Pentoxifylline in ALS

A double-blind, randomized, multicenter, placebo-controlled trial

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Abstract—*Objective:* To assess the efficacy and safety of pentoxifylline, a US Food and Drug Administration–approved drug, in patients with ALS treated with riluzole. *Methods:* The authors conducted a double-blind, randomized, placebo-controlled, multicenter trial. Four hundred patients with probable or definite ALS and vital capacity less than 100% were randomly assigned to treatment with placebo or 1.2 g pentoxifylline daily. The primary outcome was death. Secondary outcomes were rates of deterioration of ALS Functional Rating Scale–Respiratory and muscle strength. The primary intention-to-treat analysis was the survival comparison of drug vs placebo, assessed before (log-rank test) and after adjustment (Cox model) for predefined prognostic factors. *Results:* At the end of the study, after 547 days of follow-up, 103 patients (51.7%) in the pentoxifylline group and 120 (59.7%) in the placebo group were alive (unadjusted risk 1.28, $p = 0.107$; adjusted risk 1.43, $p = 0.02$). In contrast, analysis of secondary outcome functional variables did not show the same negative effect of the drug. The most common adverse reactions were nausea, dysphagia, and flushing, all reversible after stopping the drug. *Conclusions:* Pentoxifylline is not beneficial in ALS and should be avoided in patients treated with riluzole. The discrepancy between survival and measures of functional changes urges caution in equating these end points in phase III trials, and suggests that both survival and function should be used in phase III trials.

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Survival, but not function, is modestly prolonged by riluzole in ALS. No other therapies have proven to be effective.[1] Numerous mechanisms associated with motor neuron degeneration have been described in the mutated SOD1 transgenic mice,[2] leading proposals for new therapeutic strategies. A technique to detect alternative splicing suggested that an overexpression of phosphodiesterase (PDE4B) could be implicated in the process of motor neuron degeneration.[3] This enzyme hydrolyzes the cyclic nucleic acid cyclic adenosine monophosphate, which plays a crucial role in various fundamental cellular processes,[4] including apoptosis.[5] Based on these findings, we hypothesized that pentoxifylline, a PDE4B inhibitor, may be effective in patients with ALS. In addition to its effect as a PDE4B inhibitor, pentoxifylline acts on respiratory neurons circuit through protein kinase A.[6] This kinase modulates the α-amino-3-hydroxy-5-methyl-isoxazole-4-propionate-induced inspiratory drive currents in functionally active hypoglossal motoneurons[7] as well as in the pre-Bötzinger complex inspiratory neurons, which regulate respiratory rhythm in the rat.[8] Pentoxifylline also modifies inflammation implicated in motor neuron degeneration by reducing tumor necrosis factor (TNF) protein levels by inhibiting TNF messenger RNA transcription.[9]

Pentoxifylline is approved by the US Food and Drug Administration and by the French regulatory agency. Its main indication is an intermittent claudication. It is reported as a safe drug with relatively few unwanted or adverse effects.

Based on these data, we sought to investigate the efficacy and safety of pentoxifylline in patients with ALS, and we designed an exploratory, double-blind, placebo-controlled trial in Europe.

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Methods. The trial was conducted according to European guidelines for Good Clinical Practice.[10] For more details about the methods, refer to appendix E-1 (on the *Neurology* Web site at www.neurology.org).

*See the Appendix for a list of Group members.

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Table 1 *Patient distribution from randomization to end of treatment and at day 547*

	Pentoxifylline, n = 199	Placebo, n = 201	Total, n = 400
ITT population	199 (100.0)	201 (100.0)	400 (100.0)
Bulbar	45 (22.6)	44 (21.9)	89 (22.3)
Spinal	154 (77.4)	157 (78.1)	311 (77.7)
Status at the end of treatment period			
Completed treatment	92 (46.2)	102 (50.7)	194 (48.5)
Death	77 (38.7)	73 (36.3)	150 (37.5)
Discontinuation			
Any	30 (15)	25 (12.4)	55 (13.9)
Patient's decision	13 (6.5)	23 (11.4)	36 (9.0)
Adverse event	15 (7.5)	2 (1.0)	17 (4.3)
Investigator's decision	1 (0.5)	0 (0.0)	1 (0.3)
Other	1 (0.5)	0 (0.0)	1 (0.3)
Final status at day 547			
Dead	96 (48.2)	81 (40.3)	177 (44.3)
Alive	103 (51.8)	120 (59.7)	223 (55.8)

Data are number of patients (%).

ITT = intention-to-treat.

Patients and treatments. Twelve centers in four countries participated in the study. Eligible patients aged 18 to 80 years had El Escorial definite or probable ALS[11] between 6 and 47 months' duration, were stabilized on 50 mg riluzole twice a day, and had a forced vital capacity of 100% or less. Eligible patients gave written informed consent to participate in the study, and the study was approved by the appropriate ethics committees and institutional review boards.

Randomization was stratified by center and according to the site of onset, bulbar or spinal, as previously defined.[1] Patients were given 1.2 g pentoxifylline daily or placebo during 18 months.

Outcome measures. The prospectively defined primary efficacy outcome was survival during the double-blind study period, regardless of whether the patient was treated with ventilatory support (invasive or noninvasive ventilation). The secondary efficacy outcomes were function assessed every month by ALS Functional Rating Scale–Respiratory (FRS-R)[12] and manual muscle testing (MMT)[1] assessed every 3 months. At month 9, blood levels of pentoxifylline were assayed in 268 patients.

Statistical analysis. The primary analysis included all randomized patients, regardless of whether study medication was administered and regardless of the eligibility status (intention-to-treat [ITT] population). This analysis compared the survival distribution of the pentoxifylline group with that of the placebo group, using a one-sided log-rank test, stratified on site of onset and country. A one-sided test was retained because before unblinding, we had no reasons to suspect a worsening effect of pentoxifylline, which was considered to be safe and well tolerated. A Cox proportional hazards model[13] analysis of survival was performed to adjust for possible imbalance in predefined prognostic factors.

For secondary end points, slopes of deterioration of the pentoxifylline group were compared with the placebo group, using analysis of variance (ANOVA) for repeated measures and time to event analyses.

Results. Between October 3, 2002, and February 12, 2003, 400 patients were enrolled: 89 (22.3%) in the bulbar stratum and 311 (77.7%) in the limb stratum. The final trial was August 6, 2004, and results were available September 17, 2004. For more details and additional analyses, refer to appendix E-2 and table E-1 on the *Neurology* Web site at www.neurology.org

Protocol deviations were observed in four patients (1%). These patients were included in the ITT analyses. No patient was lost to follow-up (figure E-1). The distribution of subjects between groups is shown in table 1. The distribu-

Table 2 *Characteristics of patients at baseline*

	Pentoxifylline, n = 199	Placebo, n = 201	Total, n = 400
Age, y	57.1 (11.7)	56.7 (12.1)	56.9 (11.9)
Men/Women	116/83	139/62	255/145
Disease duration, mo	24.3 (11.8)	25 (11.9)	24.6 (11.8)
BMI, kg/m^2	24.3 (4.3)	24.1 (3.8)	24.2 (4.1)
ALS FRS-R	38.9 (7.1)	38.9 (6.8)	38.9 (6.9)
Manual testing	120.7 (22.3)	119.1 (23.2)	119.9 (22.8)
Vital capacity, %	71.4 (19.6)	70.5 (22.1)	70.9 (20.9)

Data are mean (SD), number of patients (men/women). Sex ratio was different across groups ($p = 0.029$).

BMI = body mass index, FRS-R = Functional Rating Scale–Respiratory.

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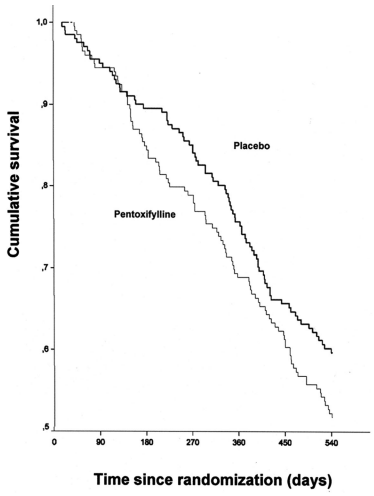

At risk						
Pentoxifylline	187	169	157	137	122	103
Placebo	191	179	170	151	132	120
Death/Censored						
Pentoxifylline	12	30	42	62	77	96
Placebo	10	22	31	50	69	81

Figure 1. Kaplan–Meier plots of survival by treatment group.

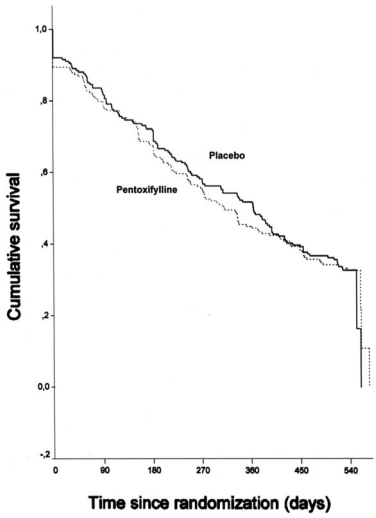

Figure 2. Kaplan–Meier plots of time to reach a predetermined threshold for ALS FRS-R Death is considered as an event.

tion of patients according to treatment was well balanced for the whole population and within strata, except for a higher proportion of women in the pentoxifylline group ($p = 0.029$; table 2).

At month 12, the interim analysis did not reach predefined significance for stopping the trial. At the end of the treatment period (day 547), 223 patients (55.8%) were alive, 103 (51.7%) in the pentoxifylline group and 120 (59.7%) in the placebo group (figure 1). Without adjustment for prognostic factors, the p value of the overall drug effect was 0.053 (one sided). The relative risk associated with the treatment effect was 1.28 (95% CI 0.94 to 1.71), corresponding to a 28% increased risk of death in the pentoxifylline group. Mean survival time was 423.43 days in the treated group (95% CI 400.60 to 446.26) and 446.38 days in the placebo group (95% CI 425.28 to 467.48).

After adjustment, the p value reached 0.02, with a relative risk of 1.43 (95% CI 1.05 to 1.96) in the treated group as compared with the placebo group. The stepwise forward Cox procedure selected six variables as independent prognostic factors (table 3). Sex was excluded from the model using univariate ($p = 0.2$) and multivariate ($p = 0.59$) survival analyses.

Analyses of the rate of deterioration in the ALS FRS-R or in MMT did not detect differences between groups using ANOVA for repeated measures (ALS FRS-R $p = 0.35$; manual testing $p = 0.14$) or time to event analyses (figures 2 and 3).

Discussion. In this study, pentoxifylline had a negative effect on survival, but with no appreciable effect on functional measures. After adjustment for prognostic factors, there was a 43% increased risk of death in the pentoxifylline group compared with the placebo group. Stopping rules for the interim analysis performed at 12 months were not reached, explaining that the trial was conducted until the end of the predefined period.

Because there was no imbalance among the two treatment groups for known prognostic variables affecting survival in ALS,[1,14-19] the possibility of an interaction with an unknown prognostic factor in the pentoxifylline group remains low. It is unlikely that the sex difference between groups explains the negative effect of pentoxifylline on survival. In the popu-

Table 3 *Survival analysis for prognostic factors (Cox model)*

Variable (dichotomized)	Relative risk (95% CI)*	p Value
Treatment	1.43 (1.05–1.96)	0.02
Age (0, ≤60 y; 1, >60 y)	0.44 (0.32–0.60)	0.000
Disease duration (0, ≤23 mo; 1, >23 mo)	2.08 (1.52–2.86)	0.000
BMI (0, >23 kg/m^2; 1, ≤23 kg/m^2)	0.62 (0.45–0.84)	0.003
ALS FRS-R (0, >40; 1, ≤40)	0.46 (0.31–0.69)	0.000
Manual testing (0, >123; 1, ≤123)	0.62 (0.43–0.90)	0.012
Vital capacity (0, ≥60%; 1, <60%)	0.54 (0.39–0.75)	0.000

* Risk of death (with 95% CI) in subgroup 0 as compared with subgroup 1 according to prognostic variables.

BMI = body mass index, FRS-R = Functional Rating Scale–Respiratory.

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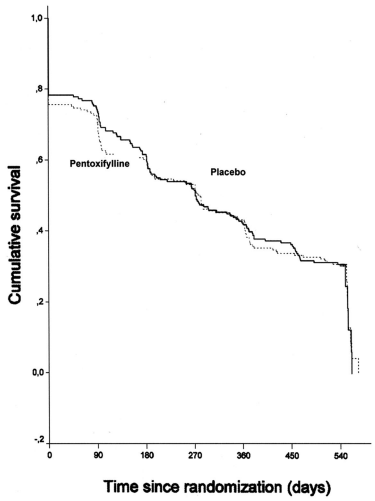

Figure 3. Kaplan–Meier plots of time to reach a predetermined threshold for manual muscle testing (MMT). Death is considered as an event.

lation studied, this variable was not retained in the Cox model, and it was not identified as a risk factor in most previous studies.[1,14-17,19] One study mentions sex as a prognostic factor in a restricted group of 198 patients.[18] One group reported two studies (published in the same year), one with an interaction[14] and the other without.[15] This variability in the results has been discussed previously[17] and is probably explained by an interaction between sex and other confounding prognostic factors.

In our study, the negative effect of the drug was observed selectively on survival and not on the functional end points. It is known that in ALS, function is closely related to survival.[19,20] This relationship has led to the assumption that functional measures can act as "surrogate markers" for survival.[21] Our data suggest that this notion may not be correct. Studies of the natural history of the disease, as well as animal models[23], reached the same conclusion.[22] When considering the large trials during the past decade, there are important reasons for suspecting that drug effects, either positive or negative, are different for survival and function. In the riluzole trial, the drug had a positive effect on survival, but no effect on function (muscle strength).[1] In the xaliproden trial (xaliproden alone without add-on therapy with riluzole), the situation was reversed, with a positive effect on function (vital capacity) but no effect on survival.[24] In the ciliary neurotrophic factor trial,[25] there was a negative effect on survival but no effect on function (muscle strength). The possibility of a negative effect on function (muscle strength, vital capacity) with no effect on survival was reported in a combined analysis of the two gabapentin trials[26] and in the topiramate trial.[27] There is no clear explanation of the discrepancy between survival and function. Possible explanations include statistical bias, problems in the study design, or a difference in drug activity. A statistical bias or problems in study design are unlikely. As previously discussed, an independence of the two measures is observed both in preclinical animal studies and in human trials. Close analysis shows that the discrepancy between survival and functional measures is present in nearly all trials conducted since the riluzole trial, while the study and statistical designs of these studies were quite different. The methods to analyze the functional end points (composite functional scales, manual testing, or quantitative muscular testing) differ largely among these studies. All studies had the statistical power to detect a difference in functional or survival end points. Currently, we can only hypothesize that neuroprotective agents may act differently on survival and function for reasons that remain obscure.

We have also no clear explanation for the negative effect of pentoxifylline on survival. However, a similar negative effect was reported with xaliproden in another study[24] using riluzole as an add-on therapy. In the latter study, there was a dose-dependent trend for a negative effect in the active treatment group on both survival and functional end points. In both studies (xaliproden with riluzole and pentoxifylline), plasma concentrations of the active drug during the trials were in the reference (expected) range. The pentoxifylline trial may indicate that there is a negative interaction between this drug and riluzole for survival. However, we cannot exclude a specific negative effect of pentoxifylline on survival. Such results suggest that physicians should avoid using riluzole and pentoxifylline together when treating patients with ALS.

Appendix

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