Factors That Impact Symptomatic Diabetic Peripheral Neuropathy in Placebo-Administered Patients From Two 1-Year Clinical Trials

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OBJECTIVE — The purpose of this study was to evaluate the change in neuropathy symptoms and disease progression in placebo-administered patients from two 1-year studies in which the impact of ruboxistaurin (RBX) in mild diabetic peripheral neuropathy (DPN) was tested.

RESEARCH DESIGN AND METHODS — Data from 262 placebo-administered patients from two identical phase 3, randomized, double-blind trials were combined and analyzed.

RESULTS — After 1 year, change in the neuropathy impairment score of lower limbs [NIS(LL)] (−0.63 points; $P = 0.005$), vibration detection threshold (VDT) (−0.42 just noticeable difference units; $P = 0.003$), and Neuropathy Total Symptom Score-6 (NTSS-6) questionnaire (−3.73 points; $P < 0.001$) improved, whereas some electrophysiology measures and heart rate deep breathing (HRDB) (−0.78 beats; $P = 0.003$) worsened compared with baseline values. There was a small but significant worsening of A1C (0.28%; $P < 0.001$), and a greater percentage of patients were using analgesics at the end of the trials (33.6%; $P = 0.003$). At 1 year, the change in NTSS-6 directly correlated with changes in NIS(LL) and VDT and inversely correlated with the peroneal nerve conduction velocity. On logistic regression analyses, a ≥50% reduction in NTSS-6 score was less likely in patients who used antihypertensive or chronic symptom medication at baseline.

CONCLUSIONS — In placebo-administered patients with mild symptomatic DPN, there was a progressive improvement in symptoms over 12 months, whereas nerve conduction studies and HRDB declined, and clinically significant worsening of DPN would require >1 year of observation.

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Abbreviations: DPN, diabetic peripheral neuropathy; HRDB, heart rate variation during deep breathing; NIS(LL), neuropathy impairment score of the lower limbs; NCV, nerve conduction velocity; NTSS-6, Neuropathy Total Symptom Score-6; RBX, ruboxistaurin; VDT, vibration detection threshold.

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*A complete list of the Ruboxistaurin Study Group members 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.

In the Rochester Diabetic Neuropathy Study cohort, the prevalence of diabetic peripheral neuropathy (DPN) was 54% in patients with type 1 diabetes and 45% in patients with type 2 diabetes (1). The two main clinical consequences of DPN, painful neuropathy and foot ulceration (sometimes leading to amputation), are associated with much patient morbidiy and mortality (2). It is well established that lack of glycemic control and a longer duration of diabetes are major risk factors for the development of DPN (3,4). In addition, a major European prospective study has recently shown that potentially modifiable, traditional markers of macrovascular disease such as hypertension, hyperlipidemia, and smoking are also independent risk factors for DPN (5).

The most consistent early abnormality in DPN is an abnormality in nerve electrophysiology. Clinical signs resulting from nerve dysfunction may include loss of light touch and pressure sensation, a decrease in vibration detection threshold (VDT), decreased motor strength, and areflexia. Symptoms may or may not develop with the onset of functional abnormalities or mild clinical impairments and are therefore not essential for the diagnosis of DPN. However, it is well recognized that pain is the most distressing symptom of DPN and the main factor that prompts the patient to seek medical advice (6). There are few studies that have examined the prevalence and progression of painful DPN, and they report a prevalence rate ranging from 7 to 26% (7,8). The variation in prevalence reporting reflects the heterogeneity of the population studied, the criteria used to define symptomatic neuropathy, and the changes in the standard of care or alternatively the degree of DPN symptoms or use of concomitant therapy in that patient population.

Virtually all clinical trials involving pain-relieving drugs have been short term and solely evaluated changes in the symptoms of DPN without careful assessment of neuropathy parameters. Thus, infor-

mation on symptomatic improvement in relation to underlying disease state progression over an extended period of time is lacking. We present data from the placebo-administered patients from two large, randomized, double-blind, identical, 12-month clinical trials to investigate which factors may impact not only the disease-state progression but also the change in symptoms in patients with mild but clinically symptomatic DPN.

RESEARCH DESIGN AND METHODS

— Two identical, phase 3, parallel, randomized, double-blind, placebo-controlled trials were performed at 64 centers to investigate the effects of 32 mg/day of the protein kinase Cβ inhibitor ruboxistaurin (RBX) mesylate compared with placebo in patients with diabetes and symptomatic DPN. The studies were conducted according to the principles expressed in the Declaration of Helsinki.

Patients studied were ≥18 years with type 1 or type 2 diabetes who had clinically diagnosed sensory symptoms due to distal symmetrical polyneuropathy. Patients needed to have mild DPN, which included a VDT ≥95th percentile, a sural sensory nerve action potential ≥1 μV, and a baseline Neuropathy Total Symptom Score-6 (NTSS-6) >6 points. Patients who had a VDT >23 just noticeable difference (JND) units, an A1C value of >12.0%, or neuropathy due to diseases other than diabetes were excluded. Assessments included the NTSS-6, VDT, neuropathy impairment score of the lower limbs [NIS(LL)], heart rate variation during deep breathing (HRDB), and electrophysiology measured by nerve conduction studies.

Measurements

To evaluate symptoms of DPN, the NTSS-6 questionnaire was used to measure frequency and intensity of neuropathic sensory symptoms (numbness and/or insensitivity, prickling sensation, aching pain, burning pain, lancinating pain, allodynia, and/or hyperalgesia) (9,10). Surface stimulation and recordings of nerve conduction were obtained from the sural, peroneal, and tibial nerves of the lower extremity. Conduction velocities were calculated from these measurements using standard methods (11). In addition, the study limb was tested for vibratory perceptions over a 30-min period. A noninvasive detector was placed at predetermined skin locations and the "4-2-1 stepping" algorithm was followed. The reading center conducted quality control assessments before data capture (12).

Concomitant medication use

All concomitant medication use was recorded on the case report form. Analgesics were permitted, and medications taken for DPN symptoms were separately noted. Chronic symptom medications were defined as medications that are typically prescribed for the treatment of DPN symptoms on an ongoing basis (>1 month). These drugs include anticonvulsants and antidepressants; some examples include gabapentin, topiramate, amitriptyline, duloxetine, and nortriptyline. For patients who required medication to relieve DPN symptoms, analgesic medications were prescribed according to the following algorithm: week 1, aspirin, acetaminophen, paracetamol, or aspirin-like compounds; weeks 2–4 (if needed and indicated), nonsteroidal anti-inflammatory medication; weeks 5–8 (if needed and indicated), class 4 controlled substances such as propoxyphene or propoxyphene combined with another analgesic such as aspirin or acetaminophen; and week 9 and beyond (if needed and indicated), codeine or codeine combined with another analgesic such as aspirin or acetaminophen. If class 2 controlled substances were required (with the exception of codeine), then the study medication was discontinued.

Patients were required to have stable glucose control before entering the study. Patients with an A1C between 9 and 12% at screening were required to lower their A1C before entering the study by use of insulin or other measures (diet and exercise with or without oral antihyperglycemic agents). Patients with an A1C >12% were excluded from the study. Patients' antihyperglycemia therapy could have been altered at any time during the trial, in accordance with good clinical practice and the local standards of diabetes care.

Analyses and statistical methods

Analyses were conducted using the intent-to-treat population, which includes all randomly assigned patients. For patients missing postbaseline measurements, the last observation carried forward approach was applied by imputing the last nonmissing postbaseline value. Pearson's correlation coefficient was used to evaluate disease progression within the placebo-administered patients by correlating the change in sensory symptoms (as measured by the NTSS-6) with the change in NIS(LL), VDT, or electrophysiological measures. Change from baseline to end point in medication use at baseline compared with postbaseline was also investigated.

Stepwise logistic regression was then conducted with the following patient characteristics included in the model: age, A1C, sex, origin (Caucasian versus non-Caucasian), diabetes type, alcohol use, tobacco use, BMI, blood pressure assessments, insulin use, and baseline measures of neuropathy. In addition, the use of the following medications was included: statins, antihypertensive agents, ACE inhibitors/angiotensin II receptor blocking agents, and chronic symptom medications. In all stepwise logistic regression models, the probability level to enter the model was set to 0.3 and the probability to remain in the model set to 0.1. The first stepwise logistic regression included the above factors; in addition, protocol was forced into the model as a factor. The second analysis was conducted in the same manner, but age and baseline A1C were also forced into the model, as these are known predictors of diabetic neuropathy disease state progression (3,4). The goal of these analyses was to assess the likelihood of clinically significant symptom improvement while adjusting for all characteristics together.

Table 1—*Patient baseline characteristics*

Characteristic	Placebo
n	262
Female sex	147 (56.1)
Type 1 diabetes	68 (26.0)
Age (years)	48.1 ± 9.4
Caucasian	207 (79.0)
BMI (kg/m^2)	30.0 ± 6.5
A1C (%)	7.6 ± 1.4
Used insulin	159 (60.7)
Duration of diabetes (years)	11.4 ± 9.2
Duration of neuropathy (years)	2.7 ± 2.8
Statin medication use	68 (26.0)
Chronic symptom medication use	38 (14.5)
Antihypertensive medication use	157 (59.9)
ACE inhibitor or ARB use	131 (50.0)

Data are means ± SD or *n* (%). ARB, angiotensin II receptor blocker

RESULTS

— Of the 519 patients randomly assigned at 64 centers, 262 received placebo and 211 of the placebo-treated patients completed the 1-year

Table 2—*Baseline to end point change at 1 year in placebo-administered patients*

Characteristic	Baseline	Baseline to end point improvement	*P* value*
NTSS-6 total score (points)	9.76 ± 3.3	3.73 ± 3.8	<0.001
NIS[LL] (points)	6.95 ± 5.0	0.63 ± 3.4	0.005
Quantitative sensory testing (JND units)	20.43 ± 2.1	0.42 ± 2.1	0.003
		Baseline to end point worsening	
HRDB (inspiration − expiration) (beats/min)	11.92 ± 6.7	0.78 ± 3.9	0.003
Peroneal NCV (m/s)	43.05 ± 4.9	0.38 ± 2.2	0.012
Tibial F-wave latency (ms)	54.93 ± 6.1	0.33 ± 2.4	0.045
Sural amplitude (μV)	9.10 ± 5.3	1.12 ± 3.7	<0.001
Sural peak latency (ms)	3.95 ± 0.49	0.058 ± 0.37	0.021
A1C (%)	7.58 ± 1.4	0.28 ± 1.2	$P < 0.001$

Data are means ± SD. To assess disease progression within the placebo-administered patients, changes from baseline to end point were assessed using a *t* test for the following neuropathy measures: NTSS-6 total score, the NIS[LL] score, VDT, the HRDB (heart rate difference between inspiration and expiration), and attributes of electrophysiology (sural, peroneal, and tibial nerves). The change from baseline to end point in A1C was also investigated. **P* values assess within placebo treatment baseline to end point change.

study (see the online appendix for the patient disposition diagram [available at http://dx.doi.org/10.2337/dc07-0608.) Baseline characteristics of the placebo group patients are presented in Table 1. Significant symptom improvement within each treatment group was demonstrated as early as 1 month and was observed throughout the course of 1 year ($P < 0.001$ in the placebo group and $P < 0.001$ in the RBX group). The combined data for the primary end point from these two clinical trials indicated that there was no significant difference between RBX-treated and placebo-administered groups for the NTSS-6 change at any point during the 1-year trials.

At baseline, placebo-administered patients had a mean NTSS-6 total score of 9.76 ± 3.3 (mean ± SD) points, NIS(LL) score of 6.95 ± 5.0 points, and VDT results of 20.43 ± 2.1 JND units. The change from baseline to end point exhibited a statistically significant mean improvement for each of the following parameters (Table 2): the NTSS-6 total score (3.73 ± 3.8; $P < 0.001$), the NIS(LL) (0.63 ± 3.4 points; $P = 0.005$), and the VDT (0.42 ± 2.1 JND units; $P = 0.003$). In contrast, the HRDB difference (inspiration – expiration at baseline = 11.9 ± 6.7 beats/min) had a statistically significant mean worsening (0.78 ± 3.9 beats/min; $P = 0.003$) from baseline to the end of the 1-year study evaluation (Table 2).

Most electrophysiology attributes numerically worsened over the 1-year study period. A statistically significant worsening was observed for peroneal motor nerve conduction velocity (NCV), tibial motor nerve F-wave latency, sural sensory nerve amplitude, and sural sensory peak latency (Table 2).

Although the change was small, a significant increase in baseline to end point A1C was observed (0.28 ± 1.2%; $P < 0.001$). The percentage of patients using insulin at baseline and at the end of the study was comparable (60.7 vs. 62.2%; $P = 0.720$), whereas the use of statins slightly increased from 26.3% at baseline to 31.7% at the end of the study ($P = 0.178$). However, the use of analgesic medications did significantly increase in the placebo-administered patients from 21.8% at baseline to 33.6% by the end of the study ($P = 0.003$). Regardless of analgesic medication use, whether never taken, taken at baseline, or initiated during the trial, there was a similar degree of improvement in the mean change from baseline in the NTSS-6 score for placebo-treated patients.

A change in sensory symptoms as measured by the NTSS-6 significantly correlated with changes in VDT ($r = 0.169$, $P = 0.010$), NIS(LL) ($r = 0.166$, $P = 0.010$), and peroneal NCV ($r = -0.213$, $P = 0.001$), although the correlations were mild. No consistent correlation was observed between change in symptoms and change in other electrophysiological measures in placebo-treated patients. In addition, no statistically significant correlation between change from baseline in each of the individual NTSS-6 symptoms and change from baseline in measures of neuropathy was observed.

As shown in Table 3, when the patient characteristics were assessed in a univariate fashion, a clinically significant (≥50%) reduction in NTSS-6 score was less likely in patients who used antihypertensive (65.2 vs. 52.8%; $P = 0.0464$) or chronic symptom medication (18.7 vs. 8.5%; $P = 0.0248$) at baseline. A similar trend was observed with the use of statins at baseline (30.3 vs. 19.8%; $P = 0.0591$). Patients who had clinically significant improvement in neuropathy symptoms at 1 year had lower mean baseline scores for NTSS-6, milder neuropathy (e.g., lower VDT, lower NIS(LL), and higher sural sensory amplitude, peroneal NCV, and tibial F-wave latency), lower BMI, type 1 diabetes, and lower systolic blood pressure and were younger. Additionally, there was a significant difference in the change in peroneal NCV between patients who had clinically significant improvement in neuropathy symptoms compared with those who did not (Table 3).

The results from the stepwise logistic regression analysis to assess the impact of patient characteristics on change in symptoms at 1 year are presented. Patients who used antihypertensive ($P = 0.025$) and chronic symptom medications ($P = 0.01$) at baseline and had a higher VDT ($P = 0.013$) at baseline were less likely to show improvement in symptoms. When the stepwise logistic regression analysis was performed with A1C and age in the model (results not shown), patients who used antihypertensive medications and chronic symptom medications at baseline were less likely to have symptom improvement. In addition, those with a higher BMI and, as anticipated, because

Table 3—*Patient characteristics that impact clinically significant improvement in neuropathic symptoms*

Characteristic	Symptom improvement ≥50%	No symptom improvement <50%	*P* value*
Baseline NTSS-6 total score (points)	9.17 ± 2.87	10.19 ± 3.58	0.0168
Baseline NIS[LL] (points)	6.45 ± 4.25	7.31 ± 5.41	0.1714
NIS[LL] changes from baseline (points)	−1.21 ± 3.37	-0.21 ± 3.41	0.0277
Baseline NIS[LL]+7 (points)	13.28 ± 5.99	15.26 ± 7.17	0.0219
NIS[LL]+7 change from baseline (points)	0.027 ± 7.7	2.51 ± 12.7	0.0969
Baseline VDT (JND units)	20.00 ± 2.06	20.71 ± 2.07	0.0087
VDT change from baseline (JND units)	−0.582 ± 2.39	−0.304 ± 1.87	0.3228
Baseline peroneal NCV (m/s)	43.34 ± 4.96	42.85 ± 4.90	0.4273
Peroneal NCV change from baseline (m/s)	0.015 ± 2.32	−0.674 ± 2.15	0.0260
Baseline tibial F-wave latency (ms)	54.54 ± 6.19	55.20 ± 6.06	0.3939
Tibial F-wave latency change from baseline (ms)	0.285 ± 2.66	0.362 ± 2.21	0.8165
Baseline sural amplitude (μV)	10.19 ± 5.44	8.34 ± 5.13	0.0076
Sural amplitude change from baseline (μV)	−1.23 ± 3.55	−1.04 ± 3.76	0.6985
Age (years)	46.30 ± 9.15	49.28 ± 9.36	0.0128
Baseline BMI (mg/kg^2)	29.07 ± 7.14	30.67 ± 5.95	0.0528
Baseline SBP (mmHg)	124.22 ± 14.21	128.26 ± 15.68	0.0361
Type 1 diabetes	33 (31.1)	34 (21.9)	0.0962
Baseline chronic symptom medication use	9 (8.5)	29 (18.7)	0.0248
Baseline antihypertensive medication use	56 (52.8)	101 (65.2)	0.0464
Baseline statin use	21 (19.8)	47 (30.3)	0.0591

Data are means ± SD or *n* (%). The patient characteristics that may predict clinically significant symptom improvement were also investigated. For these analyses, a patient was considered to have a clinically significant symptom improvement if at least a 50% reduction in the NTSS-6 total symptom score was observed from baseline to end of study. Each patient characteristic was initially evaluated using a univariate logistic regression model, with clinically significant improvement status as the dependent variable and the patient characteristic as the independent variable. A patient was considered to have a clinically significant symptom improvement if the patient had at least a 50% reduction from baseline in the NTSS-6 total symptom score. **P* values were calculated using a logistic regression analysis, with the categorical outcome (symptom improvement versus no symptom improvement) as the dependent variable and the characteristic (e.g., age) as the independent variable. SBP, systolic blood pressure.

age and A1C were forced into the model, older patients and those with a higher A1C at baseline were less likely to improve.

CONCLUSIONS — Accompanying the change in the standard of care, there has been a decrease in the incidence, prevalence, and progression of diabetic microvascular complications (10,13–15). However, the impact of improved care on neuropathy symptoms is unclear (10,13–15). It has also been conventionally assumed that the placebo effect on pain relief would be short-lived, lasting only 3–6 months. This has not been confirmed by long-term, randomized, controlled trials. Therefore, longer, randomized, controlled trials are clearly important as virtually all previous symptom-based trials have lasted <16 weeks, and information is lacking on the continued efficacy of drugs currently in use for painful DPN. This analysis addresses the evolution of neuropathy symptoms in placebo-administered patients with mild DPN over 1 year. The findings of this study may be relevant for designing future longer-term studies. In addition, the natural history and progression of the symptoms of DPN in relation to the underlying neuropathy is poorly understood (13), an issue that is also addressed by this study.

In the patients we studied, who were described as having mild DPN, we demonstrated variable progression of signs and symptoms. During the 1-year time course, there was statistically and clinically significant improvement in symptoms, signs (on neurologic examination), and sensory testing of vibration, whereas HRDB, a marker of autonomic neuropathy and small nerve fiber function, actually worsened. It is commonly believed that autonomic and sensory neuropathies are progressive complications of diabetes. We observed worsening autonomic function (HRDB), whereas sensory function (VDT) improved. This result may be due to a differential effect on large fiber sensation versus small fiber function. Additionally, electrophysiology was uniformly and numerically worse after 1 year but peroneal NCV, tibial F-wave latency, sural peak latency, and sural sensory amplitude were the only attributes to demonstrate a statistically significant worsening.

In contrast with positive results observed in the phase 2 trial investigating the effect of RBX in patients with DPN (16), the change in the NTSS-6 score was not statistically significant when RBX and placebo groups were compared in the two phase 3 studies (17). However, the change in symptoms from baseline to end point after this 1-year period was statistically significant in this patient population with mild DPN, regardless of treatment group. What could have affected symptom improvement in this study? Possibilities including the psychological effects of frequent study-required visits (18), a placebo effect (19), and changes in the diabetic and neuropathic disease states, glucose control, and use of symptom medication were considered. The improvements in symptoms as well as in the neurological examination score and VDT were unexpected because the patients' regimens (both diabetes medications and symptom medications) were stable before the study, and symptoms had been present for at least 6 months and as long as 5 years before enrollment. Although there was a slight increase in A1C at 1 year, this change could not be expected to greatly affect the clinical course. Thus, the most plausible explanation for the signif-

icant improvement in symptoms in the placebo-administered patients is likely to be the "placebo effect." The placebo effect would include the psychological effect of taking the medication as well as more frequent interactions with a team of researchers interested in the patients' well-being, thereby increasing the expectation of improvement. The placebo effect is unlikely to be explained by the increase in analgesic medication use from baseline to end point as placebo-administered patients who never received medications for symptoms of DPN during the trial also had a similar degree of improvement in the mean change from baseline in the NTSS-6 score. It is interesting that not only was the improvement in symptoms significant and progressive, but it appeared to be increasing over the 1-year time period.

Alternatively, other factors may have influenced change or improvement of symptoms in the patient population. We chose a ≥50% improvement as a clinically meaningful change (20). We used logistic regression analysis, which identified the patients with antihypertensive and chronic symptom medication use at baseline and worse VDT who were less likely to have symptom improvement. Additionally, milder symptoms and milder disease state at baseline, as defined by a composite score of nerve function, VDT, peroneal NCV change from baseline, or baseline sural sensory amplitude were identified as important. Finally, younger age, lower BMI, and lower blood pressure were associated with symptom improvement.

Similar to our previous study and distinct from the literature in this patient population, symptoms appeared to correlate positively with the neurological examination and vibration and inversely with the worsening of electrophysiological measures, such as peroneal NCV. Although this finding may support previous assertions that symptoms are unreliable in assessing neuropathy disease state progression, it also brings into question the value of other measures of neuropathic change, such as the neurological examination.

The neurological examination, which may or may not include a quantitative evaluation of sensation, has long been considered the gold standard by neurologists in making the diagnosis of DPN. The examination has subjective components that are not always amenable to a description of the presence of neuropathy or disease state progression in a strictly quantifiable manner. Moreover, it is well known that muscle strength (a prominent part of the neurological examination) cannot be fully evaluated and quantified when pain is present. Thus, the use of quantitative evaluation for the neurological examination may not accurately predict the presence or degree of neuropathy when painful symptoms are present. The recent consensus report advocating the use of the clinical examination as an important end point in defining the presence of neuropathy for clinical research purposes may be questionable (21).

Finally, in contrast to symptoms and signs, electrophysiological parameters consistently demonstrated worsening during the course of a 1-year period. Peroneal NCV, tibial F-wave latency, sural peak latency, and sural sensory amplitude were the only tests of nerve function to demonstrate a statistically significant worsening, although the remaining attributes were numerically worse. These measures are relatively objective with less variability and would thus be suitable end points for disease state progression in clinical trials (22). Clearly, several years of follow-up would be required for any clinically meaningful change even in electrophysiological measures.

This study has some limitations. These clinical trials were only 1-year studies, which may not have been long enough to observe changes in the disease state progression. Additionally, the trials screened ~8,500 patients for evidence of mild DPN with loss of vibration sensation. Enrollment into the study was limited to patients with mild DPN. Hence patients with severe symptoms and more advanced DPN were not enrolled into the trials. For this reason, only one of seven patients identified as having any severity of DPN qualified for the study. Therefore, these patients may not be representative of all patients with symptomatic DPN. Finally, the closer contact in a clinical trial setting may allow for a better patient care and glucose control, resulting in a reduction of disease state progression.

In summary, in patients with mild symptomatic DPN followed closely in a clinical trial, there was a significant and progressive improvement in symptoms over a 12-month period attributable to the placebo effect. Intervention with RBX during this 1-year period did not significantly alter symptom or disease state progression. The NIS(LL) and VDT improved from baseline to end point, whereas the more objective measures, including most electrophysiology attributes and the autonomic nerve function (HRDB), worsened over the course of 1 year. Finally, clinically significant worsening of DPN in placebo-administered patients in a clinical study would require >1 year of observation.

APPENDIX

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