INTERNATIONAL ALLIANCE OF ALS/MND ASSOCIATIONS

T Regulatory Cell Therapies
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Background

Neuroinflammation was discovered many years ago to be a key contributor to the degeneration of motor neurons in ALS. Cells called microglia that surround motor neurons and provide immune protection to a healthy central nervous system, become abnormally activated and can secrete substances that likely increase motor neuron damage. Other cells, called T cells, can exit the bloodstream into the area near motor neurons and can also play a neuroinflammatory role.

Through studying the aspects of T cells in ALS more closely it was discovered that certain types of T cells, called T regulatory cells (Tregs), can be protective and naturally reduce these neuroinflammatory effects. Furthermore, the level of effective Tregs is lower in people with ALS and the amount of Tregs is correlated with rate of disease progression (ie. more in slower progressors, less in fast). As a result, treatment strategies attempting to increase the body's production of Tregs or to provide more of them have been advanced to clinical trial in recent years. A number of trials are examining T regulatory cells as the primary means of treating ALS or as a contributor to a treatment strategy.

These include:

1) ***Dr. Stanley Appel's T regulatory cell transplants*** – Dr. Appel is the initial champion for the value of Tregs in ALS including founding research over a decade ago that demonstrated their protective effects in mouse models. In this treatment regimen, Tregs are removed from blood (a process called leukapheresis), multiplied in number outside the body (in a lab), and returned intravenously (IV) along with a low dose of a substance called interleukin-2 (IL-2), which helps stabilize the Tregs. An initial clinical trial of three individuals demonstrated very intriguing results (published here) that warranted the current 12 participant phase 2 trial. It is important to note that the first trial was extremely small and open label so interpretation of effect cannot be made at this point. The ongoing trial is a double-blind, placebo-controlled trial to primarily assess safety and Treg effect on immune and inflammatory ALS effects. There is a six month open label extension for all 12 participants after six months of study and it is no longer recruiting.
2) ***RAPA-501 Therapy*** – Rapa Therapeutics is pursuing an open label phase 1 trial of RAPA-501 T cells where T cells are removed from blood, treated outside the body (in a lab) with substances to produce Treg capabilities, followed by IV reintroduction of the cells to the participant with or without a regimen (called PC regimen) designed to assist in the Rapa T cell effectiveness. This trial is aimed as establishing safety and effective dose as the primary outcomes and will recruit 18 participants starting later in 2020.
3) ***Rapamycin (RAP-ALS)*** – An academic phase 2 trial at eight sites in Italy is studying the effects of oral rapamycin on ALS over 18 weeks of treatment, followed by 36 months of follow up. While an ability to affect ALS progression, levels of key biomarkers and other key metrics of how the treatment acts in the body will all be analyzed, the primary goal of the trial will be to measure Treg levels. Active and no longer recruiting, the trial aims to be complete in early 2021.
4) ***MIROCALS Trial*** – A joint academic effort between UK and French researchers, the Modifying Immune Response and OutComes in ALS (MIROCALS) trial is examining low dose IL-2 alone over 18 months to determine if it is sufficient to enhance a person's own Tregs. This is a large trial that was recruited across 17 clinics and is now fully enrolled with participants studied over 18 months for an effect on disease progression and survival. It is set to have results in the second half of 2021 and a website dedicated to the study can be found here. Results from an earlier Phase 2 trial were recently published here.

5) ***Nebulized RNS60*** – Revalesio Corporation is testing an inhaled experimental drug that contains oxygenated nanobubbles called RNS60, and has demonstrated anti-inflammatory and neuroprotective effects in preclinical ALS models. One of the effects demonstrated in mice was an increase in Tregs. RNS60 is soon to start in a phase 2 clinical trial of 140 participants with Treg levels as a secondary outcome to be measured. A small investigator-initiated, open label, pilot trial has previously established safety and tolerability, published here.

Recommendation

The SAC recommends that caution be taken in interpreting the effectiveness of T regulatory cells as a treatment for ALS. While promising preclinical science and data exists, and some underpowered, yet intriguing trial results as well, it is too early to know if any of these strategies are effective. Safety still needs to be assessed for Treg transplantation therapies. Each of these are exciting in their possibilities for treating ALS and the SAC looks forward to learning more from rigorous studies in the time ahead.