Compassionate use of cell products

Gil Cunha de Santis
Eugênia Maria Amorim Ubiali
Dimas Tadeu Covas

Universidade de São Paulo - USP, Ribeirão Preto, SP, Brazil

Investigational medicinal products are available to patients through two pathways. The first is by participating in a clinical trial, the second as part of a compassionate use program, which is the use of an investigational medicinal product outside a clinical trial in patients with serious or life-threatening diseases for which no other treatment is available or expected to be effective. Usually, the medicinal product is an unauthorized drug, but it could also be a cell product. Some countries have specific regulations for compassionate use of medicinal products. In the USA, Food and Drug Administration (FDA) regulations allow access to investigational medicinal products for an individual patient, and for intermediate and large-size groups of patients who otherwise do not qualify to participate in a clinical trial. In Europe, each country has its own regulations. Despite this, the European Medicines Agency adopted a guideline on this issue to facilitate access by patients to experimental treatment. Regulation (EC) No 726/2004 of the European Parliament and of the Council states that "…a common approach should be followed, whenever possible, regarding the criteria and conditions for the compassionate use of new medicinal products under Member States (MS) legislation." In Brazil there are no such regulations.

An interesting discussion on this issue took place some years ago as a round table sponsored by the Canadian Parliament. After an introductory explanation, the rights of catastrophically-ill patients were discussed. The work of Dixon was cited. He stated that "a catastrophically-ill patient has the right to be free from any paternalistic interference in electing, in consultation with his physician, any therapy whatsoever that does not cause direct harm to others"[1,2], which means that the seriously-ill individual has the right to take measures to save his own life. This should be understood as an aspect of individual right, so it cannot be forbidden. In the same document, the statement of JS Mill was cited "…the only purpose for which power can be rightfully exercised over any member of a civilized community, against his will, is to prevent harm to others"[3]. However, things are more complicated as the right to be treated means that someone else has the corresponding duty to treat or to provide the medicinal product to the patient. The right to be treated is considered a "positive right", which is the right to be subjected to an action of another person. On the contrary, the "negative right" is the right not to be subjected to an action of another person, for example, the right of a terminally-ill patient to refuse further treatment.

We believe that some conditions should be met to warrant the compassionate use of an investigational medicinal product. Its indication must have a rationale defined by pre-clinical studies or clinical trials in the same institution or elsewhere. For critically-ill patients and with no alternative treatment, risks related to the experimental therapy are not usually of great concern. The same cannot be said about patients with a less serious or chronic disease, for whom risks, known or unknown, are of utmost importance. We exemplify herein a situation in which we think the administration of an investigational cell product is warranted.

The Center for Cell Therapy of Ribeirão Preto is being required to provide mesenchymal-stromal stem cells (MSCs) for patients with severe steroid-refractory acute graft-versus-host disease (aGVHD) secondary to allogeneic hematopoietic stem cell transplantation. This condition poses a difficult problem to physicians as the prognosis is particularly somber and to date no consensus second line treatment is available[4]. Some alternatives were evaluated, such as extracorporeal photopheresis, anti-TNF antibodies, sirolimus, mycophenolate mofetil and interleukin 2 receptor antibodies[5]. Another option may be the infusion of MSCs. These undifferentiated cells, besides their capability to contribute to tissue repair, can modulate immune and inflammatory response. Because of this, MSCs were used to control the aGVHD. Le Blanc et al. were the first group to report the beneficial effect of MSCs on this condition[6]. Afterwards, others have included MSCs in a treatment algorithm for grade III-IV aGVHD[5].

Despite the evidence of the beneficial effect of this treatment, Brazilian health authorities, based on an opinion of a member of the National Research Ethics Committees (Comissão Nacional de Ética em Pesquisa - CONEP) considered that every requisition of MSCs for compassionate use has to be appraised by institutional Research Ethics Committees and ratified by CONEP, as they consider compassionate use of MSCs similar to a clinical

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Corresponding author:
Gil Cunha De Santis
Hemocentro de Ribeirão Preto, Universidade de São Paulo-USP
Rua Tenente Catão Roxo 2501, Campus universitário, Monte Alegre
14051-140 Ribeirão Preto, SP, Brazil
gil@hemocentro.fmrp.usp.br

www.rbhh.org or www.scielo.br/rbhh

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trial. But compassionate use is not a clinical trial. However, it seems reasonable to submit requests for compassionate use of MSCs to institutional Medical Ethics Committees as they are responsible for the clinical practice of an institution, but to no other official institution, as, in Brazil, there are no regulations (and no prohibitions) on this issue.

In conclusion, we consider there is an urgent need to establish in Brazil regulations for the compassionate use of medicinal products. Until then, we believe requisitions for compassionate use of MSCs should be appraised by institutional Medical Ethics Committees and not by Research Ethics Committees/CONEP as this treatment is not part of a clinical trial. Moreover, it should not be submitted to the Brazilian Health Surveillance Agency (Agência Nacional de Vigilância Sanitária - ANVISA) too, as there is no regulation that compels this procedure.

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