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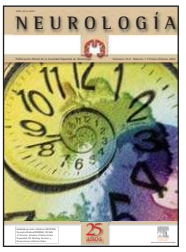

EDITORIAL

Cell therapy in amyotrophic lateral sclerosis: science and controversy

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Abstract
Stem cell therapy is seen as a possible alternative for the treatment of different degenerative diseases, among which includes amyotrophic lateral sclerosis (ALS). Despite there being basic research works with this therapy in ALS, the mechanism of action of the implanted cells are still unclear. It is also unclear which type of cells to use (bone marrow, fat, dental pulp, etc.), or the most ideal administration route. Furthermore, clinical trials with mesenchymal stem cells are not very conclusive, therefore it has not been convincingly established as an alternative therapy in ALS or any other neurodegenerative disease. Despite the scientific evidence, several clinical trials have been conducted in the last few years that offer stem cell treatments for neurodegenerative diseases, giving rise to what is known as "cellular tourism". This phenomenon has set off alarms and reactions in the scientific community. The application of these therapies must be performed following the good clinical practice guidelines in research, evidence based methodology and international ethical and scientific recommendations.

PALABRAS CLAVE
Esclerosis lateral amiotrófica;
Células madre;
Enfermedad neurodegenerativa;
Terapia celular

Terapia celular en la esclerosis lateral amiotrófica: ciencia y controversia

Resumen
La terapia con células madre se vislumbra como una posible terapia alternativa al tratamiento de diferentes patologías degenerativas, entre las cuales se encuentra la esclerosis lateral amiotrófica (ELA). En la actualidad, a pesar de que existen trabajos de investigación básica con esta terapia en la ELA, todavía quedan sin esclarecer los mecanismos de actuación de las células madre implantadas, además de no tener claro el tipo

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de células a utilizar (médula ósea, grasa, pulpa dentaria, etc.) y vía de administración más idónea. A su vez, existen ensayos clínicos con células madre mesenquimales con resultados poco concluyentes, por lo que no se ha podido establecer con contundencia como una terapia alternativa en ELA o cualquier otra enfermedad neurodegenerativa. A pesar de las evidencias científicas, en los últimos años han aparecido diferentes clínicas que ofrecen tratamientos con células madre para enfermedades neurodegenerativas, dando lugar a lo que se conoce como "turismo celular". Este fenómeno ha activado alarmas y reacciones en la comunidad científica. La aplicación de estas terapias se debe realizar siguiendo las normas de buena práctica clínica en investigación, la metodología basada en la evidencia y las recomendaciones éticas y científicas internacionales

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease with only one approved treatment, riluzole, which has only a moderate effect.[1] In recent years, cellular therapy has created great scientific and social interest, since it means exploring new therapeutic strategies in diseases that until now had no form of treatment, such as neurodegenerative diseases.[2] However, their approved indications are minimal.[2] In the case of ALS, as well as other neurodegenerative diseases, there is insufficient evidence about the effectiveness of this type of therapy,[3,4] and its safety[5] to be able to approve it, despite intense basic investigation. However, there have been some advances due to clinical trials,[6-9] mainly with mesenchymal stem cells.

There are some characteristics of ALS that make it special when considering cellular therapy. The first is that it is of unknown pathogenesis.[10] Over recent years, the importance of cells that form the environment of motor neurons[11] has also become clear in the pathogenesis of ALS. The second characteristic is how the disease spreads around the human body is currently unknown,[12] with the consequent difficulty in choosing the ideal site to implant cells.

The effect of cellular therapy in ALS could be caused by the replacement of the implanted cells by other damaged cell types. It seems logical to think that in the case of ALS, the cells being substituted are the motor neurons. This substitution would require the development of connections with other neurons and of axonal growth in the target muscle. However, these strategies only seem effective in models with static damage and not with progressive damage, as is the case in ALS.[13,14] Despite this, and because of a possible effect over other neurons, the FDA has recently approved a clinical trial with neural stem cells in patients with ALS. The replacement for astrocytes or microglia could play a larger role.[15]

Still, the most promising strategy with stem cells consists of the release of neurotrophic factors and the modulation of inflammation. When the precursor stem cells are modified to express GDNF and are implanted in SOD transgenic rats, they prevent the degeneration of motor neurons and, when administered into the muscle, they also improve motor function.[16,17]

This is the mechanism that provides neuroprotection for ALS in SOD transgenic models.[18] It was therefore possible to carry out an intramedullary clinical trial with exogenous mesenchymal cells in a thoracic location[8] and another one with cervical implementation.[9] Both trials were open and showed a modest benefit for patients.

Cells originating from the umbilical cord also showed a beneficial effect in the animal model through the immune function.[19] An autologous haematopoietic cell transplantation has been carried out in humans on a frontal level in a small number of patients.[7]

Beers et al performed a series of experiments to identify the role of microglia and of CD4+ cells in damage to motor neurons by transplanting bone marrow cells into transgenic SOD mice crossed with mice that lacked CD4+. The absence of T cells accelerated the progression of the disease, but their reintroduction through bone marrow transplant gave rise to neuroprotection.[20]

Another action strategy would be the stimulation of the endogenous neurogenesis in the neurogenic niches present in the CNS of patients with ALS (this approach has also been proposed with other diseases), but it has not been used so far.[3]

Concluding, cellular therapy in ALS is still in a very preliminary stage;. Although some clinical trials have been carried out, their results are difficult to interpret because of the small number of patients and the lack of homogeneity of their designs. It is still unknown which cellular type is ideal, which anatomical site is optimal for the introduction of cells and which method of administration should be used. Therefore, the majority of the groups consider that further basic studies are needed before advancing to the clinical stage.[21]

Cellular tourism

Despite the early stage that cellular therapy is currently in, many clinics have appeared in the past few years offering treatment with stem cells for different pathologies, mostly neurodegenerative diseases. These clinics are located mainly in countries with favourable laws. The cost of these treatments is generally quite high, not to mention that the patient must relocate to those countries.

In 2008, scientists from Alberta University[22] carried out a brilliant study that caused great impact on the scientific

community. In this study, they analysed, through the Internet by performing a Google search, the clinics that offered treatment with stem cells. This search found that all of the clinics except for one offered treatment for non-approved indications and that the majority offered a clear overestimation of effectiveness and underestimation of risks. This article led to the International Society for Stem Cell Research (ISSCR) publishing a guide for responsible investigation with stem cells.[23]

An article was recently published about a patient who presented multiple CNS tumours years after having received stem cell transplantation. After being analysed, the tumours presented male and female genotypes, so they were collected from at least two different donors.[5] This case has fuelled the controversy about the use of such therapies.

In our opinion, cellular therapy must continue being studied through basic studies and well-designed clinical trials. Its application outside of these environments has to be controlled and reviewed externally to ensure that quality, safety and ethical standards are met following the ISSCR guidelines.[23]

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