



## Special article

# Associação Brasileira de Hematologia, Hemoterapia e Terapia Celular Consensus on genetically modified cells. Special article: compassionate use and clinical trial on CAR-T cells

Gil Cunha De Santis \*

Hemocentro de Ribeirão Preto, Ribeirão Preto, SP, Brazil

## ARTICLE INFO

## Article history:

Received 26 August 2021

Accepted 14 September 2021

## Keywords:

Compassionate use

Clinical trial

CAR T-cell therapy

Cell therapy

## ABSTRACT

There are only two ways for a patient to gain access to treatment with an experimental product, such as CAR-T cells: participate in a clinical trial or receive a product in a compassionate basis. In the first case, the main beneficiary is society itself, which may in turn obtain a new treatment paradigm for a specific disease. In the second case, the use of a medicinal product has the objective of care in benefit of patients in grave clinical condition, for which no approved medicinal products exist, or for which all the possibilities for benefit from standard therapies have been exhausted. The CAR-T cell therapy may be included in one or the other types of access. The compassionate use is not a specific type of clinical research and should therefore not have its use appreciated by a research ethics committee, but rather by the medical ethics committee at the institution where the treatment will take place and by the regulatory agency.

© 2021 Published by Elsevier España, S.L.U. on behalf of Associação Brasileira de Hematologia, Hemoterapia e Terapia Celular. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

## Introduction

There are two paths for a patient to obtain access to a medicinal product (drug, cells or tissue) of experimental use (whose benefits or risks have not yet been well established, thus not having been approved by the regulatory agency for the intended purpose): clinical trial or expanded access program, when dealing with a group of patients, or compassionate use, when dealing with a sole individual.<sup>1</sup>

\* Corresponding author at: Hemocentro de Ribeirão Preto, Hospital das Clínicas da Faculdade de Medicina de Ribeirão Preto da Universidade de São Paulo (HCFMRP-USP), Av Tenente Catão Roxo, 2501, Vila Monte Alegre, Ribeirão Preto, SP, Brazil.

E-mail address: [gil@hemocentro.fmrp.usp.br](mailto:gil@hemocentro.fmrp.usp.br)

<https://doi.org/10.1016/j.htct.2021.09.009>

2531-1379/© 2021 Published by Elsevier España, S.L.U. on behalf of Associação Brasileira de Hematologia, Hemoterapia e Terapia Celular. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

The use of medicinal products in the research project aims to establish the therapeutic efficacy of the product, approved or not for commercial use, for a determined clinical condition for which there is a reasonable expectation that it will provide benefits. What is intended with a clinical trial, more than individually benefit the participants in the research, is to benefit society itself with the definition of new therapeutic paradigms. One of the problems is the relative scarcity of available clinical trials, in addition to the limited number of openings for participants in each study. Moreover, the inclusion criteria of clinical trials are usually rigid, as they seek to limit the inclusion of participants solely to those whose characteristics best favor a response for the scientifically formulated inquiry, commonly excluding, for example, the individuals of the age extremes, patients with determined comorbidities, or those

whose very grave clinical condition disqualifies them as candidates for the participation in the trial.

There are two conditions to be attended to for the compassionate use of a medicinal product: grave or incapacitating disease, with a high risk for death or sequelae, and the absence of an available standard treatment, or upon deciding that all the possibilities for providing benefits have been exhausted. There are many possible examples which attend to these two conditions, for example, a patient who has been submitted to various treatment lines for cancer or has one of the so-called “orphan” diseases, whose rarity practically impedes the execution of controlled clinical trials.

The compassionate use and the off-label use do not have exactly the same meaning. In the case of the off-label, there is the indication for a medicinal product, approved or not for commercial use, however indicated for another clinical condition and whose efficacy has not yet been clearly established, but for which there is a reasonable expectation of benefit for the patient. The compassionate use of a medicinal product is a common (and very old) medical practice stemming from the fact that the product in question has not yet been approved by a governmental regulatory agency for the intended use. It is believed that approximately 20% of the medications prescribed in the world are for compassionate use, a percentage even higher for specific groups, such as children, pregnant women or HIV-infected or cancer patients.<sup>2</sup> A study conducted at M.D. Anderson showed that one-third of the metastatic breast cancer patients were submitted to treatment with off-label drugs.<sup>3</sup> Some specific medications additionally have off-label use most of the time, such as rituximab, whose indication at a determined service was not specified in the insert 75% of the time.<sup>4</sup>

The reasons for such fact in the oncological field are various:

- 1- Multiplicity of types of cancer, each with a specific treatment.
- 2- Difficulty in including the patients in controlled clinical trials, especially in Brazil.
- 3- Absence of controlled clinical trials, for example, due to the rarity of the cancer in question (i.e., sinonasal undifferentiated carcinoma (SNUC)).
- 4- Rapid diffusion of the international clinical trials, prior to the regulatory agencies having had time to evaluate the new product.
- 5- Elevated number of drugs or products made available every year.
- 6- Delayed product approval by the regulatory agency.
- 7- Lack of interest on the part of the pharmaceutical company in seeking the approval of the use of a drug for a specific disease or condition, which is not included in the insert, and for which the patent has expired.

As the compassionate use is of an exceptional and individual character, as it is not included in clinical research, at least at the moment it is proposed, its appreciation by a research ethics commission is not to be expected, as medical practice assessment is not included in its scope. However, for this

type of treatment to be put into practice, it is necessary to obtain the formal consent of the patient, or of his or her legal guardian, in general by means of a free and informed consent form (FICF), which contains, in addition to the explanation for the lack of a therapeutic alternative for the disease, the potential benefits and risks, known or presumed, as well as the allusion to the possibility of the occurrence of adverse effects not predicted at the time of its administration, especially in the case of a genetically modified product. Furthermore, the FICF should contain the information that it is an experimental treatment of a disease for which it was not indicated. In general, the basis for compassionate use of medicinal products is established on an individual basis and the responsibility for its indication is of the attending physician, but also of the institution which sanctioned the use of the product.

The chimeric antigen receptor T cell (CAR-T cell) has been used in the treatment of patients with grave neoplastic disease, generally relapsed or refractory to the standard therapies. The most common indications for this cellular product are lymphoma B and acute lymphoid leukemia, which express the CD19 antigen, the most frequently used target.<sup>5,6</sup> The compassionate use of CAR-T cells has its reason to be, as does any type of medication or cellular product. Strictly speaking, there is no avoiding the compassionate use of CAR-T cells. The implementation of the clinical trial with this cellular product implies in, almost inevitably as a “subproduct”, its administration out of the study context. The principal requirement is that its manufacture be in accordance with local norms for the confection of the advanced cellular product therapy. Furthermore, the manufacturing institution should have a sanitary license for this activity. The regulatory agencies permitting of the compassionate use of CAR-T cells has been questioned, however, it does not matter if the agencies permit it or not, but it is rather an irrevocable right of the patients to request treatment with this product.

One of the most difficult points to put into practice refers to the institutional criteria for the selection of patients eligible for an expanded access program or compassionate use, which must be egalitarian in the favoring of candidates presenting themselves and in accordance with the capacity of the service to attend to the demand. By the way, the compassionate use criteria, which depend primarily on the discernment of the assistant physicians and what they consider necessary to respond to the scientific question, must be more difficult to establish than those of the clinical trial.

Another also interesting point, but whose scope is beyond that of this article, refers to up to what point the therapeutic modality, which has existed for a decade, is still considered experimental. In other words, what would be the dividing line between what is considered experimental and that which is clearly established. There is no clear and unique answer to this question, but there is almost always a scale between one state and the other. In the case of the CAR-T cells, some clinical trials have been published which attest to its efficacy, which has led at least two regulatory agencies to approve its use. Another important point to consider is the possibility that court orders may be issued for the use of CAR-T cells, as this type of treatment certainly will have its benefits amply divulged, which, as a matter of fact, has already been occurring. Until the regulatory

agency approves the CAR-T cell product in Brazil, its use will have to be classified as compassionate.

Finally, despite the compassionate use having an eminently charitable nature, the divulging of the results of the outcomes of its administration should be stimulated, as outcome information thus obtained may contribute to the better comprehension, not only of its potential benefit, but also of its adverse effects, which could contribute to adjustments in an eventual clinical research project, or even in its administration in new cases of compassionate use.

---

## Regulatory agencies

The governmental regulatory agencies promulgate the rules for compassionate use of, or expanded access to, a medicinal product in their countries. The three agencies that will be briefly covered here are the American Food and Drug Administration (FDA), the European Medicines Agency (EMA) and, lastly, the Brazilian *Agência Nacional de Vigilância Sanitária* (Anvisa), or “National Sanitary Vigilance Agency”.

### FDA

In the USA, the appreciation of the requisitions for cellular product (and other types of medicinal products) for compassionate use is performed by the FDA agency, both for individual use and for expanded access by a group of patients. This agency receives over 1,000 requests per year for the compassionate use of some product, increasing year by year; for example, in 2014, the number of requests was double that of 2005. The requests are mostly for individual use, their entreaty being mostly for oncological use, accepted in over 99% of the cases.<sup>7,8</sup> When a requisition is for emergency use, the agency response usually returns within 24 hours. In non-emergency cases, besides the FDA appreciation, it is customary to require the appreciation by the medical ethics commission (CEM) at the institution. Albeit, in May 2018, the American Congress promulgated the law Right to Try Act, which permits the patient to request the compassionate use of a product, prescinding the FDA proceedings, as the American society considered as just the individual’s endeavor to gain access to an experimental product without the interference of a state agent.<sup>9</sup> The objective of this law is to facilitate patient access to experimental medications. In this case, it is also recommended that consent be obtained from the institution’s CEM, despite not being obligatory, but the solicitation should be based on at least a phase I clinical study.<sup>10</sup> The institutional CEM consent, as often as possible, should be obtained because after all, the institution might be cited in the chain of responsibilities in an eventual lawsuit and would thus have the right to testify as to the treatment proposed and administrated at its facilities. Furthermore, the requesting physician may not have knowledge of the existence of an open clinical trial, nor of all the alternative therapeutics approved and available, which may be, in this manner, revealed by the referred commission. The CEM can further nominate a representative, generally a specialist in the disease for which the product has the intended use, can analyze

the case and issue a consubstantiating official opinion to provide a basis for his or her decision.

Critics of the law Right to Try fear that its implementation might discourage patients from participating in clinical trials, as they could be allocated to the control group which receives the placebo, in addition to the attribution load imposed on them (exams and return visits to attend to the necessities of the study), as well as by the pharmaceutical industry for sponsoring them.<sup>9</sup> Another concern refers to the risks for the patient that the use of an experimental product could entail, as the requisition of its use would not have been scrutinized by the agency, whose staff boasts qualified professionals to analyze each case. Moreover, the attending physician would not have the commitment to inform the agency of eventual adverse effects related to the use of the product.

### EMA

In Europe, the EMA agency additionally has the attribution of evaluating the requisitions for the compassionate use of an experimental product, however, each member-state has its own system for dealing with this issue, more or less liberally.<sup>11,12</sup>

The general rules include the obligation of the physician requesting the treatment to contact the responsible authority to obtain authorization to use the product. Once this solicitation is accepted, the physician should maintain the registers of the case, which will include eventual adverse effects following the experimental treatment. Additionally, it is the duty of the attending physician to verify the existence of an open clinical trial in which the patient could be included. When the medicinal product in question has already been approved for use in a clinical trial by the ethics in research committee, its compassionate use is usually easier to justify. This approach appears reasonable to us, as it increases the process safety. The EMA has constituted a Commission to deal with this issue called Committee for Medicinal Products for Human Use,<sup>13</sup> which can supply recommendations on the compassionate use of products to all the countries in the European Union, including suggestions on which type of patients could benefit from this type of treatment. In the European countries, where there are local regulations on this type of treatment, the therapeutic proposal is not appreciated by the ethics in research commission, but by medical ethics or an entity of specialist-representatives in the area.

### Anvisa

In Brazil, the regulations for the compassionate use of products were promulgated by Anvisa in 2013.<sup>14</sup> Originally, the understanding was that the resolution dealt with the compassionate use exclusively for medications, excluded from which, therefore, were the cases of cellular product use, as is suggested in the section “Approves the regulation for the programs of expanded access, compassionate use and supply of post-study medications”. More recently, Anvisa resolved, of its own volition, to broaden the reach of the referred Resolution of the Collegiate Directorate (RDC) to the advanced cellular therapy products, such as for example, the CAR-T cell product, as it came to consider this product as a medication.

The RDC article 6 determines furthermore that “There must be a guaranteed supply of medication authorized in the programs of expanded access, compassionate use and post-study medication for chronic cases in which there is benefit to the patients, as per medical criteria”, an imposition which may have the power to inhibit the adherence of pharmaceutical companies or institutions which manufacture cellular products to programs of expanded access or compassionate use. Another limiting factor is the RDC article 12 that determines that the solicitation for the product must be based on a “phase III study in development or concluded for the same indication solicited for the patients”, a more restrictive requisite than those imposed, for example, by the FDA and the European Parliament.<sup>15</sup> One more significant aspect of the RDC is the non-existence of the mention of deadlines to comply with the regulatory agency, even in the case of emergency treatment, in which a response of great celerity would be expected. The agency distributes incumbencies to the interested parties, but almost none to itself.

## Conclusion

The two manners of obtaining access to the experimental cellular product, such as the CAR-T cells, are the clinical trial and the compassionate use, for which the objectives are different. The former endeavors to establish new treatment paradigms for a disease, while the latter endeavors to treat specific patients who have a grave disease, with no expectation of gaining control of it with standard therapy. In Brazil, advanced cellular therapies, both the clinical trial and compassionate use of CAR-T cells projects, require processing by the regulatory agency Anvisa for the evaluation of their pertinence. In the case of the clinical trial with humans, in addition to the appreciation by the regulatory agency, the project should additionally be submitted for evaluation by the Committees on Ethics in Research/National Council of Ethics in Research (CEP/CONEP) system. The attainment of the FIGF of the patient is also considered obligatory in compassionate use.

## Conflicts of interest

The author declares no conflicts of interest.

## REFERENCES

1. De Santis GC, Ubiali EM, Covas DT. Compassionate use of cell products. *Rev Bras Hematol Hemoter.* 2013;35(2):144–5.

2. Lerosé R, Musto P, Aieta M, Papa C, Tartarone A. Off-label use of anti-cancer drugs between clinical practice and research: the Italian experience. *Eur J Clin Pharmacol.* 2012 May;68(5):505–12.
3. Dean-Colombo W, Fang S, Smith W, et al. Off-label drug use in women with breast cancer. *J Clin Oncol.* 2009;27(15 suppl). abstract 1016.
4. Kocs D, Fendrick AM. Effect of off-label use of oncology drugs on pharmaceutical costs: the rituximab experience. *Am J Manag Care.* 2003 May;9(5):393–400. quiz 401-2.
5. Neelapu SS, Locke FL, Bartlett NL, Lekakis LJ, Miklos DB, et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. *N Engl J Med.* 2017;377(26):2531–44.
6. Locke FL, Ghobadi A, Jacobson CA, et al. Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1-2 trial. *Lancet Oncol.* 2019;20(1):31–42.
7. Jarow JP, Lemery S, Bugin K, Khozin S, Moscicki R. Expanded access of investigational drugs: The experience of the center of drug evaluation and research over a 10-year period. *Ther Innov Regul Sci.* 2016;50(6):705–9.
8. Jarow JP, Lemery S, Bugin K, Lowy N. Ten-year experience for the center for drug evaluation and research, part 2: FDA’s role in ensuring patient safety. *Ther Innov Regul Sci.* 2017;51(2):246–9.
9. Chapman CR, Eckman J, Bateman-House AS. Oversight of right-to-try and expanded access requests for off-trial access to investigational drugs. *Ethics Hum Res.* 2020;42(1):2–13. <https://doi.org/10.1002/eahr.500038>.
10. Borysowski J, Górski A. Compassionate use of unauthorized drugs: Legal regulations and ethical challenges. *Eur J Intern Med.* 2019;65:12–6. <https://doi.org/10.1016/j.ejim.2019.04.008>.
11. Balasubramanian G, Morampudi S, Chhabra P, Gowda A, Zomorodi B. An overview of compassionate use programs in the European Union member states. *Intractable Rare Dis Res.* 2016;5(4):244–54.
12. Borysowski J, Górski A. Ethics framework for treatment use of investigational drugs. *BMC Med Ethics.* 2020;21(1):116. <https://doi.org/10.1186/s12910-020-00560-9>.
13. European Medicines Agency (Committee for Medicinal Products for Human Use). Guideline on compassionate use of medicinal products, pursuant to article 83 of regulation (EC) no 726/2004 Available at [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Regulatory\\_and\\_procedural\\_guideline/2009/10/WC500004075.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004075.pdf)
14. Brasil. Ministério da Saúde. Agência Nacional de Vigilância Sanitária. Resolução (RDC) n. 38, de 12 de agosto de 2013. Aprova o regulamento para os programas de acesso expandido, uso compassivo e fornecimento de medicamento pós-estudo.
15. Regulation (EC) no 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency. 2004. Available from: <https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex%3A32004R0726>