The effect of edaravone on corticospinal hyperexcitability (CSHE) in ALS and the utility of SICI as a pharmacodynamic biomarker

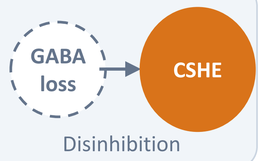
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RESEARCH QUESTION **Does edaravone reduce corticospinal hyperexictability (as measured by TMS SICI) over time in patients with ALS?**

INTRODUCTION

1 Corticospinal hyperexcitability (CSHE) is an early, upstream phenomenon in ALS, resulting from the loss of GABA interneurons



2 SICI measures cortical inhibition

Paired-pulse TMS SICI is a measure of $GABA_A$ mediated inhibition. Higher SICI = stronger inhibition.

3 SICI declines as ALS progresses

Natural history: progressive increase in CSHE with average SICI decline over 12 months of follow-up (mean, 95% CI; Krishnan et al., 2025).

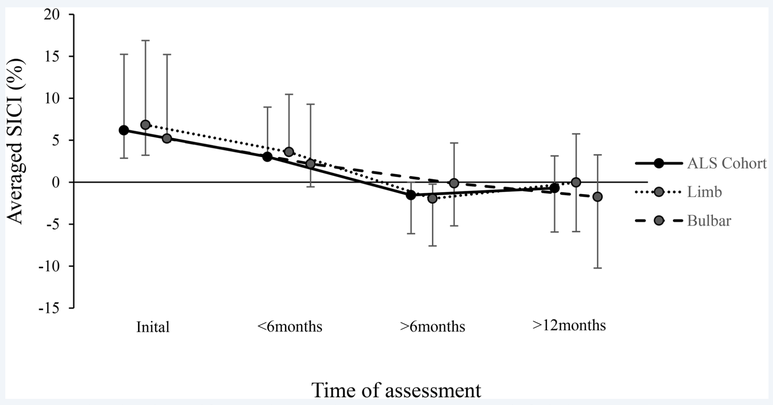
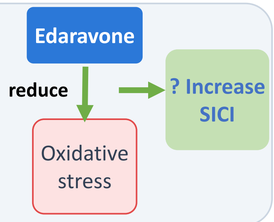


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4 Can Edaravone reduce CSHE?

Free-radical scavenger: can it reduce oxidative stress and improve neuronal bioenergetics, reducing CSHE and increasing SICI?



METHODS

A) Study design

- Consecutively recruited at the Sunnybrook ALS clinic, Toronto, Canada. Recruitment ongoing.
- ALS patients eligible for standard-of-care edaravone: disease duration ≤24 months, ALSFRS-R ≥2 in each item, FVC ≥80% predicted.
- Prospective visits every 4–6 months, drug-naive and on-drug.
- Never-on-edaravone controls will be recruited from a European site



Each visit: dotted box: encouraged, but not mandatory

SICI | ALSFRS-R | sNfL | Neuro exam | ^{31}P-MRS

B) Sample size calculation

Full study: naive vs on edaravone

SD: **8.65%** (ALS patients off edaravone, n = 57)
α = 0.05 (two-sided); power = 80%
Difference of 10%: **n = 13 per group (26 total)**
Difference of 5%: **n = 48 per group (96 total)**

METHODS (continued)

C) Statistics

SICI Trajectories

Linear mixed-effects models, random intercept and slope per patient; outcome: SICI; variable: time (months on edaravone)

ALSFRS-R

Linear mixed-effects model, outcome: ALSFRS-R; variables: Months × group interaction (exploratory).

SICI = mean of 1, 2.5 and 3 ms interstimulus intervals; higher = stronger inhibition. SICI measured with threshold tracking technique (T-SICI).

RESULTS

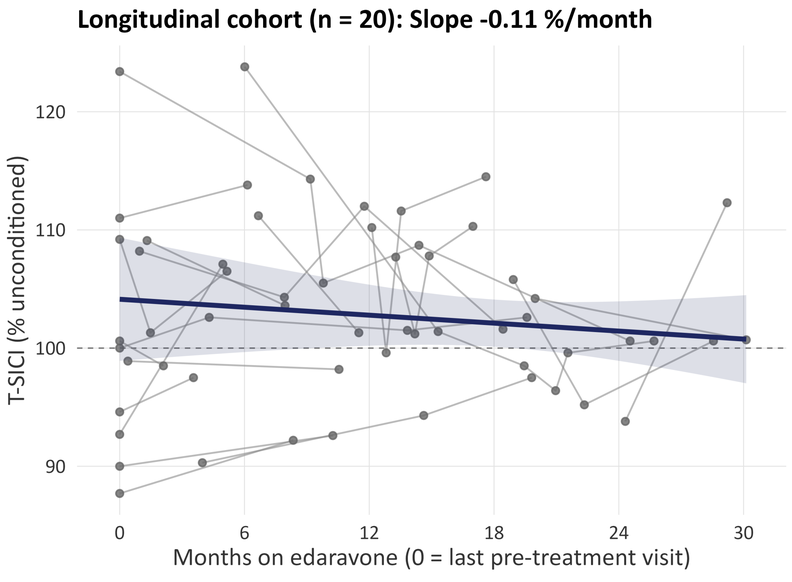
Enrolled at the time of preliminary analysis: **n = 44**
Longitudinal cohort (≥2 SICI visits, at least one on edaravone): **n = 20**
Data from only **4** patients never on edaravone were available at the time of preliminary analysis and were not included

Table 1. Baseline characteristics, longitudinal cohort

	Longitudinal cohort (n=20)
Age at edaravone start, years	61.6 ± 8.0
Male sex	13/20 (65%)
Onset: spinal / bulbar / respiratory	19 / 1 / 0
Disease duration, months	19.0 ± 11.9
Riluzole use	11/20 (55%)
Edaravone-naive at first TMS	9/20 (45%)
Baseline ALSFRS-R	41.4 ± 4.4
Baseline SICI, % unconditioned	103.6 ± 10.3
Baseline sNfL, pg/mL	60.2 [38.8–78.0] (n=17)

Mean ± SD, n/N (%), or median [IQR]. Baseline = earliest measurement; on-treatment for patients entering the study already on drug. ΔFRS = (48 − baseline ALSFRS-R) / months from symptom onset.

Figure 1. Prelim pooled SICI over time



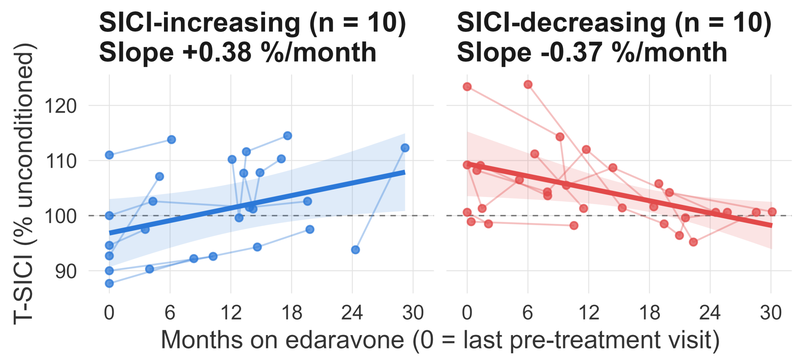
95% CI −0.38 to 0.15 %/month

Thin lines: patients. Bold line and band: mixed model, 95% CI.

The pooled 95% CI crossed zero, so we asked whether patients differed in SICI direction: each patient's SICI slope defined **SICI-increasing** (slope > 0, n = 10) and **SICI-decreasing** (slope ≤ 0, n = 10) groups.

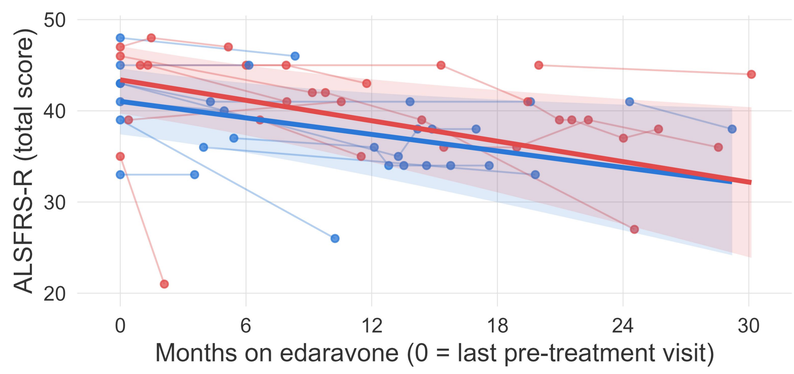
RESULTS (continued)

Figure 2. SICI over time by trajectory group



Thin lines: patients. Bold line and band: within-group mixed model, 95% CI. Dashed: SICI = 100%.

Figure 3. ALSFRS-R slope by SICI trajectory group: trend toward slower decline with rising SICI



ALSFRS-R slope, points/month (mixed model; exploratory, 10 vs 10):
Full cohort (n = 20): −0.32 (95% CI −0.49 to −0.15)
SICI-increasing: −0.30 (95% CI −0.56 to −0.05)
SICI-decreasing: −0.37 (95% CI −0.63 to −0.11)

CONCLUSIONS

1 SICI is a marker of CSHE and can be measured longitudinally in patients with ALS

2 In edaravone treated patients SICI trajectories were heterogenous, with 50% of the patients presenting an increase

3 Patients on edaravone with an increase in SICI had a slower ALSFRS-R slope (-0.30) than SICI-decreasing group (-0.37)

Limitations

- Preliminary analysis; small sample (20 with longitudinal data); no untreated comparison group.

Next steps

- Continued enrolment (updated numbers, Oct 12th):

	n	Edaravone-naïve
Enrolled	100	45
With imaging	46	20
≥1 follow-up visit	39	11

- Enrollment of never on edaravone control group from European collaborators.
- ^{31}P-MRS to assess neuronal bioenergetics: ongoing processing pipeline development.

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References.
1. Krishnan D, Talbot DL, Ashhurst JF, Park SB, Vucic S, Timmins HC, et al. Longitudinal assessment of cortical motor function in amyotrophic lateral sclerosis. Sci Rep. 2025;15(1):16978. doi:10.1038/s41598-025-01570-6
2. Khademullah CS, Aqrabawi AJ, Place KM, Dargaei Z, et al. Cortical interneuron-mediated inhibition delays the onset of amyotrophic lateral sclerosis. Brain. 2020; doi: 10.1093/brain/awaa034