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Possible clinical usefulness of embryonic stem cells

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Abstract Are embryonic stem cells being used for therapeutic purposes?

The aim of this short report is to review to what extent are embryonic stem cells currently used for therapeutic purposes.

To the best of our knowledge, only four clinical trials have been authorised so far to use human embryonic stem cells for therapeutic purposes; two of these are included in the ClinicalTrials.gov data base, and the other two, the study sponsored by Geron and the last one initiated by Advanced Cell Technology in the United Kingdom, are not.

But, in addition, Geron withdrew the clinical trial which had been originally proposed by the company itself.

This brief review focuses the debate on the use of embryonic stem cells in human cell therapy. To the best of our knowledge, only three trials are ongoing with therapeutic purposes thus far, with not all of them having begun to include patients, and of course without any of them yet having obtained evaluable clinical results.

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Posible utilidad clínica de las células progenitoras embrionarias

Resumen ¿Se están usando las células progenitoras embrionarias con objetivos terapéuticos?

El objetivo de este informe breve es revisar hasta qué punto las células progenitoras embrionarias se utilizan en la actualidad con objetivos terapéuticos.

Hasta lo que mejor conocen los autores, hasta la fecha sólo se han actualizado cuatro ensayos clínicos para usar las células progenitoras embrionarias humanas con objetivos terapéuticos; dos de estos se incluyen en la base de datos ClinicalTrials.gov; y los otros dos, el estudio financiado por Geron y el último iniciado por Advanced Cell Technology en el Reino Unido, carecen de patrocinio.

Sin embargo, además, Geron retiró el ensayo clínico propuesto originalmente por la propia empresa.

En esta breve revisión se presta atención al debate sobre el uso de las células progenitoras embrionarias en el tratamiento con células humanas. Hasta lo que conocen los autores, hasta

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la fecha, están en curso tan sólo tres ensayos con objetivos terapéuticos, aunque no todos se han iniciado para incluir a pacientes, y naturalmente ninguno de ellos ha obtenido todavía resultados clínicos evaluables.

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There is little doubt about the importance that regenerative medicine has, and above all will have, in the XXI century.¹⁻³ A basic instrument for the practice of regenerative medicine is the use of stem cells, which as we know, can be embryonic, adult or derived from reprogrammed somatic cells, so-called iPS cells.⁴ In this exciting medical field, no less exciting ethical debate is related to the advisability of using one of the three aforementioned cell types, but with a particular focus on the therapeutic use of embryonic stem cells; this is because a human embryo in its blastocyst phase must certainly be destroyed in order to obtain them,⁵ which in the opinion of many is not ethically acceptable. In this regard, we feel that it is of interest to mention the ruling by the Court of Justice of the European Union on 18 October 2011, which covers article 6, section 2c of Directive 98/44/CE of the European Parliament and the Council dated July 1998, concerning the legal protection of biotechnological inventions. This sentence defines the biological nature of human embryos, stating: "*any human ovum, must, as soon as fertilised, be regarded as a 'human embryo'; a non-fertilised human ovum into which the cell nucleus from a mature human cell has been transplanted and a non-fertilised human ovum whose division and further development have been stimulated by parthogenesis 5 must also be classified as a 'human embryo'*".

Some try to ignore the difficulty entailed in the use of embryonic stem cells, claiming that the good of being able to use them for therapeutic purposes somehow counteracts this inherent ethical difficulty.

However, before delving into this debate, we need to ask, "Are embryonic stem cells currently being used for therapeutic purposes, or is this a semantic manipulation to try to facilitate their use ethically?"

This is the aim of this short report; we intend to ascertain the extent embryonic stem cells are currently used for therapeutic purposes, i.e. whether there are any ongoing clinical trials with this particular objective.

If we go look at the website ClinicalTrials.gov, which is widely used when searching for data on ongoing clinical trials, we can see that on 6th October, there were 110,468 ongoing clinical trials worldwide, in 171 countries; of these, 3601 were using adult stem cells and 11 embryonic stem cells. However, the question, is, "are these 11 clinical trials actually aimed at evaluating the therapeutic capacity of embryonic stem cells?"

To that end, we analysed each of these eleven clinical trials in detail, and found (Table 1) that only two of them (nos. 9 and 10) are using embryonic stem cells for therapeutic purposes; both are phase I trials, and their objectives are focused on evaluating the safety and tolerability of cell transplant, not its clinical efficacy, which can only be known at the end of the clinical trial which is expected to last several years. Another three trials (nos. 1, 2 and 7) are using embryonic stem cells, but their purpose is

experimental rather than clinical, since in the first (no. 1), the aim is to derive good quality embryonic stem cells, so that in the future they may be useful for clinical purposes, focusing specifically on not using animal products in the culture medium, which will doubtless benefit their clinical use. In the second (no. 2), the objective is to derive stem cells from embryos with different diseases, which would allow a deeper understanding of these conditions. The third (no. 7) seeks to identify factors which may contribute to the differentiation of embryonic stem cells to germ cells; however, in addition to the fact that this trial does not have a clinical purpose, its direct objective is to assess the safety of the process only.

Three further studies (nos. 3, 5 and 6) use adult and not embryonic stem cells. Indeed, the first (no. 3) uses mesenchymal or autologous bone marrow stem cells, in order to facilitate cardiomyoplasty of a damaged ischaemic heart. The second (no. 5) compares the level of circulating adult stem cells between normal subjects and patients with heart failure, to evaluate whether this has any significance in the evolution of the disease. The third (no. 6) compares the effect of autologous mesenchymal stem cells with the same type of allogeneic stem cells, to determine their cardiomyoplastic efficacy in patients with chronic ischaemic heart disease secondary to myocardial infarction.

Another two studies (8 and 11) are using umbilical cord stem cells, i.e. adult stem cells, to evaluate their effect in patients with type 1 diabetes.

Finally, the last study (no. 4) is attempting to obtain iPS cells from the adult somatic cells of patients with neurological diseases.

All of the above confirms that in the ClinicalTrials.gov review that we mentioned, only two trials (nos. 9 and 10) that it includes are using embryonic stem cells for therapeutic purposes. However, as well as said report being erroneous in what it says, it is incomplete, as it does not include other currently ongoing clinical trials which are really using embryonic stem cells and which have a therapeutic objective. Let us consider these latter trials.

On 23rd January 2009, the North American Food and Drug Administration (FDA) gave the green light to the first clinical trial in the world conducted with embryonic stem cells.⁶ It was aimed at the treatment of traumatic spinal cord injury, and was to include 11 patients who had suffered the cord injury no more than 15 days earlier.⁷ In other words, it was aimed at patients with a recent spinal cord injury. At first it was reported that the trial might be concluded towards the end of 2011;⁸ however, the first patient was not enrolled until March this year and the fourth was recruited right in the middle of last September, so it will undoubtedly take a few more years before the outcome is known. In any case, it should be specified that the immediate aim of the trial is not therapeutic, but rather is to assess whether the cell transplant has any negative effects.

Table 1 Clinical usefulness of embryonic stem cells.

Essay number	Date	Title	Institution	Situation in which it is	Cell type used	Aim of the essay	Is it a trial with embryonic stem cells and therapeutic purpose?
1	July 2002	Derivation of new embryonic stem cell lines for clinical use	Hadassah Medical Organization	Ongoing	embryonic stem cells	Obtaining cell lines from human embryos	No
2	April 2004	Obtaining human embryonic stem cells	Hadassah Medical Organization	Ongoing	embryonic stem cells	Obtaining cell lines from human embryos	No
3	August 2008	Using adult stem cells in myocardial infarction	University of Miami	Ongoing	Autologous adult stem cells	Repair the damaged myocardium	No
4	April 2009	Obtaining iPS cells from patients with neurological diseases	Hadassah Medical Organization	Ongoing	iPS cells	Deriving iPS cells from patients with neurological diseases	No
5	December 2009	Evaluation of the number of circulating adult stem cells in cardiac patients	Monash University	Recruiting patients	Adult stem cells	To evaluate the levels of circulating adult stem cells in cardiac patients	No
6	March 2010	Evaluation of the effect of adult stem cells in myogenesis	National Heart, Lung and Blood Institute	Recruiting patients	Progenitor cells	To evaluate the myogenic effect of adult stem cells	No
7	October 2010	Derivation of new embryonic stem cell lines	Soroka University Medical Center	Not yet started	Embryonic stem cells	To study the factors that contribute to its development	No
8	September 2010	Assessment of adult stem cells in type I diabetes	University of Illinois	Recruiting patients	Umbilical cord blood	Assessment of effect in patients with type I diabetes	No
9	April 2011	Evaluation of safety and tolerability of using embryonic stem cells in patients with macular degeneration	Advanced Cell Technology	Recruiting patients	Embryonic stem cells	Assess the safety and tolerability in patients with macular degeneration	Yes
10	April 2011	To evaluate the effect of embryonic stem cells in Statgadt disease	Advanced Cell Technology	Recruiting patients	Embryonic stem cells	Assess the safety and tolerability in patients with Statgardt disease	Yes
11	July 2011	Assessment of adult stem cells in type I diabetes	University of Illinois	Recruiting patients	Umbilical cord blood	Assessment of the effect in patients with type I diabetes	No

On 14th July this year, the North American company Advanced Cell Technology, located in Marlborough, MA, announced that the FDA had authorised it to begin two clinical trials with embryonic stem cells in two groups of patients with ocular lesions,⁹ the first with Stargardt's macular dystrophy and the second with age-associated macular degeneration. Stargardt's disease affects young people, gradually leading to visual disorders, which in adulthood may cause blindness due to degeneration of the epithelial pigment of the retina.

The first trial proposes to enrol 12 patients.⁹ Two have been included to date, and are being treated at the David Geffen School of Medicine at UCLA; they will have to be followed up for six weeks to ensure that the cell transplant is not accompanied by negative side effects.

The second trial, aimed at treating age-associated macular lesions, a disease which likewise can lead to blindness, also has an estimated enrolment of 12 patients, with objectives similar to those in the previous trial.

However, last 22nd September, the news became public that the United Kingdom Medicines and Healthcare Products Regulatory Agency had authorised the first clinical trial with human embryonic stem cells outside the United States.¹⁰

The study is also aimed at patients with Stargardt's macular dystrophy and will be conducted at Moorfields Eye Hospital in London. They also want to include 12 patients, and are intending to treat the first one at the end of this year.

Therefore, to the best of our knowledge, four clinical trials have been authorised so far to use human embryonic stem cells for therapeutic purposes; only two of these are included in the ClinicalTrials.gov review, while the other two, the study sponsored by Geron⁶ and the last one initiated by Advanced Cell Technology in the United Kingdom,¹⁰ are not.

We must add a further important consideration regarding the low therapeutic potential of human embryonic stem cells. It involves Geron's withdrawal from stem cell research,¹¹ after investing several hundred million dollars in the clinical trial which had been originally proposed by the company itself. The company mentioned financial reasons, namely low profitability of the research. It is our view, however, that this move is due to the fact that no functional improvements have been observed in the four spinal cord patients who received stem cell transplants.

This brief review focuses the debate on the use of embryonic stem cells in human cell therapy, since only three clinical trials are ongoing thus far, with not all of them having begun to include patients, and of course without any of them yet having obtained evaluable clinical results.

We believe that this shows the limited value of human embryonic stem cells in relation to cell therapy in humans,

as opposed to adult stem cells, which as we know are already being used in more than 3000 clinical trials, to which we must add those that use iPS cells.

However, it should be noted that, regardless of the four clinical trials initiated with human embryonic stem cells, two major technical problems will first have to be solved in order to use them safely. First human embryonic stem cells are, although to a limited extent, immunogens. Stem cells are allogeneic biological material and the cells may create rejection problems. Thus, most probably patients who use this type of treatment will have to take immunosuppressive therapy for life. The second problem is that, due to their own lack of differentiation, they have definite teratogenic potential,¹² which is undoubtedly an obvious difficulty for use in humans.

Conflict of interest

The author have no conflict of interest to declare.

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