With Tofersen, a first effective treatment is becoming available for ALS!

After decades of repeatedly negative clinical trial results, more than hope is emerging for ALS patients. Indeed, data from the VALOR study, a phase III clinical trial of tofersen in patients with ALS based on an SOD1 mutation, appeared in the prestigious journal *The New England Journal of Medicine* edition of September 21 2022. The study shows that the therapy reduces motor nerve cell damage and that patients show stabilization in their disease progression.

Amyotrophic Lateral Sclerosis, or ALS, gained name recognition in 2014 thanks to the "ice bucket challenge". In 10% of patients, the disease runs in the family. Mutations in the superoxide dismutase 1 gene (SOD1), are a frequent cause of this hereditary form of ALS. In Europe, SOD1 mutations occur in 20% of patients with familial ALS, in total about 2% of all ALS patients.

Tofersen is an antisense oligonucleotide, a small piece of hereditary material, which binds to the messenger molecule of the SOD1 gene, preventing the mutated SOD1 protein from being formed. Tofersen should be administered monthly through an epidural. It is being developed by the company Biogen. The phase I study already showed that tofersen treatment resulted in a decrease of the SOD1 protein in the spinal fluid and that the treatment was well tolerated. Four European groups participated in this study.

The VALOR study is a phase III study that then investigated the long-term effect of tofersen. The results published on September 21 2022 confirm that the treatment results in a decrease in the SOD1 protein in the lumbar fluid and a significant decrease in neurofilaments (a measure of nerve damage). After six months of treatment, no significant effect was seen between the treated and untreated group, but with long-term treatment, effects on functional decline, on lung function and on survival became evident. In some patients, complete stabilization occurs and sometimes even some improvement in muscle strength. "We have never seen this before in ALS studies, it is a milestone in ALS research," said Prof. Van Damme, member of the EUpALS Scientific Expert Board. Evy Reviers, Chairwoman of EUpALS, fully agrees "It shows that ALS is a treatable disease after all."

Tofersen can only be used in patients with an SOD1 mutation and the detection of this mutation can be done via a test. Now it remains to be seen how quickly EMA will approve tofersen's registration and how soon it can come to market. In the interim period, Biogen is committed to already making tofersen available to patients through an "Early Access Program."

With these positive clinical trial results for tofersen in SOD1-ALS, the state-of-the-art has clearly been progressed in ALS clinical research. Following Biogen, several other pharmaceutical companies are currently conducting similar antisense nucleotide-based clinical trials in other genetic subgroups of ALS patients.

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