New insights from first clinical trial of potential treatment for motor neurone disease

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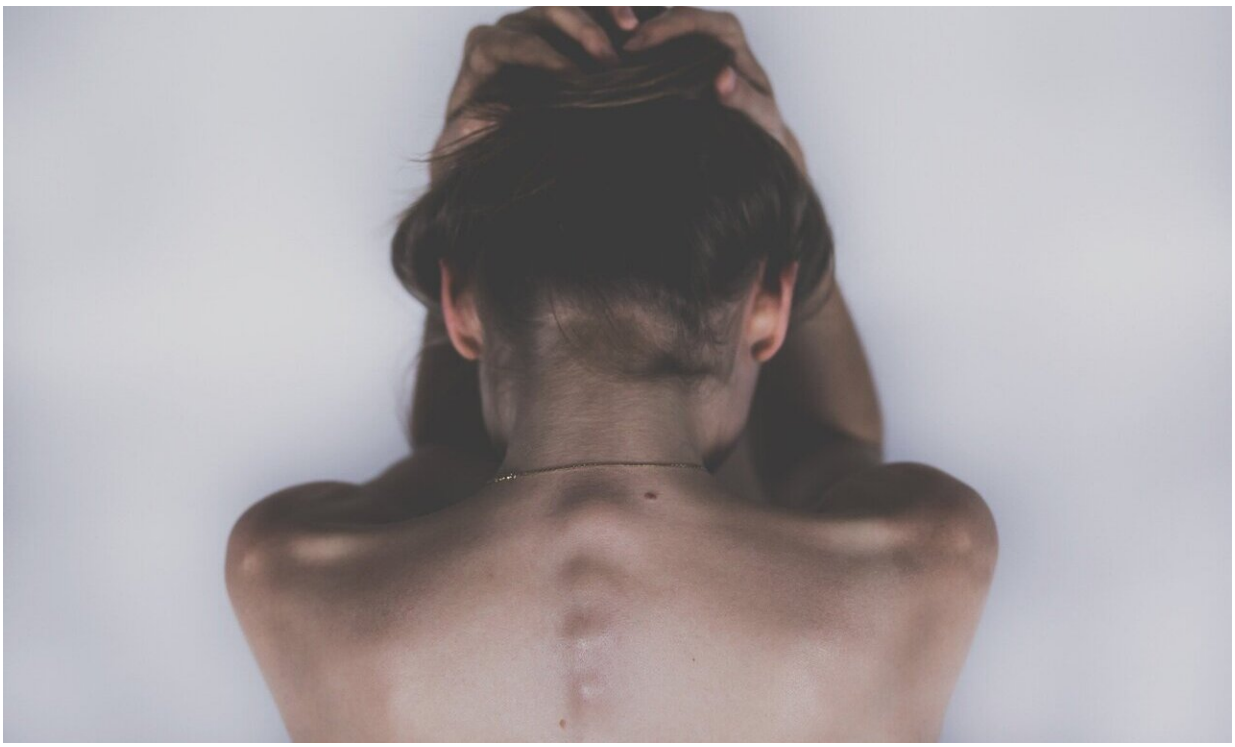

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Results from a randomized clinical trial have shown that a potential new treatment can help control the immune response of patients with motor neuron disease (MND), which could reduce further damage in the brain

and spinal cord.

MND is the name for a group of diseases which affects the nerves (motor neurons) in the brain and spinal cord causing muscles to weaken, stiffen and waste. It can affect how a person living with the disease can walk, talk, eat, drink and breathe, and there is currently no known cure.

Although the causes of MND (also known as amyotrophic lateral sclerosis, or ALS) are not fully understood, it is known that inflammatory mechanisms influence motor neuron damage in the brain and spinal cord. Circulating regulatory T cell lymphocytes (Tregs) contribute to the control of this inflammatory response.

Researchers from the Sheffield Institute of Translational Neuroscience (SITraN) were part of an international consortium contributing to the trial, IMODALS: Immune Modulation in ALS, the first of its kind for the potential treatment of ALS.

The study—published in *EBio Medicine*—investigated whether interleukin-2 (IL-2) – can control the immune response of patients with MND and found that as Tregs are dependent on IL-2 for survival and function. Treatment of IL-2 at low doses, as used in IMODALS, was found to be well tolerated and increases Treg numbers and function in the blood.

The IMODALS study had three main goals:

- To demonstrate in MND patients that low doses of IL-2 (ld IL-2) amplify Treg numbers and function in relation to dose.
- To ensure that ld IL-2 at the chosen doses would be safe to use in people with MND.
- That the study provided an opportunity to investigate the potential of ld IL-2 to modify immune mechanisms in ways that

might be beneficial in MND.

This third goal required regular blood sampling over the period of the trial to measure the numbers, function, and types of Tregs and of other circulating immune cells, and to test the hypothesis that ld IL-2 should alter the levels of blood markers (e.g., chemokines, cytokines and neurofilament proteins) of nerve cell damage in MND.

Professor Janine Kirby, Professor of Neurogenetics at SITraN, said: "Researchers in Sheffield looked at blood samples taken from patients over the course of the trial and saw what changes were occurring in the genes being expressed in blood cells. These results correlated with those changes viewed in the types of cells seen, such as an increase in the number of T cell regulatory cells, which are a type of immune cell."

The double-blinded study involved 36 people with MND, randomly assigned to three groups of 12 participants. Each group received one of two doses of ld IL-2, or placebo over five days every month over three months. Observations on safety continued for a further three months.

The main findings were that ld IL-2 significantly increased the numbers of circulating Tregs, as predicted, and foremost improved their ability to control other immune cell responses that contribute to nerve cell damage. This double benefit of 'more Tregs' and 'better Tregs' indicates that ld IL-2 therapy is fully functional in MND patients. Furthermore this response was related to the dose of IL-2.

Secondly, ld IL-2 was safe and well tolerated by the MND trial participants.

Thirdly, changes in blood cytokines and chemokines were in keeping with the notion that ld IL-2 reduces the harmful effects and enhances the beneficial effects of immune activity in the nervous system in MND.

Professor Dame Pam Shaw Professor of Neurology, Director of SITraN and Director of the NIHR Sheffield Biomedical Research Center said: "This was a pilot study to see if three cycles of low dose IL-2 treatment increased the number of T cell regulatory cells, as these types of cells are normally reduced in patients with MND. The treatment did increase the number of these cells, and importantly was also found to be safe to use in patients. These results allowed funding to be secured for a larger and longer Phase II Clinical Trial called MIROCALS to be undertaken."

She added: "The MIROCALS trial is currently underway across Europe and the Sheffield team is a key partner. The ultimate aim of this longer trial is to see whether low dose IL-2 improves life expectancy and quality of life of MND patients, and to obtain a biomarker read-out of the effectiveness of the treatment in individual patients."

Overall, the study findings strongly support the further investigation of ld IL-2 in MND and provide crucial insights on which to base larger trials designed to detect improvement in day to day activity and survival in MND.

More information: William Camu et al. Repeated 5-day cycles of low dose aldesleukin in amyotrophic lateral sclerosis (IMODALS): A phase 2a randomized, double-blind, placebo-controlled trial, *EBioMedicine* (2020). DOI: 10.1016/j.ebiom.2020.102844

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