August 2020 MND Research Article summary - Jessica Allsop, Research Assistant, University of Sheffield

Results from a clinical trial looking at using artificially engineered RNA (single stranded DNA) to reduce the levels of a mutant protein involved in some cases of MND

Phase 1-2 Trial of Antisense Oligonucleotide Tofersen for SOD1 ALS (Miller et al., July 2020, The New England Journal of Medicine, Vol 383, No. 2)
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MND is a currently incurable neurodegenerative disorder, that affects motor neuron function. Around 10% of cases are familial, thus having a genetic component, with mutations in the superoxide dismutase (SOD1) gene accounting for 2% of these cases. The mechanism in which this mutation works is thought to be via a toxic gain of function, thus increasing the amount of mutant protein in the body, which can be harmful. There are currently multiple clinical trials that are underway which are aiming to find a potential therapy, including this ascending-dose trial (a trial with multiple groups, each being given a higher dose than the last). In this trial, they designed the antisense oligonucleotide, Tofersen, an artificially engineered piece of RNA (a single stranded piece of DNA used in the making of proteins) to identify mutant SOD1 RNA. This then broke down the mutant SOD1 RNA by activating enzymes (proteins that speed up chemical reactions in the body) to do so. This meant that the mutant SOD1 protein couldn’t be made, thus reducing the levels of mutant SOD1 in the body.

By using individuals affected by MND, with this trial focusing on those affected by mutant SOD1, researchers at multiple universities across the world, in conjunction with the University of Sheffield, aimed to use the antisense oligonucleotide Tofersen to reduce the effects of MND by targeting the mutant form of SOD1, and decreasing the production of this protein. They did this by randomly assigning 50 patients in a 3:1 ratio, with one patient going to the placebo (a deliberately ineffective treatment) group, to each of the following dose groups: Placebo, 20mg, 40mg, 60mg and 100mg. Milligrams (mg) are 1/1000th of a gram, e.g. 20mg is equal to 0.02 grams. Each patient then got 5 injections of their assigned dose into their spinal cord over the course of 12 weeks.

48/50 patients got all 5 doses successfully. There was a reduction in the concentration of the mutant SOD1 protein in the spinal cord in all cases, including the placebo group with a 3% decrease, but the largest decrease was in the 100mg group where there was a 36% decrease in SOD1 concentrations in the cerebrospinal fluid from baseline levels. Cerebrospinal fluid is a clear fluid in the central nervous system that cushions the brain and spinal cord from injury, and also provides nutrients. There was also no difference in the effects of Tofersen with those who were classed as fast-progressing MND and those who weren’t.

This stage of the study could not go beyond this level of analysis. Overall, this therapy provides an interesting target, which does show some benefits. These benefits show a slowing in the decrease of the ALSFRS-R score (ALS Functional Rating Scale Revised), slow vital capacity (volume of air expired in an unforced manoeuvre), and the handheld dynamometry score (measurement of strength in 16 muscle groups), with 100mg Tofersen treatment. However, as they are descriptive tests, it is hard to draw conclusions from this data. Phase 3 of this trial is currently underway monitoring the safety and effectiveness of Tofersen, and the long term effects.