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Special article

[Translated article] New challenges in advanced therapies

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ABSTRACT

The huge development that advanced therapy medicinal products (AMTPs) have experienced in recent years, both commercial and research, represent a challenge for hospital pharmacy at all levels. The aim of this article is to describe the implementation of an advanced therapies unit (AUT) and the process of preparation of the AMTPs according to the "good manufacturing practices" (GMP), as well as the results obtained in a tertiary hospital, as an example of the challenges posed by MTA's academic production.

The AUT meets the requirements established in the GMP by guaranteeing that the medicines produced therein are of the quality required for the use for which they are intended, and also provides support to various research groups involved in the development of AMTPs. The AUT is composed of a highly qualified multidisciplinary team, qualified and trained in GMP, and is authorized for the preparation of 5 types of AMTPs consisting of allogeneic virus-specific T cells (VST) with various viral specificities. A circuit has been established in collaboration between the UTA and the pharmacy service with the hematology service for the assessment of the clinical indication, the request, and preparation of VST, which allows the treatment of patients receiving hematopoietic stem cell transplants who present viral reactivations resistant or refractory to standard treatment, or who cannot tolerate it due to toxicity. Preliminary results from these AMTPs suggest that VSTs are an effective and safe alternative.

Academic AMTPs have special interest in orphan indications or in the absence of alternative treatments, and their production through the "hospital exemption" can favor early access in the initial phases of development and at a lower cost. It is essential to promote the training of hospital pharmacists in GMP and their participation in collaboration with other clinicians and researchers to develop AMTPs that meet all logistical and regulatory requirements.

Nuevos retos de las Terapias Avanzadas

Palabras clave:
medicamentos de terapias avanzadas
normas de correcta fabricación
terapia celular
criopreservación

RESUMEN

El enorme desarrollo que están experimentado en los últimos años los medicamentos de Terapias Avanzadas (MTA) tanto industriales como en investigación suponen un reto para la Farmacia Hospitalaria a todos los niveles. El objetivo del trabajo es describir la puesta en marcha de una Unidad de Terapias Avanzadas (UTA) y el proceso de elaboración de los MTA según las «normas de correcta fabricación» (NCF), así como los resultados obtenidos en un hospital terciario, como ejemplo de los retos que supone la producción académica de MTA.

La UTA cumple los requisitos establecidos en las NCF garantizando que los medicamentos que en ella se producen son de la calidad requerida para el uso al que están destinados, y además, proporciona apoyo a diversos grupos de investigación involucrados en el desarrollo de MTA. La UTA está compuesta por un equipo

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multidisciplinario altamente calificado, capacitado y entrenado en NCF, y está autorizada para la elaboración de cinco tipos de MTA que consisten en linfocitos T virus-específicos (VST) alogénicos con diversas especificidades víricas. Se ha establecido un circuito en colaboración entre la UTA y el Servicio de Farmacia con el Servicio de Hematología para la valoración de la indicación clínica, la solicitud y la elaboración de VST, lo que permite el tratamiento de pacientes receptores de trasplante de progenitores hematopoyéticos que presenten reactivaciones víricas resistentes o refractarias al tratamiento farmacológico habitual, o que no puedan tolerarlo debido a la toxicidad. Los resultados preliminares de estos MTA sugieren que las VST son una alternativa efectiva y segura.

Los MTA académicos tienen especial interés en indicaciones huérfanas o en ausencia de tratamientos alternativos, y su producción a través de la «exención hospitalaria» puede favorecer su acceso precoz en las fases iniciales de desarrollo y a un menor coste. Es fundamental promover la formación de los farmacéuticos hospitalarios en NCF y su participación en colaboración con otros clínicos e investigadores para desarrollar MTA que cumplan con todos los requisitos logísticos y regulatorios.

Introduction

Advanced therapy medicinal products (ATMPs) are drugs for human use based on genes (gene therapy), cells (cell therapy), or tissues (tissue engineering). The development of both industrially manufactured and academic ATMPs has experienced a significant growth in the last few years, to the extent that they are the subject of nearly half of the 2093 clinical trials on advanced therapies underway globally.[1] Hospital pharmacists are responsible for ensuring the safe and effective use of all medicines,[2] including ATMPs, which involves managing the entire pharmacotherapeutic process, from procurement of the drug to its administration to the patient. Hospital pharmacists are therefore part and parcel of the Spanish National Health System's *Advanced Therapies Implementation Plan* as the professionals ultimately responsible for managing both commercial (industrially-manufactured) and academic (developed by hospitals and research institutions) ATMPs.[3]

The manufacturing of ATMPs, as is the case with any other kind of medicine, must follow established good manufacturing practices (GMPs).[4] In November 2017, the European Commission adopted a series of specific GMPs for ATMPs,[5] which cover both industrially manufactured and hospital pharmacy-compounded formulations. As regards non-industrially manufactured ATMPs, Royal Decree 477/2014 establishes the possibility that they may be compounded by hospital pharmacies under the hospital exemption rule,[6] provided that specific quality standards are met and that the process is carried out under the responsibility of a medical practitioner, in order to comply with an individual medical prescription for a custom-made product for an individual patient.

ATMPs are complex products associated with several risks which vary as a function of the type of drug, the characteristics of the starting materials, and the manufacturing process employed. For that reason, GMPs for ATMPs are founded on a risk-based approach, with manufacturers being responsible for establishing the organizational, technical, and structural measures needed to ensure the quality of the final product.[4,6] The European Union has recently published a new version of Annex I of its GMPs (not specific for ATMPs), which emphasizes the importance of quality risk management and of a proactive identification of the risks associated with drug production.[7]

This article discusses the main challenges inherent in the compounding of ATMPs in hospital pharmacy departments. We shall use the implementation of a GMP-compliant multidisciplinary advanced therapies unit (ATU) in a third-level hospital, and the results it has obtained so far, as an example of the galenic production of ATMPs.

Design of an advanced therapies unit

The ATU described in this study is a platform shared by the La Fe University and Polytechnical Hospital (HUP La Fe) and the La Fe Healthcare Research Institute (IIS La Fe). It was designed under the regulatory framework governing the conduct of clinical and preclinical studies as a unit responsible for supporting different research groups in the development of academic ATMPs.

The ATU, established in 2017, covers an area of 177.25 m^2, distributed into 3 independent class B compounding rooms, 5 class C rooms, an area dedicated to vapor-phase LN2 cryopreservation, and a quality control laboratory (Fig. 1). The unit meets all the requirements established in the EU's GMPs, assuring the quality, safety, and efficacy of the medicines produced.

The ATU boasts a highly-qualified multidisciplinary team steeped in the particulars of GMPs, which includes hematologists, biologists, and pharmacists, both from IIS La Fe and from HUP La Fe. At present, the unit is led by a hospital pharmacist, who is responsible for authorizing the production of every batch of ATMPs once its compliance with the approved specifications has been ascertained. AMTP-producing units must meet the following requirements to ensure compliance with GMPs:[5]

- Personnel: Highly qualified staff with clear attribution of responsibilities.
- Facilities and equipment: The facilities and equipment must be fit for purpose and regularly maintained. Facilities producing more than one ATMP (multi-product facilities) should either assign a separate area for each ATMP produced, or distribute the production of different ATMPs across different time slots, ensuring the implementation of strict cleaning systems to avoid cross-contamination.
- Documentation system: Facilities must be in possession of comprehensive specifications for all bulk and finished materials and intermediate products, as well as of a detailed description of the production process and all the associated records.
- Compounding process: The consistency of the production process, the quality of the products compounded, and the compliance with all specifications must be duly guaranteed.
- Quality assurance: Quality assurance systems must be independent from the production system.
- Prospective evaluation of change: Any changes must be planned for and be approved prior to their implementation.
- Quality defects and deviations from the required specifications must be identified as early as possible and action must be taken to investigate the causes and implement the corrective and/or preventive measures.
- Traceability: It is indispensable to ensure full traceability of final products and of starting and critical materials.

Along the same lines, new Annex 1 of the EU GMPs seeks to tighten the requirements related to the prevention, control, and tracking of pharmaceutical products, and to improve the quality assurance and

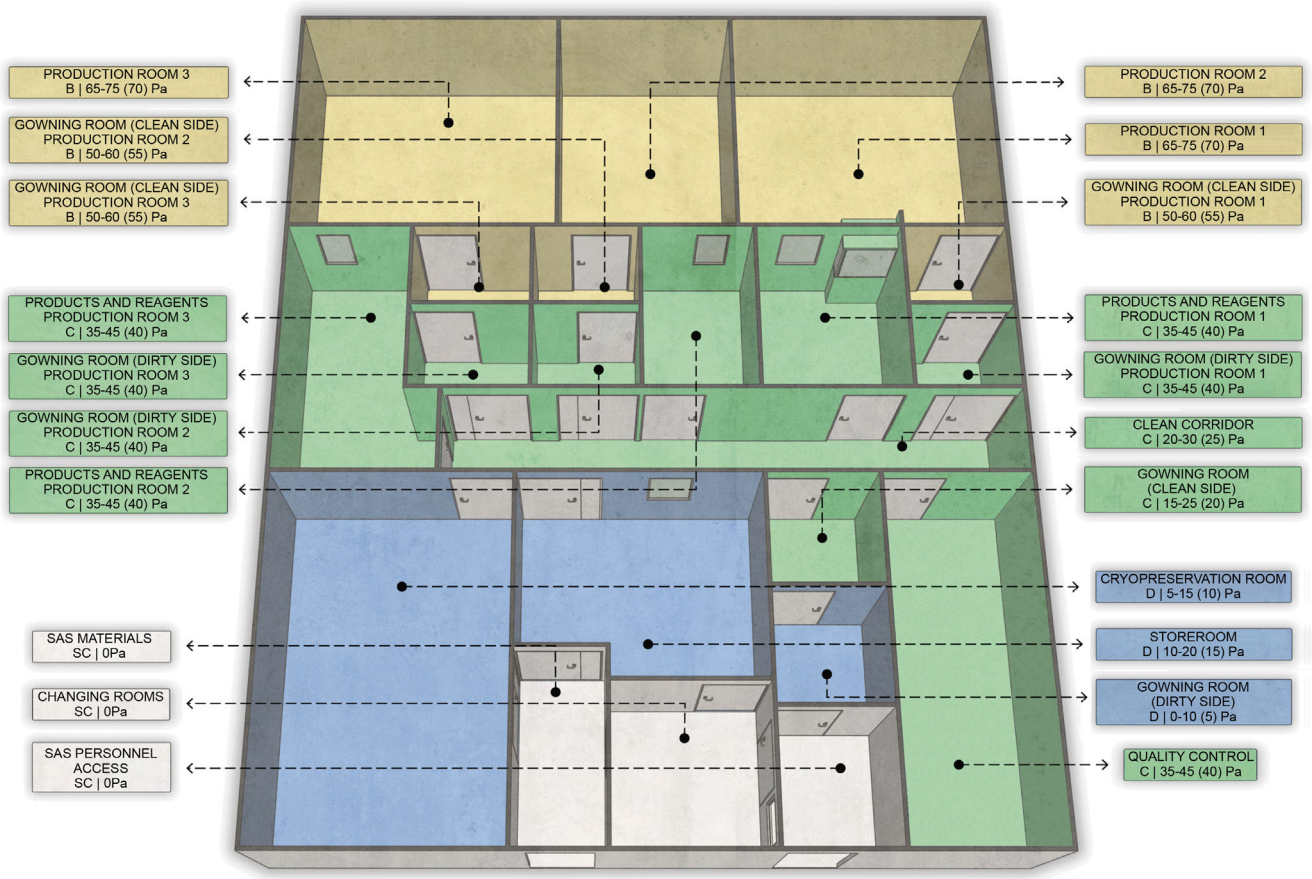

Fig. 1. Layout and equipment of the advanced therapies unit.

information management systems used. With regard to cleanrooms, it emphasizes the importance of cleaning systems, of maintaining an aseptic and controlled environment, of properly designing facilities and materials to avert the risk of contamination, and of ensuring that the staff are properly trained and qualified.[7]

Qualification and maintenance of compounding facilities

Qualification of air treatment systems (according to ISO 14644-1 and ISO 14644-2 standards) and cleanrooms is carried out yearly by an external company. In addition, an environmental monitoring program exists that allows evaluation of the effectiveness of the contamination control measures adopted. The environmental monitoring program includes viable and non-viable particle monitoring:

Surface sampling: Carried out by means of contact plates to control for aerobic bacteria, fungi, and yeasts.

Environmental sampling: Performed by specialized teams, it is used to control for aerobic bacteria, fungi, and yeasts. It may be carried out with an air sampler or with sedimentation plates.

Non-viable particle counts: This procedure is aimed at checking for 0.5–5-μm particles. The system used must allow continuous control of the cleanroom.

Differential pressure: The theoretical pressures defined for each cleanroom must be verified with a system that allows for continuous monitoring.

Number of air changes per hour: A system is used to ensure that the minimum number of air changes established for each room is complied with.

The ATU staff monitors for the presence of viable particles every 3 weeks. The results of the analysis are examined by the HUP La Fe Microbiology Department, with which an internal collaboration agreement has been concluded.

Aseptic process validation

Aseptic process simulation tests, also known as *media fill tests*, consist in the performance of an aseptic manufacturing routine based on a sterile microbiological growth medium and/or a placebo to determine if the procedures employed during drug compounding are capable of avoiding microbial contamination.

Media fill tests must follow the usual compounding procedure and be carried out in the same place as the actual production is performed, with a particular focus on processes involving non-sterile stages, and considering all possible interventions.

Securing the approval of the Spanish Medicines and Health Products Agency (AEMPS) to produce an ATMP requires performing 3 consecutive media fill tests per operator and production process, with satisfactory results. In addition, a media fill test must be conducted every year in active ATUs, with an additional test being required if the ATU has not produced ATMPs for 6 months and 3 additional tests being mandatory if a whole year has gone by without the ATU producing an ATMP.

Applying for authorization to produce an advanced therapy medicinal product

The application procedure established by HUP La Fe for ATMPs for which the ATU holds an AEMPS-issued compounding authorization comprises the following stages (Fig. 2):

1. The attending physician submits a standardized application report to the hematopoietic stem cell transplantation (HSCT) and cell therapy

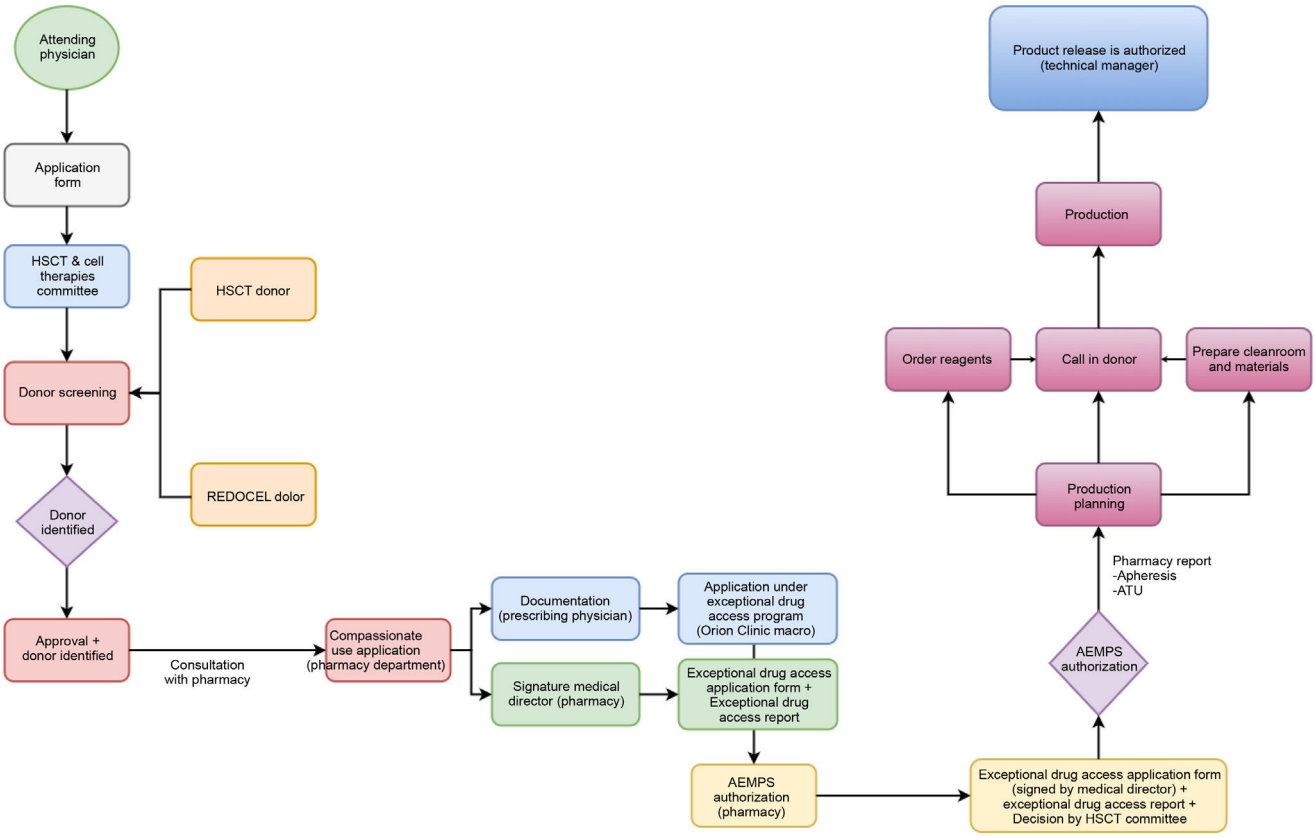

Fig. 2. Applying for an authorization to compound advanced therapy medicinal products.

committee. The committee, made up of a multidisciplinary team, meets weekly to analyze applications for HSCT and ATMPs, including both commercial T-cell therapies with chimeric antigen receptors (CAR-Ts) and in-development or academic ATMPs. At those meetings, the different therapeutic alternatives available are discussed and the potential indication for an ATMP is evaluated. In case of acceptance, a search for the most appropriate donor commences.

2. The HSCT and cell therapy committee selects the most appropriate donor, which may be the previous HSCT donor, a family member with appropriate HLA compatibility, or a third-party donor from the REDOCEL cell donor network, a collaborative project with the Transfusion Center of the Valencia Region (CTCV) and the Blood and Tissue Bank of Cataluña (BST). The donor must meet the donation standards for hematopoietic products as determined by the blood bank/apheresis unit. Eligibility is also determined depending on the presence of T-cell immunity against the virus of interest. This assessment is conducted by the hematology diagnostic unit by means of *in-vitro* assays and cytometry.
3. Once a donor has been determined eligible, the attending physician submits an application under the exceptional drug access program, attaching the minutes of the committee meeting where approval was granted. Subsequently, a consultation is made with the hospital's pharmacy department to discuss the possibility to administer the drug under the compassionate use rule if the treatment is not part of an active clinical trial. All of these documents are submitted to the hospital's medical director, together with an application under the exceptional drug access program prepared by the pharmacy department.
4. The pharmacy department must upload all the required documents (application by the hematology unit, approval by the committee, application of the pharmacy department with the hospital medical director's, and the ATU technical manager's authorization to produce the ATMP) to the AEMPS exceptional drug access program website to obtain an authorization to use the drug in individual patients. In addition, the product's PEI (investigational new drug) authorization number, as assigned by AEMPS, must be stated and any clarifications requested by AEMPS about the product must be addressed.
5. Once AEMPS' authorization has been secured, both the hospital's apheresis unit and the ATU can set about planning the production process. The former must call in donors and schedule the lymphocyte apheresis procedure, while the latter must secure the reagents needed and prepare the compounding room, the batch documentation and the required materials.
6. The ATMP can now be produced. This procedure, which will be explained in detail below, basically includes obtaining a donor sample, compounding the ATMP in GMP conditions, dosing and packaging the drug, the release of the end product by the technical manager and, last but not least, administration of the ATMP.

Experience of the advanced therapies unit of the La Fe University Polytechnical Hospital

The HUP's hematology department contacted the ATU for the production of several ATMPs in GMP conditions. All of such ATMPs were to be based on T-cells specifically targeted at viruses related to publicly-funded projects within a multicenter clinical trial (Nr EudraCT 2018-000911-25).

The ATU has since 2019 been accredited by AEMPS for the production of 4 different kinds of allogeneic T-cells specifically targeted to cytomegalovirus (CMV), Epstein–Barr virus (EBV), adenovirus (AdV), and BK polyomavirus (BKV), obtained from peripheral blood. Moreover, the ATU has recently been authorized to produce T-cells targeted at JC polyomavirus (JCV) for the treatment of progressive multifocal leukoencefalopathy.

These ATMPs, known as *virus-specific T cells* (VSTs), are indicated for the treatment of viral reactivations either refractory to standard pharmacological treatment or unable to receive it because of toxicity issues.

Infusion of VSTs endows the receptor with virus-specific immunity without increasing the risk of them developing graft-versus-host disease (GvHD). The selection of donor T-cells takes place by antigenic stimulation with a viral peptide and immunomagnetic capture of the specific IFNɣ-producing cells, using the automated CliniMACS Prodigyce:sup]® platform.

Production of virus-specific T-cells

The VST production process can be broken down into the following stages.

Stage 1: Reception of the starting material and volume adjustments

The starting material is obtained through leukapheresis of a donor who is seropositive for the virus of interest. It must contain between 1.0 and 1.5×10^9 nucleated cells and, following the performance of a series of tests to verify its integrity and eligibility for the process it will undergo, it is adjusted to a final volume of ≤100 ml. A sterile connector is used to transfer the starting material to the tubes in the CliniMACS Prodigy® system, keeping the circuit closed for the duration of the process to avoid any potential contamination.

Stage 2: Antigen stimulation with a viral peptide and immunomagnetic capture through IFNɣ production

The T-cells specific for the virus of interest are selected from the total pool of donor lymphocytes by antigen stimulation with a viral peptide and immunomagnetic capture through IFNɣ production, using the CliniMACS Prodigy® platform. This process takes place over a period ranging between 4 and 6 h at 37 °C.

Stage 3: Dosing and packaging of the final product

Once analyzed by flow cytometry, the total volume of the final product is dosed taking into consideration the weight of the recipient and the specifications of the final product (viability, purity, maximum dose, and maximum content of impurities). The processing and packaging of the final product takes place in a grade A environment using a horizontal laminar flow cabinet located in a grade B cleanroom.

Production of the 5 types of VST results in a single dose, which is prepared by wet compounding and administered at once. For that reason, the production process does not involve cryopreservation of the final product.

Stage 4: Release of the final product

The release of the final product takes place in 2 stages: an early phase, based on partial results, and a final phase, once all the results are available. The critical stages of the process are controlled by analyzing both the intermediate products and the final product.

Before early release of an ATMP a quality control procedure is implemented, which consists of a microbiologic assay (Gram-positive cultures) and a flow cytometry test (post-stimulation and final product), where counts and viability analyses of lymphocyte and IFNɣ-marked T-cell populations are performed. Such analyses make it possible to ensure that only T-cells specifically targeted against the virus of interest have been selected and that they comply with pre-determined purity criteria. The quality examination required before the ATMP can be released is completed with a series of sterility, mycoplasma and endotoxin assays.

The product is then transported at a temperature ranging between 2 and 8 °C. A maximum of 24 h may elapse between early release of the ATMP and its infusion into the patient's bloodstream. The production process spans a maximum period of 36 h (range: 22–36) and takes place in an almost entirely closed system, except for the reconstitution and reagent addition phases. In our case, the process was performed in a grade A environment in a grade C cleanroom. Production was automated (CliniMACS Prodigy®) and all reagents were filtered before use.

Results of the production of virus-specific T cells and future projects

Since February 2021, the ATU has produced 6 VST ATMPs, which have been used to treat 6 patients, 5 of them for CMV infection (4 adults and 1 pediatric patient), and 1 for BKV infection (a pediatric patient). Tolerance was optimal in all cases. Three patients were treated for CMV infection within the context of a phase Ib/II clinical trial (NCT04018261), whose preliminary results (20 patients) were presented at the American Society of Hematology (ASH) 2022 Annual Meeting.[8] VST treatment was shown to be effective in 14 patients, with 61.2% positive responses at week 8 and without any new viral reactivations. As regards toxicity,11 severe VST-related adverse reactions were observed, including infections ($n = 5$), hematological toxicity ($n = 3$), and 1 case of mild reversible cutaneous GvHD. In the 3 remaining patients, 2 of them with CMV infection and the other with BKV infection, the ATMP was used under the compassionate use rule. All of these patients responded at week 8. The 2 patients with CMV infection did not experience new viral reactivations, whereas the one with BKV infection never tested negative for the virus. No adverse reactions associated with the administration of ATMPs were observed.

The ATU is also a compounding center under the first Spanish bank containing CMV- and EBV-directed T-cells to be immediately used to address post-transplantation opportunistic infections. This collaborative project, funded by RETOS (RTC-2017-6368-1), is aimed at providing the National Health System with a bank of T-cells directed against CMV and EBV to be applied in patients lacking a compatible donor. These 2 viral infections are of particular concern given the high morbidity and mortality rates they are responsible for in the context of allogeneic hematopoietic stem cell and solid organ transplantations. It is expected that the corresponding clinical trial will be initiated at the beginning of 2024.

The ATU is at present immersed in validating an open-system procedure for the production of platelet-rich plasma (PRP) for different trauma surgery indications, where PRP has traditionally been prepared using the open system. Being able to prepare PRP using the open technique will result in significant cost savings as compared with the closed technique and will allow a better characterization of the product, increasing its versatility and number of potential uses.

Future projects of the ATU include the development of an expanded natural-killer cell-based ATMP to prevent and treat tumor recurrence and viral infections as well as the design of an academic CAR-T cell therapy targeted at acute leukemia.

Discussion

Under the hospital exemption rule, non-industrial ATMPs are set to become a safe and effective alternative for patients with diseases with few or no therapeutic options. Against this background, the role of hospital pharmacy departments in promoting, developing, and implementing both industrial and academic ATMPs in clinical practice is likely to be crucial.[9]

The current European and Spanish regulations require that a set of GMPs,[4–7] as well as a risk management system, be established for the compounding of ATMPs with a view to ensuring that the drug's quality is high enough to achieve its therapeutic purpose with optimal safety and effectiveness. Implementing a GMP system calls for intensive staff training, in addition to a significant investment in facilities and equipment. As stated in Royal Decree 16/2012[10] and the *Best-practice guidelines for the compounding of drugs in hospital pharmacy departments*,[11] collaboration of hospital pharmacists in ATMP compounding projects also involving clinicians and researchers will be extremely helpful going forward, given their long experience with GMPs, particularly

regarding the formulation and packaging of medicines in cleanrooms. The new Annex 1 of the EU's GMPs for sterile products underscores the need to establish a pharmaceutical quality system that ensures an integrated management of risks in order to minimize contamination risks and implement a contamination-control strategy.[7]

As was the case for CAR-T-cell therapy, the initial development of ATMPs was circumscribed to the academic sphere and only later taken up by pharma companies, partly due to the logistic and regulatory requirements inherent in complying with GMPs and promoting clinical trials.[12–14] The crucial participation of clinicians and researchers in the early stages of development of ATMPs demonstrates their ability to design these therapies from scratch as well as the need to work in near-GMP conditions from the initial preclinical stages to facilitate the transition towards industrial production.[3] More and more hospitals and healthcare research institutes are creating their own ATUs with the aim of promoting a kind of translational medicine that allows quick and safe access to ATMPs in their early development phases.

The expertise and the complex equipment required for compounding ATMPs warrant concentrating the process in specialized centers, which can then produce the drugs for third parties making it possible for a larger number of patients to avail themselves of these therapies. In order to promote collaboration between ATMP-producing facilities, the Carlos III Institute has set up the Consortium Network for the Development of Advanced Therapy Medicinal Products (CERTERA).[15] HUP La Fe's ATU is one of the centers that has applied to join CERTERA and is awaiting publication of the final list of admitted centers. The legal details concerning how the collaboration will work and how the products will be billed to third parties remain to be decided as these ATMPs are not commercially available, unlike other non-industrial ATMPs such as CART-T ARI-0001 used for acute lymphoblastic leukemia and NC1 used for spinal cord lesions, which are available through AEMPS' exceptional drug access program.

As regards the results obtained by HUP La Fe's ATU, it should be mentioned that the VST therapies produced have achieved efficacy and toxicity levels akin to those of other academic endeavors also based on the CliniMACS Prodigy®[16,17] system or on VST banks, with positive responses ranging between 80% and 100% and a low incidence of GvHD.[18–20] It should be mentioned that a phase II clinical trial on 58 patients for posoleucel,[21] a multi-virus VST therapy against 6 different viruses (CMV, EBV, AdV, BKV, JCV, and human herpes virus 6) with indications similar to those of the ATMP produced in our facility, produced an objective response rate of 95% at 6 weeks and 13 cases of GvHD (10 grade 1, 2 grade 2, and 1 grade 3). Both academic productions, as well as posoleucel, have demonstrated the key role played by VST therapy in refractory viral infections following an allogeneic HSCT.

In a nutshell, production of ATMPs under the hospital exemption rule is set to constitute a formidable technical, educational, and logistic challenge for hospital pharmacies. However, if all technical requirements are met and the current regulations are conformed to, and if the work is placed in the hands of multi-disciplinary teams, success will lie within our reach. Given that the future of therapeutics will be based on the use of both industrial and academic ATMPs, hospital pharmacists, as those responsible for managing the entire pharmacotherapeutic process, should also be able to ensure that ATMPs are compounded in GMP conditions.

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CRediT authorship contribution statement

Juan Eduardo Megías-Vericat: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Visualization, Writing – original draft, Writing – review & editing. **Ana Bonora-Centelles:** Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Writing – original draft, Writing – review & editing. **Tomás Palanques-Pastor:** Investigation, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Cristóbal Eduardo Aguilar Gallardo:** Conceptualization, Formal analysis, Investigation, Methodology, Resources, Validation, Visualization, Writing – original draft, Writing – review & editing. **Manuel Guerreiro:** Conceptualization, Formal analysis, Investigation, Methodology, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Inés Gómez Seguí:** Conceptualization, Investigation, Methodology, Supervision, Validation, Visualization, Writing – review & editing. **Javier De La Rubia:** Supervision, Validation, Writing – original draft, Writing – review & editing. **José Luis Poveda Andrés:** Supervision, Validation, Visualization, Writing – review & editing.

Declaration of competing interest

The authors have declared that they have no interests that may be perceived as posing a conflict or bias.

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