Immune tolerance in patients with Multiple Sclerosis and Neuromyelitis Optica by peptide-loaded tolerogenic dendritic cells: final results of the phase 1b clinical trial and extension

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Objective:
To verify the safety and signs of efficacy of the administration of tolerogenic dendritic cells (tolDCs) in patients with Multiple Sclerosis and Neuromyelitis optica spectrum disorder.

Background: Multiple sclerosis (MS) and Neuromyelitis Optica Spectrum Disorders (NMOSD) are autoimmune diseases of the central nervous system leading to significant disability. The presence of autoimmune responses to myelin-derived peptides in MS and aquaporin-4 (AQP4) in NMOSD in humans support the development of antigen-specific tolerance induction therapies such as tolDCs.

Design/Methods: We conducted a first in human Phase Ib clinical trial testing increasing concentrations of autologous tolDCs (50 to 300 10^6 cells i.v. divided into 3 doses administered every 2 weeks) loaded with 7 myelin and one aquaporin-4 peptides in 12 patients, 8 with MS and 4 with NMOSD. The primary end-point was the safety and tolerability of the intervention and secondary end-points were clinical outcomes (relapses and disability), imaging (MRI and OCT) and immunological markers (cell subsets, cell proliferation and cytokine secretion for specific peptides).

Results:
Therapy with tolDCs was well tolerated, without serious adverse events and with no therapy-related reactions. Patients remained stable at the clinical level in terms of relapses and disability scales, as well as at the imaging level. We observed a significant increase in the production of IL-10 levels in PBMCs stimulated with the peptides as well as an increase in the frequency of Tr1 cells by week 12 of follow-up. No significant differences were observed in terms of cell proliferation. These results were validated in 8 additional cases (5 MS and 3 NMO) treated with the higher dose, confirming the good tolerability of the therapy and the induction of immune tolerance by the treatment.

Conclusions:
The intravenous administration of peptide-loaded DCs vaccination is safe, feasible and effective in eliciting antigen specific IL-10 production by T regulatory cells in MS and NMOSD patients.