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Progressive increase in brain glucose metabolism after intrathecal administration of autologous mesenchymal stromal cells in patients with diffuse axonal injury

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Abstract

Background aims. Cell therapy in neurological disability after traumatic brain injury (TBI) is in its initial clinical stage. We describe our preliminary clinical experience with three patients with diffuse axonal injury (DAI) who were treated with intrathecal administration of autologous mesenchymal stromal cells (MSCs). *Methods.* Three patients with established neurological sequelae due to DAI received intrathecally autologous MSCs. The total number of MSCs administered was 60×10^6 (one patient), 100×10^6 (one patient) and 300×10^6 (one patient). *Results.* All three patients showed improvement after cell therapy, and subsequent studies with 18F-fluorodeoxyglucose (18F-FDG) positron emission tomography (PET) showed a diffuse and progressive increase in brain glucose metabolism. *Conclusion.* Our present results suggest benefit of intrathecal administration of MSCs in patients with DAI, as well as a relationship between this type of treatment and increase in brain glucose metabolism. These preliminary findings raise the question of convenience of assessing the potential benefit of intrathecal administration of MSCs for brain diseases in which a decrease in glucose metabolism represents a crucial pathophysiological finding, such as Alzheimer's disease (AD) and other dementias.

Key Words: *alzheimer's disease, brain metabolism, cell therapy, diffuse axonal injury, mesenchymal stromal cells*

Introduction

Cell therapy is a hope for patients suffering neurological disability, but there are still many unknowns about its mechanism of action, type and dose of stem cells to be used or best route of administration. In recent years, there is evidence suggesting that cell therapy using autologous bone marrow mesenchymal stromal cells (MSCs) can improve quality of life in patients with spinal cord injury (SCI) [1,2] and previous pre-clinical and clinical studies suggest also a role for cell therapy with MSCs for the treatment of established neurological disability secondary to traumatic brain injury (TBI) [3–5]. In addition to a possible long-term replacement of damaged cells, the release of neurotrophic factors by the transplanted stem cells may induce therapeutic mechanisms that include neuroprotective effects, induction of axonal sprouting, neovascularization or activation of endogenous neurogenesis [2,3]. In this report we present our experience with three patients diagnosed with diffuse axonal injury (DAI) treated using intrathecal administration of autologous MSCs. The finding of a progressive increase in brain glucose metabolism suggests a new effect of MSCs after their intrathecal transplantation, and a possible explanation for the clinical benefit.

Methods

We used a cell therapy medicament (NC1) approved as a medicament under clinical investigation by the Spanish Agency for Medicaments and Health Products (AEMPS). It consists of autologous bone marrow–derived MSCs and autologous plasma as its excipient.

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Additional details, culture of MSCs, formulation, packaging and phenotypic characterization of this cell therapy medicament have been previously described [1]. NC1 was currently used for the treatment of sequelae of SCI in clinical trials approved by the Ethical Committee for Clinical Research (ECCR) of the Puerta de Hierro-Majadahonda Hospital (ClinicalTrials.gov identifiers: NCT01909154, NCT02165904 and NCT02570932). After considering that patients described in this report had exhausted their chances of recovery, we solicited authorization to AEMPS for intrathecal administration of our cell therapy medicament. Ethical aspects and possible benefits were considered, and authorization was obtained from both the AEMPS and Medical Management.

In the three patients, informed consent, adapted from protocols previously approved by our ECCR, was obtained from their families, after explaining the experimental nature of the treatment and the previous experience obtained after intrathecal administration of NC1 medicament in patients with neurological sequelae due to SCI.

Criteria for selecting the doses were biosafety. Out first patient received doses of 30×10^6 MSCs in order not to exceed the authorized dose in our clinical trials NCT01909154 and NCT02165904, and after our clinical experience with the clinical trial NCT02570932, showing absence of adverse events after intrathecal administration of 100×10^6 MSCs, we selected these doses for our Cases 2 and 3. Thus, the overall number of MSCs administered ranged between 60×10^6 (Case 1) and 300×10^6 (Case 2).

18F-fluorodeoxyglucose (18F-FDG) positron emission tomography (PET) computed tomography (CT) scans were performed using a Siemens Biograph 6 True Point PET-CT (Siemens-CTI). A 300–400 MBq 18F-FDG dose was administered 45–60 min before image aquisition. Brain PET images were acquired at 20 min/bed position. The reconstruction was performed using iterative method and attenuation/scatter correction. Given the overall increase in brain metabolism obtained after cell therapy, a qualitative assessment of the results of 18F-FDG-PET was performed. In the images, blue areas indicate hypometabolism, green areas indicate normal metabolism, yellow areas indicate slightly high metabolism and red areas indicate high metabolism.

Report of cases

Case 1

This 30-year-old woman had a severe TBI, with multiple zones of brain hemorrhagic contusions and DAI on April 3, 2015. In June 2015, she presented a minimally conscious state, disconnection with the environment, staring, extreme spasticity in lower extremities, extreme contracture of the neck and inability to speak or make sounds. Neurophysiological studies showed slowing of brain waves and severe alteration of somatosensory evoked potentials (SSEP). 18F-FDG-PET showed brain hypometabolism in multiple zones, mainly in parietal and temporal areas, and in cerebellum. On July 24, 2015, a first dose of 30×10^6 autologous MSCs was administered into the lumbar subarachnoid space through lumbar puncture, without adverse events. Increased reactivity and reduced spasticity were noted in the following days and SSEP and electroencephalogram (EEG) showed significant improvements. On August 24, 2015, the patient began to respond to simple commands and emit monosyllables. On September 3, 2015, a new 18F-FDG-PET showed an overall increase in brain metabolism, without obvious change in the hypometabolic areas disclosed in the previous study. A second subarachnoid administration of 30×10^6 MSCs was performed on September 11, 2015. In the following days, the patient experienced a progressive clinical improvement, answering verbal commands, connecting with her environment and maintaining a coherent language. Neck contracture disappeared completely and a progressive improvement in spasticity was appreciated. In the following months she was able to walk unaided, eat alone and showed progressive sphincter control, to reach a situation of normal neurological status in November, 2015. On May 5, 2016, a new 18-FDG-PET showed higher brain metabolism compared with previous studies. Now, the patient is symptom-free and performs normal life activities, but continues rehabilitation exercises for slight residual spasticity in his left hand. During the months of follow-up, progressive improvement in the Disability Rating Scale (DRS) [6] was recorded, showing scores of 22, 11, 11, 6 and 3 in July, August, September, October and November 2015, respectively. Figure 1 shows images of sequential 18F-FDG-PETs.

Case 2

This 57-year-old male patient suffered a severe TBI on November 6, 2015, with multiple hemorrhagic brain contusions, acute subdural hemorrhage and DAI. The patient was subjected to craniectomy and evacuation of the subdural clot. Cranial bone was not replenished by severe brain edema. In January 2016, after overcoming the phase of brain edema, the patient showed a minimally conscious state, with disconnection with the environment, and unable to speak. At this time, 18F-FDG-PET showed brain hypometabolism, mainly in frontal and temporal areas of both cerebral hemispheres. On February 18, 2016, 100×10^6 autologous MSCs were administered into subarachnoid space by lumbar puncture. Three days later, a