Title:

Safety and feasibility of a tolerogenic dendritic cell-based treatment for multiple sclerosis (MS): a comparison of intranodal and intradermal cell administration in two phase I clinical trials

Authors:

Barbara Willekens1, 2†, Silvia Presas-Rodríguez3, 4, Maria José Mansilla5, 6, Judith Derdelinckx1, 2†, Wai Ping Lee1, Griet Nij1, Maxime De Laere1, Inez Wens1, Patrick Cras2, Paul Parizel6, Wim Van Hecke8, Annemie Ribbens9, Geert Adams10, Marie-Madeleine Couttenye11, Juan Navarro-Barriuso5, 6, Aina Teniente-Serra5, 6, Bibiana Quirant-Sánchez5, 6, Ascension Lopez-diaz De Cerio12, Susana Inogós12, Felipe Prosper13, 14, Catharina C. Gross15, Heinz Wiendl15, S. Marieke Van Ham16, Anja Ten Brinke16, Herman Verheij17, Anke Kip17, Ana Marian Barriocanal18, Anna Massuet-Vilamajó19, Niel Hens20, 21, Zwi Berneman1, 2†, Eva Martínez-Cáceres5, 6, Cristina M. Ramo-Tello3 and Nathalie Cools1, 7 on behalf of RESTORE

Affiliations:

1 Laboratory of Experimental Hematology, University of Antwerp, Belgium, 2 Antwerp University Hospital, Department of Neurology, Belgium, 3 Hospital Germans Trias i Pujol, Spain, 4 Departamento de Medicina, Facultad de Medicina, Universidad Autónoma de Barcelona, Spain, 5 Hospital Germans Trias i Pujol, Spain, 6 Department of Cell Biology, Physiology and Immunology, Autonomous University of Barcelona, Spain, 7 Center for Cellular Therapy and Regenerative Medicine, Antwerp University Hospital, Belgium, 8 Department of Radiology, Antwerp University Hospital, Belgium, 9 Icometrix (Belgium), Belgium, 10 C-Clear Partners, Belgium, 11 Department of Nephrology, Antwerp University Hospital, Belgium, 12 Clínica Universidad de Navarra, Spain, 13 Área de Terapia Celular, Clínica Universidad de Navarra, Spain, 14 Centro de Investigación Médica Aplicada (CIMA), Spain, 15 Klinik für Allgemeine Neurologie, Universitätsklinikum Münster, Germany, 16 Sanquin Diagnostic Services, Netherlands, 17 Lygature, Netherlands, 18 Institut d’Investigació en Ciències de la Salut Germans Trias i Pujol (IGTP), Spain, 19 Hospital Germans Trias i Pujol, Spain, 20 Centre for the Evaluation of Vaccination, University of Antwerp, Belgium, 21 Center for Statistics, University of Hasselt, Belgium

Introduction: Most disease-modifying treatments for multiple sclerosis (MS) give rise to side-effects, ranging from mild to severe. Hence, an unmet need for treatments that combine excellent safety and high efficacy remains. Antigen-specific tolerization with autologous tolerogenic dendritic cells (tolDC) is a promising approach to meet this need.

Objectives: We assess the safety and feasibility of the therapeutic use of autologous tolDC in a well-defined population of MS patients in two single-center clinical trials, comparing intradermal (i.d., MS-tolDC, NCT02618902) and intranodal (i.n., TOLERVIT-MS, NCT02903537) administration.

Methods: Autologous monocytes are extracted via a leukapheresis procedure and cultured, stimulated and loaded with 7 myelin-derived antigens (MBP13-32, MBP111-129, MBP154-170, PLP139-154, MOG1-20, MOG35-55 and MBP83-99) and frozen, compliant with good manufacturing practice (GMP). According to a best-of-five design, six administrations at consecutive intervals are planned in 3 cohorts receiving incremental doses of tolDC. The number of adverse events (AE) and relapses,
neurological disability and magnetic resonance imaging (MRI) endpoints are evaluated to assess safety.

**Results:** Until September 12, 2018, 15 patients have been screened, of which 4 have been included in the clinical trial with i.d. administration of tolDC and 6 in the clinical trial with i.n. administration. Six patients received the investigational product and are currently in the treatment and safety follow-up phase. Four of the treated patients were diagnosed with relapsing remitting MS (1 male and 3 female) and two with primary progressive MS. The age ranged between 30 and 43 years and the baseline EDSS between 1.5 and 6.0. To date, no serious adverse events have been reported. Most adverse events were considered to be treatment unrelated, except for mild-moderate local reactions seen at the injection site. Two patients experienced a mild MS relapse (not meeting protocol defined criteria for confirmed MS relapse).

**Conclusions:** The interim results of the first dose cohort do not show an important safety signal to date. Further treatment and follow-up of patients is ongoing.

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**Trial registration:** Both studies are registered at clinicaltrials.gov: NCT02618902 and NCT02903537 (EudraCT numbers: 2015-002975-16 and 2015-003541-26, respectively).

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