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Cell therapy with autologous mesenchymal stromal cells in post-traumatic syringomyelia

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Abstract

Background aims. Recently, clinical studies show that cell therapy with mesenchymal stromal cells (MSCs) improves the sequelae chronically established in paraplegic patients, being necessary to know which of them can obtain better benefit. *Methods.* We present here a phase 2 clinical trial that includes six paraplegic patients with post-traumatic syringomyelia who received 300 million MSCs inside the syrinx and who were followed up for 6 months. Clinical scales, urodynamic, neurophysiological, magnetic resonance (MR) and studies of ano-rectal manometry were performed to assess possible improvements. *Results.* In all the cases, MR at the end of the study showed a clear reduction of the syrinx, and, at this time, signs of improvement in the urodynamic studies were found. Moreover, four patients improved in ano-rectal manometry. Four patients improved in neurophysiological studies, with signs of improvement in evoked potentials in three patients. In the American Spinal Injury Association (ASIA) assessment, only two patients improved in sensitivity, but clinical improvement in neurogenic bowel dysfunction was observed in four patients and three patients described improvement in bladder dysfunction. Spasms reduced in two of the five patients who had them previous to cell therapy, and spasticity was improved in the other two patients. Three patients had neuropathic pain before treatment, and it was reduced or disappeared completely during the study. Only two adverse events ocurred, without relation to the cell therapy. *Conclusions.* Cell therapy can be considered as a new alternative to the treatment of post-traumatic syringomyelia, achieving reduction of syrinx and clinical improvements in individual patients.

Key Words: *cell therapy, mesenchymal stromal cells, paraplegia, post-traumatic syringomyelia, spinal cord injury*

Introduction

At present, cell therapy with autologous mesenchymal stromal cells (MSCs) seems to be a therapeutic promise for patients with established spinal cord injury (SCI), but these techniques are still subject to uncertainties related to the disparity of protocols and subject selection. When cell therapy is applied to patients with SCI, a strategy may be the intralesional or intrathecal administration of MSCs. This type of cell therapy is safe and effective for patients with chronic paraplegia [1,2]. However, if MSCs are administered into a great cavity, the possibility that transplanted cells die by a mechanism of anoikis [3], as an apoptotic response to the absence of cell-matrix interactions, must be taken into account. The present clinical trial studies if, in the case of paraplegic patients with extensive syringomyelia, some type of clinical improvement can be expected after MSC administration or if these patients should be excluded from any attempt at improvement. Thus, in the present article we show the experience obtained with a phase 2 clinical trial

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(EudraCT: 2015-002383-16; Clinical Trials.gov NCT02807142), which includes six patients with chronic paraplegia and an extensive post-traumatic syringomyelia.

Methods

Cell therapy medicament

We used a cell therapy medicament (NC1) developed after pre-clinical studies by our group and currently approved as a medicament under clinical investigation (PEI number 12–141) by the Spanish Agency of Medicament and Health Products (AEMPS). This medicament consists of autologous MSCs and autologous plasma as its excipient. Previous to medicament preparation, a sample of peripheral blood was retrieved from each patient for genomic studies to rule out chromosomal abnormalities that could discourage cell expansion and to obtain a genetic fingerprint (KaryoNIM Stem Cells and KaryoNIM STR test, respectively; NIMGenetics).

Data about the cell therapy medicament, including genetic studies, culture, formulation, packaging and phenotypic characterization of the MSCs, are provided in the Supplementary Material (Supplementary Figure S1).

Study design and treatment

The clinical trial protocol was approved by the ethics committee of Puerta de Hierro-Majadahonda Hospital and by the AEMPS. It was conducted in accordance with the principles of the Declaration of Helsinki [4] and good clinical practice guidelines [5]. A flow chart of the patients can be seen in Supplementary Material (Supplementary Figure S2). Adverse events were collected throughout the follow-up and classified according to the Medical Dictionary for Regulatory Activities (MedDRA version 18.1).

This clinical trial included six male patients. Age ranged between 30 and 50 years (mean ± standard deviation [SD], 39 ± 7.6 years). The time elapsed from the SCI until the moment of initiating the cell therapy ranged between 5.75 and 27.68 years (mean ± SD, 13.73 ± 8.65 years). According the American Spinal Injury Association Impairment Scale (AIS), three patients (50%) were American Spinal Injury Association (ASIA) A, two patients (33.3%) were ASIA B and one patient (16.6%) was ASIA D. With regard to the level of SCI, two patients (33.3%) had the lesion at D5 level, and the remaining four patients had the level of SCI at D3, D4, D8 and L1, respectively (Table I).

Table I. Clinical data of the patients.

Patient code	01	02	03	04	05	06
Age (y)	**30**	**50**	**43**	**38**	**42**	**31**
Time since SCI (y)	**5.75**	**27.68**	**17.01**	**6.16**	**17.72**	**8.07**
Vertebral level	**D3**	**D8**	**L1**	**D5**	**D4**	**D5**
AIS grade	**A**	**A**	**D**	**B**	**B**	**A**

In magnetic resonance (MR), all of the patients had a large syringomyelic cavity on either side of the SCI area. In length, the extension of the syrinx ranged between 87 and 300 mm (mean ± SD, 210.3 ± 90.94 mm). In the medium sagittal plain, the width of the syrinx ranged between 10 and 20 mm (mean ± SD, 12.05 ± 3.97 mm). The measurements were taken by means of software associated with MR-3T equipment (Philips Intera Achieva XR, v 263.9; Philips Healthcare) on sagittal T2-weighted images and MR-myelography images achieved with sequences of "turbo spin-echo".

Treatment consisted in the administration, inside of the syrinx, of 300 x 10^6 autologous expanded MSCs, supported in autologous plasma (month 1 of the study; Supplementary Figures S3, 4 and 5). The patients were followed up until month 6.

Clinical scores were obtained from each patient by means of the following scales: the scale provided by the ASIA [6], the SCI functional rating scale of the International Association of Neurorestoratology (SCI Functional Rating Scale of the International Association of Neurorestoratology [IANR-SCIFRS] scale) [7], the Visual Analog Scale (VAS) for the evaluation of neuropathic pain [8], the Penn [9] and the modified Ashworth [10] scales for the evaluation of spasms and spasticity, respectively, the Geffner scale [11] for the study of bladder function and the scale described by Krogh *et al.* [12] for the study of neurogenic bowel dysfunction (NBD). MR and studies of neurophysiology, urodynamic and ano-rectal manometry were also performed before and after the treatment. Additional details are provided in the Supplementary Material.

Statistical analysis

To study the differences between the scores of the clinical scales, the nonparametric Wilcoxon rank test has been used, comparing the result of each time period with results at baseline. Descriptive analysis was performed for urodynamic, neurophysiological and ano-rectal manometry parameters. Safety analysis was analyzed by means of frequencies and percentages. The graphs were made with the GraphPad Prism program for Windows (version 5.04; GraphPad Software). All inferential procedures used $\alpha = 0.05$ as the level of risk.

Results

In our present clinical trial, the cell expansion process did not involve any alteration to the genome of the cells in any of the cases, according to the results