Clinical Efficacy of Fidarestat, a Novel Aldose Reductase Inhibitor, for Diabetic Peripheral Neuropathy

A 52-week multicenter placebo-controlled double-blind parallel group study

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OBJECTIVE — The purpose of this study was to evaluate the efficacy of fidarestat, a novel aldose reductase (AR) inhibitor, in a double-blind placebo controlled study in patients with type 1 and type 2 diabetes and associated peripheral neuropathy.

RESEARCH DESIGN AND METHODS — A total of 279 patients with diabetic neuropathy were treated with placebo or fidarestat at a daily dose of 1 mg for 52 weeks. The efficacy evaluation was based on change in electrophysiological measurements of median and tibial motor nerve conduction velocity, F-wave minimum latency, F-wave conduction velocity (FCV), and median sensory nerve conduction velocity (forearm and distal), as well as an assessment of subjective symptoms.

RESULTS — Over the course of the study, five of the eight electrophysiological measures assessed showed significant improvement from baseline in the fidarestat-treated group, whereas no measure showed significant deterioration. In contrast, in the placebo group, no electrophysiological measure was improved, and one measure significantly deteriorated (i.e., median nerve FCV). At the study conclusion, the fidarestat-treated group was significantly improved compared with the placebo group in two electrophysiological measures (i.e., median nerve FCV and minimal latency). Subjective symptoms (including numbness, spontaneous pain, sensation of rigidity, paresthesia in the sole upon walking, heaviness in the foot, and hypesthesia) benefited from fidarestat treatment, and all were significantly improved in the treated versus placebo group at the study conclusion. At the dose used, fidarestat was well tolerated, with an adverse event profile that did not significantly differ from that seen in the placebo group.

CONCLUSIONS — The effects of fidarestat-treatment on nerve conduction and the subjective symptoms of diabetic neuropathy provide evidence that this treatment alters the progression of diabetic neuropathy.

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Abbreviations: AR, aldose reductase; FCV, F-wave conduction velocity; MNCV, motor nerve conduction velocity; SNCV, sensory nerve conduction velocity.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Diabetic neuropathy is a degenerative disorder triggered by persistent hyperglycemia. The degenerative changes, consisting of axonal atrophy, demyelination, nerve fiber loss, and disordered nerve fiber repair, develop and progress even in the early stage of diabetes. Axonal atrophy, demyelination, and disordered repair can be clinically assessed as a decline in nerve conduction velocity. During hyperglycemia, nerve maturation secondary to nerve fiber loss is also disturbed. Abnormal excitement of these immaturely regenerated nerve fibers causes spontaneous pain, numbness, and paresthesia (1–3). In the majority of patients, these changes, characteristic of diabetic neuropathy, considerably deteriorate the quality of life.

After the onset of subjective symptoms, only palliative treatments are currently available. Accordingly, early diagnosis and treatment before the onset of subjective symptoms is considered essential. Diabetic neuropathy is a long-term complication of diabetes that should not be underestimated, because the progress of the disease may lead to foot ulcers, foot gangrene, foot amputation, or even sudden death caused by cardiovascular autonomic neuropathy.

Aldose reductase (AR) inhibitors have received considerable attention as potential treatments for diabetic neuropathy, and a number of them have been developed (4). However, these agents have not achieved worldwide use because of limited efficacy or unacceptable adverse effects.

The present study explored the clinical utility of a novel AR inhibitor, fidarestat (SNK-860; Sanwa Kagaku Kenkyusho, Nagoya, Japan) (5–12), in patients with diabetic neuropathy. In animal models of diabetic neuropathy, fidarestat was demonstrated to be one of the most potent AR inhibitors yet identified. We have evalu-

ated the utility of fidarestat based on electrophysiological measurements of nerve function and an assessment of subjective symptoms. The safety of this compound was evaluated with a complete laboratory panel of measurements (chemistry, hematology, and urinalysis) and assessment of adverse events.

RESEARCH DESIGN AND METHODS

— A total of 279 patients, 139 in the fidarestat group and 140 in the placebo group, who met all of the following criteria were enrolled in the trial. Patients were included if their motor nerve conduction velocity (MNCV) in the tibial nerve ranged between 30 and 48 m/s, and their sensory nerve conduction velocity (SNCV) in median nerve (in the distal area) ranged between 35 and 55 m/s. Patients in whom the F-wave response had disappeared were excluded. Patients with the following subjective and objective nerve symptoms were included: those who complained of paresthesia or hypesthesia in all four limbs or in the lower extremities or those who had neurological abnormalities, including abnormal Achilles reflex and the absence of vibration sense in the lower extremities.

This study was designed and conducted based on a per-protocol analysis. Therefore, efficacy was assessed only in those subjects who complied with the protocol and only when data met acceptable technical standards. Efficacy was quantifiable in 192 patients; the exclusion rate was approximately equal in the placebo and fidarestat-treated groups. The main reasons for exclusion from efficacy analysis were lack of electrophysiological measurement and medication noncompliance.

Study design

The effects of fidarestat on nerve function and subjective symptoms in patients with diabetic neuropathy were evaluated in a double-blind placebo-controlled 52-week multicenter (78 institutions) parallel group study. Before the trial, the study protocol was approved by the institutional review board at each of the participating medical institutions, and written consent was obtained from all of the enrolled patients. Data for electrophysiological measurement, but not symptomatic assessments, were collected from patients who used medication to control pain.

Clinical evaluation method

The patients were treated with either one tablet of the trial drug (fidarestat 1 mg) or one matching placebo tablet once daily before breakfast for 52 weeks. The primary end points for clinical efficacy were the differences between baseline and posttreatment electrophysiological measurements of the median motor nerve (F-wave minimum latency, MNCV, and FCV), the tibial motor nerve (F-wave minimum latency, MNCV, and FCV), and the median sensory nerve (forearm SNCV and distal SNCV). The method to measure nerve function was that according to Kohara et al. (13), with a minor modification. The results of the electrophysiological measurements were systematically assessed by the Nerve Function Evaluating Committee. This independent committee evaluated the electrophysiological measurements with respect to the quality of the tracings in terms of signal-to-noise ratio, artifacts, selection of an appropriate potential for measurement, correct scoring of latencies and amplitudes, transcriptional errors, pattern errors, and adherence to the protocol.

Symptoms were assessed using a standardized and comprehensive questionnaire at baseline and following 4, 8, 12, 24, 36, and 52 weeks of treatment. The symptoms assessed included measures of numbness, pain, rigidity, alterations in temperature perception, paresthesia, hypesthesia, and weakness. For most symptoms (e.g., spontaneous pain in the lower extremity) both "severity" and "extent" (i.e., distal-to-proximal gradient) were scored on an ascending 0–4 scale. Other subjective symptoms (e.g., "sensation as if walking on sand") were scored only for severity on the same 5-point scale. For each symptom category, data were analyzed for all subjects in the efficacy pool who reported the symptom during the course of the study. Because not all symptoms were present in each subject, different subsets of subjects were included for each symptom. Analysis focused on change in symptoms, assigning a value of 0 for the level reported at baseline for each subject and calculating the mean change from baseline for each time point.

The specific scoring of symptoms was as follows for severity: 0 = none (disappeared); 1 = very slight (sometimes but it causes no problem at all in daily life); 2 = slight (always but it causes no problem in daily life); 3 = moderate (always and it sometimes troubles daily activity); and 4 = severe (it troubles daily activity). For extent, the scoring was as follows: 0 = none; 1 = only fingertips or ends of toes; 2 = from wrist to fingertip or from ankle to toe; 3 = from elbow to fingertip or from knee to toe; and 4 = from above the elbow or above the knee.

Statistical analysis

To analyze for homogeneity in patient demographics, data on variables were analyzed with a two-sample *t* test, data on rank were analyzed with Wilcoxon's rank-sum test, and data on categories were analyzed with χ^2 test or Fischer's exact probability test. The level of significance to detect bias between the two treatment groups for subject demographic characteristics was 15% (two-tailed). Electrophysiological measurements were analyzed as follows: within-group comparisons between baseline and posttreatment values were performed with a one-sample paired *t* test, and between-group comparisons were performed with a two-sample *t* test. Changes in the subjective symptom score were analyzed with a two-way analysis of variance for interaction. The level of significance was 5% (two-tailed).

For the safety analysis, a 95% CI for the difference in the incidence of adverse events was applied.

RESULTS

Patient demographics

Table 1 shows the demographics for 192 patients included in the efficacy assessments, 102 treated with placebo and 90 treated with fidarestat, in whom baseline and posttreatment efficacy could be compared. There were no statistically significant differences between the two groups in any of the demographic variables.

Change in HbA_{1c}

Using the method of Shima et al. (14), HbA_{1c} levels at baseline and after 52 weeks of fidarestat treatment (n = 89) were 7.7 ± 0.1 and 7.9 ± 0.1%, respectively. HbA_{1c} levels at baseline and after 52 weeks of placebo treatment (n = 101) were 7.9 ± 0.2 and 7.9 ± 0.2%, respectively. There was no significant difference between the two groups at either time point (P = 0.27).

Table 1—*Selected characteristics of subjects included in the efficacy analysis*

Characteristic	Placebo	Fidarestat	*P*
n	102	90	—
Age (years)	56.7 ± 0.7	57.3 ± 0.9	0.60
Sex			0.48
Male	55 (53.9)	54 (60.0)	
Female	47 (46.1)	36 (40.0)	
BMI (kg/m^2)	23.3 ± 0.4	22.9 ± 0.3	0.39
Duration of diabetes (months)	180.4 ± 10.0	169.7 ± 9.4	0.44
Type of diabetes			1.00
Type 1	5 (4.9)	4 (4.4)	
Type 2	97 (95.1)	86 (95.6)	
HbA_{1c} (%)	8.0 ± 0.2	7.7 ± 0.1	0.23
Treatment for diabetes			0.99
No medication	6 (5.9)	6 (6.7)	
Oral hypoglycemic agent	47 (46.1)	40 (44.4)	
Insulin	41 (40.2)	37 (41.1)	
Oral hypoglycemic agent/Insulin	8 (7.8)	7 (7.8)	
Diabetic retinopathy			0.76
No	36 (35.3)	37 (41.1)	
Simple	31 (30.4)	19 (21.1)	
Preproliferative	15 (14.7)	17 (18.9)	
Proliferative	20 (19.6)	17 (18.9)	
Diabetic proteinuria			0.68
No	62 (60.8)	52 (57.8)	
Intermittent	20 (19.6)	19 (21.1)	
Persistent	20 (19.6)	19 (21.1)	

Data are *n*, means ± SEM, or n (%).

Electrophysiological measurement

Table 2 outlines each electrophysiological measure (means ± SEM) at the baseline and end-of-treatment time points. Six measures assessed function in motor nerves, including maximal conduction velocity, F-wave latency, and FCV in the median and tibial nerves. In the fidarestat group, five of the six measures demonstrated significant improvement ($P < 0.05$) over the 52-week treatment period. As expected, no electrophysiological measure of motor function significantly improved in the placebo group, and one measure (i.e., median FCV) significantly deteriorated over the study period. At baseline, the median FCV was 56.7 m/s in both the placebo and the fidarestat groups; this value improved by 0.9 m/s in the fidarestat group and deteriorated by 0.6 m/s in the placebo group, resulting in an end-of-treatment group difference of 1.5 m/s ($P < 0.001$). The two measures of sensory function, median NCV in distal and proximal segment, also improved in the fidarestat group, but the changes from baseline were not significant.

Changes in subjective symptoms over time

Figure 1 shows some of the changes in the score for subjective symptoms, in which a significant difference between the two treatment groups was observed. As shown in the figure, the difference between the two groups gradually increased with continuous treatment. Fidarestat was significantly superior to placebo for the treatment effects on numbness of upper extremities (severity $P < 0.05$, extent $P < 0.001$; Fig. 1*A* and *B*, respectively), hypesthesia in lower extremities ($P < 0.05$; Fig. 1*C*), spontaneous pain in upper extremities (extent $P < 0.01$; Fig. 1*D*), and paresthesia in the sole upon walking (a sensation as if walking on sand, $P < 0.05$; a sensation as if walking on an uneven road, $P < 0.05$; Fig. 1*E* and *F*, respectively). Although the data are not shown in Fig. 1, numbness in lower extremities (severity), sensation of rigidity of lower extremities, and heaviness in the foot were significantly improved in the fidarestat-treatment group compared with the placebo group ($P < 0.05$, 0.05, and 0.001, respectively). There was no significant difference between the two treatment groups in the sensation of coldness or flushes.

Safety

For this study, abnormalities that were evaluated by the investigators as "related" or "probably related" to the study drug were reported as the adverse events. The incidence of adverse experience was 5.8% in the fidarestat group and 5.0% in the placebo group, with no significant difference (95% CI −5.3 to 6.8%) between the two groups. No serious adverse experience requiring treatment discontinuation occurred during the course of the study. The incidence of abnormal laboratory values was 6.5% in the fidarestat group and 5.0% in the placebo group, with no significant difference (−4.7 to 7.6%) between the two groups. No serious abnormal laboratory values requiring treatment discontinuation were observed in either treatment group.

CONCLUSIONS — Diabetic neuropathy is a long-term complication of diabetes that develops early in the course of the disease and is observed in 60–70% of all diabetic patients (15). It is known that diabetic neuropathy is a nerve degenerative disease characterized by axonal degeneration, nerve fiber demyelination, and a reduction in the number of medium-to-large diameter nerve fibers, particularly in peripheral nerves. The clinical data obtained from the Diabetes Control and Complications Trial (DCCT) (16,17) and other studies have shown that it is possible to prevent or delay the progression of diabetic neuropathy, but it is difficult to restore nerve function, even in patients under strict blood glucose control.

Observations from animal models suggest that diabetic neuropathy is triggered by hyperglycemia, which leads to a persistent accelerated flux of glucose through the polyol pathway. The rate-limiting enzyme in this pathway is aldose reductase. The increased flux through the polyol pathway is followed by abnormal protein kinase C metabolism (18), oxidative stress (19), accelerated glycation (20), and decreased endoneural capillary perfusion (21), leading eventually to nerve degeneration. On the basis of this hypothesis, AR inhibitors have been proposed as treatments for diabetic neuropa-

Table 2—*Baseline and posttreatment nerve function test values*

Parameter	Placebo	Fidarestat	Difference (95% CI)	*P*†
MNCV in median				
n	95	86		
Baseline (m/s)	51.4 ± 0.5	51.8 ± 0.4		
End of treatment (m/s)	51.2 ± 0.5	51.8 ± 0.4		
Difference (m/s)	−0.2 ± 0.4	−0.0 ± 0.4	0.2 (−0.8 to 1.2)	0.74
95% CI	(−0.9 to 0.5)	(−0.8 to 0.7)		
*P**	0.55	0.90		
F wave minimum latency in median				
n	96	88		
Baseline (m/s)	31.3 ± 0.3	31.3 ± 0.3		
End of treatment (m/s)	31.6 ± 0.3	30.8 ± 0.3		
Difference (m/s)	0.3 ± 0.2	−0.5 ± 0.2	0.8 (−1.2 to −0.3)	<0.001
95% CI	(−0.1 to 0.6)	(−0.8 to −0.2)		
*P**	0.11	<0.01		
FCV in median				
n	96	88		
Baseline (m/s)	56.7 ± 0.4	56.7 ± 0.5		
End of treatment (m/s)	56.1 ± 0.4	57.6 ± 0.5		
Difference (m/s)	−0.6 ± 0.3	0.9 ± 0.3	1.6 (0.8 to 2.4)	<0.001
95% CI	(−1.2 to −0.1)	(0.3 to 1.5)		
*P**	<0.05	<0.01		
MNCV in tibial				
n	95	81		
Baseline (m/s)	40.2 ± 0.5	40.1 ± 0.4		
End of treatment (m/s)	40.3 ± 0.5	40.8 ± 0.4		
Difference (m/s)	0.1 ± 0.4	0.8 ± 0.3	0.7 (−0.3 to 1.6)	0.15
95% CI	(−0.6 to 0.8)	(0.2 to 1.3)		
*P**	0.81	<0.01		
F wave minimum latency in tibial				
n	99	86		
Baseline (m/s)	54.8 ± 0.5	56.0 ± 0.6		
End of treatment (m/s)	54.4 ± 0.6	55.1 ± 0.6		
Difference (m/s)	−0.4 ± 0.3	−0.9 ± 0.3	−0.5 (−1.3 to 0.4)	0.31
95% CI	(−1.0 to 0.2)	(−1.5 to −0.2)		
*P**	0.21	<0.05		
FCV in tibial				
n	99	86		
Baseline (m/s)	47.7 ± 0.4	47.0 ± 0.5		
End of treatment (m/s)	48.1 ± 0.5	47.6 ± 0.5		
Difference (m/s)	0.4 ± 0.3	0.6 ± 0.3	0.2 (−0.6 to 1.0)	0.63
95% CI	(−0.2 to 1.0)	(0.1 to 1.1)		
*P**	0.19	<0.05		
SNCV in median (distal)				
n	82	67		
Baseline (m/s)	47.8 ± 0.8	48.5 ± 0.9		
End of treatment (m/s)	47.6 ± 0.9	48.8 ± 0.8		
Difference (m/s)	−0.1 ± 0.5	0.3 ± 0.5	0.4 (−1.0 to 1.9)	0.55
95% CI	(−1.2 to 0.9)	(−0.7 to 1.3)		
*P**	0.81	0.54		
SNCV in median (forearm)				
n	86	76		
Baseline (m/s)	57.4 ± 0.6	57.0 ± 0.7		
End of treatment (m/s)	57.4 ± 0.6	57.6 ± 0.6		
Difference (m/s)	−0.0 ± 0.5	0.6 ± 0.5	0.6 (−0.8 to 2.0)	0.37
95% CI	(−1.1 to 1.0)	(−0.3 to 1.5)		
*P**	0.93	0.21		

Data are means ± SEM unless otherwise indicated. **P* is the result of one-sample paired *t*-test within-group comparisons between baseline and posttreatment values, and †*P* is the result of two-sample *t*-test comparison between groups.

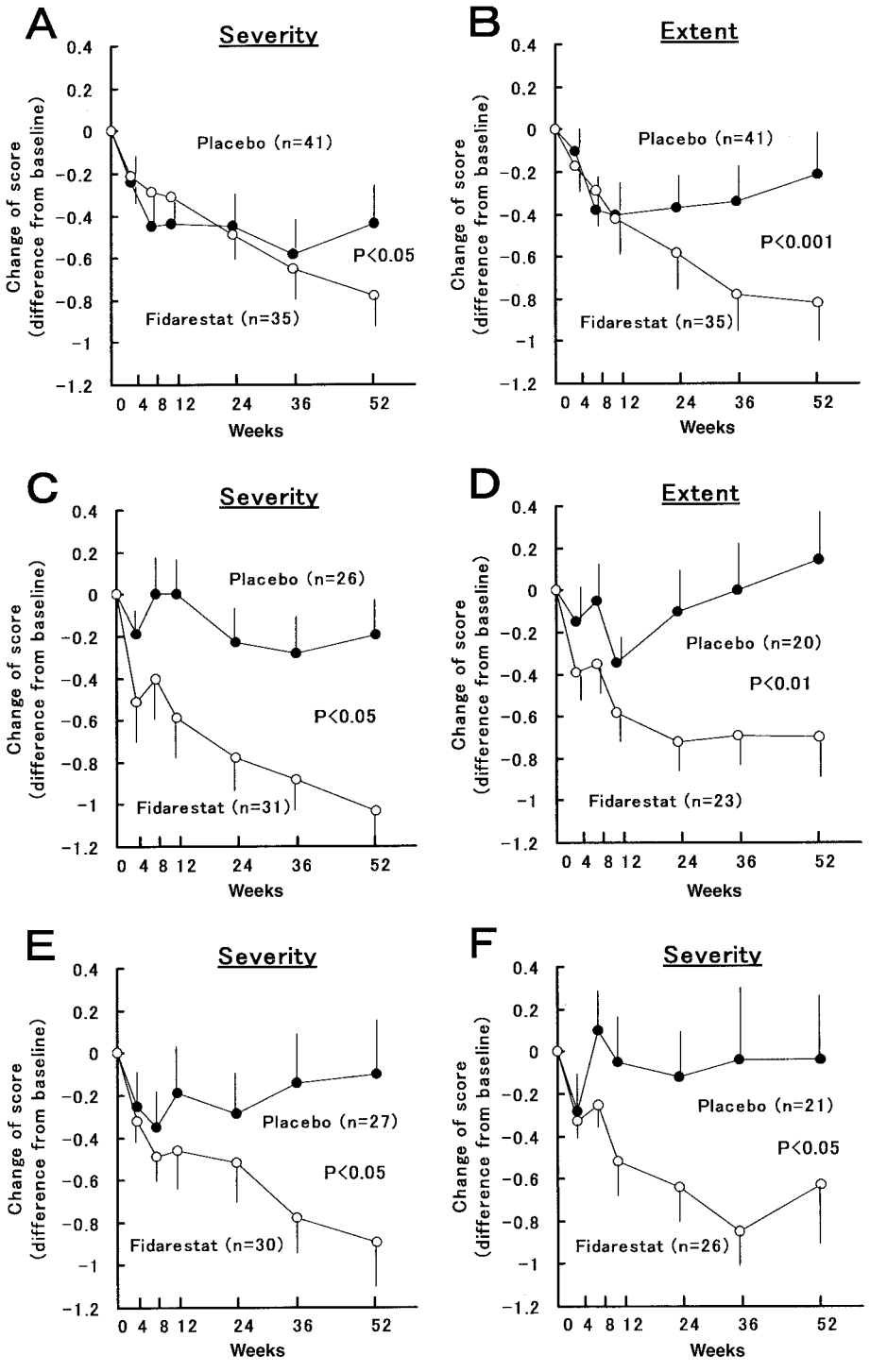

Figure 1—*Effect of fidarestat on subjective nerve symptoms for numbness of upper extremities* (A *and* B)*, hypesthesia in lower extremities* (C)*, spontaneous pain in upper extremities* (D)*, and paresthesia in the sole upon walking (a sensation as if walking on sand* [E] *or a sensation as if walking on an uneven road* [F]*). Data are means ± SEM.*

thy. Only one compound has been successfully developed. Epalrestat is marketed for the treatment of diabetic neuropathy, but only in Japan (22).

There are a number of reports supporting the beneficial effects of AR inhibitors in animal models for diabetic neuropathy (23–25). In these models, fidarestat has been shown to produce persistent AR inhibition in peripheral nerves, where its elimination half-life is ~190 h (9). When tested in streptozotocin-induced diabetic rats at a daily dose of 2 mg/kg/day for 15 months, fidarestat treatment improved nerve polyol metabolism and prevented the decline of nerve conduction velocity observed in untreated diabetic animals. It also prevented the onset and progression of nerve fiber degeneration, including demyelination, collapse in the region around the node of Ranvier, axonal atrophy, and a decrease in nerve fiber circularity (11).

During the last 20 years, a number of AR inhibitors have been evaluated in clinical studies. Sural nerve biopsies collected from patients with diabetic neuropathy who had been treated for >12 months with an AR inhibitor provided evidence that sorbinil (26) and tolrestat (27) significantly increased nerve fiber regeneration, whereas zenarestat (28) and sorbinil (26) significantly increased nerve fiber density. Clinical studies with these compounds have also provided evidence of beneficial effects on nerve electrophysiology. In animal studies, AR inhibitor effects on nerve function have been attributed to decreased axonal atrophy, increased thickening of the myelin layer in large-diameter nerve fibers, decreased edema in the node of Ranvier, and a restoration of microcirculation in the endoneurium (18–21,23–25).

Fidarestat demonstrated a significant improvement compared with placebo in F-wave minimum latency and FCV of the median nerve. The improvement of nerve conduction velocity, however, was smaller than that reported in the zenarestat study (28). This difference in the magnitude of the treatment effect may be caused by several factors, including differences in the severity of neuropathy and the duration of diabetes in the patients evaluated in each study. For example, the zenarestat study targeted patients with mild or moderate neuropathy. Subjects with absent sural sensory responses or with proliferative or preproliferative retinopathy were excluded. These subjects, who likely have relatively severe neuropathy, were included in the present study, resulting in a population with a ~40% prevalence of retinopathy. In addition, the duration of diabetes was ~5 years longer in our subjects compared with those participating in the zenarestat study. Some investigators (29) have speculated that the ability to prevent further deterioration or to reverse

the functional deficits in neuropathy may be limited by disease severity. Although small and not present in every nerve, the observed significant change in electrophysiological measures, combined with the improvement in symptoms, is especially encouraging in the diabetic population included in the present study.

In the median nerve, FCV significantly declined in the placebo group. This result is consistent with a recent estimate, based on population studies, that nerve conduction velocity decreases by ~0.5 m/s annually in diabetic patients (30). Improvement of nerve conduction function was considered to result in the effect of nerve degeneration, such as axonal atrophy in diabetic neuropathy (30). These results suggest that fidarestat can delay the progressive deterioration of nerve function secondary to diabetic neuropathy.

The reproducibility of nerve conduction velocity measurements in efficacy evaluations of drugs for diabetic neuropathy has varied considerably, prompting considerable efforts at standardization in multicenter studies (13,30,31). The greater reproducibility of measurements of F-wave minimum latency and FCV versus MNCV measurements suggests that the former measurements may have a greater utility in multicenter studies of diabetic patients, particularly in patients with an advanced form of the disease (13). F-wave measurements are also particularly useful because they can detect abnormalities in any region of a peripheral nerve (31). Differences in the reproducibility of F-wave minimum latency and FCV versus MNCV measurements may account for the greater sensitivity of the former measurements for detecting evidence of disease progression and fidarestat treatment effects in the present study.

In the present trial, changes in the severity of each of the subjective symptom scores were also used in the evaluation of treatment efficacy. For numbness and spontaneous pain, the extent and severity of the symptom were included in the evaluation. During the course of the study, the difference in the subjective symptom scores between the fidarestat and placebo groups increased over time. Fidarestat treatment appeared to significantly improve subjective symptom scores compared with placebo, particularly numbness, sensation of rigidity, paresthesia in the sole upon walking, spontaneous pain, heaviness in the foot, and hypesthesia. This phenomenon is not commonly observed with symptomatic therapy but is characteristic of a radical therapy that eliminates the cause of disease. In diabetic neuropathy, although nerve fiber regeneration after nerve fiber loss is frequently observed in peripheral nerves, the process of regeneration appears to be delayed, and thus some regenerated nerve fibers remain immature. Abnormal excitement of these immature regenerated nerve fibers is thought to lead to numbness, spontaneous pain, and paresthesia upon walking (1–3). Fidarestat treatment improved these symptoms, suggesting that it may accelerate the nerve regenerative process in diabetic patients. Hypesthesia, a negative symptom, is the loss of sensitivity to stimulation that develops when the regenerative ability is lost and the number of functional nerve fibers is reduced. Care should be taken, particularly at the onset of this symptom, because hypesthesia can often lead to the development of foot lesions.

The safety of AR inhibitors in patients with diabetic neuropathy has severely limited their widespread clinical use. The marketing and development of several AR inhibitors shown to have benefit in clinical trials have been discontinued because of adverse reactions in patients. Sorbinil caused a hypersensitivity response and skin rash in as many as 10% of the participating patients in a number of relatively small clinical trials (32), whereas the carboxylic AR inhibitors tolrestat and zenarestat caused serious hepatic dysfunction (33) and renal toxicity (34), respectively. In the large multicenter placebo-controlled study described here, there were no reports of skin rash caused by fidarestat treatment, even though fidarestat is in the same hydantoin chemical class of compounds as sorbinil. The incidences of adverse experiences and abnormal laboratory values whose causality with the trial drug could not be ruled out were similar between the fidarestat and placebo groups. Neither serious adverse experiences nor serious abnormal laboratory values that required the discontinuation of the study treatment were reported with fidarestat treatment. Accordingly, fidarestat appears to be well tolerated with long-term use. The safety of fidarestat is thought to be due to *1*) its rapid distribution into tissues and its selective binding to AR protein (12), *2*) its limited metabolism and excretion via the kidney, *3*) the absence of direct pharmacological effects other than AR inhibition, and *4*) the absence of effects on hepatic drug-metabolizing enzymes (5).

As mentioned above, fidarestat treatment not only improved nerve conduction velocity decreased by diabetic neuropathy, but also improved a variety of subjective symptoms associated with this progressive disabling disorder. These findings support the hypothesis that the polyol pathway plays a central role in the onset and progress of diabetic neuropathy in human subjects. Furthermore, the putative mechanism of action and clinical efficacy of fidarestat suggest that by its persistent inhibition of the hyperglycemia-accelerated polyol metabolism, it induces the maturation of immature regenerated nerve fibers, stimulates the repair, and halts further nerve fiber degeneration. The effects of fidarestat treatment on subjective symptoms as well as other measures of nerve function, together with its safety profile, provide evidence that fidarestat, a novel AR inhibitor, may be clinically useful for the radical treatment of diabetic neuropathy.

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