Tofersen for Amyotrophic Lateral Sclerosis: A Step Forward or Another False Hope?

Sir,

Amyotrophic lateral sclerosis (ALS) is an uncommon and terminal neurological disease characterised by the gradual breakdown of motor neurons in the central nervous system. Hallmarks of this disease include muscle weakness and paralysis, subsequently leading to death.[1] Approximately 2% of ALS cases are due to mutations in the *superoxide dismutase 1* (*SOD1*) gene.[2] Tofersen, a novel antisense oligonucleotide, is responsible for the degradation of *SOD1* messenger RNA which causes a reduction in the synthesis of toxic SOD1 protein. This characteristic underlies its potential utility in the treatment of *SOD1*-mutated ALS.[3,4]

In April 2023, the U.S. Food and Drug Administration (FDA) granted accelerated approval for Tofersen as a treatment for *SOD1*-ALS, following the disclosure of findings from the phase III, international, double-blind, randomised controlled trial, namely the VALOR C study.[3,4] In this trial, 108 participants with *SOD1*-ALS were randomly assigned into two groups in a 2:1 ratio. The Tofersen group included 72 participants who were treated with 100 mg of Tofersen as an intervention. In comparison, the control group included 36 participants who received artificial cerebrospinal fluid (CSF) as a placebo. Both regimens were administered intrathecally in bolus injections. After 28 weeks, the primary endpoint was assessed by examining changes in the ALS Functional Rating Scale-Revised (ALSFRS-R) scores among 60 participants who showed rapid progression of ALS. From baseline to week 28, the average change in total ALSFRS-R score was a decline of -6.98 points in the Tofersen group, compared to a decline of -8.14 points in the placebo group. This demonstrated an insignificant difference in the efficacy between the two groups. However, the analysis of secondary endpoints showed a significant decrease in SOD1 protein levels in CSF and a reduction in neurofilament light chain concentrations in plasma. Both of these markers are considered important prognostic indicators for the progression of ALS.[4]

Despite failing to achieve its primary endpoint, Tofersen was approved by the FDA based on a favourable clinical risk-benefit balance. An extension phase of the VALOR trial is ongoing to compare the effects of early *versus* delayed initiation of the medicine at 3.5 years of follow-up. Preliminary findings from the extended study at only 52 weeks follow-up predicted better outcomes with early intervention of Tofersen. Procedural pain and headache were commonly reported adverse effects with Tofersen. A few patients developed neurological manifestations including myelitis, elevated intracranial pressure, aseptic or chemical meningitis, lumbar radiculopathy, and papilloedema.[4]

Besides Tofersen, two other medicines, namely Edaravone and Riluzole, have been approved by the FDA. However, they assist only in the symptomatic treatment of the disease.[5] Tofersen is the sole gene therapy available for ALS, highlighting the necessity for continued research and investigation. Nonetheless, the approval of Tofersen provides compelling evidence of advancements in the treatment of ALS and reflects our growing understanding of its pathophysiology.

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