

A multicentre trial of the aldose-reductase inhibitor, tolrestat, in patients with symptomatic diabetic neuropathy*

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Summary. The effects of the aldose-reductase inhibitor, tolrestat, on chronic symptomatic diabetic sensorimotor neuropathy were studied during a placebo-controlled, randomised, 52-week multicentre trial. Of the four tolrestat doses investigated, only the highest dose group, 200 mg once daily, showed subjective and objective benefit over baseline and placebo, and further analyses are confined to this group ($n = 112$) and placebo ($n = 107$). Painful and paraesthetic symptoms were analysed separately: improvement in paraesthetic symptoms were seen at one year ($p = 0.04$), though painful symptoms improved on both placebo and active therapies. Significant improvement in both tibial and peroneal motor nerve conduction velocities were seen at 52 weeks. Tolrestat 200 mg once daily was significantly better than

placebo in producing concordant improvements in both motor nerve conduction velocities and paraesthetic symptom scores at 24 weeks ($p = 0.01$), 42 weeks ($p = 0.01$) and 52 weeks ($p = 0.02$). Long-term benefit [concordant improvement at 24 weeks maintained until 52 weeks] was seen in 28% of treated patients compared to 5% on placebo ($p = 0.001$). It is concluded that some sustained improvement in symptomatic diabetic neuropathy may be obtained following aldose-reductase inhibition with tolrestat 200 mg once daily.

Key words: Diabetic neuropathy, aldose-reductase inhibitors, nerve conduction.

Peripheral neuropathy is one of the major complications of diabetes with a prevalence rate that approaches 20% even when strict clinical and electrophysiological criteria are applied [1]. There is increasing evidence to implicate both metabolic and vascular abnormalities in the aetiology of this condition [2–7]. Interest has increasingly been focussed on one metabolic consequence of hyperglycaemia in the nerve: increased activity of the enzyme aldose reductase which leads to tissue accumulation of sorbitol, in association with depletion of myo-inositol [2, 4]. A considerable body of animal data now confirms a pivotal role for the polyol pathway in the aetiology of experimental diabetic neuropathy [2, 4, 8]. Treatment with an aldose-reductase inhibitor (ARI) or myo-inositol supplementation in diabetic animal models can improve motor conduction velocity [9]. Although early studies on the effects of ARIs on human diabetic neuropathy were encouraging [10, 11], not all reports demonstrated benefit [12, 13]. However, many of these studies were hampered by their very short-term treatment period, the longest period being 6 months.

Tolrestat (N-[[5-trifluoromethyl]-6-methoxy-1-naphthalenyl]-thiomethoxy]-N-methylglycine), is an aldose-reductase inhibitor with a 10-h half-life [14], allowing once-daily administration, which has a favourable safety

profile [15]. In order to investigate the potential of this novel drug in the treatment of chronic, sensorimotor neuropathy, we evaluated the efficacy and safety of tolrestat in a placebo-controlled, randomised, double-blind trial in 550 patients during a 52-week period.

Subjects and methods

Subjects

Five hundred and fifty patients with either Type 1 (insulin-dependent) or Type 2 (non-insulin-dependent) diabetes of at least four months' duration were recruited in 19 centres. Inclusion criteria were: male or post-menopausal female patients; stable diabetes (judged clinically and by glycosylated haemoglobin and fasting plasma glucose results prior to entry); symptoms of stable or increasing severity caused by peripheral neuropathy; and abnormal motor or sensory nerve conduction results in at least three of six tested nerves.

Patients with other possible causes of polyneuropathy were excluded by clinical and laboratory investigations (hepatic or renal disease; any malignant disease; excessive alcohol intake; abnormal serum B12; abnormal serological tests for syphilis).

The groups were all comparable as to numbers of patients, duration of diabetes and neuropathy. During the study, patients continued on their usual diabetic therapy, including oral hypoglycaemic agents or insulin. No other treatment for peripheral neuropathy (eg., tricyclic drugs, phenytoin) was permitted, except for occasional, as needed, non-narcotic analgesic drugs.

Informed consent was obtained from all patients, and ethical committee approval was granted at every centre.

* Prepared by the authors for the North American tolrestat in neuropathy research group.

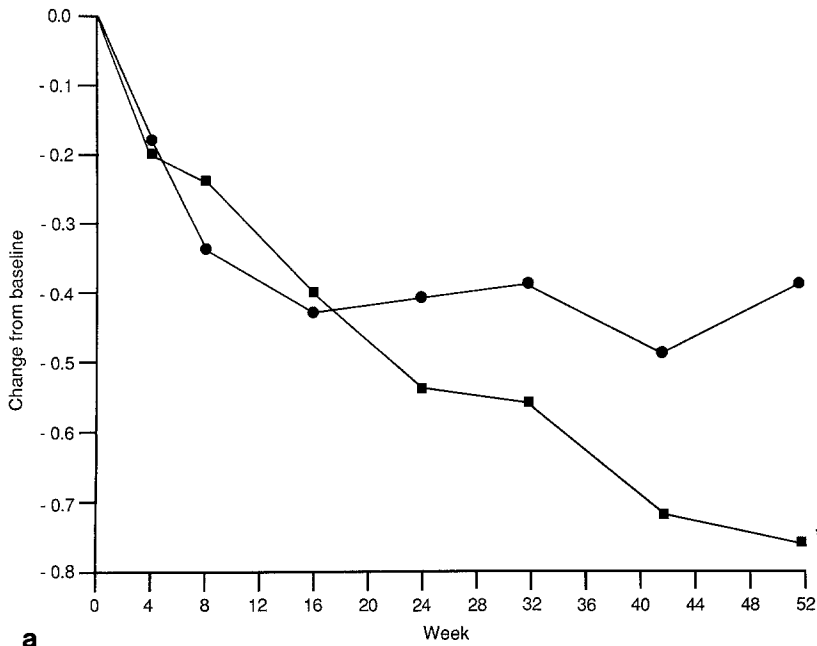
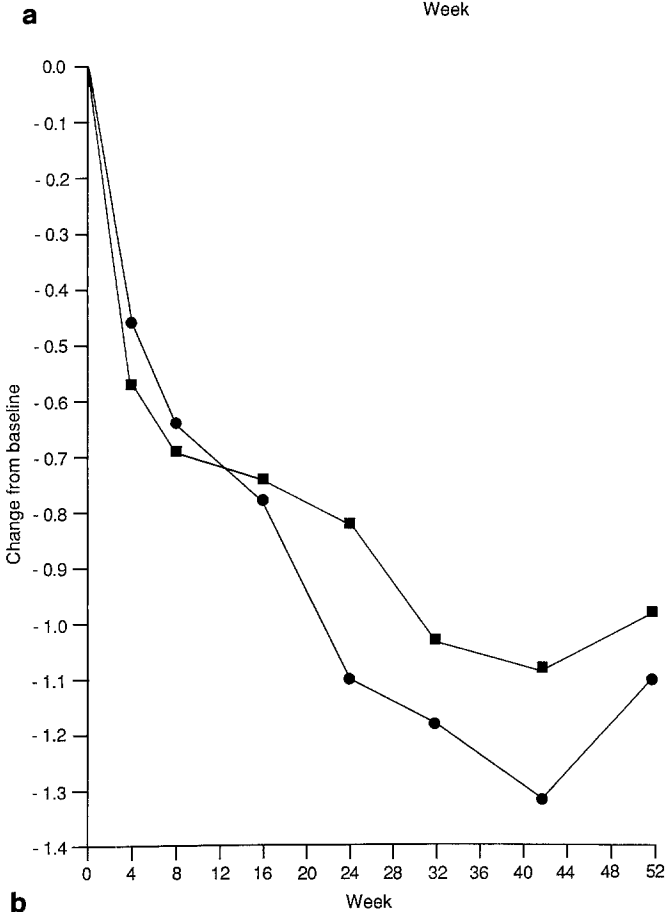


Fig. 1 a, b. The effect of tolrestat 200 mg once daily on the severity of the (a) paresthetic symptoms and (b) painful symptoms: least squares mean change from baseline. ● = placebo; ■ = tolrestat. * $p = 0.04$ compared with placebo



The study was conducted on an outpatient basis, with visits at weeks 2, 4, 8, 12, 16, 20, 24, 32, 42 and 52. The efficacy and safety assessments detailed below were repeated at some or all visits.

Efficacy assessments

Symptomatic assessments. The patients were asked to grade the present severity of the three most troublesome neuropathic symptoms of either pain or paraesthesiae on a 5 point scale: 0 = absent, 1 = mild, 2 = moderate, 3 = severe and 4 = very severe. Symptoms were characterised as pain (eg., burning, deep aching, tenderness) or paraesthesiae (eg., pins and needles, asleep feeling) by the investigator at the time of assessment. These symptoms were assessed separately as most patients complained of both pain and paraesthesiae. Changes in symptom scores were assessed at weeks 4, 8, 16, 24, 32, 42 and 52.

Objective measurements. Changes in nerve function were assessed by nerve conduction velocity measurements. Four motor (peroneal, tibial, median, and ulnar) and two sensory nerves (median and sural) were assessed at baseline and after 8, 24, 42 and 52 weeks of therapy. Surface electrodes were used with skin temperature maintained between 33 ° and 35 °C, and averaging was applied as needed.

In order to account for baseline differences and differences between investigative sites in the range of normal nerve conduction values, the percentage change from baseline was determined and used for all statistical evaluations. In addition, the average percentage change in motor nerve conduction velocity (MCV) for each patient at a given visit was calculated in order to analyse the concordance between objective and subjective changes. An analysis was also performed on the number of motor nerves improved per patient out of a total of the four nerves that were tested.

Clinical response. In order to define a relationship between objective and subjective symptomatic improvements, patients were categorised as follows: responders showed improvement in both motor nerve conduction velocity and neuropathic symptom scores, failures showed deterioration or no change in both neuropathic indices, and all other patients were considered to be partial responders. This analysis was done at weeks 8, 24, 42 and 52 using paraesthetic symptoms and painful symptoms. In addition to exploring the possible relationship between objective and subjective responses, this concordance analysis assesses the relevance of objective changes and can identify improvement or prevention of further deterioration.

Drug administration

Patients were randomised to receive one of five treatments for up to 52 weeks: tolrestat 50, 100 or 200 mg once daily, tolrestat 100 mg twice daily or placebo. Each patient received morning and evening doses taken 30 min before breakfast or dinner. In those patients receiving tolrestat once daily, the active drug was given in the morning. Patient compliance was assessed by counting returned tablets: no significant differences between groups were observed during the trial.

Table 1. The effect of tolrestat 200 mg once daily on motor nerve conduction velocity (metres/second): least squares mean percentage change from baseline \pm SEM (*n*) [baseline m/s]

Motor nerve	Treatment group	Week			
		8	24	42	52
Peroneal	Placebo	-0.25 \pm 1.29 (72) [35.49]	0.80 \pm 1.15 (68) [35.73]	1.18 \pm 1.99 (54) [35.63]	-3.23 \pm 2.32 (45) [36.89]
	Tolrestat	-0.14 \pm 1.14 (77) [35.94]	1.89 \pm 1.15 (66) [36.46]	3.09 \pm 1.77 (55) ^a [36.70]	2.94 \pm 2.29 (45) ^b [37.80]
Ulnar	Placebo	-0.15 \pm 1.24 (89) [47.33]	-0.55 \pm 0.99 (85) [47.16]	3.93 \pm 1.62 (71) ^c [46.87]	1.34 \pm 1.70 (60) [47.48]
	Tolrestat	1.55 \pm 1.17 (92) [47.70]	2.31 \pm 0.96 (84) ^{d, e} [47.70]	3.47 \pm 1.55 (72) ^f [47.23]	2.50 \pm 1.57 (61) [47.07]
Tibial	Placebo	0.81 \pm 1.58 (75) [35.65]	2.38 \pm 1.55 (71) [35.61]	3.54 \pm 2.14 (59) ^g [35.48]	-0.53 \pm 2.25 (52) [35.92]
	Tolrestat	2.34 \pm 1.38 (80) ^h [35.44]	3.47 \pm 1.50 (71) ⁱ [35.88]	4.82 \pm 2.01 (63) ^j [35.73]	5.43 \pm 2.07 (53) ^{k, l} [36.08]
Median	Placebo	0.96 \pm 0.93 (88) [47.05]	1.28 \pm 0.82 (84) [47.02]	1.73 \pm 1.19 (69) [46.60]	2.67 \pm 1.72 (60) [47.12]
	Tolrestat	1.08 \pm 0.87 (92) [47.56]	2.44 \pm 0.79 (84) ^m [47.51]	1.70 \pm 1.13 (73) [47.49]	0.45 \pm 1.59 (61) [47.56]

^a $p = 0.041$ compared with baseline; ^b $p = 0.030$ compared with placebo; ^c $p = 0.008$ compared with baseline; ^d $p = 0.019$ compared with placebo; ^e $p = 0.008$ compared with baseline; ^f $p = 0.013$ compared with baseline; ^g $p = 0.050$ compared with baseline; ^h $p = 0.046$ compared with baseline; ⁱ $p = 0.011$ compared with baseline; ^j $p = 0.009$ compared with baseline; ^k $p = 0.026$ compared with placebo; ^l $p = 0.005$ compared with baseline; ^m $p = 0.001$ compared with baseline

Long-term clinical response. Patients with a long-term response were required to show a clinical response at the week 24 visit that continued at the week 42 and 52 visits. Similar criteria were used to define long-term failures and partial responders.

Drug safety

Safety parameters were assessed throughout the study and all patients were included in these analyses. In addition to subjective complaints and clinical examinations, the following laboratory investigations were performed at every visit: Hb, full blood count, fasting blood glucose, HbA_{1c}, urea and electrolytes, liver function tests and urinalysis. Creatinine clearance was measured at baseline and thereafter at weeks 8, 16, 24, 32, 42 and 52.

Statistical analysis

The parametric variables (such as nerve conduction velocity and symptom score) were subjected to a two-way analysis of variance. This model, which evaluates treatment, investigator, and treatment by investigator effects, was employed to test for significant changes from baseline within treatment groups and for significant differences between each tolrestat group and the placebo group in change from baseline. The tests involving efficacy variables were one-tailed. An investigator was required to contribute a minimum of one eligible patient to each treatment group at each visit in order to be included in the efficacy analysis for that visit. Changes from baseline in the parametric variables are expressed as least squares means. The least squares mean is generated by the analysis of variance model, and it adjusts for the effects of unequal sample sizes among the investigators.

Categorical analyses were performed on the clinical response using the Cochran-Mantel-Haenszel test and on the frequency of abnormal laboratory values and patient complaints using the Chi-Square test.

Results

Of the 550 patients who entered the trial, 80% were male and 45% were judged to have Type 1 (insulin-dependent) diabetes by clinical assessment. Mean age was 55 years, duration of diabetes 14.8 years and of symptomatic neuropathy 6.9 years. No significant differences were observed between any of these parameters or in glycaemic control at entry or after randomisation, for any of the therapeutic groups.

Significant improvements over both baseline values and placebo-treated patients were only seen in those treated with tolrestat 200 mg once daily, and subsequent results refer only to this treatment group ($n = 112$) and placebo ($n = 107$).

Symptomatic response

The effects of tolrestat 200 mg once daily on paraesthetic and painful symptoms are shown in Figures 1 a and b, respectively. No benefit of the drug over placebo was seen for painful symptoms. In contrast, no further improvement in paraesthetic symptoms was seen with the placebo after 8 weeks, and a significant improvement in paraesthetic symptoms over placebo was seen at the end of the trial in tolrestat-treated patients ($p = 0.04$).

Objective assessments

The effects of tolrestat 200 mg once daily on MCVs are summarised in Table 1. Significant improvements over baseline were seen in all nerves at one or more assessment visits, and improvement over placebo was seen in both

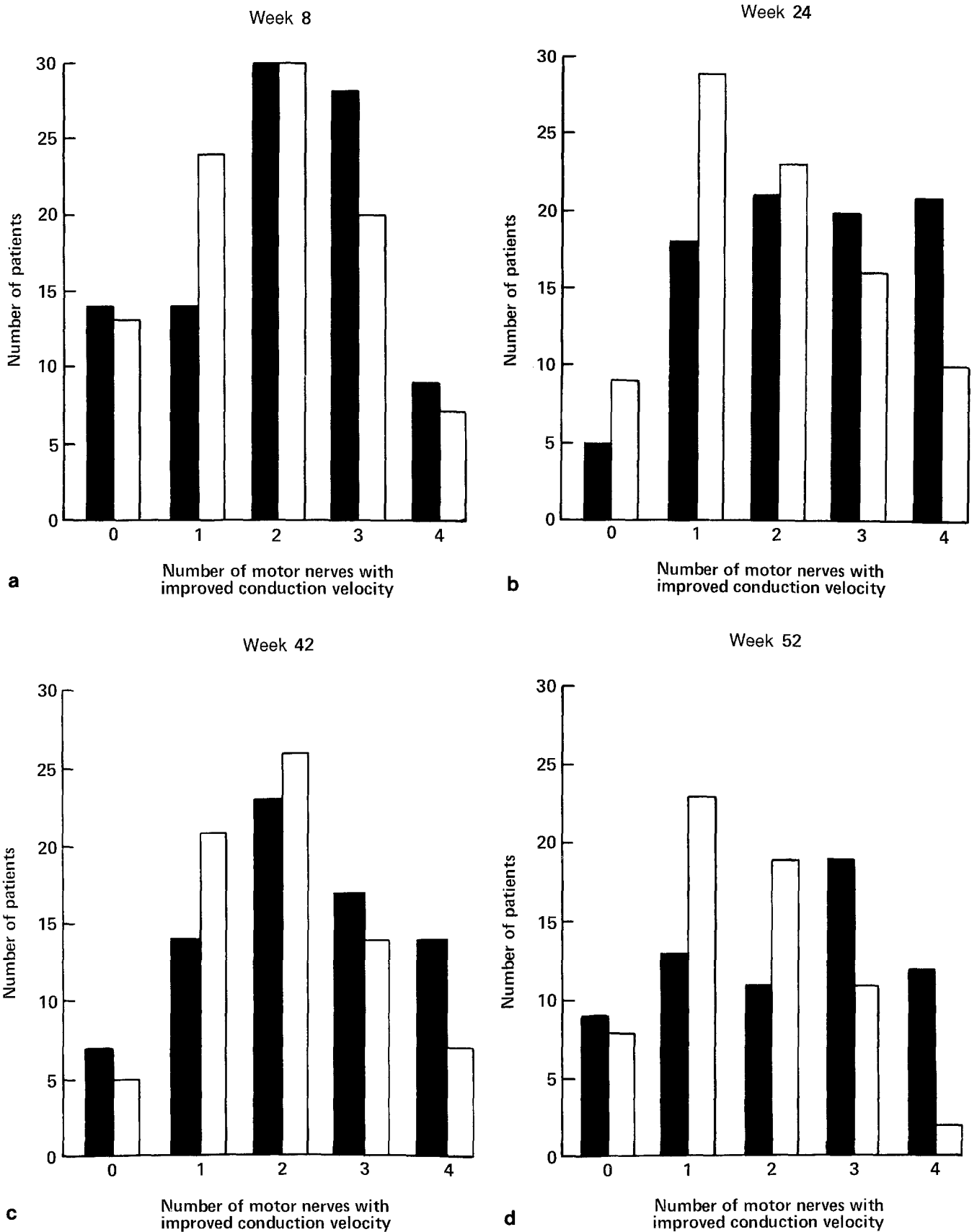


Fig. 2a-d. The effect of tolrestat 200 mg once daily on the frequency distribution of motor nerves with improved conduction velocity compared with baseline (four nerves tested) at (a) week 8, (b) week 24, (c) week 42, and (d) week 52. Improvement defined as greater than 0 m/s. ■ = tolrestat; □ = placebo. Total number of pa-

tients in tolrestat group at week 8, 24, 42, and 52 was 95, 85, 75, and 64, respectively. Total number in placebo group was 94, 87, 73, and 63, respectively. Significance testing for tolrestat compared with placebo: week 8, $p = 0.11$; week 24, $p = 0.002$; week 42, $p = 0.08$; week 52, $p = 0.003$

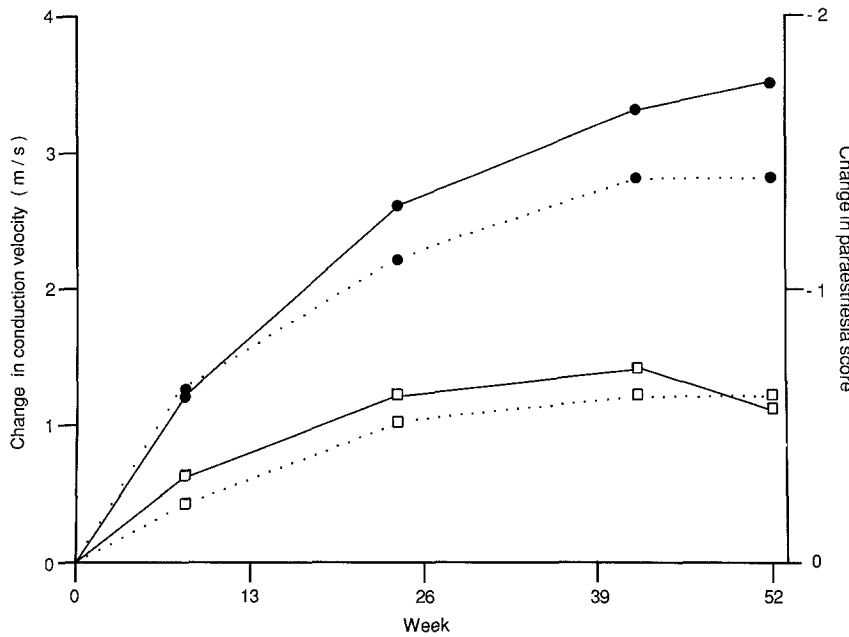


Fig. 3. The effect of tolrestat 200 mg once daily on the mean motor nerve conduction velocity and paraesthesia score. Long-term responders: ●-● = motor nerve conduction velocity; ●-● = paraesthesia score. All patients: □-□ = motor nerve conduction velocity; □-□ = paraesthesia score

lower limb nerves at 52 weeks, and additionally in the ulnar nerve at 24 weeks. Highly significant changes in favour of tolrestat were seen when the number of motor nerves showing improvement was analysed and compared with placebo ($p = 0.002$ at 24 weeks; $p = 0.003$ at 52 weeks; Fig. 2). No significant changes were observed in either of the sensory nerves tested.

Clinical response

The effect of tolrestat on the occurrence of concordant improvement in MCV and symptomatic severity was analysed, using paraesthesiae as the symptomatic index. Tolrestat treatment was associated with a significantly more favourable outcome at weeks 24, 42 and 52 ($p = 0.012, 0.103$ and 0.018 , respectively; Table 2). No benefit was demonstrated when pain was used as the symptomatic index.

Long-term clinical response

Since improvement in paraesthetic neuropathy may be a gradual response that becomes established after 24 weeks of treatment, a satisfactory long-term clinical response

was defined as a continued improvement of both paraesthetic symptoms and MCV during the second 6 months of treatment, that is, at weeks 24, 42 and 52. Treatment failures showed no improvement in symptoms or MCV over the same time period, and all other subjects were considered long-term partial responders. Analysis of the frequency of patients in each category revealed a highly significant difference in favour of tolrestat compared with placebo (long-term clinical response 28% tolrestat vs 5% placebo; treatment failures 6% vs 19%; $p = 0.001$).

The time course of the change in average nerve conduction velocity and paraesthesiae in all patients and in the subset of long-term clinical responders is shown in Figure 3.

Safety

Dizziness was the only drug-related patient complaint which occurred with a greater frequency in patients receiving tolrestat than in those receiving the placebo. In the case of the tolrestat 200 mg once daily group, there was an 11% incidence compared with 3% on placebo ($p < 0.05$).

Table 2. The effect of tolrestat 200 mg once daily on the occurrence of concordant improvements in functional (conduction velocity) and symptomatic (paresthesia severity) indices of nerve function

Outcome	Treatment	Week			
		8 ^a	24 ^b	42 ^c	52 ^d
Response, n, (%)	Placebo	7 (9.6)	15 (21.7)	13 (23.2)	13 (26.5)
	Tolrestat	15 (19.2)	24 (34.3)	24 (39.3)	21 (40.4)
Partial response, n, (%)	Placebo	49 (67.1)	34 (49.3)	30 (53.6)	20 (40.8)
	Tolrestat	39 (50.0)	35 (50.0)	29 (47.5)	24 (46.2)
Failure, n, (%)	Placebo	17 (23.3)	20 (29.0)	13 (23.2)	16 (32.7)
	Tolrestat	24 (30.8)	11 (15.7)	8 (13.1)	7 (13.5)

^a $p = 0.38$; ^b $p = 0.012$; ^c $p = 0.013$; ^d $p = 0.018$.

p values refer to significance testing in the mean scores of tolrestat compared with placebo

An evaluation of routine laboratory values was carried out. Compared with placebo, occasional increases in the least squares mean values of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) were seen in patients taking tolrestat 100 mg once daily, 200 mg once daily, and 100 mg twice daily. At no time did the least squares mean increase in ALT or AST exceed 22 U/L. The number of dropouts from the study because of elevated hepatic enzymes (AST and ALT) was small: 2 patients on placebo, 2 on tolrestat 50 mg once daily, 4 on 100 mg once daily, 4 on 200 mg once daily, and 5 on 100 mg twice daily. In no instance was there evidence of severe hepatic dysfunction, and the changes in hepatic enzymes were reversible within 8–16 weeks of drug discontinuation. No changes in any other biochemical parameter were observed in any treatment group throughout the trial.

There were no significant changes in heart rate in any treatment group during the trial. However, there were minor but significant decreases ($p < 0.05$) from baseline of 3.8 to 6.6 mmHg in systolic blood pressure and 2.2 to 3.4 mmHg in diastolic blood pressure in the tolrestat treatment groups. There were no changes from baseline in systolic or diastolic blood pressure in the placebo group.

Discussion

There is currently no therapy for chronic sensorimotor diabetic neuropathy that modifies biochemical abnormalities in peripheral nerves, with the possible exception of strict glycaemic control, which is notoriously difficult to maintain over a prolonged period of time [16]. Thus, the only effective treatment is for symptomatic relief, with imipramine having been demonstrated to be efficacious in double-blind trials [17]. However, such therapies are not known to influence the natural history of the condition, which is of gradual progression over years with persistence of symptoms and some reduction in MCVs [18, 19]. It is against this background that any trials of new therapies must be considered and compared.

In the present study, whereas no positive effects were seen in three treated groups, minor though consistent improvement in peripheral nerve function has been demonstrated following one year of treatment with tolrestat 200 mg once daily in patients with long-standing sensorimotor diabetic neuropathy. Similar results have been reported using other aldose-reductase inhibitors for at least 6 months [13], as it is likely that any benefit will be gradual in onset, which might explain the disappointing results of some short-term trials [12]. This is further supported by data from the European multicentre trial of tolrestat [20], which has recently demonstrated results very similar to those in the present trial.

In assessing any therapy for chronic sensorimotor diabetic neuropathy it is important to recognize that structural damage has occurred, and that measurable recovery might take weeks or months to be detected. Sima and co-workers recently confirmed that improvement of the neuropathological lesions can occur following aldose-reductase inhibitor therapy for one year in patients with established neuropathy [21]. The present data are also con-

sistent with the data on glycaemic control [22–25], which demonstrated that several weeks or months were required for significant improvements in nerve function to be seen. Moreover, the lack of significant changes in sensory nerve function is also similar to that seen in trials of strict glycaemic control, where little or no changes were observed [22–25]. In general, change in conduction is technically more difficult to detect in sensory nerves [26].

An important question raised by the present study and the literature is the magnitude of the change in motor nerve conduction velocity that can be expected in patients with long-standing neuropathy. The positive studies of aldose-reductase inhibitors and strict glycaemic control have generally shown MCV increases of 1–4 m/s [10, 13, 22–25]. This is also consistent with the tolrestat results in this study of approximately 1–2 m/s. Both the modest response and its variability are to be expected in view of the severity of the disease, in that, while some patients may improve, others may not worsen and some may not respond at all. These problems of objective assessment are further compounded when evaluating symptoms. Although symptoms vary from day to day, may be difficult to recall or describe and are subject to a marked placebo response, their assessment is essential in clinical trials [16]. It is also possible that symptoms improve because of a progression rather than an improvement of the underlying pathology. It was in order to exclude this possibility that a concordance analysis was performed, which takes into account individual patient outcome and identifies patients with equivocal responses who tend to obscure overall group changes. The results of this analysis demonstrated the superior effects of tolrestat throughout the second half of the study, using paraesthesiae as the symptomatic index. The long-term responders demonstrated the greatest objective improvement, but no baseline clinical characteristic such as duration of diabetes or neuropathy could be identified that accurately predicted which patients might best respond to tolrestat therapy. The fact that a similar outcome was not observed using pain as the symptomatic index may reflect the recognized difficulties in the assessment of pain in a placebo controlled trial [27].

It is difficult to explain why significant changes were seen in patients treated with tolrestat 200 mg once daily, whereas 100 mg twice daily failed to provide any response. When the same dose is given once daily, higher initial levels are seen which should relate to drug effect [14]. As blood glucose flux is greater during the day, the fact that drug levels are greater during these hours on the 200 mg once daily regimen might explain the observed difference in the results for these different dosages. A further inconsistency in the results from this trial is the fact that different nerves show significant improvement during the trial. However, similar findings are seen in most reports of the effect of strict glycaemic control on peripheral nerve function [22–25], and these are probably explained by the chronicity and natural history of the condition together with the recognised problems with repeated electrophysiologic measurements in multicentre studies.

The only significant side-effect during the study was dizziness which was experienced by 11% of patients receiving tolrestat 200 mg once daily; however, this was not

severe as no patient was dropped from the studies because of this complaint. There was no increased incidence of skin rash or a hypersensitivity reaction which has been observed with another aldose-reductase inhibitor [11, 13]. The only other problem encountered which is of clinical relevance in tolrestat treated patients has been an elevation of hepatic transaminases, which appeared to be drug related in approximately 2% of patients and which was reversible upon discontinuation of the drug [15].

In conclusion, the results of the present study suggest that a proportion of patients with established sensorimotor neuropathy benefited from tolrestat therapy, with approximately 30% demonstrating a clinical response. It is possible that aldose-reductase inhibition may become an important addition to glycaemic control in the treatment of neuropathy. However, it is unlikely that trials similar to this in patients with well-established neuropathy will provide useful additional information. There is now a need for long-term trials, either of prevention in diabetic patients without objective evidence of neuropathy, or of intervention in very early neuropathy.

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