



SPECIAL ARTICLE

## A protocol proposition of cell therapy for the treatment of chronic obstructive pulmonary disease<sup>☆</sup>



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### KEYWORDS

Cell therapy;  
Chronic obstructive  
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**Abstract** The main feature of pulmonary emphysema is airflow obstruction resulting from the destruction of the alveolar walls distal to the terminal bronchioles. Existing clinical approaches have improved and extended the quality of life of emphysema patients. However, no treatment currently exists that can change the disease course and cure the patient. The different therapeutic approaches that are available aim to increase survival and/or enhance the quality of life of emphysema patients. In this context, cell therapy is a promising therapeutic approach with great potential for degenerative pulmonary diseases. In this protocol proposition, all patients will be submitted to laboratory tests, such as evaluation of heart and lung function and routine examinations. Stem cells will be harvested by means of 10 punctures on each anterior iliac crest, collecting a total volume of 200 mL bone marrow. After preparation, separation, counting and labeling (optional) of the mononuclear cells, the patients will receive an intravenous infusion from the pool of Bone Marrow Mononuclear Cells (BMMC). This article proposes a rational and safe clinical cellular therapy protocol which has the potential for developing new projects and can serve as a methodological reference for formulating clinical application protocols related to the use of cellular therapy in COPD. This study protocol was submitted and approved by the Brazilian National Committee of Ethics in Research (CONEP – Brazil) registration number 14764. It is also registered in ClinicalTrials.gov (NCT01110252).

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**PALAVRAS-CHAVE**

Terapia celular;  
Doença pulmonar  
obstrutiva crônica;  
Enfisema pulmonar;  
Células-tronco

**Proposta de um protocolo de terapia celular para o tratamento da doença pulmonar obstrutiva crônica**

**Resumo** O enfisema pulmonar apresenta como principal característica a obstrução do fluxo aéreo resultante da destruição das paredes alveolares distais ao bronquíolo terminal. As abordagens terapêuticas clínicas existentes têm contribuído para o prolongamento e melhora na qualidade de vida dos portadores de enfisema. Porém, até o momento nenhum tratamento clínico existente tem sido capaz de alterar o curso da doença e resultar em cura do doente. As diferentes estratégias terapêuticas têm como objetivo o aumento da sobrevida e/ou a melhora na qualidade de vida dos doentes com enfisema pulmonar. Neste contexto, a terapia celular apresenta-se como uma alternativa terapêutica promissora, com grande potencial de aplicabilidade em doenças degenerativas do pulmão. Nesta proposta de protocolo, todos os pacientes serão submetidos a testes laboratoriais, como a avaliação das funções cardíaca e pulmonar e exames de rotina. A colheita das células-tronco será realizada por meio de 10 punções em cada crista ilíaca, totalizando um volume final de 200 mL de medula óssea coletada. Após a preparação, separação, contagem e marcação (opcional) das células mononucleares, os pacientes receberão uma infusão intravenosa de uma suspensão de Células Mononucleares da Medula Óssea (CMMO). Pretende-se, neste artigo, a proposta de um protocolo de terapia celular racional e seguro com potencial para o desenvolvimento de novos projetos, que sirva como referencial metodológico para a formulação de protocolos de aplicação clínica relacionados ao uso de terapia celular para a DPOC. O protocolo proposto neste artigo foi submetido e aprovado pelo Comitê Nacional de Ética em Pesquisa (Conep – Brasil) registrado como o número 14.764. Também está registrado no Clinical Trials.gov (NCT01110252).

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**Introduction**

Pathological states characterized by gradual, nonreversible airflow impairment come under the general heading of chronic obstructive pulmonary disease (COPD).<sup>1-3</sup> Within the COPD spectrum, there are two nosological entities: chronic bronchitis and emphysema. Chronic bronchitis is characterized by fibrosis, luminal plugs, increased airways resistance and airways inflammation. The main feature of pulmonary emphysema is the destruction of the alveolar walls distal to the terminal bronchiole, without significant pulmonary fibrosis.<sup>1-6</sup>

The treatment of COPD and emphysema includes bronchodilators, short-acting and long-acting,  $\beta_2$ -agonists, anticholinergics, xanthines, corticosteroids, mucolytics and antibiotics. Other clinical support measures include rehabilitation therapies, oxygen therapy and ventilation strategies. New clinical and pharmacological approaches have significantly prolonged and improved the quality of life of patients with emphysema; however, there are no effective or curative treatments. Surgical treatment, such as lung transplantation, is an option which is theoretically effective; however, it is a high risk procedure and involves complex surgery; in addition it is severely affected by the scarcity of donors.<sup>1-8</sup>

In this context, cell therapy with adult stem cells (ASC) has not been thoroughly explored or studied, despite its great potential for the treatment of pulmonary degenerative diseases. A large number of previous studies in animal models have suggested that adult stem cells (hematopoietic and mesenchymal) would be able to migrate to injured areas and promote morphological and/or functional regeneration of the pulmonary parenchyma.<sup>9-12</sup>

The main objective of this article is to propose a rational and safe clinical cell therapy protocol employing Bone Marrow Mononuclear Cells (BMMC). This new methodological approach is expected to represent a potentially interesting and consistent reference for the development of new protocols for clinical application in COPD.

The protocol proposed in this article refers to the project registered in ClinicalTrials.gov (NCT01110252) and the Brazilian National Committee of Ethics in Research (CONEP – Brazil) – registration number 14764.

**Methods/design****Study design**

This study corresponds to a phase I clinical trial (safety evaluation of the procedure) with methodological and operational support from the University of the State of São Paulo – UNESP (Assis, SP, Brazil). The participants received written and verbal information explaining the study and written consent was obtained from all participants before beginning the procedure.

The protocol design was based on previous studies that have indicated that the procedures for collection, separation and infusion of BMMC are virtually free of adverse effects.<sup>11-17</sup> The selection criteria were based on the fact that the patients, despite being in an advanced stage of COPD, presented good clinical, laboratory and psychological conditions (cardiac function, nutritional condition, psychosocial and emotional profile and family support) (Fig. 1).

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