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Is edaravone harmful? (A placebo is not a control)

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Abstract

Edaravone is delivered by long-term daily intravenous infusions, yet the risk of infusion was not considered in the design or analysis of studies examining the efficacy of edaravone in ALS. A reappraisal of the pivotal edaravone study (Study 19) on which claims of efficacy are based suggests that this risk cannot be dismissed, that the efficacy of edaravone may be over-estimated, and that some differences between edaravone and placebo may not implicate the ALS disease process. When trial conditions may be harmful to both arms of a placebo-controlled trial, not only is it necessary that treatment prove superior to placebo, but also that treatment is better than no intervention. In Study 19, edaravone performed better than placebo, but both placebo and edaravone likely did worse than no intervention, an interpretation more in keeping with previous trial experience of drugs with similar mechanisms of action, and with previous trial experience with edaravone. Edaravone, as presently delivered, may be both ineffective and harmful.

Keywords: *Edaravone*; *ALS*; *clinical trial design*

Mitochondrial dysfunction and oxidative stress play a role in ALS pathogenesis, and at least nine compounds supporting mitochondrial function and/or acting as anti-oxidants have been studied in controlled human trials. Unfortunately, in spite of a sound rationale and supportive pre-clinical studies, all have been negative (1). Edaravone, a free radical scavenger that should share similar actions, was advanced to further investigation after an open-label phase 2 study showed an improvement in the rate of decline in the revised ALS Functional Rating Scale (ALSFRS) (2). A confirmatory phase 3 trial (Study 16) had negative results (2), but a *post hoc* analysis of Study 16 trial participants suggested that edaravone might be helpful in a small subset of patients. Consequently a second phase 3 trial (Study 19) was undertaken using highly restrictive inclusion criteria, and this showed that the ALSFRS of patients treated with edaravone declined about 1/3 slower than placebo over 6 months (3), a remarkable and surprising result. On this basis, edaravone has been approved in ALS in the USA, and is submitted for regulatory approval in Canada.

There are caveats in the interpretation of the Study 19 trial. As the investigators acknowledge, the main outcome measure was a self-reported functional scale without survival data, and factors that might be expected to positively affect scale measures (such as strength, FVC) were unchanged. The trial was small and of short duration, and there were imbalances at randomization favoring edaravone (e.g. disease severity was worse in the placebo group). As such, it is possible but not definite that edaravone is superior to placebo even in this highly selected population, and there have been calls for additional trials using larger numbers for longer duration with confirmatory endpoints (4).

However, a far greater question and one that has received little attention is whether edaravone is better than no treatment at all. Specifically, is the decline in the placebo group consistent with the natural rate of decline in these patients?

In most trials the ALSFRS of placebo-treated patients declines in an approximately linear fashion with time. In this trial, however, there was a sharp downward inflection after randomization. The average rate of decline in the placebo group during the 12-week lead-in phase was 0.61 units/month, but after randomization the placebo group declined 2.2 times more rapidly at 1.35 units/month, a relative worsening of 121%. The edaravone group worsened, from 0.61 units/month in

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the lead-in phase to 0.91 units/month after randomization, a worsening of 49%. Thus, after randomization both groups showed a worsened decline, less marked in the edaravone group. At face value, worsening decline after treatment is not compatible with treatment efficacy and raises concerns of safety.

However, a worsened decline could have at least three explanations, not all troublesome.

First, perhaps the natural rate of change in the ALSFRS in the highly selected population of Study 19 is not linear but biphasic or convex downwards, and the worsening in rate of decline at about 3 months reflects the natural progression, which by happenstance coincides with the time of randomization. Since patients were accepted into the trial with a disease duration of up to 2 years, a synchronous decline at randomization is unlikely. Using the Pro-Act database (5) and attempting to replicate the trial entry criteria as much as possible, decline in control populations appears roughly linear over nine months (i.e. matching the 3 months lead-in and 6 months treatment in the Study 19 trial) (Figure 1). However, the numbers are small and there are several difficulties in modeling.[1] When examined using all patients in the Pro-Act database, Proudfoot et al. (6) concluded that the individual rate of decline was linear, but with time there was an amelioration in the aggregate rate of decline due to drop-out of sicker patients (i.e. the opposite of Study 19). Using the ALS database at Pitié-Salpêtrière, Gordon et al. (7) conclude that the ALSFRS declines in a curvilinear fashion, but again, with an amelioration over time in the rate of decline. Thakore (8) estimated the "pre-slope" of patients in the Pro-Act database by assuming an ALSFRS of 48 at the time of first symptom, and found that symptom onset was better predicted by including a quadratic time term. In this model, the decline in the ALSFRS could be concave or convex depending on the magnitude of the pre-slope, and assuming that the edaravone lead-in phase might equate to the pre-slope, the modeled progression would bracket concave and convex profiles, with the average slightly convex. Two studies (9,10) have incorporated lead-in phases in their design and both show a worsening of slope in the placebo groups after randomization. However, the deviation from linearity is small (declines of 22% for TCH346 and 28% for minocycline) and 4–5 times less than the decline seen in Study 19. Thus, a worsened decline of the magnitude seen in the edaravone study after randomization should not be expected as natural history, based on published data and available modeling.

Second, perhaps the decline is indeed linear or nearly so but the worsening in slope after randomization is a statistical aberration and falls within the confidence limits extrapolated from the linear regression of the ALSFRS over the lead-in period. Confidence limits cannot be calculated from aggregate data, but the standard errors of the mean calculated from the reported standard deviations during the lead-in are very small (0.27 ALSFRS units), the same patients continue from the lead-in to the randomized period, and the average slopes of both edaravone and control patients worsen substantially after randomization. As such, while the play of chance might explain a decline in slope for any one individual, it would be very unlikely to do so in the aggregate. A better estimate of this likelihood could be derived from the trial data using individual slopes and these were not reported. However, further answers can be found in the FDA review of edaravone (11). Figure 2 shows the individual declines in the ALSFRS after randomization, and the results are concerning. About 60% of patients continued to decline within the selection parameters established in the lead-in phase of the trial (−1 to −4 ALSFRS units per 12 weeks), but a significant minority of patients experienced a much more rapid decline -indeed some approaching 1 unit per week. As such, the prima facie case is that there is a worsening in slope in both groups after randomization that is not spurious, and that some patients in both placebo and treatment arms experience an accelerated decline.

We are then left with a third possibility – that a factor common to both groups has caused a worsening in some or all patients coincident with randomization, greater in the placebo group. In this case, one would argue that edaravone is possibly effective, but not sufficiently effective to overcome any deleterious experimental factor(s) common to both placebo and treatment arms.

One does not have to look too hard to find such a factor. All patients in the Study 19 trial received daily intravenous infusions of edaravone or placebo, two weeks on and two weeks off, for 6 months following randomization, and thereafter on

[1]Interrogating the Pro-Act database for a control group matched to the Study 19 placebo group is not straightforward. There are inclusion criteria in the edaravone trial that cannot be matched, either because they do not exist (Japan ALS severity classification) or because they are not included (age). Moreover, the constituent trials in Pro-Act are not identified, and the database includes patients in the ceftriaxone trial, which required central venous access. With these caveats, 9640 patients could be identified as being treated with either drug or placebo, and of these 2028 had ALSFRS-R values (and 2647 had ALSFRS). Of the 2028, 627 had an FVC of 80% or more at randomization, and of these 145 had known symptom onset of 2 years or less, and a score of 2 or more in each subscale of the ALSFRS. Of these, very few had ALSFRS-R scores measured at 84 days, and using linear interpolation over 100 days to estimate slope, only 49 had slopes corresponding to a drop of −1 to −4 units over 12 weeks. The change in ALSFRS-R for these patients over 36 weeks is shown in Figure 1, with the regression line weighted according to the numbers contributing to each data point. (The median of individual slopes over the same period is −0.02462, very close to the slope of the regression line).

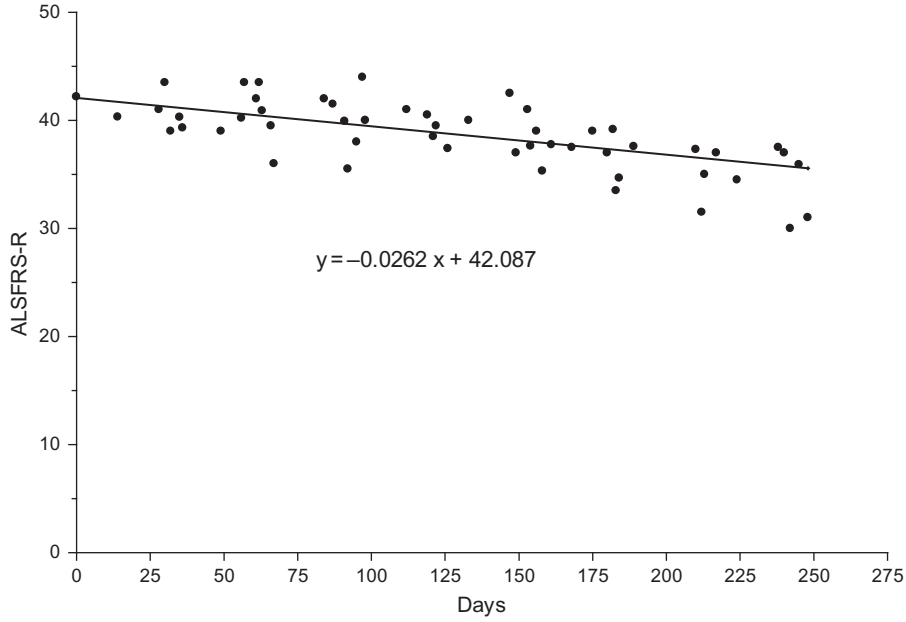

Figure 1. The change in the ALSFRS over 9 months in a subset of patients from the Pro-Act database matched as much as possible to the entry criteria of the Study 19 edaravone trial.

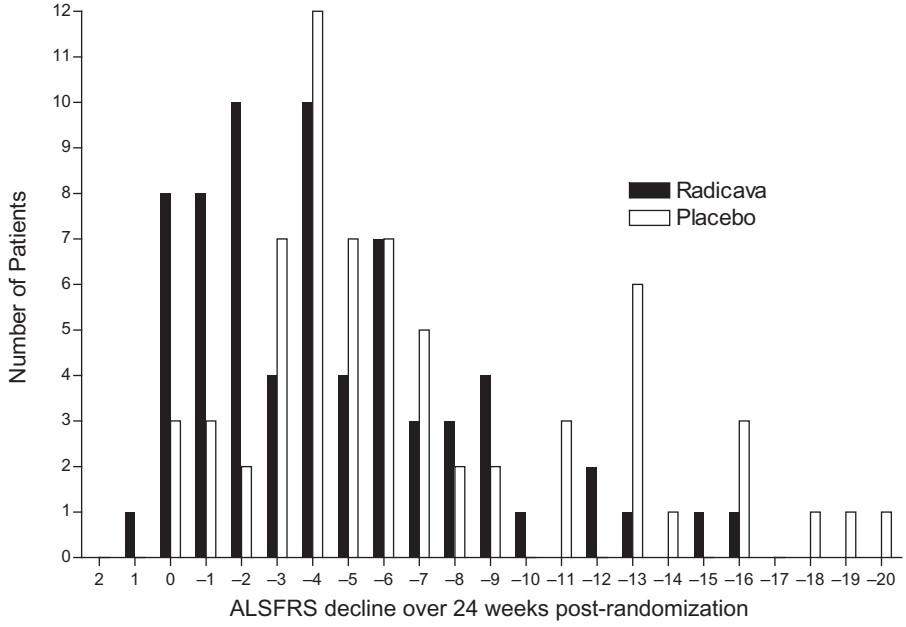

Figure 2. The change in ALSFRS after randomization for all patients in edaravone Study 19, redrawn from the FDA Summary review on edaravone, figure 2.

open label. The method of intravenous delivery is not stated in the trial report, but one can suppose that some patients received infusions through repeated temporary (perhaps one or several days) short intravenous upper extremity access, while others might have done so through a semi-permanent indwelling intravenous access, either peripherally inserted central catheter (PICC) or a surgically-inserted central venous catheter.

Leaving aside the potential negative impact of daily drug infusions on a subjective functional rating scale, there are biological reasons why both placebo and treatment arms would decline with chronic intravenous infusions. Some are best appreciated from studies in animal models where experimental conditions can be isolated. In mouse models of ALS, toxicity is highly dependent on the physical state, both clinically and pathologically. SOD1 mice live longer if provided with a running wheel in the cage (12), and the effect of swimming exercise equals or exceeds any therapeutic intervention reported in these mice, and is accompanied by preservation of spinal motor neurons and beneficial changes in glia (13). The reasons for this state dependent toxicity are unclear and likely multifactorial. It seems likely that patients with

temporary or semi-permanent iv access would swim, run, cycle, or go to the gym less often or not at all, and a change in physical state could lead to physical and functional decline.

Perhaps more directly, serious thrombotic side effects are associated with all forms of chronic intravenous access; indeed, reports attesting to the safety of chronic infusions under any circumstances are elusive. In one study of 332 patients, PICC-DVT was symptomatic in 3.6–4.3%, but ultrasound-detected asymptomatic thrombosis occurred in 71.9%, with thrombosis usually beginning soon after insertion (14). After a literature review, Fallouh et al. (15) conclude that "PICC-DVT is common, costly and morbid". The figures are almost identical with surgically implanted systems: 73% thrombosis at first ultrasound evaluation (16). Temporary access through peripheral iv is associated with a surprisingly high risk of thrombosis that seems almost counter-intuitive (17–19). Tagalakis et al. (20) estimated the average rate of infusion thrombophlebitis with peripheral access to be 25–35%. Indeed, in a randomized trial in an ICU setting, there were more complications in the 128 patients assigned to short-term peripheral iv access than those with central lines, including five who developed superficial thrombosis and five developed DVT in the upper extremities (21). On a surgical ward, 11.1% of patients with an indwelling peripheral iv developed thrombosis, all asymptomatic (22); prolonged paresis during surgery was felt to be a contributing factor in peripheral iv associated thrombosis (23). At least in the lower extremities, 25% of patients with superficial thrombosis progressed to DVT (24), and 77.1% of DVT causing fatal PE were asymptomatic (25).

Clearly, all modes of chronic iv access are associated with a significant risk of thrombosis, nearly all asymptomatic. It is likely that patients in these studies were at high risk of thrombosis, as common indications for infusions include malignancy and immunological disorders, with potentially prolonged infusions of irritating infusates. However, it is also reasonable to assume that thrombosis and thromboembolism would be more prevalent in paretic limbs, more likely with repeated or prolonged iv use, more problematic in patients with already compromised respiratory function, and might cause disproportionate difficulties in some patients over others. It is thus unclear whether chronic infusions of edaravone and its associated excipients[2] would be of lower, similar, or higher risk than those reported, but an accelerated decline in the average ALSFRS slope following daily intravenous infusions should not be surprising or unexpected, could be of significant magnitude, and could have biological as well as psychological explanations.

Because of this risk of thrombosis, it is necessary to add a further caveat to the interpretation of the primary results of Study 19. Edaravone has multiple points of interaction with thrombosis pathways (26) and may have antithrombotic or thrombolytic action. In two *in vitro* models, edaravone added to alteplase reduced capillary occlusion by thrombus, in one by 69.9% (27,28). In a study of cardiogenic cerebral embolism, treatment with edaravone led to hemorrhagic transformation with an adjusted OR of 9.25 over control (26). Edaravone may lead to suppression of platelet adhesion and platelet aggregation through altered nitric oxide synthase and P-selectin (27,29). The most common treatment-related side effect in Study 19 was contusion and bruising (19%). As such, there is an underappreciated risk of thrombosis and embolism with chronic infusion, and the possibility that edaravone might ameliorate this risk but through mechanisms independent of the ALS disease process.

So where does this leave us? We have a concerning and anomalous situation, wherein edaravone was brought forward for further clinical study because of improvement in the rate of decline in the ALSFRS in a phase 2 trial, yet in the confirmatory Study 19 phase 3 trial the rate of decline worsened. The worsening is unlikely to be artefactual, has two plausible mechanisms, and is unlikely to be compatible with therapeutic efficacy. Yet in the same trial we have a significant relative benefit over placebo in the ALSFRS (albeit with multiple caveats that temper this conclusion and no assurance that the benefit reflects an improvement in the underlying ALS disease process). This paradox does have an explanation, as both observations may be true. When trial conditions may be harmful to both arms of a placebo-controlled trial, it is not only necessary that treatment is superior to placebo, but also that treatment is better than no intervention. Based on the reported results of the Study 19 trial, the default interpretation should be that in a highly selected population edaravone performed better than placebo, but that both placebo and edaravone did worse than no intervention. As such, there is a real possibility that edaravone, as delivered in the trial, is both ineffective and harmful.

It is possible that the above concerns will prove misplaced, and in time it may be shown that chronic infusions of edaravone can be accomplished without harm, that the decline seen after randomization in Study 19 falls within expected limits, and that there is a satisfactory biological explanation why edaravone is efficacious in a small

[2]Each infusion of edaravone also contains 20 mg L-cysteine, 40 mg sodium bisulfite, phosphoric acid, and sodium hydroxide, adjusted to a pH of 4 (11). The first two are antioxidants on their own, albeit at low dose. Sodium bisulfite infusion causes thrombosis when delivered into rabbit ear veins (30). Acid solutions of this pH are a risk factor for infusion thrombophlebitis (31).

subset of ALS patients but not most. At present, however, none of these are established.

All of this underscores the urgent need for confirmatory trials of edaravone in ALS before more widespread use, and with a trial design that incorporates more appropriate controls. It bears emphasizing that the inclusion of survival data could better establish the effectiveness of edaravone over placebo, but would do nothing to establish the effectiveness of edaravone over control.

Moreover, and in contradistinction to most drug trials, there is a wealth of experience with failed ALS trials of compounds similar to edaravone and with failed ALS trials of edaravone itself (Study 16, Study 18), suggesting a low a priori likelihood of success amenable to Bayesian analysis.

Along the same lines, at most 2.5% of the patients in the Pro-Act database would have met the entry criteria for Study 19, and in the *post hoc* analysis of Study 16 those patients who would not have met the Study 19 trial criteria did numerically worse on edaravone than placebo (11). Consequently, there is no evidence that the Study 19 results can be generalized to the larger ALS population (indeed, some evidence to the contrary). If more patients in current practice are receiving edaravone through a semi-permanent central iv access than in the Study 19 trial, then the risk/benefit profile could be further worsened. Efficacious treatment for ALS is a goal shared by ALS patients, providers, and pharmaceutical firms alike, but surely first, we must do no harm.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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   "Data used in the preparation of this article were obtained from the Pooled Resource Open-Access ALS Clinical Trials (PRO-ACT) Database. In 2011, Prize4Life, in collaboration with the Northeast ALS Consortium, and with funding from the ALS Therapy Alliance, formed the Pooled Resource Open-Access ALS Clinical Trials (PRO-ACT) Consortium. The data available in the PRO-ACT Database has been volunteered by PRO-ACT Consortium members."
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    There are 2 points at least of potential interest: Statistical review-executive summary (p6): "Study 19 does not seem very persuasive on it's own since many of the secondary analyses were not nominally significant although the study was small. Some alternative subjective interpretation (e.g., risk benefit considerations or orphan drug status) would seem necessary if one was to view this submission as sufficient for approval …."

    Summary Review (p16): "In Study 16, the group of patients that did not meet the criteria for less severe disease (of the post hoc analysis) fared numerically worse than placebo, and an exploratory study conducted by the applicant in patients with more advanced disease (Study 18) also showed numerically worse results for edaravone than for placebo. Although these results do not definitely establish that edaravone has deleterious effects in more advanced patients, they certainly raise concern that edaravone efficacy decreases as ALS gets more severe."
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