Creatinine as a Biomarker of Disease Subtype, Disease Progression, and Drug Response in Patients with ALS in the Phase 3 Empower Study

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Introduction

ALS is heterogeneous disease with a highly variable clinical course, including survival ranging from a few months to 10 years or more. Validated ALS biomarkers are needed to aid diagnosis, measure and predict disease progression, and serve as surrogate markers of drug response.

Changes in serum creatinine concentrations have previously been correlated with disease progression, suggesting creatinine as a candidate biomarker for ALS progression.[1] Creatinine is a measure of both muscle degradation and of metabolic function. Dexpramipexole has demonstrated neuroprotective properties through a mechanism believed to be associated with enhanced bioenergetic efficiency. [2]

We retrospectively analyzed data sets from the EMPOWER Phase 3 trial of dexpramipexole, the largest clinical trial ever conducted in ALS (n=943), to assess potential correlations of creatinine concentrations to disease progression, treatment effects, and outcomes of treatment-responsive subgroups.

Methods

Baseline clinical laboratory values for creatinine were correlated with baseline clinical characteristics, including ALSFRS-R score and classification of definite ALS by El Escorial Criteria (EEC). Changes from baseline in creatinine levels were correlated with clinical outcomes by treatment groups.

Dexpramipexole and riluzole effects on creatinine were estimated using a mixed effects repeated measures model to compare effects averaged over time through month 12. The model included terms for treatment, visit, and treatment by visit interaction, baseline laboratory value and baseline laboratory value by visit interaction. The coefficient for treatment main effect represented the mean change in creatinine averaged over each visit (time-averaged creatinine loss). The difference in the coefficients for treatments (placebo minus dexpramipexole) represented the time-averaged-difference (TAD) in creatinine loss.

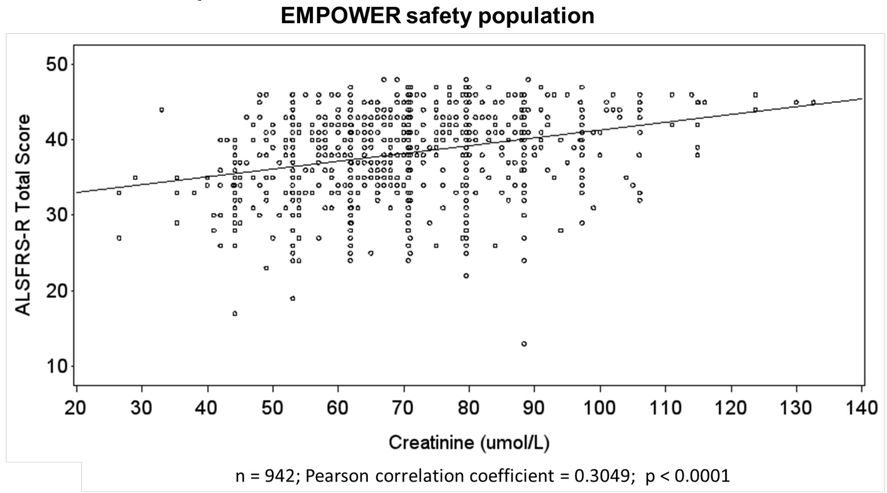
References

1 Paillisse C et al. Amyotrop Lateral Scler. 2005 Mar;6(1):37-44

2 Bozik M, Gribkoff V. CNS Neurosci Ther. 2008 Fall;14(3):215-26.

Results

Scatter plot of baseline creatinine vs. ALSFRS-R total score, EMPOWER safety population

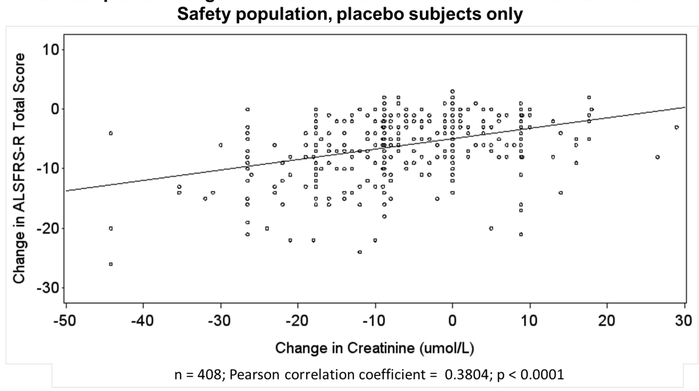


EMPOWER baseline creatinine levels correlated significantly with baseline ALSFRS-R scores

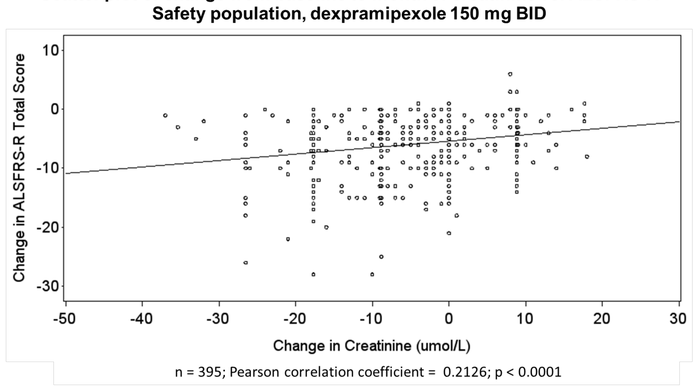
In EMPOWER, a strong correlation existed between levels of creatinine at baseline and baseline ALSFRS-R, with greater creatinine levels associated with higher ALSFRS-R at randomization. (Pearson correlation coefficient = 0.3049, p < 0.0001). In addition, mean baseline creatine was significantly lower in subjects classified with definite ALS by El Escorial Criteria (p = 0.01, data not shown).

Loss of function and change in creatinine correlated significantly in the EMPOWER placebo group, while dexpramipexole treatment diminished this correlation

Scatter plot of change from baseline to month 6: creatinine vs. ALSFRS-R Safety population, placebo subjects only



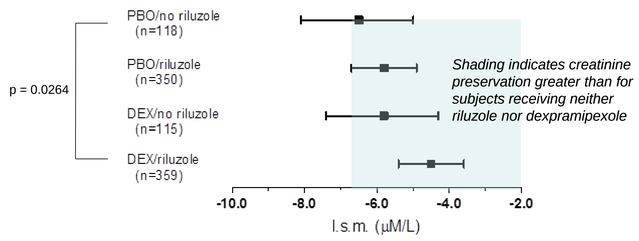
Scatter plot of change from baseline to month 6: creatinine vs. ALSFRS-R Safety population, dexpramipexole 150 mg BID



A significant correlation existed between reduction in creatinine and decline in ALSFRS-R at month 6 (left panel). This correlation was significantly reduced with dexpramipexole treatment (right panel, p = 0.0447). Time-averaged creatinine loss from baseline through month 12 (data not shown) was also greater for placebo participants than dexpramipexole participants (-6.0 µm/l vs -4.8 µm/l, p=0.0359). This finding is consistent with the phase 2 study of dexpramipexole in ALS (data not shown), in which participants receiving dexpramipexole 300 mg daily had reduced creatinine loss at month 3 compared with placebo participants (0.0 µm/l vs -5.3 µm/l, p=0.011).

Riluzole and dexpramipexole showed additive creatinine-preserving effects

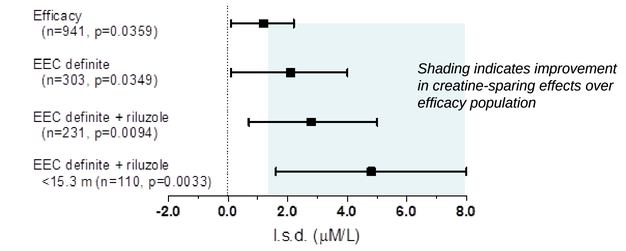
Time-Averaged Creatinine Change from Baseline to Month 12



Creatinine loss was greatest for EMPOWER placebo subjects not receiving riluzole (-6.5 µm/l, 95% CI -8.1,-5.0), followed by dexpramipexole-treated subjects not on riluzole (-5.8 µm/l, 95% CI -7.4,-4.3) and placebo participants on riluzole (-5.8 µm/l, 95% CI -6.7,-4.9). Creatinine preservation was greatest for dexpramipexole-treated subjects on riluzole (-4.5 µm/l, 95% CI -5.4,-3.6). This suggests an additive benefit of riluzole and dexpramipexole on creatinine preservation, consistent with outcome benefits seen in subjects receiving dexpramipexole plus riluzole in EMPOWER *post hoc efficacy* analyses, as reported elsewhere (Bozik et al, MNDA, 2013).

Dexpramipexole-responder subgroups experienced reduced creatinine loss

Time-Averaged Creatinine Difference from Baseline to Month 12



Creatinine-sparing effects of dexpramipexole by treatment-responder subgroups, measured by the least-square difference between dexpramipexole treatment and placebo. Creatinine preservation in the efficacy population (1.2 µm/l; 95% CI 0.1,2.2) increased in the the EEC definite subgroup (2.1 µm/l; 95% CI 0.1,4.0), further increased in the EEC definite + riluzole subgroup (2.8 µm/l; 95% CI 0.7,5.0), and was greatest for EEC-definite subjects receiving riluzole who entered the study in the lower median (<15.3 months) of symptom duration (4.8 µm/l; 95% CI 1.6,8.0) This creatinine-sparing effect by subpopulation is consistent with outcome benefits seen with EMPOWER *post hoc* analyses, as reported elsewhere (Bozik et al, MNDA, 2013),

Conclusions

In EMPOWER, creatinine levels correlated significantly with disease severity at baseline and over 12 months of study. Creatinine-sparing effects were associated with both dexpramipexole and riluzole treatment, with the combination of drugs significantly attenuating creatinine loss. Preservation of creatinine was most significant in the subpopulation of dexpramipexole responders defined by EEC-definite classification, concomitant riluzole use, and lower-median symptom duration at study start.

These analyses strengthen the hypothesis that creatinine is a biomarker of ALS progression and potentially of positive treatment effect. Both hypotheses require prospective confirmation in well-controlled clinical studies. Further research is also needed to strengthen the mechanistic association between creatinine loss and disease progression.