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MEsenchymal StEm cells for Multiple Sclerosis (MESEMS): a randomized, double blind, cross-over phase I/II clinical trial with autologous mesenchymal stem cells for the therapy of multiple sclerosis.

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Abstract

BACKGROUND:

Multiple sclerosis (MS) is an inflammatory disease of the central nervous system with a degenerative component, leading to irreversible disability. Mesenchymal stem cells (MSC) have been shown to prevent inflammation and neurodegeneration in animal models of MS, but no large phase II clinical trials have yet assessed the exploratory efficacy of MSC for MS.

METHODS/DESIGN:

This is an academic, investigator-initiated, randomized, double-blind, placebo-compared phase I/II clinical trial with autologous, bone-marrow derived MSC in MS. Enrolled subjects will receive autologous MSC at either baseline or at week 24, through a cross-over design. Primary co-objectives are to test safety and efficacy of MSC treatment compared to placebo at 6 months. Secondary objectives will evaluate the efficacy of MSC at clinical and MRI levels. In order to overcome funding constraints, the MEsenchymal StEm cells for Multiple Sclerosis (MESEMS) study has been designed to merge partially independent clinical trials, following harmonized protocols and sharing some key centralized procedures, including data collection and analyses.

DISCUSSION:

Results will provide patients and the scientific community with data on the safety and efficacy of MSC for MS. The innovative approach utilized to obtain funds to support the MESEMS trial could represent a new model to circumvent limitation of funds encountered by academic trials.

TRIAL REGISTRATION:

Andalusia: NCT01745783 , registered on Dec 10, 2012. Badalona: NCT02035514 EudraCT, 2010-024081-21. Registered on 2012. Canada: ClinicalTrials.gov, NCT02239393 . Registered on September 12, 2014. Copenhagen: EudraCT, 2012-000518-13 . Registered on June 21, 2012. Italy: EudraCT, 2011-001295-19, and ClinicalTrials.gov, NCT01854957 . Retrospectively registered on May 16, 2013. London: Eudra CT 2012-002357-35, and ClinicalTrials.gov, NCT01606215 . Registered on May 25, 2012. Salzburg: EudraCT, 2015-000137-78 . Registered on September 15, 2015. Stockholm:

ClinicalTrials.gov, NCT01730547 . Registered on November 21, 2012. Toulouse: ClinicalTrials.gov, NCT02403947 . Registered on March 31, 2015.

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Mesenchymal Stromal Cell-Based Therapy: New Perspectives and Challenges.

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Abstract

Stem cells have been the focus of intense research opening up new possibilities for the treatment of various diseases. Mesenchymal stromal cells (MSCs) are multipotent cells with relevant immunomodulatory properties and are thus considered as a promising new strategy for immune disease management. To enhance their efficiency, several issues related to both MSC biology and functions are needed to be identified and, most importantly, well clarified. The sources from which MSCs are isolated are diverse and might affect their properties. Both clinicians and scientists need to handle a phenotypic-characterized population of MSCs, particularly regarding their immunological profile. Moreover, it is now recognized that the tissue-reparative effects of MSCs are based on their immunomodulatory functions that are activated following a priming/licensing step. Thus, finding the best ways to pre-conditionate MSCs before their injection will strengthen their activity potential. Finally, soluble elements derived from MSC-secretome, including extracellular vesicles (EVs), have been proposed as a cell-free alternative tool for therapeutic medicine. Collectively, these features have to be considered and developed to ensure the efficiency and safety of MSC-based therapy. By participating to this Special Issue "Mesenchymal Stem/Stromal Cells in Immunity and Disease", your valuable contribution will certainly enrich the content and discussion related to the thematic of MSCs.

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Bench-to-bedside optimization of mesenchymal stem cell isolation, processing, and expansion for *in vivo* administration.

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Abstract

Aim: In this study, we aimed at identifying the optimal conditions for isolation, processing and expansion of mesenchymal stem cells (MSCs). **Methods:** Porcine bone marrow was obtained from either small- or large-volume bone marrow aspirate (BMA). Next, three BMA processing methods were compared. Finally, the best condition was selected from various culture parameters, including basal media, supplementation and seeding density. **Results:** Our results demonstrate that a small-volume BMA and direct plating yields significantly higher concentration of MSCs. Basal media supplementation with 10% platelet lysate and seeding density of 1000 cells/cm^2 can generate large numbers of

multipotent MSCs with augmented function and low population doublings. **Conclusion:** This work provides guidance for preparation of robust MSCs for future clinical trials.

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Defining mesenchymal stromal cell (MSC)-derived small extracellular vesicles for therapeutic applications.

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Abstract

Small extracellular vesicles (sEVs) from mesenchymal stromal/stem cells (MSCs) are transiting rapidly towards clinical applications. However, discrepancies and controversies about the biology, functions, and potency of MSC-sEVs have arisen due to several factors: the diversity of MSCs and their preparation; various methods of sEV production and separation; a lack of standardized quality assurance assays; and limited reproducibility of *in vitro* and *in vivo* functional assays. To address these issues, members of four societies (SOCRATES, ISEV, ISCT and ISBT) propose specific harmonization criteria for MSC-sEVs to facilitate data sharing and comparison, which should help to advance the field towards clinical applications. Specifically, MSC-sEVs should be defined by quantifiable metrics to identify the cellular origin of the sEVs in a preparation, presence of lipid-membrane vesicles, and the degree of physical and biochemical integrity of the vesicles. For practical purposes, new MSC-sEV preparations might also be measured against a well-characterized MSC-sEV biological reference. The ultimate goal of developing these metrics is to map aspects of MSC-sEV biology and therapeutic potency onto quantifiable features of each preparation.

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Mobilization of Transplanted Bone Marrow Mesenchymal Stem Cells by Erythropoietin Facilitates the Reconstruction of Segmental Bone Defect.

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Abstract

Reconstruction of segmental bone defects poses a tremendous challenge for both orthopedic clinicians and scientists, since bone rehabilitation is requisite substantially and may be beyond the capacity of self-healing. Bone marrow mesenchymal stem cells (BMSCs) have been identified as an optimal progenitor cell source to facilitate bone repair since they have a higher ability for proliferation and are more easily accessible than mature osteoblastic cells. In spite of the potential of BMSCs in regeneration medicine, particularly for bone reconstruction, noteworthy limitations still remain in previous application of BMSCs, including the amount of cells that could be recruited, the compromised bone migration of grafted cells, reduced proliferation and osteoblastic differentiation ability, and likely tumorigenesis. Our current work demonstrates that BMSCs transplanted through the caudal vein can be mobilized by

erythropoietin (EPO) to the bone defect area and participate in regeneration of new bone. Based on the histological analysis and micro-CT findings of this study, EPO can dramatically promote the effects on the osteogenesis and angiogenesis efficiency of BMSCs in vivo. Animals that underwent EPO+BMSC administration demonstrated a remarkable increase in new bone formation, tissue structure organization, new vessel density, callus formation, and bone mineral density (BMD) compared with the BMSCs alone and control groups. At the biomechanical level, we demonstrated that combing transplantation of EPO and BMSCs enhances bone defect reconstruction by increasing the strength of the diaphysis, making it less fragile. Therefore, combination therapy using EPO infusion and BMSC transplantation may be a new therapeutic strategy for the reconstruction of segmental bone defect.