

Long-Term Clinical Effects of Epalrestat, an Aldose Reductase Inhibitor, on Diabetic Peripheral Neuropathy

The 3-year, multicenter, comparative Aldose Reductase Inhibitor-Diabetes Complications Trial

NIGISHI HOTTA, MD¹
YASUO AKANUMA, MD²
RYUZO KAWAMORI, MD³
KEMPEI MATSUOKA, MD⁴
YOSHITOMO OKA, MD⁵
MOTOAKI SHICHIRI, MD⁶

TAKAYOSHI TOYOTA, MD⁷
MITSUYOSHI NAKASHIMA, MD⁸
ISAO YOSHIMURA, PHD⁹
NOBUO SAKAMOTO, MD¹
YUKIO SHIGETA, MD¹⁰
THE ADCT STUDY GROUP*

OBJECTIVE — We sought to evaluate the long-term efficacy and safety of epalrestat, an aldose reductase inhibitor, on diabetic peripheral neuropathy.

RESEARCH DESIGN AND METHODS — Subjects with diabetic neuropathy, median motor nerve conduction velocity (MNCV) ≥ 40 m/s, and HbA_{1c} $\leq 9\%$ were enrolled in this open-label, multicenter study and randomized to 150 mg/day epalrestat or a control group. After excluding the withdrawals, 289 (epalrestat group) and 305 (control group) patients were included in the analyses. The primary end point was change from baseline in median MNCV at 3 years. Secondary end points included assessment of other somatic nerve function parameters (minimum F-wave latency [MFWL] of the median motor nerve and vibration perception threshold [VPT]), cardiovascular autonomic nerve function, and subjective symptoms.

RESULTS — Over the 3-year period, epalrestat prevented the deterioration of median MNCV, MFWL, and VPT seen in the control group. The between-group difference in change from baseline in median MNCV was 1.6 m/s ($P < 0.001$). Although a benefit with epalrestat was observed in cardiovascular autonomic nerve function variables, this did not reach statistical significance compared with the control group. Numbness of limbs, sensory abnormality, and cramping improved significantly with epalrestat versus the control group. The effects of epalrestat on median MNCV were most evident in subjects with better glycemic control and with no or mild microangiopathies.

CONCLUSIONS — Long-term treatment with epalrestat is well tolerated and can effectively delay the progression of diabetic neuropathy and ameliorate the associated symptoms of the disease, particularly in subjects with good glycemic control and limited microangiopathy.

Diabetes Care 29:1538–1544, 2006

From the ¹Chubu Rosai Hospital, Nagoya, Japan; the ²Institute for Adult Diseases Asahi Life Foundation, Tokyo, Japan; the ³Department of Medicine, Metabolism, and Endocrinology, Juntendo University School of Medicine, Tokyo, Japan; the ⁴Saiseikai Shibuya Satellite Clinic, Tokyo, Japan; the ⁵Division of Molecular Metabolism and Diabetes, Tohoku University Graduate School of Medicine, Sendai, Japan; the ⁶Research Institute of Lifestyle-Related Diseases, Osaka, Japan; the ⁷Tohoku Rosai Hospital, Sendai, Japan; the ⁸Hamamatsu Institute of Clinical Pharmacology and Therapeutics, Hamamatsu, Japan; the ⁹Faculty of Engineering, Tokyo University of Science, Tokyo, Japan; and the ¹⁰Shiga University of Medical Science, Otsu, Japan.

Address correspondence and reprint requests to Nigishi Hotta, MD, PhD, Chubu Rosai Hospital, 1-10-6 Komei, Minato-ku, Nagoya 455-8530, Japan. E-mail: hotta@chubuh.rofuku.go.jp.

Received for publication 5 December 2005 and accepted in revised form 20 March 2006.

Abbreviations: ADCT, Aldose Reductase Inhibitor-Diabetes Complications Trial; ARI, aldose reductase inhibitor; MFWL, minimum F-wave latency; MNCV, motor nerve conduction velocity; VPT, vibration perception threshold.

*A list of ADCT Study Group members from Japan can be found in the APPENDIX.

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

DOI: 10.2337/dc05-2370

© 2006 by the American Diabetes Association.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked "advertisement" in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Although several pivotal trials have shown that strict glycemic control reduces the occurrence and progression of diabetes-related complications (1–3), this approach alone does not completely eliminate complications. Thus, the development of new drugs to manage diabetes complications remains a high priority.

Diabetic neuropathy is a common complication of diabetes often associated with considerable morbidity and mortality (4); it appears relatively early in the disease process. One important metabolic factor underlying diabetic peripheral neuropathy is an enhanced polyol pathway (5–8); suppression of this pathway may be an important key to efficient treatment for diabetic peripheral neuropathy. As aldose reductase is a key enzyme of the polyol pathway, aldose reductase inhibitors (ARIs) have received much attention worldwide. Although many ARIs have been developed, most have been ruled out as potential therapies because of unacceptable adverse effects or weak efficacy. Currently, ranirestat is being tested in clinical trials in Japan and the U.S.; fidarestat is preparing for phase III testing in Japan and the U.S. Epalrestat (Ono Pharmaceuticals, Osaka, Japan), approved in Japan in 1992, is the only ARI currently available commercially. Epalrestat is easily absorbed into neural tissue (9–12) and potently inhibits aldose reductase (9) with minimum adverse effects (13,14).

Although several published reports have described the efficacy and safety of epalrestat (13–17), including a double-blind, placebo-controlled study (13), no long-term or large population studies have been conducted. Therefore, the Aldose Reductase Inhibitor-Diabetes Complications Trial (ADCT) was initiated to evaluate the efficacy and safety of long-term administration of epalrestat in subjects with mild diabetic neuropathy.

RESEARCH DESIGN AND METHODS

The ADCT was conducted at 112 medical facilities in Japan between 1997 and 2003. The protocol was approved by the Institutional Review Board of each medical facility. Informed consent was obtained after a detailed explanation of the study purpose and methods.

Adults aged ≥ 20 years were diagnosed in each facility as mild diabetic peripheral neuropathy based on subjective symptoms, no foot ulcer, and neurological dysfunctions (at least two parameters: MNCV [indispensable] and VPT or Achilles tendon reflex, etc.). Patients were enrolled for study if they had a median motor nerve conduction velocity (MNCV) ≥ 40 m/s (seemingly reversible) and stable glycemic control (HbA_{1c} [A1C] $\leq 9\%$, with $\pm 0.5\%$ variation in the previous 3 months). Subjects were excluded if their primary cause of neurologic disorder was not diabetes (alcoholic neuropathy, carpal tunnel syndrome, sequelae of cerebrovascular disease, etc.), if they had arteriosclerosis obliterans (ankle brachial pressure index of ≤ 0.8) or severe hepatic or renal disorder, if they were participating in other interventional studies, or if they were receiving other experimental medications for diabetic neuropathy, prostaglandin E₁ preparations, or any other medication that affects symptoms of diabetic neuropathy.

In this 3-year, open-label study, participants were randomized to epalrestat or a control group. The randomization sequence was generated by an independent organization (Bell System 24, Tokyo, Japan) and randomization was stratified by sex, age (20 to <40 , 40 to <65 , and ≥ 65 years), A1C (<7.5 and 7.5 – 9%), and median MNCV (40 to <50 and ≥ 50 m/s) using the minimization method. A central telephone and fax service was used to implement the sequence allocation. Epalrestat (50 mg) was orally administered three times daily before each meal (150 mg/day). Both groups continued conventional therapy (diet treatment, hypoglycemic agents, insulin, and hypotensive agents). With the exception of rescue medication, new medication to aid neuropathy control was prohibited.

Study end points and measures of outcome

Study visits occurred at 6 monthly intervals. **Somatic nerve function.** The primary end point was change from baseline to study end in median MNCV in the patient's nondominant arm. The arm was

chosen to avoid any bias due to possible lower limb impairment caused by Japanese lifestyle (a tendency to sit straight). Secondary end points included changes from baseline to study end in minimum F-wave latency (MFWL) of the median motor nerve and vibration perception threshold (VPT). Nerve conduction and MFWL were measured using electromyography at 32–34°C based on Kohara et al. (18). F-wave was measured 16 times, and the minimum was adopted. VPT was measured on the medial malleolus in the low extremities using a 128-Hz tuning fork by measuring the number of seconds until the patient could no longer feel the vibrations after the tuning fork was placed on the medial malleolus (15).

Cardiovascular autonomic nerve function. The coefficient of variation of the R-R interval at rest (CV_{R-R}) was measured by electrocardiograph. Variation in resting heart rate during deep breathing was also measured.

Other measures of outcome. Changes in strength of Achilles tendon and quadriceps reflexes were measured. Changes in subjective symptoms of diabetic neuropathy were evaluated using a 100-mm visual analog scale at 3 years, and the percentage change from baseline was calculated. Reductions in symptom levels of $\geq 50\%$ or $<50\%$ were considered an improvement or semi-improvement; no reduction was considered unchanged, and an increase was considered to be aggravation.

Retinopathy assessments were performed by an ophthalmologist using a fundus photograph. Patients' eyes were graded as no retinopathy, simple (mild or moderate nonproliferative) retinopathy, or either preproliferative or proliferative retinopathy based on the Davis classification (19). Changes after 3 years were defined as improved, unchanged, or deteriorated. Microalbuminuric state was classified at baseline as normal, microalbuminuria, or clinical albuminuria, according to the microalbuminuria diagnostic standards of the American Diabetes Association (20). Change after 3 years was evaluated as improved, unchanged, or deteriorated.

Safety

Safety assessments included adverse event (AE) reporting and routine laboratory tests. All reported AEs were recorded with severity graded as mild, moderate, or severe, and relationship to treatment was assigned. AEs were monitored in epalrestat recipients only.

Statistical analysis

Assuming the population SD of median MNCV is 6 m/s, ~ 300 subjects were needed for each treatment group to have a two-sided α level of 0.05 and a power of 0.95 to detect between-group differences.

Efficacy analyses were performed in subjects who had data for at least 1 year, with the last-observation-carried-forward method used. This method corrects bias by using the last available value for a missing value (21,22).

Statistical methods used included χ^2 tests for nominal scale, Mann-Whitney *U* tests for ordered categorical scale, two-sample *t* tests for comparison of mean values between groups, paired *t* tests for comparison of mean values within groups, and two-way repeated ANOVA for changes in glycemic control. The Cochran-Mantel-Haenszel method was performed in order to calculate the improvement of subjective symptoms when a significant group difference was seen at baseline. ANCOVA was performed for the adjusted data using baseline values as covariates. Normalization for the multiplicity of subgroup analyses was not performed. All analyses were carried out using SAS version 8.02 (SAS Institute, Cary, NC). $P < 0.05$ was considered statistically significant.

RESULTS

Demographic profile of the subjects

A total of 634 subjects were enrolled and allocated; 31 patients withdrew before starting the trial, leaving 295 and 308 patients in the epalrestat and control groups, respectively. Six (epalrestat) and three (control) patients were excluded for major protocol deviations. Thus, 289 (epalrestat) and 305 (control) patients were included in the analyses. Patient clinical characteristics are provided in Table 1. There were no significant differences between the two groups. Of these, 55 and 31 withdrew after <1 year; reasons for withdrawal were a change in hospital (12 in each group), complications in comorbid illnesses (7 in each group), amelioration of symptoms (2 epalrestat), AEs (20 epalrestat), deterioration in symptoms (7 control), or other (14 epalrestat and 5 control). Both amelioration of symptoms and AEs were likely to be experienced in the epalrestat group only, resulting in the higher withdrawal rate in this group. Additionally, 53 (epalrestat) and 59 (control) patients had ineligible data for the primary efficacy analysis, generally be-

Table 1—Patient clinical characteristics

	Control	Epalrestat	P
n	305	289	
Sex			0.742*
Male	174 (57.0)	161 (55.7)	
Female	131 (43.0)	128 (44.3)	
Age (years)	61.5 (± 9.1)	61.5 (± 9.8)	0.958†
BMI (kg/m ²)	23.0 (± 3.4)	23.1 (± 3.2)	0.706†
Type of diabetes			0.299*
Type 1	6 (2.0)	9 (3.1)	
Type 2	295 (96.7)	279 (96.5)	
Other	4 (1.3)	1 (0.3)	
Duration of diabetes (years)	12.4 (± 8.0)	13.3 (± 8.9)	0.221†
A1C (%)	7.0 (± 1.0)	7.1 (± 1.0)	0.214†
Diabetes therapy			0.977‡
Diet alone	40 (13.1)	44 (15.2)	
Oral hypoglycemic agent	151 (49.5)	133 (46.0)	
Insulin	114 (37.4)	112 (38.8)	
Duration of neuropathy (years)	3.1 (± 3.5)	3.5 (± 4.6)	0.387†
Median MNCV (m/s)	52.5 (± 4.9)	52.1 (± 5.1)	0.277†
Diabetic retinopathy			0.171‡
No	157 (51.5)	135 (46.7)	
Simple	82 (26.9)	79 (27.3)	
Preproliferative	26 (8.5)	27 (9.3)	
Proliferative	40 (13.1)	48 (16.6)	
Proteinuria			0.826‡
No	224 (73.4)	209 (72.3)	
Microalbuminuria	30 (9.8)	33 (11.4)	
Clinical albuminuria	51 (16.7)	47 (16.3)	

Data are means ± SD or n (%). P values were calculated using * χ^2 test, †two-sample t test, and ‡Mann-Whitney U test. Duration of neuropathy refers to mean patient-reported duration of neuropathy symptoms.

cause of the unavailability of an electromyogram or a problem with measuring technique. Thus, the primary efficacy analysis included 181 and 215 patients in the epalrestat and control groups, respectively.

Changes in glycemic control

Changes in glycemic control of the patients whose median MNCV, the primary end point, were followed for 3 years. In the control group (n = 214), A1C (means ± SD) at baseline, 1, 2, and 3 years, was 7.1 ± 1.0, 7.2 ± 1.2, 7.3 ± 1.3, and 7.2 ± 1.3%, respectively. Corresponding values in the epalrestat group (n = 180) were 7.2 ± 1.1, 7.2 ± 1.1, 7.3 ± 1.2, and 7.3 ± 1.3%, respectively. One patient in each group was lost to follow-up. There were no significant differences between the two groups at any time points.

Change in nerve function

Table 2 shows changes from baseline in somatic nerve function at years 1, 2, and 3. After 3 years, no statistically significant

deteriorations in median MNCV or VPT were observed in the epalrestat group, with a significant improvement in MFWL of the median motor nerve. Conversely, significant deterioration in these parameters was observed in the control group. To account for between-group differences in baseline median MNCV, an ANCOVA model using baseline values as covariate was applied to the 3-year data; there were significant differences in median MNCV, MFWL of the median motor nerve, and VPT between the groups, largely owing to deterioration of function in the control group.

Analysis of cardiovascular autonomic nerve function showed a significant deterioration in CV_{R-R} interval at rest after 3 years in the control group but not with epalrestat; however, the between-group difference was not statistically significant (Table 2). When subjects with a CV_{R-R} interval ≥5% were excluded (23), there was a significant between-group difference at year 2 (change from baseline; means ± SD: control group [n = 146] −0.18 ± 1.06% vs. epalrestat [n = 119]

+0.17 ± 1.04%; P = 0.007). The same trend was observed after 3 years (data not shown).

No significant between-group differences were observed for change in variation in resting heart rate (Table 2) or Achilles tendon and quadriceps reflexes (data not shown).

Change in subjective symptoms

At baseline, there were no significant differences between the groups, with the exception of cramping (P = 0.009, variation adjusted by the Cochran-Mantel-Haenszel method), in terms of the proportion of subjects experiencing symptoms of peripheral neuropathy. After 3 years, the epalrestat group exhibited significantly greater amelioration of the numbness of upper (P = 0.042) and lower (P = 0.030) extremities, paresthesia or hypesthesia (P = 0.015), and cramping (P = 0.024) compared with the control group. There were no statistically significant between-group differences in spontaneous pain of upper and lower extremities, dizziness, coldness, abnormal sweating, and constipation. The levels of improvement in subjective symptoms were as follows: numbness of upper extremities (control group [n = 93]: improved 28.0%, semi-improved 18.3%, unchanged 18.3%, and aggravated 35.5%; epalrestat group [n = 89]: 41.6, 19.1, 13.5, and 25.8%, respectively); numbness of lower extremities (control group [n = 190]: 33.7, 19.5, 15.3, and 31.6%, respectively; epalrestat group [n = 166]: 40.4, 23.5, 16.3, and 19.9%, respectively); paresthesia or hypesthesia (control group [n = 114]: 23.7, 17.5, 17.5, and 41.2%, respectively; epalrestat group [n = 94]: 37.2, 17.0, 19.1, and 26.6%, respectively); cramping (control group [n = 92]: 27.2, 13.0, 26.1, and 33.7%, respectively; epalrestat group [n = 89]: 42.7, 10.1, 16.9, and 30.3%, respectively).

Effects on diabetic microangiopathy

In subjects with no or simple retinopathy at baseline, an improvement at year 3 was seen in 1 of 114 (0.88%) and 7 of 99 (7.07%) subjects in the control and epalrestat groups, respectively. In contrast, 19 (16.67%) and 10 (10.10%) subjects in the control and epalrestat groups, respectively, had a deterioration in retinopathy. The difference between groups in improvement and deterioration rate was statistically significant (P = 0.026).

Of subjects with microalbuminuria at

Table 2—Change in nerve function over time

Variables	n	Baseline	1 year		2 years		3 years		Adjusted at 3 years†
			Δ	P*	Δ	P*	Δ	P*	
Median MNCV (m/s)									
Control	215	53.34 ± 4.40	-0.49 ± 3.05	0.019	-0.93 ± 3.31	<0.001	-1.49 ± 3.91	<0.001	51.42 ± 3.49
Epalrestat	181	51.96 ± 4.49	+0.29 ± 3.11	0.214	+0.28 ± 3.70	0.310	+0.11 ± 3.54	0.687	52.57 ± 3.50
P‡		0.002	0.013		<0.001		<0.001		0.001
MFWL of median motor nerve (ms)									
Control	131	26.66 ± 2.46	+0.12 ± 1.17	0.242	+0.19 ± 1.34	0.112	+0.35 ± 1.37	0.004	27.15 ± 1.30
Epalrestat	125	27.00 ± 2.68	-0.28 ± 1.14	0.008	-0.31 ± 1.31	0.010	-0.26 ± 1.31	0.026	26.59 ± 1.30
P‡		0.283	0.007		0.003		<0.001		<0.001
VPT (s)									
Control	113	8.78 ± 3.83	-0.21 ± 3.18	0.492	-0.61 ± 3.16	0.043	-0.79 ± 3.89	0.033	7.83 ± 3.50
Epalrestat	84	8.01 ± 3.43	+0.57 ± 3.21	0.110	+0.58 ± 3.40	0.121	+0.63 ± 3.96	0.150	8.86 ± 3.50
P‡		0.147	0.095		0.012		0.013		0.041
CV _{R-R} interval at rest (%)									
Control	159	2.51 ± 1.44	-0.04 ± 1.13	0.691	-0.20 ± 1.53	0.105	-0.26 ± 1.31	0.013	2.22 ± 1.01
Epalrestat	134	2.34 ± 1.32	+0.04 ± 1.38	0.761	+0.04 ± 1.37	0.707	-0.17 ± 1.27	0.113	2.21 ± 1.01
P‡		0.299	0.629		0.158		0.565		0.923
Variation in resting heart rate (bpm)									
Control	101	8.38 ± 5.73	-0.60 ± 4.94	0.224	-0.34 ± 5.12	0.505	-0.58 ± 5.38	0.279	7.51 ± 3.89
Epalrestat	83	7.01 ± 4.52	-0.10 ± 4.08	0.824	+0.54 ± 5.04	0.333	-0.39 ± 3.80	0.354	6.98 ± 3.90
P‡		0.072	0.452		0.244		0.776		0.369

Data are means ± SD unless otherwise indicated. Δ, change vs. baseline. P values were calculated using *paired *t* test, †two-sample *t* test, and ‡ANCOVA including baseline values as covariates. VPT was measured on the medial malleolus in the low extremities using a 128-Hz tuning fork by measuring the number of seconds until the patient could no longer feel the vibrations after the tuning fork was placed on the medial malleolus.

baseline, an improvement at year 3 was seen in 6 of 69 (8.70%) and 7 of 66 (10.61%) subjects in the control and epalrestat groups, respectively, whereas 15 (21.74%) and 8 (12.12%) subjects had a deterioration in albuminuria (not statistically significant), respectively.

Stratified subgroup analyses on median MNCV

Stratified subgroup analyses were performed to examine the relationship between change from baseline in median MNCV and glycemic control, grade of retinopathy, and grade of proteinuria (Fig. 1). **A1C levels.** In the control group, median MNCV deteriorated significantly over the 3 years, regardless of level of glycemic control during this study (Fig. 1A). In variation between groups, the epalrestat group showed a statistically significant prevention of deterioration of MNCV at years 2 and 3 in subjects with A1C <7% and at years 1, 2, and 3 in those with A1C ≥7% to <9% for the control group. In subjects with A1C ≥9%, there were no significant differences between the two groups. However, in the variation within groups, though median MNCV of the

control group deteriorated significantly compared with baseline at years 2 and 3 ($P < 0.050$ and 0.010 , respectively), the epalrestat group did not show such significant deterioration.

The median MNCV in control group subjects with a baseline A1C <7%, ≥7 to <8%, and ≥8% deteriorated over time (data not shown). However, in epalrestat recipients with baseline A1C <7% ($n = 73$), there was almost no deterioration, with significant differences compared with the control group ($n = 96$) at year 1 ($P = 0.055$), 2 ($P = 0.002$), and 3 ($P < 0.001$).

Grade of retinopathy. In subjects with no or simple retinopathy at baseline, the median MNCV deteriorated over time in the control group but not the epalrestat group, with significant between-group differences at years 1, 2, and 3 (Fig. 1B). Median MNCV deteriorated over time in subjects with preproliferative or proliferative retinopathy, regardless of group assignment.

Grade of proteinuria. In subjects with no proteinuria at baseline, median MNCV deteriorated over time in the control group but not in the epalrestat group. Sig-

nificant between-group differences were reported at years 1, 2, and 3 (Fig. 1C). Median MNCV deteriorated in subjects who had microalbuminuria or clinical albuminuria at baseline, regardless of treatment. Although deterioration was less in the epalrestat group, this did not reach significance relative to the control group.

Safety

In the epalrestat group, 26 of 295 subjects (8.8%) reported AEs; these occurred within the 1st year of treatment in 22 of the 26 subjects. AEs included hepatic function abnormalities (seven cases), gastrointestinal symptoms such as nausea and diarrhea (eight cases), skin rash/eczema (two cases), and one case each of vertigo, light-headedness, dorsal pruritus, hot flushes, hand stiffness, weakness of a lower extremity, edema in a lower extremity, thirst, and cerebral infarction. There were no severe AEs, and no AEs were thought to be directly related to the long-term administration of epalrestat.

CONCLUSIONS — Of patients with diabetic neuropathy, 60–70% will develop serious complications that culmi-

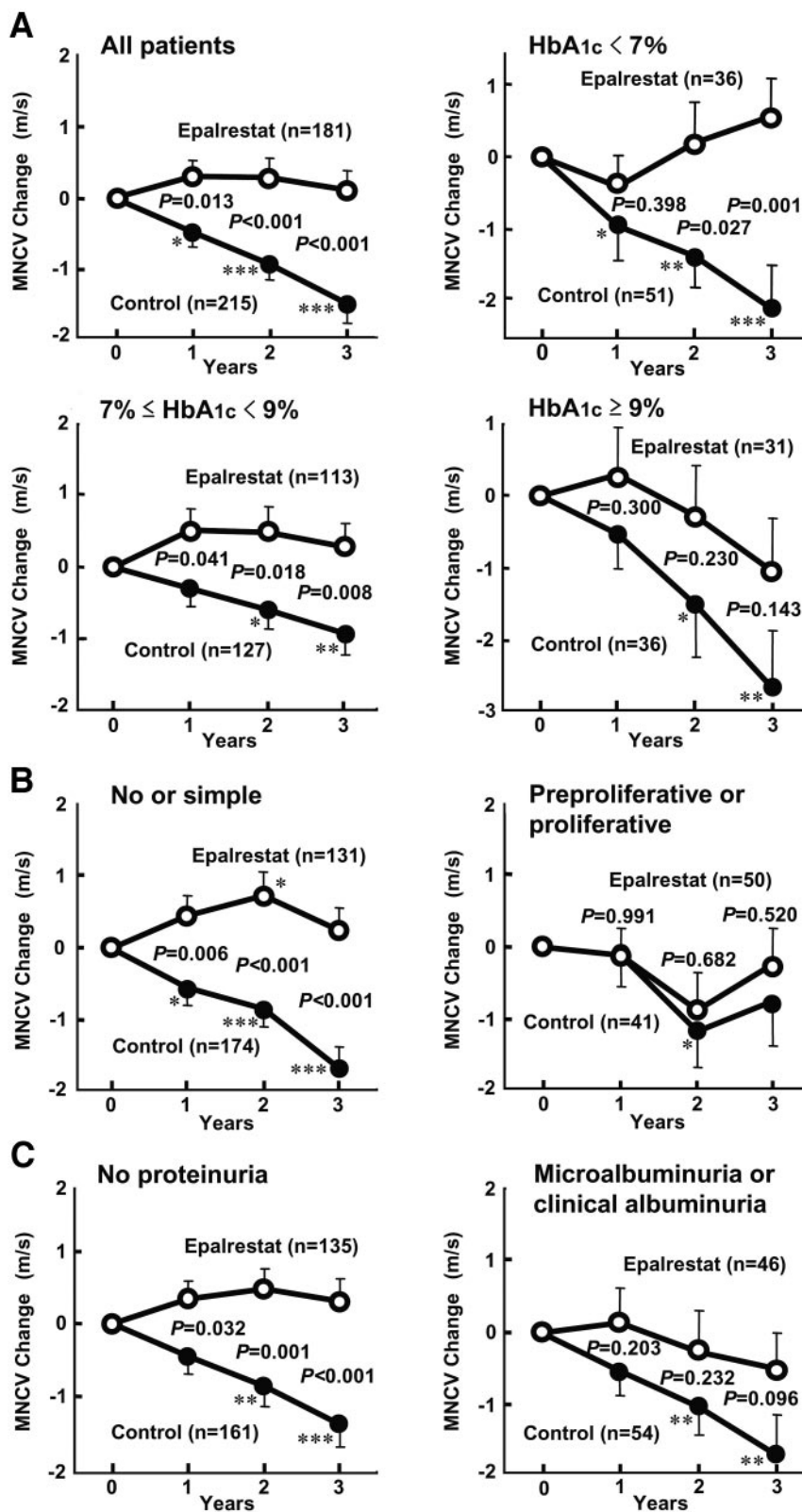


Figure 1—Effects of epalrestat on median MNCV according to A1C over 3 years (A), baseline level of retinopathy (B), and baseline level of proteinuria (C). ○, epalrestat group; ●, control group. Data are reported as means ± SE. P values were calculated using the two-sample t test. *P < 0.050, **P < 0.010, and ***P < 0.001 were calculated for each baseline using the paired t test.

nate in the amputation of an appendage (24). It is therefore of paramount importance to treat diabetic neuropathies appropriately.

Generally, median MNCV decreases with time in patients with diabetic neuropathy. Partanen et al. (25) reported a significant decrease of 2.9 m/s in the median MNCV over a 10-year period in patients with type 2 diabetes, which converts to a reduction over 3 years of 0.87 m/s. In our study, the control group showed a deterioration of 1.49 m/s over 3 years, exceeding the deterioration in Partanen et al. Conversely, the median MNCV of the epalrestat group has quickened slightly (+0.11 m/s over 3 years). The between-group difference of 1.6 m/s over 3 years indicates that epalrestat can prevent the deterioration of diabetic neuropathy.

MFWL may also be a useful index to evaluate diabetic neuropathy (17,18). In our study, epalrestat was associated with a significantly shorter MFWL of the median motor nerve compared with the control group, which is in agreement with another study with mild neuropathy (17). Other ARIs, including fidarestat, ranirestat, and zenarestat, have also been reported to improve MNCV and MFWL. Although a 52-week study of fidarestat did not show a significant effect on median MNCV, the median nerve F-wave conduction velocity and minimal latency were improved significantly (26). Moreover, in another 52-week study (27), zenarestat considerably improved peroneal MNCV. Similarly, ranirestat was shown to improve sensory nerve conduction by ≥1 m/s over 12 weeks (28) and improved peroneal MNCV following 60 weeks of treatment (29).

Short-term treatment with fidarestat (28 weeks) remarkably improved performance in arm and leg VPT (30), an indicator of sensory nerve disturbance (31). Ranirestat also improved VPT at the first toe following 60 weeks of treatment (29). In our study, VPT deteriorated over time in the control group but did not change significantly in the epalrestat group, suggesting that epalrestat is effective in preserving the sensory function. This is further supported by the improvement in subjective symptoms (numbness of limbs, sensory abnormality, and cramping) with epalrestat therapy, although such improvements are difficult to evaluate in an open-label study.

The existence of bias cannot be ruled out due to the open-label trial design.

However, because the nerve function inspection by the medical technologist and the assessment of the electromyogram by the specialized physician were carried out under masked conditions, it is thought that bias has been minimized.

There was an apparent imbalance in the number of analyzed subjects between the control ($n = 215$) and the epalrestat ($n = 181$) groups resulting from more withdrawals in the epalrestat group for events deemed treatment specific.

In performing a stratified analysis using median MNCV as an index, epalrestat was most effective in subjects with good glycemic control. Hyperglycemia-induced hyperactivity of polyol pathway links to the augmentation of the metabolic disorders, like glycation, oxidative stress, and others, contributing to the deterioration of diabetic neuropathy. However, these disorders are not completely caused from the hyperactivity of polyol pathway (5–8). Therefore, our data suggest good glycemic control may be important to keep the better effect of ARI treatment. Epalrestat was also effective in no or mild diabetic retinopathy and urinary microalbumin levels <30 mg/g creatinine. We believe this is the first study to conduct such an analysis and that it provides useful criteria for the selection of subjects for ARI treatment.

ARIs may also be valuable in the treatment of other diabetes complications (5,6). Our results suggest that epalrestat may be effective for preventing the onset or delaying progression of simple retinopathy, supporting previous findings by Hotta et al. (32).

AEs attributed to epalrestat were previously reported in 3.0% of subjects in a 12-week study (13) and 129 of 5,249 subjects (2.5%) in a 3- to 12-month multicenter study (14). The higher incidence (8.8%) of AEs in this study may be due to the longer duration of the study. It should be noted, however, that no particularly severe events were observed, thus confirming the safety of epalrestat for long-term administration.

In conclusion, long-term treatment with the ARI epalrestat is well tolerated and can effectively delay the progression of diabetic neuropathy and ameliorate the associated symptoms of the disease. Effects are particularly evident in patients with good glycemic control and no or mild microangiopathies.

Acknowledgments—We are grateful to Dr. Masayuki Baba and Dr. Isamu Ozaki (Hirosaki University School of Medicine, Hirosaki, Japan) for the evaluation of the electromyogram and Dr. Masakatsu Fukuda (NTT West Osaka Hospital, Osaka, Japan) for retinopathy evaluations. We also thank doctors and coworkers at the 112 medical facilities in Japan for provision of clinical data.

APPENDIX

ADCT Study Group (Japan)

Dr. Yukio Shigeta (Shiga University of Medical Science, Otsu), Dr. Nobuo Sakamoto (Chubu Rosai Hospital, Nagoya), Dr. Toshio Kaneko (Yamaguchi University, Yamaguchi), Dr. Yasuo Akanuma (Institute for Adult Diseases Asahi Life Foundation, Tokyo), Dr. Yoshitomo Oka (Tohoku University Graduate School of Medicine, Sendai), Dr. Motoaki Shichiri (Research Institute of Lifestyle-Related Diseases, Osaka), Dr. Takayoshi Toyota (Tohoku Rosai Hospital, Sendai), Dr. Nigishi Hotta (Chubu Rosai Hospital, Nagoya), Dr. Kempei Matsuoka (Saiseikai Shibuya Satellite Clinic, Tokyo), Dr. Ryuzo Kawamori (Juntendo University School of Medicine, Tokyo), Dr. Yoshitomo Atsumi (Saiseikai Central Hospital, Tokyo), Dr. Shinichi Oikawa (Nippon Medical School, Tokyo), Dr. Hideki Kishikawa (Health Care Center of Kumamoto University, Kumamoto), Dr. Jiro Nakamura (Nagoya University Graduate School of Medicine, Nagoya), Dr. Masayuki Baba (Hirosaki University School of Medicine, Hirosaki), Dr. Hitoshi Yasuda (Shiga University of Medical Science, Otsu), Dr. Nobuhiro Yamada (University of Tsukuba, Tsukuba), Dr. Mitsuyoshi Nakashima (Hamamatsu Institute of Clinical Pharmacology and Therapeutics, Hamamatsu), Dr. Isao Yoshimura (Tokyo University of Science, Tokyo), and Dr. Yoshio Goto (Tohoku Kosei-Nenkin Hospital, Sendai).

References

1. Diabetes Control and Complications Trial Research Group: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 329:977–986, 1993
2. Ohkubo Y, Kishikawa H, Araki E, Miyata T, Isami S, Motoyoshi S, Kojima Y, Furuyoshi N, Shichiri M: Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-depen-

- dent diabetes mellitus: a randomized prospective 6-year study. *Diabetes Res Clin Pract* 28:103–117, 1995
3. UK Prospective Diabetes Study (UKPDS) Group: Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 352:837–853, 1998
4. Vinik AI, Mehrabyan A: Diabetic neuropathies. *Med Clin North Am* 88:947–999, 2004
5. Hotta N: New concepts and insights on pathogenesis and treatment of diabetic complications: polyol pathway and its inhibition. *Nagoya J Med Sci* 60:89–100, 1997
6. Oates PJ, Mylari BL: Aldose reductase inhibitors: therapeutic implications for diabetic complications. *Expert Opin Investig Drugs* 8:2095–2119, 1999
7. Cameron NE, Eaton SE, Cotter MA, Tesfaye S: Vascular factors and metabolic interactions in the pathogenesis of diabetic neuropathy. *Diabetologia* 44:1973–1988, 2001
8. Oates PJ: Polyol pathway and diabetic peripheral neuropathy. *Int Rev Neurobiol* 50:325–392, 2002
9. Terashima H, Hama K, Yamamoto R, Tsuboshima M, Kikkawa R, Hatanaka I, Shigeta Y: Effects of a new aldose reductase inhibitor on various tissues in vitro. *J Pharmacol Exp Ther* 229:226–230, 1984
10. Kikkawa R, Hatanaka I, Yasuda H, Kobayashi N, Shigeta Y, Terashima H, Morimura T, Tsuboshima M: Effect of a new aldose reductase inhibitor, (E)-3-carboxymethyl-5-[(2E)-methyl-3-phenylpropenylidene]rhodanine (ONO-2235) on peripheral nerve disorders in streptozotocin-diabetic rats. *Diabetologia* 24:290–292, 1983
11. Sawada M, Terashima H, Okegawa T, Kawasaki A: Pharmacokinetic study of epalrestat (ONO-2235). In *Current Concepts of Aldose Reductase and Its Inhibitions*. Sakamoto N, Kinoshita JH, Kador PF, Hotta N, Eds. Amsterdam, Excerpta Medica, 1990, p. 111–118
12. Kamon N, Mabuchi H, Takeda R, Terashima H: Effects of aldose reductase inhibitor (ONO-2235) on human erythrocyte sorbitol concentrations in 75 g oral glucose tolerance tests. *Horm Metab Res* 23:226–229, 1991
13. Goto Y, Hotta N, Shigeta Y, Sakamoto N, Kikkawa R: Effects of an aldose reductase inhibitor, epalrestat, on diabetic neuropathy: clinical benefit and indication for the drug assessed from the results of a placebo-controlled double-blind study. *Biomed Pharmacother* 49:269–277, 1995
14. Hotta N, Sakamoto N, Shigeta Y, Kikkawa R, Goto Y, Diabetic Neuropathy Study Group in Japan: Clinical investigation of epalrestat, an aldose reductase inhibitor,

- on diabetic neuropathy in Japan: multicenter study. *J Diabetes Complications* 10: 168–172, 1996
15. Uchida K, Kigoshi T, Nakano S, Ishii T, Kitazawa M, Morimoto S: Effect of 24 weeks of treatment with epalrestat, an aldose reductase inhibitor, on peripheral neuropathy in patients with non-insulin-dependent diabetes mellitus. *Clin Ther* 17:460–466, 1995
 16. Ikeda T, Iwata K, Tanaka Y: Long-term effect of epalrestat on cardiac autonomic neuropathy in subjects with non-insulin dependent diabetes mellitus. *Diabetes Res Clin Pract* 43:193–198, 1999
 17. Nakayama M, Nakamura J, Hamada Y, Chaya S, Mizubayashi R, Yasuda Y, Kamiya H, Koh N, Hotta N: Aldose reductase inhibition ameliorates pupillary light reflex and F-wave latency in patients with mild diabetic neuropathy. *Diabetes Care* 24:1093–1098, 2001
 18. Kohara N, Kimura J, Kaji R, Goto Y, Ishii J, Takiguchi M, Nakai M: F-wave latency serves as the most reproducible measure in nerve conduction studies of diabetic polyneuropathy: multicentre analysis in healthy subjects and patients with diabetic polyneuropathy. *Diabetologia* 43: 915–921, 2000
 19. Davis MD, Myers FL, Bresnick GH, Venecia G: Natural evolution. In *Current Diagnosis and Management of Chorioretinal Diseases*. L'Esperance FA Jr, Ed. St. Louis, MO, C.V. Mosby, 1977, p. 179–184
 20. Molitch ME, DeFronzo RA, Franz MJ, Keane WF, Mogensen CE, Parving HH, Steffes MW: Diabetic nephropathy. *Diabetes Care* 26 (Suppl. 1):S94–S98, 2003
 21. Gillings D, Koch G: The application of the principle of intention-to-treat to the analysis of clinical trials. *Drug Info J* 25:411–424, 1991
 22. Department of Health and Human Services Food and Drug Administration: International conference on harmonisation: guidance on statistical principles for clinical trials: availability–FDA. Notice. *Fed Regist* 63:49583–49598, 1998
 23. Kageyama S, Mochio S, Taniguchi I, Abe M: A proposal of a quantitative autonomic function test. *Jikeikai Med J* 28:81–85, 1981
 24. Boulton AJM: Treatments for diabetic neuropathy. *Curr Diab Rep* 1:127–132, 2001
 25. Partanen J, Niskanen L, Lehtinen J, Mervaala E, Siitonen O, Uusitupa M: Natural history of peripheral neuropathy in patients with non-insulin-dependent diabetes mellitus. *N Engl J Med* 333:89–94, 1995
 26. Hotta N, Toyota T, Matsuoka K, Shigeta Y, Kikkawa R, Kaneko T, Takahashi A, Sugimura K, Koike Y, Ishii J, Sakamoto N, the SNK-860 Diabetic Neuropathy Study Group: Clinical efficacy of fidarestat, a novel aldose reductase inhibitor, for diabetic peripheral neuropathy: a 52-week multicenter placebo-controlled double-blind parallel group study. *Diabetes Care* 24:1776–1782, 2001
 27. Greene DA, Arezzo JC, Brown MB: Effect of aldose reductase inhibition on nerve conduction and morphometry in diabetic neuropathy: Zenarestat Study Group. *Neurology* 53:580–591, 1999
 28. Bril V, Buchanan RA, the AS-3201 Study Group: Aldose reductase inhibition by AS-3201 in sural nerve from patients with diabetic sensorimotor polyneuropathy. *Diabetes Care* 27:2369–2375, 2004
 29. Bril V, Buchanan RA, the Ranirestat Study Group: Long-term effects of ranirestat (AS-3201) on peripheral nerve function in patients with diabetic sensorimotor polyneuropathy. *Diabetes Care* 29:68–72, 2006
 30. Hotta N, Yasuda K, Sumita Y, Sano T, Kakuta H, Nagashima M, Hayashi Y, Yamamoto M, Wakao T, Okuyama M, Kobayashi M, Mori K: Effects of a novel aldose reductase inhibitor, fidarestat (SNK-860), on vibration perception threshold and subjective symptoms in patients with diabetic polyneuropathy: an open-label pilot study. *Clin Drug Invest* 24:671–680, 2004
 31. Sakakibara H, Hirata M, Hashiguchi T, Toibana N, Koshiyama H, Zhu SK, Kondo T, Miyao M, Yamada S: Digital sensory nerve conduction velocity and vibration perception threshold in peripheral neurological test for hand-arm vibration syndrome. *Am J Ind Med* 30:219–224, 1996
 32. Hotta N, Kakuta H, Ando F, Sakamoto N: Current progress in clinical trials of aldose reductase inhibitors in Japan. *Exp Eye Res* 50:625–628, 1990