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Letter to the Editor: New Observation

Tofersen Treatment Normalizes Neurofilament Levels in Autosomal Recessive *SOD1* Amyotrophic Lateral Sclerosis

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Pathogenic variants in the superoxide dismutase 1 (*SOD1*) gene account for approximately 2% of cases of amyotrophic lateral sclerosis (ALS).[1] The inheritance is typically autosomal dominant, except for ALS associated with the *SOD1* p. Asp91Ala and p. Asp97Asn substitutions, which appear to cause recessively inherited disease.[2,3] Tofersen, an antisense oligonucleotide that reduces the synthesis of SOD1 protein, was recently shown to decrease neurofilament levels in people with *SOD1* ALS, and open-label extension data showed slowed clinical decline in people initially randomized to tofersen.[4] However, this study included only two people with the p. Asp91Ala variant. Case reports of such people treated with tofersen are scarce.[5,6] Here, we describe a person with a homozygous p. Asp91Ala *SOD1* variant in which neurofilament levels rapidly normalized with initiation of tofersen.

This case involved a 49-year-old female who noticed fasciculations in her legs 1 year prior to presentation. This was followed by progressive difficulty climbing stairs, fasciculations in her arms and a decrease in grip strength (left hand more than right). She had no bulbar or respiratory symptoms. Her past medical history was notable for relapsing remitting multiple sclerosis (MS), presenting 14 years earlier with diplopia and paresthesias, and brain MRI demonstrating typical MS lesions. In the following years, she had two additional typical MS relapses with sensory symptoms and new demyelinating lesions on MRI, the last of which was 3 years prior to her diagnosis of ALS. Following these relapses, she had no persistent symptoms or deficits and was never started on disease-modifying treatment. She was taking no medications, and her medical history was otherwise unremarkable. She had a brother and a sister with leukemia, but no family history of ALS. Her exam 12 months after the onset of ALS demonstrated a relatively symmetric quadriparesis with normal muscle tone and no apparent focal atrophy. Cranial and bulbar muscles were spared. There was symmetric hyperreflexia in the arms, including positive Hoffmann's signs, and normal reflexes in the legs. Brain MRI showed no active lesions. MRI of the C-spine also did not show active lesions and just a T2 hyperintense lesion within the ventral aspect of the cord at the C5 level that had been present and unchanged for 7 years and had not been accompanied by weakness or hyperreflexia/spasticity on exams in the MS clinic in the past. Electromyography showed widespread active denervation potentials and a chronic neurogenic pattern in cervical, thoracic and lumbar segments. The trapezius was sampled as a cranial muscle and was normal. Genetic testing was performed using a 31-gene panel for ALS (Prevention Genetics, Marshfield, WI) and identified a homozygous variant in *SOD1* (c.272A >C, p. Asp91Ala, rs80265967 in dbSNP). She was started on tofersen treatment 15 months after symptom onset. Her ALS functional rating scale revised (ALSFRS-R) was 38/48 at that time, her vital capacity (VC) was 77% predicted and neurofilament light chain (NfL) was unmeasurably high (>10.000 pg/mL) in CSF and 142.8 pg/mL in serum (the upper limit of normal is 21.4 pg/mL for her age category of 41–65 years) using a simoa assay (MitogenDx LDT, Calgary, AB). After the start of treatment, her serum NfL levels rapidly normalized (Figure 1A). CSF NfL levels were repeated once at 16 months post-treatment initiation and had also normalized (640.11 pg/mL; reference value range 0.316–890 pg/mL). At 13 months, her VC had improved slightly to 82% predicted, and her manual muscle strength testing had declined from a Medical Research Council sum score of 46/60 to 40/60. At 16 months, her ALSFRS-R score had decreased by three points to 35/48 (Figure 1B). She did not experience any side effects, except for elevated CSF protein (ranging from 0.47 to 1.10 g/L, median 0.76, interquartile range (IQR) 0.31) and total nucleated cells (ranging from 8 to 46 10^6/L, median 33, IQR 9.5) throughout the observed treatment period, which has been described before.[4] One month after the start of tofersen, she was also started on riluzole.

The autosomal recessive disease associated with the homozygous p. Asp91Ala substitution tends to be milder, with a slower progression than typical autosomal dominant *SOD1* ALS, which corresponds with the disease history and findings in our case. The mechanism of disease in *SOD1* ALS is not yet entirely elucidated, but mutated SOD1 protein is generally considered to cause ALS through a toxic gain of function.[1] However, it is unclear if the autosomal recessive mutated SOD1 protein also has a toxic gain of function (and would therefore respond to treatment with tofersen), especially

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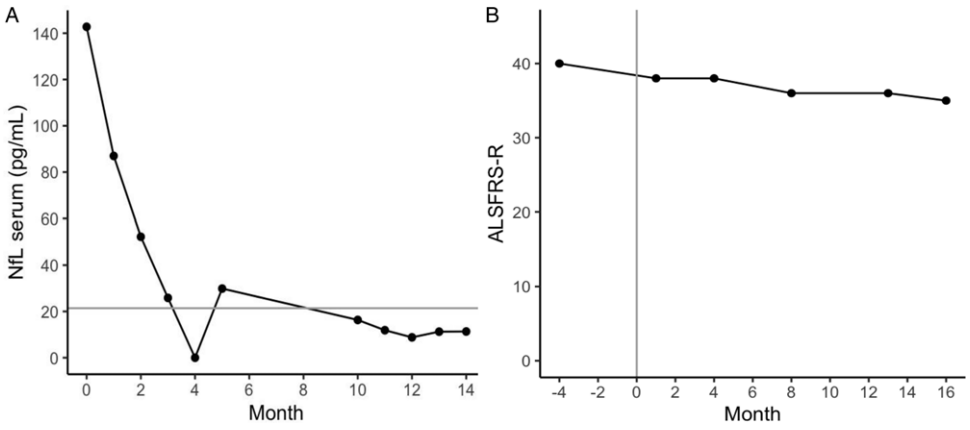

Figure 1. (A) Serum neurofilament light chain (NfL) evolution from the start of tofersen treatment at month 0. The horizontal line depicts the upper limit of normal of serum NfL (21.4 pg/mL) according to the laboratory reference values for this patient's age category (41–65 years). **(B)** Amyotrophic lateral sclerosis functional rating scale revised (ALSFRS-R) score evolution from 4 months before the start of tofersen treatment (first available measurement) to 16 months afterward. The vertical line indicates the start of tofersen treatment at month 0.

given the conflicting reports regarding the pathogenicity of heterozygous p. Asp91Ala variants.[5] Nevertheless, a recent pathology study demonstrated that people with homozygous p. Asp91Ala variants also have inclusions of misfolded SOD1 protein in motor neurons and glial nuclei in the spinal cord and brainstem.[7] One could thus hypothesize that a reduction of SOD1 protein by tofersen could also have a positive effect in this subgroup of people.

Neurofilaments in people with ALS have been studied extensively and are correlated with disease progression rate and survival, which suggests that a therapy that reduces neurofilament levels could have a positive effect on these factors.[4,8] It should be noted that NfL levels can be elevated in MS, although the lack of MS disease activity clinically and the drop in NfL after initiation of tofersen therapy would support that the NfL levels and subsequent changes were likely unrelated to her prior MS diagnosis. Apart from the decrease in neurofilament levels, VC stabilized, and the ALSFRS-R deteriorated only slightly during follow-up in this case. Since slow disease progression is expected in people with homozygous p. Asp91Ala *SOD1* variants, it may be too soon to conclude that there has been a clinical disease-modifying effect in this person. There were no missed doses of tofersen to explain the transient fluctuation in serum NfL at month 5 (Figure 1A).

In conclusion, the findings of our report add to the body of evidence that tofersen decreases neurofilament levels in people with homozygous p. Asp91Ala *SOD1* variants, which may be a biomarker of treatment response, suggesting that they should be considered for treatment.

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References

1. Bunton-Stasyshyn RK, Saccon RA, Fratta P, Fisher EM. SOD1 function and its implications for amyotrophic lateral sclerosis pathology: new and renascent themes. *Neuroscientist*. 2015;21(5):519–529.
2. Andersen PM, Forsgren L, Binzer M, et al. Autosomal recessive adult-onset amyotrophic lateral sclerosis associated with homozygosity for Asp90Ala CuZn-superoxide dismutase mutation: a clinical and genealogical study of 36 patients. *Brain*. 1996;119(4):1153–1172.
3. Hand CK, Mayeux-Portas V, Khoris J, et al. Compound heterozygous D90A and D96N SOD1 mutations in a recessive amyotrophic lateral sclerosis family. *Ann Neurol*. 2001;49(2):267–271.
4. Miller TM, Cudkowicz ME, Genge A, et al. Trial of antisense oligonucleotide tofersen for, *SOD1* ALS. *N Engl J Med*. 2022;387(12):1099–1110.
5. Weishaupt JH, Körtvélyessy P, Schumann P, et al. Tofersen decreases neurofilament levels supporting the pathogenesis of the SOD1 p.D91A variant in amyotrophic lateral sclerosis patients. *Commun Med*. 2024;4(1):150.
6. Meyer T, Schumann P, Weydt P, 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(6):515–521.
7. Forsberg KM, Graffmo KS, Stenvall E, et al. Widespread CNS pathology in amyotrophic lateral sclerosis homozygous for the D90A SOD1 mutation. *Acta Neuropathol*. 2023;145(1):13–28.
8. Shahim P, Norato G, Sinaii N, et al. Neurofilaments in sporadic and familial amyotrophic lateral sclerosis: a systematic review and meta-analysis. *Genes*. 2024;15(4):496.

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