MESENCHYMAL STROMAL CELLS

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 syring 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 occurred, 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

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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 (EudraCT: 2015-002383-16; Clinical [Trials.gov](https://www.clinicaltrials.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 $\pm$ 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 $\pm$ SD, 13.73 ± 8.65 years). According to 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

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

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](#)).

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 $\pm$ SD, 210.3 ± 90.94 mm). In the medium sagittal plain, the width of the syrinx ranged between 10 and 20 mm (mean $\pm$ 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 300×10^6 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

Table II. Different scores in ASIA scale.

	Months	Mean	SD	p-value	Effect size	
Total Score	Before treatment	143.00	16.20	-	-	
	At 3 months FU	144.3	16.69	0.37	-	
	At 6 months FU	149.00	17.18	0.12	-	
Pin Prick Score	Before treatment	41.67	5.27	-	-	
	At 3 months FU	43.17	6.36	0.25	-	
	At 6 months FU	44.67	7.03	0.06	-	
Light Touch Score	Before treatment	50.33	11.76	-	-	
	At 3 months FU	50.17	11.55	> 0.99	-	
	At 6 months FU	53.33	11.94	0.25	-	

Wilcoxon test was applied comparing each month with baseline. Tendency to improvement was observed but without statistical significance.

FU, follow-up.

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 obtained after analysis by the Array—comparative genomic hybridization platform.

Adverse events

During the study, two patients suffered some type of adverse event (AE); patient 02 had an episode of bronchopneumonia and patient 04 had accidental burns on the legs. In both cases, these AEs had no relationship with the treatment.

Sensitivity and motor assessment

Sensitivity and motor assessments, according to the ASIA scale, did not show changes in motor scores during the follow-up in any of the patients. In sensitivity, only two patients showed improvement. Patient 02 changed the light touch score from 46 (baseline and at the third month) to 59 at the end of the study. Patient 03 changed the light touch score from 53 (baseline) to 57 at the end of the study, and the pin prick score from 43 (baseline) to 50 at the third month and to 55 at the end of follow-up. The statistical study failed to obtain significant differences between sensitivity scores at the end of the follow-up compared with the pre-treatment scores ($P = 0.25$ in light touch score assessment, and $P = 0.06$ in pin prick score assessment). Table II shows the scores of sensitivity obtained in the ASIA scale previous to treatment, at the third month

Table III. Scores in IANR-SCIFRS scale.

	Months	Mean	SD	p-value	Effect size	
IANR SCIFRS	Before treatment	29.33	7.86	-	-	
	At 3 months FU	32.33	6.31	0.06	-	
	At 6 months FU	34.83	3.86	0.06	-	

Wilcoxon test was applied comparing each month with baseline. Tendency to improvement was observed but without statistical significance.

after MSC administration and at the end of the follow-up (month 6).

Spinal cord function assessed using the IANR-SCIFRS scale

The IANR-SCIFRS scale evaluates the global spinal cord function through nine sections, with a final section that only applies to men and assesses sexual function. When statistical study was performed, the average score in IANR-SCIFRS before treatment was 29.33 points (SD, 7.86 points), and, at the end of the study, it was 34.83 points (SD, 3.86 points), showing a tendency to improvement, but without statistical significance ($P = 0.06$ at the third and sixth months; Table III).

The assessment of sexual function, according to the IANR-SCIFRS scale, failed to show improvement in any of the patients.

At the end of follow-up, the two patients who showed improvement in sensitivity in the ASIA assessment reported better sphincter function in the evaluation of the IANR-SCIFRS, which evaluates from 0 to 6 points this parameter (patient 02 changed from 0 to 2 points, and patient 03 changed from 0 to 3 points).

According to the analysis of global IANR-SCIFRS scale, two patients showed a "slight handicap," before treatment, and four patients showed a "medium handicap," while, at the end of the follow-up, five patients showed a "slight handicap" and the remaining patient showed a "medium handicap" (Figure 1).

Spasms and spasticity

Previous to cell therapy, all the patients showed variable degree of spasms and/or spasticity measured using the Penn and Ashworth scales, respectively. In four patients, these manifestations improved during the treatment, but no differences with statistical significance were found. Tables IV and V show the tendency to improvement in spasms (Penn scale) and spastic-

ity (Ashworth scale) but statistical analysis between scores before treatment and at the end of follow-up failed to obtain significance ($P = 0.50$).

Neuropathic pain

Prior to cell therapy, neuropathic pain, measured using the VAS scale, was present in three patients. In all of them, it decreased or disappeared completely during the time of follow-up. Table VI shows the evolution in the scores of neuropathic pain measured using the VAS scale, with a tendency to improvement, but statistical analysis between scores before treatment and at 6-month time points failed to obtain significance ($P = 0.25$).

Effect of cell therapy on bladder and bowel dysfunction

We analyzed the possible clinical improvement of bladder and bowel dysfunction using the scales of Geffner and NBD, respectively. In the Geffner scale (Table VII), which values bladder function, improvement was observed in three patients, but statistical analysis failed to obtain significant differences between scores at the end of the follow-up compared with the pre-treatment scores ($P = 0.25$).

In the NBD scale, which values neurogenic bowel dysfunction, improvement was also observed in four patients, but statistical analysis failed also to obtain significant differences between scores at the end of the follow-up compared with the pre-treatment scores ($P = 0.12$; Table VIII).

When the NBD rating scale was analyzed, we observed that previous to cell therapy, one patient had a very minor NBD, one patient had a minor NBD, one patient had a moderate NBD and three patients had a severe NBD. At 3 months of follow up, two patients had a very minor NBD, one patient had a minor NBD, two patients had a moderate NBD and one patient had a severe NBD. At the end of the follow-up, three patients had a very minor

Figure 1. Improvements of patients in the IANR-SCIFRS scale. Previous to cell therapy, two patients had a slight handicap and four patients had a medium handicap. At the end of the study, five patients had a slight handicap and one patient had a medium handicap.

NBD, one patient had a minor NBD, one patient had a moderate NBD and one patient had a severe NBD (Figure 2).

Studies of ano-rectal manometry

Table IX shows the improvement obtained for each patient in the studies of ano-rectal manometry. In comparison with the baseline study, at the end of the follow-up, four patients showed improvement either in sensitivity (first sensation at filling) or achieving a higher pressure in anal contraction or higher pressure of rectal sphincter at rest. Additional information is provided in the Supplementary Material (Supplementary Table S1).

Urodynamic studies

At the end of the study, all of the patients improved in some urodynamic parameters, in comparison with the studies carried out previous to administration of cell therapy. Table X shows the improvements obtained for each patient. At the end of the study, four patients improved in first sensation at filling, four patients improved in maximum cystometric capacity, three patients showed decrease in detrusor pressure at filling and four patients improved in postmictional residue. Furthermore, three patients improved in bladder compliance. Additional information is provided in the Supplementary Material (Supplementary Table S2).

Table IV. Scores in Penn scale.

	Months	Mean	SD	p-value	Effect size	
PENN	Before treatment	1.66	1.21	-		
	At 3 months FU	1.33	1.03	> 0.99	-	
	At 6 months FU	1.16	0.75	0.50	-	

Wilcoxon test was applied comparing each month with baseline. Tendency to improvement was observed but without statistical significance.

Table V. Scores in Ashworth scale.

	Months	Mean	SD	p-value	Effect size	
ASHWORTH	Before treatment	1.75	1.17	-		
	At 3 months FU	1.58	1.35	> 0.99	-	
	At 6 months FU	1.50	0.83	0.50	-	

Wilcoxon test was applied comparing each month with baseline. Tendency to improvement was observed but without statistical significance.

Neurophysiological studies

Neurophysiological improvements were obtained in four patients. In comparison with the neurophysiological studies performed previous to cell therapy, at the end of follow-up, improvement in somatosensory evoked potentials, in latency and/or amplitude, was recorded in two patients. One patient improved in motor evoked potentials. Two patients improved in sensitive nerve conduction, and one patient improved in motor nerve conduction. Furthermore, at the end of the study, one patient showed improvement in voluntary muscle contraction, and two patients showed electromyographical signs of infralesional active muscle reinnervation. Table XI shows the improvement for each patient in neurophysiological studies.

Neuroimaging studies

In all of the cases, MR performed at the end of follow-up showed a decrease in the length and/or width of the syrinx. The measurements were obtained by means

of the software associated with the imager, and they must be considered as approximate due to the difficulty of obtaining strictly superimposable images in sequential studies. Although a decrease in length and width of syrinx was observed at the end of follow-up, statistical significance was only found for the changes in syrinx width ($P = 0.003$). When the syrinx/canal index was studied, as an index that indirectly values intramedullary tension [13], it ranged between 0.60 and 1.30 in the basal studies (mean $\pm$ SD, 0.84 ± 0.24) and between 0.13 and 0.68 (mean $\pm$ SD, 0.33 ± 0.19) at the end of the study ($P = 0.003$). Figure 3 shows syrinx changes after cell therapy. Additional information is provided in the Supplementary Material (Supplementary Table S3 and Supplementary Figure 6).

Summary of clinical improvements

Table XII summarized the improvements obtained in the patients of the study. All of the patients showed variable improvement in clinical scales, mainly in the

Table VI. Scores in VAS scale.

	Months	Mean	SD	p-value	Effect size	
VAS	Before treatment	2.00	3.16	-	-	
	At 3 months FU	1.33	2.42	0.25	-	
	At 6 months FU	1.00	2.44	0.25	-	

Wilcoxon test was applied comparing each month with baseline. Tendency to improvement was observed but without statistical significance.

Table VII. Scores in Geffner scale.

	Months	Mean	SD	p-value	Effect size	
GEFFNER	Before treatment	1.83	1.47	-	-	
	At 3 months FU	2.50	1.22	0.50	-	
	At 6 months FU	2.83	1.47	0.25	-	

Wilcoxon test was applied comparing each month with baseline. Tendency to improvement was observed but without statistical significance.

Table VIII. Scores in NBD scale.

	Months	Mean	SD	p-value	Effect size	
NBD	Before treatment	14.67	6.91	-	-	
	At 3 months FU	9.83	3.92	0.12	-	
	At 6 months FU	8.50	5.54	0.12	-	

Wilcoxon test was applied comparing each month with baseline. Tendency to improvement was observed but without statistical significance.

Figure 2. Improvement in NBD throughout the study. Previous to cell therapy, three patients had a severe NBD, and at the end of the study only one patient had a severe NBD.

Table IX. Improvement for each patient obtained in parameters of ano-rectal manometry.

Patient code	01	02	03	04	05	06
Increase in mean pressure of rectal sphincter in rest	No	Yes	No	No	Yes	No
Increase in mean pressure of anal contraction	Yes	Yes	Yes	No	Yes	No
Improvement in first sensation of rectal filling	No	Yes	Yes	No	Yes	No

Table X. Improvement for each patient obtained in urodynamic parameters.

Patient code	01	02	03	04	05	06
Improvement in first sensation at filling	Yes	No	Yes	Yes	No	Yes
Increase in bladder capacity at filling	No	Yes	No	Yes	Yes	Yes
Decrease in detrusor pressure at filling	No	Yes	Yes	No	Yes	No
Improvement in bladder compliance at filling	No	Yes	Yes	No	Yes	No
Decrease in postmictional residue	Yes	No	Yes	Yes	Yes	No

Table XI. Improvement for each patient obtained in neurophysiological parameters.

Patient code	01	02	03	04	05	06
Improvement in SSEP	No	Yes	No	Yes	No	No
Improvement in MEP	No	No	No	No	No	Yes
Improvement in sensitivity conduction	No	No	No	Yes	Yes	No
Improvement in motor conduction	No	No	No	Yes	No	No
Improvement in voluntary muscle contraction	No	No	No	No	Yes	No
Presence of infralesional active muscle reinnervation	No	No	No	No	Yes	Yes

scales related to sphincter dysfunction and neuropathic pain.

Discussion

It is well known that between 1% and 4.45% of paraplegic patients can develop in a late phase large intramedullary cavities extending several segments at distance from the area of SCI, which is known as “post-traumatic syringomyelia” or “post-traumatic cystic myelopathy”. The syringomyelic cavity may be asymptomatic or associated with a worsening of previously established neurological deficit, such as development of supraspinal sensory disorders, autonomic dysreflexia or increase of neuropathic pain or spasticity [14–19]. At present, there is no evi-

dence that the drainage of these cavities provides benefit, and surgery is recommended only in paraplegic patients with post-traumatic syringomyelia who developed worsening of symptoms, which were associated with an enlargement of previous intramedullary cavities [15,17]. Various surgical techniques, such as subarachnoid-peritoneal shunt, subarachnoid-subarachnoid bypass or arachnolysis with untethering and duraplasty at the level of underlying trauma, have been used in post-traumatic syringomyelia [17]. Because shunting exposed the patients to a higher rate of clinical recurrence and reoperation, at present, duraplasty and arachnolysis seem to be the most widely accepted treatment, but with doubtful long-term benefit.

On the other hand, cell therapy with MSCs seems to provide new promise for patients with SCI and it is necessary to know the selection of patients who can get benefit from these new techniques [20]. We have recently described how a paraplegic patient who received surgical administration of MSCs in the SCI zone improved in the ASIA assessment and in sphincter control, and, at the same time, an associated supraspinal syrinx was reduced [21]. Due to the experience obtained with said patient, the present clinical trial was designed to study if patients with large syringomyelic cavities should be submitted to cell therapy, hoping for some kind of benefit. Although the limited follow-up and the small number of patients can be clear limitations of the present study, our previous experience shows that, after cell therapy in patients with SCI, the clinical benefit, mainly in sensitive improvement, is observed in the course of the first 2 months after MSC administration. For this reason only a short follow-up period was chosen. Similarly, only six patients were chosen for the study because this number of patients was considered sufficient to know a possible individual benefit or a trend toward a benefit, although we did not expect to obtain improvements with statistical significance.

The analysis of our present findings shows the safety and feasibility of intrathecal administration of MSCs in post-traumatic syringomyelia, obtaining diverse individual improvement in the few patients studied. In comparison with previous studies of cell therapy in chronic paraplegic patients [1,2], the scarce response to treatment in scores of sensitivity is strange. It can be explained by the presence of a sustained intramedullary tension due to syrinx, which determines an atrophy of the spinal cord, as it can be seen in our patients when the reduction of the syrinx after cell therapy allows a correct identification of the cord. On the other hand, the progressive tendency to improvement obtained in the IANR-SCIFRS, Penn, Ashworth, Geffner, VAS and NBD scales is similar to the tendency to improvement showed in

clinical trials that used intrathecal cell therapy in paraplegic patients [2].

It is difficult to explain the fact that after administration of MSCs in the syrinx, without aspirating its content, syrinx reduction can be obtained, suggesting that after cell therapy a redistribution of cerebrospinal fluid is achieved. When syrinx is reduced, a thinned spinal cord is frequently observed, and, considering that an atrophied spinal cord is associated with poor response to cell therapy [22], if cell therapy is considered for post-traumatic syringomyelia, it should be done early before intramedullary pressure can cause or increase the atrophy of the injured spinal cord. In

Table XII. Clinical improvement for each patient obtained at the end of the follow-up.

CODE PATIENT	01	02	03	04	05	06
ALS grade	A	A	D	B	B	A
Sensitivity						
Global SC function						
Spasms						
Spasticity						
Neuropathic pain						
Bowel dysfunction						
Bladder dysfunction						

Green: Patients who improve. Yellow: Patients who neither improve nor worsen.

SC, spinal cord.

Figure 3. Syrx changes after cell therapy. (A, B and C) Graphs with the improvements in the syrx size. Statistical significance was obtained after cell therapy for the syrx width and for S/C index ($P = 0.03$). (D and E) Changes obtained in the syrx in patient 06. (D) MR-myelography previous to cell therapy, showing the SCI at D5 vertebral level (bar) and an extensive syrx, mainly at infralesional levels. (E) Changes in the syrx at the end of the follow-up. Spinal cord is now identified, and at supraslesional level a thinned spinal cord can be seen, with increased subarachnoid space (arrow).

our patients, individual improvements were also observed in the studies of urodynamic, neurophysiology, neuroimaging and ano-rectal manometry. These improvements can be observed previous to clinical improvements, and they support a possible benefit of the cell therapy.

Conclusions

In conclusion, in paraplegic patients with post-traumatic syringomyelia, the administration within the syrinx of a single dose of 300 million autologous MSCs supported in autologous plasma is safe. It can reduce syrinx and provide individual benefits. In any case, new studies with a greater number of cases are required.

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Appendix: Supplementary material

Supplementary data to this article can be found online at doi:10.1016/j.jcyt.2018.04.006.