MESEMS: A randomized, double blind placebo-controlled cross-over study to evaluate safety and efficacy of intravenous administration of autologous mesenchymal stem cells in patients with multiple sclerosis

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Introduction

Mesenchymal stem cells (MSC) are stromal cells residing in many tissues, including the bone marrow (BM), where they support hematopoiesis. MSC have been demonstrated to ameliorate experimental autoimmune encephalomyelitis through the induction of immune tolerance and promotion of tissue repair. Clinical experience with MSC, either autologous or heterologous, in other disease settings different from MS, and particularly in the treatment of graft-versus-host disease, showed a favorable safety profile. From these considerations, the first trials with BM-derived MSC for the treatment of MS were performed and published starting from 2007. These trials involved a limited number of subjects, with moderate to severe disability and active or progressive disease, treated with autologous, BM-derived MSC either administered by lumbar puncture (intrathecally) or intravenously (IV), at variable dosages. Due to the low number of treated subjects, most trials were underpowered for drawing conclusions on efficacy and reported only data about the safety profile, which was overall favorable. Based on this background, the International Mesenchymal Stem Cells Transplantation Study Group generated a scientific consensus through a shared network approach devising a protocol for a potential phase II trial with MSC for active MS not responding to available treatments. Here we describe the protocol for a phase II trial assessing safety and efficacy of MEsenchymal StEm cells for the treatment of Multiple Sclerosis (MESEMS). The IMSCTSG network approach is based on the idea of carrying out an international trial, based on the shared consensus previously released by the network and intended as a group of partially independent national clinical trials.

Methods

Trials belonging to the MESEMS network share: trial design and primary outcomes of the study, a central randomization procedure, central collection of data through a unique Contract Research Organization (CRO) utilizing a common electronic CRF, centralized collection and analysis of MRI images (MIAC, Basel , Switzerland) and common funding of some centralized procedures by non-profit organizations. In detail, funding was obtained nationally through foundations and MS Societies, while the Italian MS Foundation, MSIF and ECTRIMS have financially supported coordination and centralized activities. However, local trials have obtained independent authorization by national authorities, have been independently registered to trial databases (either EudraCT or Clinicaltrials.gov), employ MSC isolated and expanded by local cell factories and may slightly differ in the patients population. The design will permit pooled analysis of data for the evaluation of primary and secondary objectives. While the primary and secondary objectives are shared among the single trials of the MESEMS network and are going to be the object of a single publication, freedom is given to all centers to perform independent, ancillary studies to be published separately.

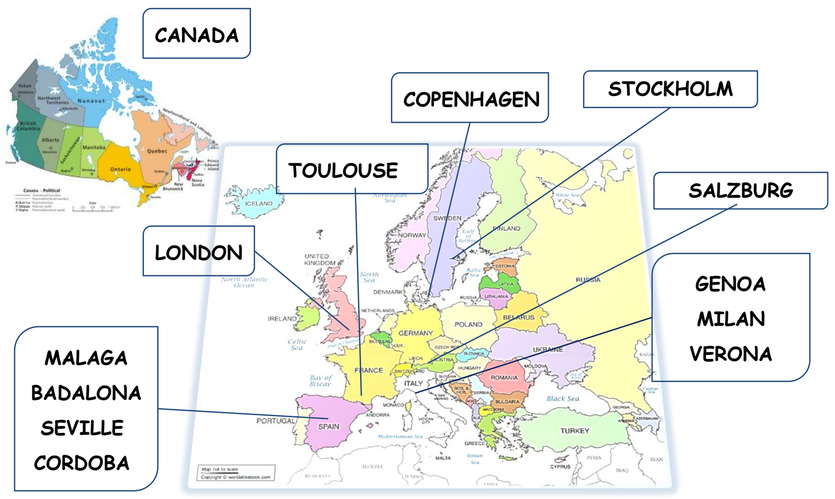

Figure 1: Countries where the MESEMS trial is being investigated

Aim	Measures
Safety of IV therapy with autologous MSC in RRMS, SPMS, and PPMS patients.	Number and severity of adverse events within each treatment arm
Activity of autologous MSCs in MS patients	Reduction as compared to placebo in the total number of contrast-enhancing lesions (GEL) at MRI acquired on conventional MRI scans (minimum magnetic field intensity: 1.5 T) over 24 weeks.

Table 1: Primary objectives of the MESEMS trial and related measures

RRMS with one of the following
≥ 1 clinically documented relapse in past 12 months
≥ 2 clinically documented relapses in last 24 months
≥ 1 GEL at MRI performed within the last 12 months or ≥ 1 new T2 lesion in last 12 months
SPMS with:
An increase of ≥1 EDSS point (if at randomization EDSS ≤ 5.0) or 0.5 EDSS point (if at randomization EDSS ≥ 5.5) in the last 12 months AND ≥ 1 clinically documented relapse or ≥ 1 GEL at MRI within the last 12 months
PPMS with all the following
An increase of ≥ 1 EDSS point (if at randomization EDSS ≤ 5.0) or 0.5 EDSS point (if at randomization EDSS ≥ 5.5), in the last 12 months
≥ 1 GEL at MRI performed within the last 12 months
Positive cerebrospinal fluid (CSF) (oligoclonal banding)

Table 2: Inclusion criteria for the MESEMS trial

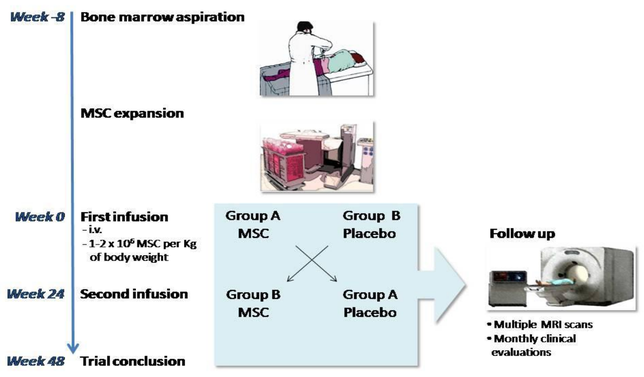

Figure 2: Schematic depiction of the MESEMS trial design (from ref. 6)

Results

MESEMS is being investigated in 8 countries, with an anticipated enrollment of 160 MS patients. The MESEMS protocol is a double-blind, randomized, sham-controlled cross-over trial. The primary endpoints are safety (measured as number and severity of adverse events-AE) of IV treatment with autologous MSC and efficacy at MRI within the first 24 weeks after treatment. In detail, efficacy will be then defined as reduction in the number of gadolinium-enhancing lesions (GEL) at 24 weeks in those who received MSC at week 0 compared to those who received placebo. Secondary endpoints include safety and efficacy at 48 weeks, comparison of early vs delayed treatment, and clinical efficacy at 24 and 48 weeks (**Table 1**: primary objectives of the MESEMS project). Secondary outcomes aim to gather preliminary information of the efficacy on other MRI metrics, clinical, immunological, neuropsychological and neuro-ophthalmological parameters. The main inclusion criteria for the MESEMS trial are: relapsing-remitting, secondary progressive or primary progressive MS displaying disease activity by clinical and MRI parameters, age 18-50, EDSS 3.0-6.5 and disease duration 2-10 years **(Table 2).** Thirty patients have been enrolled in Italy so far in the three Italian Clinical Centers of University of Genova, San Raffaele Institute in Milan, and University of Verona. Upon informed consent, patients undergo central randomization and a BM aspirate at week (-8). The Cell Factory "Lanzani" , Ospedale Papa Giovanni XXIII, Bergamo, expands the BM-derived MSC up to a number of 1-2 millions per Kg of patient's body weight and, after the appropriate quality checks, freezes one IV bag of MSC in infusion medium and another IV bag containing infusion medium only (i.e. placebo). According to the central randomization code, patients receive one bag at baseline (week 0) and the other at week 24. For evaluation of safety, AEs occurrence and severity are registered monthly since inclusion according to the CTC-AE classification. For evaluation of efficacy, patients undergo a contrast-enhanced brain MRI at baseline and then at six further timepoints.

Conclusions

Getting reliable data on safety and efficacy of stem cells based therapies, obtained by large, phase II clinical trials conducted within the principles of the good clinical practice, is particularly important for patients and for the scientific community but is not easy, mainly due to economic constraints. This novel approach to a collaborative trials was devised in order to overcome some key issues that would otherwise prevent from performing a typical multicenter study: first of all, the international nature of such effort would have required a large economical support, far beyond the possibility of an academic network such as the IMSCTSG and almost impossible to obtain entirely from supranational funding agencies in a reasonable amount of time, thus seriously putting at risk the clinical and rigorous development of this innovative therapeutic approach; secondly, and related to the particular nature of the investigational product (autologous, BM-derived cells), costs-, time- and space-constraints would have not permitted to isolate and expand MSC from all enrolled subjects in a single cell factory, unless using allogeneic cell products prepared in large scale by a pharmaceutical company. This would have also increased the chance that national regulatory issues would have impeded the use of cells products produced according to procedures not fully complying with local regulations for advanced therapy medicinal products (ATMP). The involvement of different national cell factories, in turn, despite bringing some minor differences in cell preparation from nation to nation, guarantees full complying to national laws, sometimes slightly different among countries, and standard operation procedures approved by national authorities, a requirement to obtain authorization for MSC expansion. Results of the MESEMS trial will permit us to evaluate the safety and efficacy of MSC in MS and provide the rationale for designing a phase III program that will center on proving repair.

Disclosures and funding

The authors have nothing to disclose related to the topic of this abstract.

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