RESEARCH SUMMARY

Trial of Antisense Oligonucleotide Tofersen for *SOD1* ALS

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CLINICAL PROBLEM

Approximately 2% of cases of amyotrophic lateral sclerosis (ALS) are associated with mutations in the gene encoding superoxidase dismutase 1 (*SOD1*), with toxic gain of function of the mutant SOD1 protein implicated in degeneration of anterior horn cells. Tofersen, an antisense oligonucleotide, was designed to reduce SOD1 synthesis, but its effects in patients with *SOD1*-mutated ALS are unknown.

CLINICAL TRIAL

Design: An international, phase 3, double-blind, randomized, placebo-controlled trial examined the efficacy and safety of tofersen in adults with weakness attributable to ALS and a confirmed *SOD1* mutation.

Intervention: 108 participants were assigned in a 2:1 ratio to receive, through lumbar puncture, eight bolus injections of tofersen (100 mg) or placebo over a period of 24 weeks. The primary end point — the change from baseline to week 28 in the total score on the ALS Functional Rating Scale–Revised (ALSFRS-R) — was assessed in 60 participants predicted to have faster-progressing disease; ALSFRS-R scores range from 0 to 48, with higher scores indicating better function.

RESULTS

Efficacy: The mean ALSFRS-R score declined in both groups by week 28, with no significant difference between the two groups. An ongoing extension phase comparing early-start to delayed-start participants independent of rapidity of progression had suggestive but uncertain findings favoring tofersen.

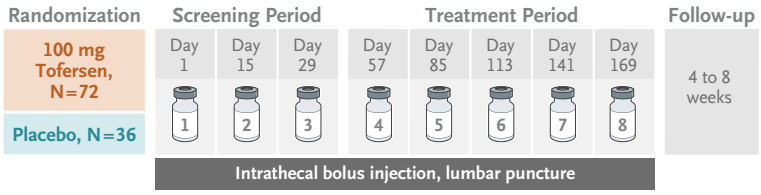
Safety: Procedural pain and headache were common. Among 104 participants who received tofersen either initially or as part of an open-label extension phase, 7 (7%) had neurologic serious adverse events, including myelitis, chemical or aseptic meningitis, lumbar radiculopathy, increased intracranial pressure, and papilledema.

LIMITATIONS AND REMAINING QUESTIONS

- Randomization was not stratified according to the baseline concentration of neurofilament light chains in plasma, which may have limited balance between the trial groups.
- The extension phase of the trial, which suggested differences between early treatment and delayed treatment, is ongoing.

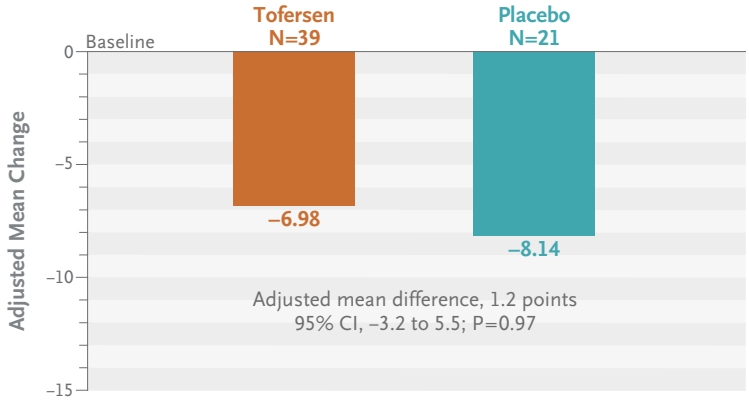
Links: Full Article | NEJM Quick Take

VALOR Trial Design

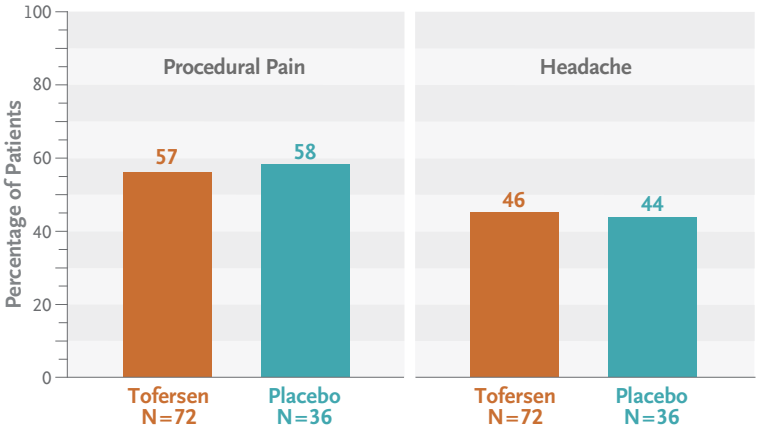


Change in ALSFRS-R Total Score at 28 Wk

(Faster-Progression Subgroup)



Most Common Adverse Events



CONCLUSIONS

Among patients with ALS and *SOD1* mutations, intrathecal treatment with the antisense oligonucleotide tofersen did not improve clinical end points over a period of 28 weeks and was associated with a limited number of serious neurologic events.