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Editorial

[Translated article] Initial achievements and remaining challenges of CAR-T cell therapy in the Spanish National Health System

Logros iniciales y retos pendientes de la terapia con células CAR-T en el Sistema Nacional de Salud Español

Chimeric Antigen Receptor T cell (CAR-T cell) therapy represents a major breakthrough in the treatment of hematological malignancies. The impact of this innovative therapy is comparable to that of the development of allogeneic hematopoietic stem cell transplantation (allo-HSCT).[1] Indeed, the antitumor activity of T-cells was first observed in the setting of allo-HSCT. Over time, donor lymphocyte infusion has been increasingly used in patients with posttrasplant relapse.[2] However, the use of CAR-T therapy poses new challenges in terms of organization, logistics and social and health costs. These challenges arise from the fact that current legislation considers substantially manipulated or genetically modified cells to be an advanced therapy medicinal product (ATMP).[3] Although CAR-T therapy has been initially used for some types of B-cell malignancies and multiple myeloma, new indications are expected to be approved in the coming years. This article briefly describes our view of the initial experience of Spanish National Health System (SNS) centers with CAR-T therapy. A summary of the main challenges and expectations about this therapeutic approach is also provided.

Biologically, the CAR receptor (generally transfected via viral vectors) is a hybrid molecule. First-generation molecules consisted of a single chain variable fragment (scFv) of a monoclonal antibody that identifies a tumor-associated antigen, a transmembrane domain, and the intracellular signaling domain derived from the CD3 molecule of the T cell receptor (CD3ζ). Second-generation CARs incorporated a co-stimulatory domain (generally CD28 or 4-1BB) that leads to T-cell activation and enhances the efficacy and persistence of the modified lymphocytes.[1] From the very first moment, anti-CD19 CAR-T cell therapy demonstrated an unprecedented efficacy in refractory B-cell malignancies (B-cell acute lymphoblastic leukemia [B-ALL] and diffuse large B-cell lymphoma [DLBCL]). The promising results obtained led to the FDA (2017) and EMA (2018) approval of the two first second-generation products (tisagenlecleucel and axicatbagen ciloleucel).[4]

In Spain, the use of CAR-T cell therapy was initially constrained to clinical trials. However, the approval of the first products by the EMA led to the development of a national strategy for the implementation of CAR-T therapy in the SNS. The strategy was named "Plan for the implementation of advanced therapies in the SNS: CAR medications" *["Plan de abordaje de las terapias avanzadas en el SNS: medicamentos CAR"]* and was approved by the Interterritorial Council in November 15, 2018.[5] The Plan was based on the tenets of equity, safety and an efficient use of CAR-T cell therapy in Spain. For such purpose, a network of centers of reference was established for the administration of CAR T cells. A Panel of Experts on the use of CAR T cell products in the SNS was also created. The mission of the Panel was to develop pharmaco-clinical protocols for the use of CAR-T cells and to evaluate treatment requests from public healthcare centers across Spain. A distinctive feature of the Spanish Model was that it included a strategy to foster and promote publicly funded research. This way, academic CAR-T cell products are incorporated into the SNS through authorized manufacturing nodes via hospital exemption. Initially, eight centers were granted authorization for treating adult patients, and three for pediatric patients. Later, three more centers were authorized (two for adults and one for pediatric patients). Extraordinary authorization was also given to another center. In 2022, the initial list was substantially extended to 20 adult centers (plus four additional centers) and 10 pediatric centers. The previous extraordinary authorization was maintained. These hospitals were primarily selected based on their experience with complex allo-HSCT, CAR-T cells, cellular apheresis, and complex cellular processing. Other requirements included holding JACIE/CAT/ONT accreditation or MTA Good Manufacturing Practice Compliance Certification; or having documented preclinical experience with immune-effector cells, among other criteria. A major requirement was also the availability of a Multidisciplinary CAR-T Cell Therapy Unit composed of the professionals involved in the process and a Clinical-Pathology Committee for the evaluation of candidate patients. The two later are essential for ensuring the safety and effective use of these treatments in all authorized centers.

Close collaboration between multiple Hospital Units has become essential to deal with the logistics and complex procedures; coordinate pre-evaluation studies; conduct follow-up; and prevent serious complications (including cytokine release syndrome or Immune-effector Cell Associated Neurotoxicity Syndrome). Apart from Hematology Units and Hospital Pharmacies, other Units actively engaged are Neurology, Intensive Medicine, Infectious Diseases, Microbiology, Radiology, Nuclear Medicine, and Pathology, among others. Nurse Case Managers or Advanced CAR-T cell Clinical Nurse Specialists also play a pivotal role in the coordination of patient journey.

One of the primary challenges is optimizing coordination between the referring hospital, the authorized center of reference, health authorities, and the CAR-T cell manufacturer to reduce the time from indication of the CAR-T cell therapy to its actual administration. Time is one of the main limitations of these therapies as compared to other

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immunotherapies such as bispecific antibodies or immunoconjugates. The percentage of patients who cannot receive a CAR-T cell therapy due to clinical deterioration during the wait or long manufacturing time of the CAR-T cell product is not negligible (7%–25% in some series, depending on the parameters considered).[6]

The rate of response to CAR-T cell therapy in patients with refractory hematological malignancies (B-ALL, DLBCL or multiple myeloma) is higher as compared to other therapeutic options.[1] The severe toxicity of the product should also be taken into consideration. Initial complications include cytokine release syndrome, ICANS, hemophagocytic lymphohistiocytosis or infections. Other complications include cytopenias, which increase morbidity and mortality associated with the procedure.[7] This added to the fact that the long-term rate of relapse after CAR-T therapy in treated patients exceeds 50%[8] highlights the need for further research for a more effective use of these medicines and the optimization of clinical outcomes. Long-term pharmacovigilance in treated patients, with a special focus on the development of secondary neoplasms, is essential in the follow-up of treated patients.[9]

The health and social cost of these therapies is still very high, despite them being publicly funded by virtue of a pay-per-result agreement. Long waiting times and limited availability add to the difficulties described above.[3] The distinctive features of CAR-T cell therapies described above may have negatively affected their level of implementation. Indeed, the initial estimates of clinicians and national and international scientific societies on the number of potential candidates to CAR-T cell therapy are inconsistent with the reported data on treated patients.[10] According to the data provided by the Autonomous Communities on the National Transplant Organization Report on Cellular Therapy Activity, a total of 535 patients received the CAR-T therapy in Spain in 2023, including participants in clinical trials.[11]

At this time (early 2025), there are four publicly-reimbursed CAR-T cell products available in the Spanish SNS. These include tisagenlecleucel (reimbursed for B-ALL and DLBCL) and axicabtagen ciloleucel (reimbursed for DLBCL [recently as second-line therapy); brexucabtagen autoleucel (for mantle cell lymphoma); and idecabtagen vicleucel, an anti-BCMA CAR-T cell product for myeloma multiple. Distinctively, the academic CAR-T therapy ARI-0001 (varnimcabtagen autoleucel) is also available in Spain. This therapy was approved for B-ALL in patients older than 25 years under the Hospital Exemption clause. More recently, ARI-0002 h (anti-BCMA) was approved for multiple myeloma. The availability of the first anti-BCMA CAR-T cells for multiple myeloma also required the extension of the Ministry Panel of Experts, thereby adding logistic needs.

Challenges are expected to escalate in the short and long term with the advent of new CAR-T cell therapies that will increase their efficacy and persistence, reduce associated toxicity and extend the indications currently approved. Ongoing clinical trials will enable progress in CAR-T cell therapy for earlier indications in those hematological malignancies for which they are currently approved (B cell neoplasms, multiple myeloma) and other hematological malignancies. These include myeloid diseases (especially acute myeloblastic leukemia[13]) and T-cell neoplasms,[14] which pose additional challenges that are being addressed in clinical trials with optimized CAR-T cells. New strategies under evaluation include third-generation CAR-T cells, which contain two costimulatory molecules, or four-generation CAR-T cells, which secrete additional molecules such as cytokines and chemokines. There are ongoing clinical trials testing autologous CAR-T cell products generated using new faster manufacturing platforms, universal allogeneic CAR-T cells, other chimeric antigen receptor cells (CAR-NK, CAR-macrophage) or CAR-T cells produced *in vivo*.[12]

Finally, regarding other areas different to Hematology, updated results for autoimmune diseases[15] and solid tumors, especially in central nervous system cancers (for which conventional therapies are hardly effective)[16] open a new therapeutic horizon for many patients and pose new and exciting challenges to our National Health System.

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Fermín Sánchez-Guijo: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Silvia Jiménez:** Writing – review & editing, Writing – original draft, Visualization, Validation, Investigation, Formal analysis, Data curation, Conceptualization.

Conflicts of interest

FS-G has received fees from Novartis, Gilead-Kite and Johnson and Johnson.

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