, as were the plasma ranirestat levels. The efficacy end points were changes in NCS, VPT, and the TCNS at the end of the extension, which is a full 60 weeks of treatment compared with entry into the biopsy study, and also changes compared with entry into the extension study. Plasma ranirestat levels were measured at weeks 14, 16, 20, 24, and 36 from entry into the biopsy study.

Adverse events were carefully documented during the study. Clinical laboratory tests were periodically performed with an electrocardiogram at entry into the extension then at weeks 36 and 60. Neurological and physical examinations were performed at entry and at the end of the extension study.

### Analytic procedures

#### Electrophysiologic measurements.

The same standardized procedures were used in the extension study as described for the 12-week biopsy study (3). The only difference was that unilateral sural nerve testing was done at week 60 from entry into the biopsy study as a sural nerve had been biopsied and no response would be expected.

#### Biochemical measurements

Plasma ranirestat levels were measured as previously described (3).

### VPT

VPT was measured at the first toe by the method of limits using a neurothesiometer (Horwell Scientific, London, U.K.).

### RESULTS

#### Demographics

Ninety-two of 94 eligible patients entered the double-blind extension phase: 34 were given placebo to 5 mg/day ranirestat, 31 were given 5 mg/day ranirestat, and 27 were given 20 mg/day ranirestat; 82.6% of patients completed the extension study (30 at placebo to 5 mg/day, 31 at 5 mg/day, and 25 at 20 mg/day). The demographic information has previously been described for entry into the biopsy study, where the three groups were shown to be...
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Table 2—Baseline NCS, VPT, and TCNS results for patients in the extension study*

<table>
<thead>
<tr>
<th></th>
<th>Placebo/5 mg</th>
<th>5 mg</th>
<th>20 mg</th>
<th>P value (5 vs. 20 mg)</th>
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<tbody>
<tr>
<td>n</td>
<td>30</td>
<td>31</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>NCV (m/s)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sural, right</td>
<td>42.2 ± 4.5</td>
<td>41.8 ± 5.3</td>
<td>39.3 ± 4.9</td>
<td>0.053†</td>
</tr>
<tr>
<td>Sural, left</td>
<td>41.6 ± 4.0</td>
<td>41.8 ± 5.9</td>
<td>39.2 ± 3.9</td>
<td>0.050†</td>
</tr>
<tr>
<td>Median sensory, elbow</td>
<td>55.0 ± 5.5</td>
<td>55.4 ± 4.8</td>
<td>53.5 ± 4.1</td>
<td>0.090†</td>
</tr>
<tr>
<td>Median sensory, wrist</td>
<td>45.6 ± 10.1</td>
<td>48.9 ± 7.2</td>
<td>48.7 ± 5.2</td>
<td>0.852</td>
</tr>
<tr>
<td>Median motor</td>
<td>49.6 ± 3.6</td>
<td>52.3 ± 3.5</td>
<td>50.4 ± 4.2</td>
<td>0.091†</td>
</tr>
<tr>
<td>Peroneal motor</td>
<td>39.1 ± 3.5</td>
<td>40.6 ± 3.4</td>
<td>38.8 ± 4.8</td>
<td>0.307</td>
</tr>
<tr>
<td>VPT (volts)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>21.7 ± 9.0</td>
<td>21.6 ± 8.5</td>
<td>21.2 ± 6.8</td>
<td>0.993</td>
</tr>
<tr>
<td>Left</td>
<td>21.6 ± 8.4</td>
<td>21.1 ± 9.1</td>
<td>21.2 ± 6.9</td>
<td>0.773</td>
</tr>
<tr>
<td>TCNS (n = 19)</td>
<td>10.2 ± 3.6</td>
<td>10.1 ± 3.0</td>
<td>9.4 ± 4.0</td>
<td>0.249</td>
</tr>
</tbody>
</table>

Data are means ± SD. *Predose data (week 0) are shown for the 5- and 20-mg ranirestat group, and data at the entry to the extension study (week 12) are shown for placebo/5-mg group. †P value <0.05. P values; Wilcoxon rank-sum test between 5 and 20 mg ranirestat. The 20-mg group appears to have slightly more severe DSP based on the above parameters, but none of the differences achieved statistical significance.

The changes in NCV at 12 and 60 weeks are shown in Fig. 1. The previous 12-week biopsy study showed that peroneal motor NCV deteriorated in the placebo group by ~0.4 m/s. Peroneal motor NCV did not significantly change in the other groups at the end of week 12. For those continuing in the extension study, peroneal motor NCV improved in the 5-mg/day group by 1.2 m/s (P = 0.04) from weeks 0 to 60 and by 1.0 m/s (P = 0.05) in those receiving 20 mg/day during this same period. In the 20-mg/day group, the NCV improved by 1.2 m/s (P = 0.007) during the extension period from weeks 12 to 60 (data not shown). In other words, the improvement in peroneal motor NCV with ranirestat treatment was not observed until treatment extended beyond 12 weeks.

The median motor NCV deteriorated in the placebo group in the 12-week biopsy study by 0.39 m/s. The NCV for the 5-mg/day group deteriorated by 1.1 m/s (P = 0.10) from entry to week 60, with an insignificant change of ~0.1 m/s (P = 0.9) in the 20-mg/day group to week 60. The right sural NCV slightly deteriorated in the placebo group in the 12-week biopsy study. The 5-mg/day group improved by 0.7 m/s (P = 0.42) at week 60. The 20-mg/day group showed an improvement of 1.3 m/s (P = 0.07) after 60 weeks of treatment. The left sural nerve was biopsied at the end of the previous 12-week biopsy study in most patients, so NCS results were not available.

The proximal median sensory NCV was unchanged in the placebo group in the 12-week biopsy study and showed some improvement for the 5-mg/day group at week 60, by 0.5 m/s (P = 0.31).

Electrophysiology

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The proximal median sensory NCV was unchanged in the placebo group in the 12-week biopsy study and showed some improvement for the 5-mg/day group at week 60, by 0.5 m/s (P = 0.31).
The 20-mg/day group improved in the 12-week biopsy study and then improved further by 3.4 m/s (P = 0.01) at week 60. There was a trend of difference (P = 0.05) between the 5- and 20-mg/day groups following 60 weeks of treatment, indicating that 20 mg/day had a greater treatment effect. The lack of improvement in the distal median sensory NCV is likely due to mechanical factors at the carpal tunnel in patients with diabetes (7).

VPT
VPT did not change significantly in the placebo or 5-mg/day groups in the 12-week biopsy study or in the extension study at 60 weeks. VPT tended to improve in both toes in those treated with 20 mg/day ranirestat, but there was some asymmetry in the changes. The left side decreased by 1.9 volts (P = 0.09) compared with 0.8 volts (P = 0.50) for the right side.

TCNS
Mean changes in the symptom, sensory test, reflex, and total scores from entry are shown in Fig. 2 by treatment group. A decrease in score indicates fewer clinical features of DSP. The symptom score (0–6) decreased by –1.0 for the 5-mg/day treatment group (P < 0.001) and by –0.6 for the 20-mg/day group (P = 0.01) from weeks 0 to 60. The sensory test score (0–6) decreased by –0.2 for the 5-mg/day treatment group (P = 0.08) and –0.4 for the 20-mg/day group (P = 0.08). The combined symptom and sensory scores (0–11) decreased by –1.2 for the 5-mg/day group (P < 0.001) and by –1.0 for the 20-mg/day group (P = 0.009) from weeks 0 to 60.

In the placebo to 5-mg/day group, the number of patients with severe neuropathy increased from five at entry into the biopsy study to eight at week 12 while receiving placebo. From weeks 12 to 60, the number with no neuropathy increased from one to three. For the 5-mg/day group, from weeks 0 to 60, the number with no neuropathy increased from one to five; those with severe neuropathy dropped from nine to seven. For the 20-mg/day group, from weeks 0 to 60, the number with no neuropathy increased from two to four, and those with severe neuropathy decreased from eight to six. This improvement is even more encouraging because the 20-mg/day group had more abnormal nerve function as shown by NCS at week 0 compared with the 5-mg/day group.

Pharmacokinetics
Plasma ranirestat levels are proportional to dose with no evidence of drug accumulation (data not shown).

Safety
Ranirestat was well tolerated for up to 60 weeks of administration. The prevalence of treatment-emergent adverse events was similar between the 5- and 20-mg groups. No clinically significant changes were observed for the other safety parameters.

CONCLUSIONS — The results of the extension study demonstrate that effective inhibition of the polyol pathway by the ARI, ranirestat, is maintained with long-term treatment. 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, as shown by the current findings, although the extension study was not powered to show changes in NCS or the TCNS.

The magnitude of NCV improvement after ranirestat therapy for 60 weeks is an indicator of the strong efficacy of this ARI in polyol pathway inhibition. In population studies, Arezzo (8) reported that motor NCV decreased by ~0.5 m/s per year in patients with diabetes. Greene et al. (9) reported a decline in peroneal motor NCV and median and sural sensory NCV of >0.25 m/s in the placebo-treated patients in a ranirestat study. Brown et al. (10) reported more detail on these same patients, indicating a decline of median forearm sensory NCV of ~0.05 m/s (n = 360), of peroneal motor NCV of ~0.2 m/s (n = 359), and of sural CV of ~0.65 m/s (n = 359) in 12 months. Other authors (11,12) have reported deterioration in NCV in patients with DSP. In this slowly progressive chronic disorder, ARI therapy would be expected to slow or halt the progression of NCV deterioration. Thus, the small deteriorations in motor and sensory NCV found in the placebo patients after 12 weeks are as expected, and greater decline would be predicted after 60 weeks. However, the improved NCV of 1 m/s for lower-limb motor and sensory nerves and of ~3 m/s in the forearm median sensory nerve following 60 weeks of treatment with 20 mg/day ranirestat are completely unexpected and indicate the strong efficacy of ranirestat. The lack of change for median distal sensory NCV is likely due to mechanical factors at the carpal tunnel in patients with diabetes (6,7).

The magnitude of change in NCV is
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greater at 60 weeks than at 12 weeks. Also, improved VPT were first evident at 60 weeks, although the changes in VPT were not statistically significant. These findings suggest that ARIs have sustained and increasing effects on nerve function and clinical sensory activity that can be observed after 12 months of therapy.

Finally, the improvement in the TCNS scores and the shift in DSP severity on a simple clinical grading scale after 60 weeks of therapy confirm the clinical relevance of the improvements in NCS and VPT testing (5). Together with improved nerve function and sensation, more patients were classified as having no neuropathy and fewer as having severe DSP at 60 weeks.

The improvement in nerve function, VPT, and DSP severity observed with 20 mg/day ranirestat in this study as well as the 83.5% inhibition of nerve sorbitol levels found in the biopsy study suggest that 20 mg/day ranirestat would be clinically effective for the management of DSP. The findings in the current study are in keeping with a previous study of zenarestat, another ARI, that showed that dose-dependent increments in sural nerve ze- narestat level and sorbitol suppression were accompanied by a significant improvement in NCV (9). In particular, ze- narestat doses producing >80% sorbitol suppression were associated with a significant increase in the density of small-diameter sural nerve myelinated fibers. Given the lack of a placebo group and statistical power in the current study, the results need to be confirmed in a placebo-controlled trial of comparable duration, i.e., 12 months. Nonetheless, the current findings support the polyol pathway as being a major pathophysiological mechanism underlying DSP (2).

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APPENDIX

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References