View Point

Tofersen: Silver Lining or Hyperbole??

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Abstract

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder of anterior horn cells with a dismal prognosis. Over a century since its description, we still do not have a cure for this disorder. Edaravone, Riluzole, and combination of phenylbutyrate and taurursodiol are a handful of FDA-approved drugs that only delay the progression of the disease by a few months. Tofersen, an antisense oligonucleotide, in SOD1 related ALS, has joined the bandwagon of FDA-approved drugs for ALS recently. It is a gene therapy that has been found to lower SOD1 concentrations and neurofilament light chain concentrations in blood and CSF, a known biomarker of ALS, leading to the accelerated approval of the drug. Although it did not show any statistically significant clinical improvement. In this article, we discuss the development and approval process of the first gene-based therapy, Tofersen, for ALS.

Keywords: Amyotrophic lateral sclerosis, gene therapy, SOD1-related ALS, Tofersen

More than a century has passed, since the first description of amyotrophic lateral sclerosis (ALS) by Jean Marie Charcot's in 1865, yet, we do not have a cure for this enigmatic disease.[1] We have not made much progress in treating ALS since the underlying pathomechanism is still unknown. Edaravone, Riluzole along with the recent addition of phenylbutyrate, and taurursodiol (PB/TURSO) are the list of FDA-approved drugs for ALS treatment with limited benefit of delaying the progression of the disease by a few months.[2-4] A recent addition to the list is a gene-based therapy, Tofersen, which got accelerated approval after the VALOR study [Table 1].[5]

The identification of ALS-related genes has advanced our understanding of disease pathogenesis and facilitated the development of therapeutics directly challenging the underlying genetic process. Superoxide dismutase 1 (SOD1) was the first ALS-related gene identified in 1993. It is seen in 2% of ALS patients with over 200 disease-causing variants, each of which can have a unique disease course.[6]

Therapies targeting the genes have come to the forefront. Tofersen is one such molecule, and it is an antisense oligonucleotide (ASO) that reduces SOD1 protein synthesis by induction of RNAse H mediated degradation of mRNA. In rodent models, Tofersen prolonged survival and improved motor performance.[7]

The phase 1–2 ascending dose trial of Tofersen in SOD1 mutation ALS patients reported that high dose Tofersen (Dose-100 mg intrathecal administration, 100 g/15 ml, every 15 days for 3 doses and then every 28 days) led to a decrease in CSF SOD1 concentration compared to placebo.[8] There was a reduction of 3% SOD1 protein concentrations in the placebo group vs. 36% in the 100 mg dose group at day 85. On post-hoc analysis of fast progressors (defined as the participants carrying a mutation known to have a fast-progressing disease course and having the pre-randomization slope of the ALSFRS-R score of at least 0.2 points per month) vs. other participants, no significant difference in baseline or magnitude of reduction in the CSF SOD1 concentrations was observed.[8]

The adverse effects reported were headache, procedural pain, lumbar puncture syndrome, back pain, pain in limbs, and neck pain, which were largely related to the lumbar puncture.

An increase in CSF leukocytes and proteins was noted with the ascending dose without any clinical or radiological signs or symptoms of myelitis, the cause of which was unclear. CSF cells of more than 10/cm were seen in 42% of the combined Tofersen group (maximum–144 cells) compared to 8% of placebo group.

Though this study was not conducted to ascertain the clinical efficacy as it was not powered to test the same, the patients did show a delay in the progression of the disease while on the treatment as indicated by the exploratory outcomes. Change in the Amyotrophic lateral sclerosis functional rating scale—Revised (ALSFRS-R = −1.19 vs 5.63), change in vital capacity (VC = −7.08 percentage points vs. −14.46 percentage points) and change in the handheld dynamometry (HD = −0.03 vs − 0.26) was reduced more in the 100 mg Tofersen group

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Table 1: FDA-Approved drugs for ALS

Drug Name	FDA approval Year	Landmark trial	Mechanism of action	Dose	Adverse effects
Riluzole Oral suspension riluzole (Tiglutik™) Oral film riluzole (Exservan™)	1995 2018 2019	A controlled trial of riluzole in ALS. ALS/Riluzole Study Group.(3)	Inhibition of glutamic acid release, non-competitive block of N-methyl-D-aspartate (NMDA) receptor Direct action on the voltage-dependent sodium channel	100 mg/day in two divided doses	Asthenia, dizziness, gastrointestinal disorders, and elevations in liver enzyme activities
Edaravone (Radiclava) Oral suspension (Radiclava ORS)	2017 2022	Safety and efficacy of edaravone in well defined patients with ALS: a randomized, double-blind, placebo-controlled trial(2)	Free radical scavenger	1st cycle—60 mg in 100 ml saline intravenously once daily for 14 days followed by 14-day drug-free interval 2nd cycle onwards—60 mg in 100 ml saline intravenously once daily For 10 days within 14 days period followed by 2 weeks drug-free interval	Injection site contusion, gait disturbance, and headache Allergic reaction
Tofersen (Qalsody)	2023	Tofersen in adults with SOD1-ALS: phase 3 VALOR trial and open-label extension results(9)	Antisense oligonucleotide (ASO) that reduces SOD1 protein synthesis by induction of RNAse H mediated degradation of mRNA	100 mg intrathecal administration, 100 g/15 ml, every 15 days for 3 doses and then every 28 days	Injection site pain, headache, fatigue, arthralgias, myelitis, radiculitis, aseptic meningitis, and elevated intracranial pressure
Sodium phenylbutyrate-taurursodiol	September 2022	Effect of sodium phenylbutyrate/ taurursodiol on tracheostomy/ ventilation-free survival and hospitalization in ALS: long-term results from the CENTAUR trial (4)	Sodium phenylbutyrate histone deacetylase inhibitor—reduces adaptive stress response in endoplasmic reticulum. Taurursodiol—increase the threshold of cellular apoptosis by maintaining mitochondrial integrity Reduces cell death	Sodium phenylbutyrate 3g and taurursodiol 1g suspension dissolved in 250 milliliters of water per orally once daily for three weeks, then twice daily thereafter	Diarrhea, abdominal pain, nausea, upper respiratory tract infection, fluid retention, drug interactions (inhibits CYP2C8 and CYP2B6 induces CYP1A2, CYP2B6, and CYP3A4)

when compared to the placebo group. It was also noted the rate of progression returned with treatment cessation.[8]

Part C of the above trial, the VALOR study, evaluating the safety and efficacy of Tofersen was recently concluded (July 2021) and published in the National England Journal of Medicine (NEJM-September 2022). A total of 108 patients (Tofersen–72, placebo–36) were randomized for the initial 52 weeks subsequently followed by an open-label extension phase (N = 95). The primary end point, that is the change in the ALSFRS R score change at 28 weeks in the faster progression group (N = 60), was not significantly reduced in the Tofersen group compared to the placebo (−6.98 points vs. –8.14 points, $P = 0.97$, CI= −3.2 to 5.5). Due to the lack of statistical significance observed in the primary end point, the subsequent analysis was also deemed non-significant, and as a result, no *P* value was reported.

However, the concentrations of SOD1 and Neurofilament light chain (NfL) decreased by 29% and 60% in the Tofersen group, while they increased by 16% and 20% in the placebo group.

The percentage decline in the slow vital capacity and the change in handheld dynamometry megascore was less in Tofersen group compared to placebo (VC-14.3 vs. 22.2 points, HD-−0.34 vs. 0.37).

Early vs. delayed starters were analyzed in the open-label extension phase. It was observed that the decline in SOD1 and NfL concentrations was more in early starters and the decline in slow vital capacity, handheld dynamometer mega scores, and ALSFRS-R was less in early starters.[9]

Though the results of the trial were negative for the primary clinical endpoint, the drug was given accelerated approval by the FDA for SOD1-related ALS in April 2023, contingent on the evidence of clinical benefit in confirmatory trials for continued approval.

These findings were replicated in a small case series (n = 6) where patients received Tofersen for 5 months under the expanded access program. All patients showed a decline in the NfL concentrations, with a decline in the rate of progression observed in two patients.[10]

The significance of the decline in NfL concentration arises from the fact that NfL was established as a biomarker for ALS with the Presymptomatic familial ALS Study (PrefALS study). It is an ongoing longitudinal natural history and biomarker

study of at-risk populations who are carriers of ALS-related genes (SOD1, C9orf72, TARDBP, FUS, VCP), initiated in 2007. Ten phenoconverters, that is, participants who develop unequivocal symptoms, or subclinical signs of disease detected through detailed neuromuscular examination or EMG that clearly indicated disease, were identified in this study, of which 9 were carriers of SOD1 mutation (A4V mutation being the most prevalent).

Elevated levels of serum neurofilament light (NfL) chains were observed 11.8 months before conversion and continued to rise 6 months afterward, whereas longitudinal levels remained stable in established ALS patients included in the study. Although the cross-sectional level at the baseline was significantly higher in the control and at-risk population. Annual increase of NfL with age was negligible with no correlation to the gender or mutation type.[11]

To confirm the clinical efficacy of the Tofersen, a trial of Tofersen in presymptomatic SOD1 carriers is ongoing, the ATLAS trial. It will assess whether it delays the ALS clinical manifestations. It is designed based on the result of a PreFALS study, which demonstrated a presymptomatic phase of 6–12 months before phenoconversion, characterized by gradual elevation of NfL concentrations.

ATLAS trial proposes to determine whether early initiation of Tofersen in the presymptomatic individual at high risk of phenoconversion will lead to a delay in the onset of clinical manifestations or a reduction in longitudinal functional decline.

It will be conducted in two parts—Part A (the run-in period) and Part B (the recruitment phase). Patients will be recruited once the NfL reaches a predefined threshold, that is, 44 pg/ml or > 10 pg/ml rise from baseline. Once the patient manifests the clinical disease, they can participate in an open-label extension of Part C. Primary endpoints are the percentage of participants who develop phenoconversion at 12 and 24 months of randomization in Part B and the time to development of ALS from baseline in Part B. The research group has also focused on the psychosocial effects of presymptomatic genetic testing and the emerging knowledge of novel SOD1 variants.[12]

This trial will not only determine the potential of initiating the treatment in the presymptomatic phase, it also gives an opportunity to study other potential biomarkers and neurophysiological markers that can be used in other subsets of the ALS population. Despite only being relevant to 2% of ALS patients with SOD1 mutation, the results are eagerly awaited, as this will pave the way for future drug development and research strategies.

The development of this drug can be attributed to the natural history studies of diseases like ALS with ambiguous pathogenetic processes. This underscores the significance of this research in advancing our understanding and potential treatments for such conditions. The accelerated approval of the drugs showing evidence of a decline in biomarkers without clinical impact is commonplace; the lack of clinical benefit may be due to the short duration of the trials and lack of assessment of patient-reported outcomes. These points can be incorporated into the future trials for a holistic assessment.

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Conflicts of interest

There are no conflicts of interest.

References

1. Meininger V. ALS, what new 144 years after Charcot? Arch Ital Biol 2011;149:29-37.
2. Writing Group, Edaravone (MCI-186) ALS 19 Study Group. Safety and efficacy of edaravone in well defined patients with amyotrophic lateral sclerosis: A randomised, double-blind, placebo-controlled trial. Lancet Neurol 2017;16:505-12.
3. Bensimon G, Lacomblez L, Meininger V. A controlled trial of riluzole in amyotrophic lateral sclerosis. ALS/Riluzole Study Group. N Engl J Med 1994;330:585-91.
4. Paganoni S, Hendrix S, Dickson SP, Knowlton N, Macklin EA, Berry JD, *et al*. Long-term survival of participants in the CENTAUR trial of sodium phenylbutyrate-taurursodiol in amyotrophic lateral sclerosis. Muscle Nerve 2021;63:31-9.
5. Trial of Antisense Oligonucleotide Tofersen for SOD1 ALS | NEJM. Available from: https://www.nejm.org/doi/full/10.1056/NEJMoa2204705. [Last accessed on 2023 Aug 07].
6. Kim G, Gautier O, Tassoni-Tsuchida E, Ma XR, Gitler AD. ALS genetics: Gains, Losses, and implications for future therapies. Neuron 2020;108:822-42.
7. McCampbell A, Cole T, Wegener AJ, Tomassy GS, Setnicka A, Farley BJ, *et al*. Antisense oligonucleotides extend survival and reverse decrement in muscle response in ALS models. J Clin Invest 2018;128:3558-67.
8. Miller T, Cudkowicz M, Shaw PJ, Andersen PM, Atassi N, Bucelli RC, *et al*. Phase 1–2 trial of antisense oligonucleotide tofersen for SOD1 ALS. N Engl J Med 2020;383:109-19.
9. Miller TM, Cudkowicz ME, Genge A, Shaw PJ, Sobue G, Bucelli RC, *et al*. Trial of antisense oligonucleotide tofersen for SOD1 ALS. N Engl J Med 2022;387:1099-110.
10. Meyer T, Schumann P, Weydt P, Petri S, Koc Y, Spittel S, *et al*. Neurofilament light-chain response during therapy with antisense oligonucleotide tofersen in SOD1-related ALS: Treatment experience in clinical practice. Muscle Nerve 2023;67:515-21.
11. Benatar M, Wuu J, Andersen PM, Lombardi V, Malaspina A. Neurofilament light: A candidate biomarker of presymptomatic amyotrophic lateral sclerosis and phenoconversion. Ann Neurol 2018;84:130-9.
12. Benatar M, Wuu J, Andersen PM, Bucelli RC, Andrews JA, Otto M, *et al*. Design of a randomized, placebo-controlled, phase 3 trial of tofersen initiated in clinically presymptomatic SOD1 variant carriers: The ATLAS study. Neurother J Am Soc Exp Neurother 2022;19:1248-58.