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REVIEW

Clinical application of cell, gene and tissue therapies in Spain☆

P. Gálvez-Martín*, A. Ruiz, B. Clares

Departamento de Farmacia y Tecnología Farmacéutica, Facultad de Farmacia, Universidad de Granada, Granada, Spain

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Abstract Scientific and technical advances in the areas of biomedicine and regenerative medicine have enabled the development of new treatments known as ''advanced therapies'', which encompass cell therapy, genetics and tissue engineering. The biologic products that can be manufactured from these elements are classified from the standpoint of the Spanish Agency of Medication and Health Products in advanced drug therapies, blood products and transplants. This review seeks to provide scientific and administrative information for clinicians on the use of these biologic resources.

PALABRAS CLAVE
Célula madre;
Terapia celular;
Terapia génica;
Ingeniería tisular;
Terapias avanzadas;
Medicina regenerativa

Aplicación clínica de las terapias con células, genes y tejidos en España

Resumen Los avances científicos y técnicos en el área biomédica y la medicina regenerativa han permitido el desarrollo de nuevos tratamientos, denominados «terapias avanzadas», que engloban la terapia celular, la génica y la ingeniería tisular. Los productos biológicos que pueden fabricarse a partir de estos elementos se clasifican desde el punto de vista de la Agencia Española del Medicamento y Productos Sanitarios en medicamentos de terapias avanzadas, productos derivados de la sangre y trasplantes. Esta revisión pretende aportar información científica y administrativa, de utilidad para el clínico, sobre el uso de estos recursos biológicos.

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* Corresponding author.
E-mail address: galmafarma@gmail.com (P. Gálvez-Martín).

Background

Advances in regenerative medicine have enabled the development of biological therapies, based on the application of cells, genes and tissues as therapeutic elements, therapies that have been called ''advanced therapies''. These therapies constitute an emerging area in the treatment of numerous diseases such as malignancies,[1] myocardial infarction,[2] diabetes mellitus,[3] osteochondral lesions[4] and nervous system lesions.[5]

Since 2007, regulatory agencies at the national (Spanish Agency for Medicines and Medical Devices [AEMPS]) and European (European Medicines Agency [EMA]) level have enacted legislation governing the classification and human use of biological elements included in the concept of advanced therapies.

In this review, we describe the main aspects that define and classify the drugs based on cells, genes or tissues for human use in Spain, with the objective of facilitating their daily clinical application.

Definition and classification of advanced therapies

The term ''advanced therapies'' includes cell therapy, gene therapy and tissue engineering, which are based on the use of cells, genes and tissues, respectively.[6] The development of these products entails a manufacturing process in which the safety and quality of the biological material must be rigorously controlled.

The first phase consists of obtaining a biological sample or biopsy, which can be of autologous, allogeneic or xenogeneic origin.[7] The active biological product is then isolated, manipulated and converted into the final product. Quality control is then performed, as well as characterization of the cells, genes or tissues for therapeutic goals. The product is then transported and, finally, administered to the patient (Fig. 1).

Cell therapy

The objective of cell therapy is to repair, replace or recover the biological function of a damaged tissue or organ, using specialized cells or stem cells.[6]

Stem cells are nonspecialized cells that are capable of dividing (self-renewal) over indefinite periods during an individual's life. Under appropriate microenvironment conditions, these cells proliferate *ex vivo* and *in vivo*[8] through asymmetric divisions, differentiating into cells of distinct lineages with specialized characteristics and functions (e.g., erythrocytes, myocytes, neurons and hepatocytes).

Depending on the type of tissue that originates the cells, stem cells are classified as totipotent, pluripotent, multipotent and unipotent.[9] Depending on their origin, the cells are classified as an embryonic stem cell (ESC), adult stem cell (ASC) or induced pluripotent stem cell (iPS)[10] (Fig. 2).

Embryonic stem cells

These are pluripotent stem cells from the embryo in the blastocyst phase, which has approximately 100–200 cells. ESCs are characterized by their capacity to remain in an undifferentiated proliferative state for an extended period.[11] ESCs are the most polyvalent and have the capacity for originating all cell types of the 3 germ layers: endoderm, mesoderm and ectoderm.[11]

The first ESCs were isolated from mice bone marrow by Evans and Kaufman in 1980.[12] In 1998, Thomson et al. isolated ESCs from human embryos, from *in vitro* fertilization clinics.[13] Experimentally, ESCs have been used successfully in various animal models for regenerating liver cells, hematopoietic stem cells, neuronal tissue and cardiac tissue.[14] The clinical application of ESCs in humans is still limited, however, due to ethical considerations regarding the use of embryos and the uncertainty in terms of their safety, the risk of formation of teratomas and immune transplant rejection.[15]

Adult stem cells

These cells encompass a large variety of undifferentiated cells located in adult tissues, regardless of the individual's age. These cells have the capacity for single or multiple differentiation. ASCs are characterized by their high proliferative potential and their capacity for self-renewal and differentiation into at least one cell type.[16]

ASCs divide in a balanced manner, both asymmetrically and symmetrically. Their capacity to undergo asymmetric mitotic divisions produces two differentiated daughter cells for generating progenitors, which subsequently differentiate into mature cell types with specialized functions. Alternatively, ASCs undergo symmetrical divisions in a stochastic manner to produce new stem cells, maintaining their capacity for self-renewal.[17]

The first type of isolated ASC was the hematopoietic stem cell, which is capable of self-renewal and differentiation into multipotent hematopoietic cells.[18] Subsequently in 1968, Friedenstein et al. described another stem cell population with similar characteristics, which they called ''fibroblast colony-forming units'', currently known as mesenchymal stem cells (MSC).[19] It is important to note that, to date, ASCs have been identified in practically all organs and tissues of the adult body (e.g., skin, liver, pancreas, blood, kidney, intestine, blood vessels, central nervous system, dental pulp, adipose tissue, skeletal muscle and heart).[17,20]

From the clinical standpoint, ASCs are the most widely used stem cells due to their safety, efficacy and the ease with which they are obtained.[21,22] Nevertheless, the use of ASCs has numerous limitations, such as the identification of the molecular signals that start their activation, the introduction of isolation protocols and simpler cultures, as well as *in vitro* differentiation that increases their plasticity, the increase in the end product's cellular viability and the cultures' genetic stability.[23]

Induced pluripotent stem cells

These are pluripotent stem cells derived from non-pluripotent somatic stem cells, manipulated by inserting transcription factors.[24] The first trials on nuclear genetic material transfer to a somatic cell were conducted with oocytes, inducing their pluripotency by electrochemical stimuli.[25] In 2006, this technique was improved by Takahashi