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ISCT Committee Reports

Current challenges in cell and gene therapy: a joint view from the European Committee of the International Society for Cell & Gene Therapy (ISCT) and the European Society for Blood and Marrow Transplantation (EBMT)

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ABSTRACT

Cell and gene therapy poses evolving challenges. The current article summarizes the discussions held by European Regional Committee of the International Society for Cell & Gene Therapy and the European Society for Blood and Marrow Transplantation (EBMT) on the current challenges in this field, focusing on the European setting. This article emphasizes the imperative assessment of real-world cell and gene therapy activity, advocating for expanded registries beyond hematopoietic transplantation and chimeric antigen receptor–T-cell therapy. Accreditation's role in ensuring standardized procedures, as exemplified by JACIE (The Joint Accreditation Committee of ISCT-Europe and EBMT), is crucial for safety. Access to commercial products and reimbursement variations among countries underscore the need for uniform access to advanced therapy medical products (ATMPs). Academic product development and point-of-care manufacturing face barriers to patient access. Hospital Exemption's potential, demonstrated by some initial experiences, may increase

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patient accessibility in individual situations. Regulatory challenges, including the ongoing European ATMPs legislation review, necessitate standardized criteria for Hospital Exemption and mandatory reporting within registries. Efforts to combat unproven therapies and fraud involve collaboration between scientific societies, regulatory bodies and patient groups. Finally, is important to highlight the vital role of education and workforce development in meeting the escalating demand for specialized professionals in the ATMP field. Collaboration among scientific societies, academic institutions, industry, regulatory bodies and patient groups is crucial for overcoming all these challenges to increase gene and cell therapy activity in Europe.

Introduction

Cellular therapy, considered as a whole, has emerged as an evolving but challenging tool for addressing diseases with unmet medical needs. The shift in European legislation in the first decade of the 21st century, which introduced the legal definition of advanced therapy medicinal products (ATMPs), presented a significant challenge for academic centers involved at that time in cellular therapy and increased the attention of the pharmaceutical industry toward this therapeutic field [1,2]. The advent of chimeric antigen receptor (CAR)–T cells has exponentially amplified the interest of stakeholders in this area of biomedicine, along with the accompanying challenges and future imperatives. Consequently, with a focus on the European-specific landscape, the European Regional Committee of the International Society for Cell & Gene Therapy (ISCT) and the European Society for Blood and Marrow Transplantation (EBMT) have convened several meetings to jointly discuss the challenges pertaining to cell and gene therapy within this region, ultimately arriving at a consensus on potential strategies to address them. The culmination of these discussions is summarized within this article.

Assessment and Documentation of Real-World Cell and Gene Therapy Activity

It is acknowledged that the comprehensive assessment of real-world practices surrounding the application of ATMPs is pivotal for advancing the field, as strategic analysis and planning invariably necessitate a foundation in such data. For the past three decades, the EBMT registry has established itself as the premier resource within Europe for evaluating hematopoietic transplant activities and outcomes [3]. The registry, predominantly encompassing institutions engaged in hematopoietic transplantation, accumulates data from all EBMT-affiliated centers. Most recently, the registry has integrated a newly designed “Cell Therapy Form” to register patients and capture their outcomes. CAR-T therapy has been prioritized since it was widely introduced on the European Union market. Nevertheless, EBMT is also planning to register patients and capture their outcomes following treatment with other forms of cellular or gene therapies manufactured from hematopoietic stem cells, various types of immune effector cells and mesenchymal stromal cells [4]. Other types of ATMPs that are used to treat other than hematologic conditions or are manufactured from other tissues than the bone marrow are generally excluded from the EBMT registry. Previous efforts have been made to join forces in accessing or estimating this information between ISCT, EBMT, the Tissue Engineering and Regenerative Medicine International Society, the International Federation for Adipose Therapeutics and the International Cartilage Repair Society, with a periodic survey from which valuable information on activity in other fields outside hematology is obtained [5–12].

A prospective approach to aggregate real-life activity, akin to the current practice for CAR-T therapy within the EBMT registry, could involve expanding this registry to comprehensively capture data from all these diverse sources within European countries. Such an undertaking, although significant in terms of economic costs, resource allocation and time, would facilitate an organized and timely aggregation of data. The alignment and endorsement of all scientific societies and stakeholders embarking upon this collective endeavor are imperative.

Accreditation, Quality Assurance and Benchmarking

A critical prerequisite for ensuring safety of the entire cellular therapy manufacturing and treatment process, which spans from patient/donor selection to patient care, is that the procedures are executed in a standardized manner. It is required that such activities occur within experienced healthcare centers, guided by optimal protocols and conditions. Accreditation systems stand as the foundation for ensuring these standards. Within Europe, JACIE (The Joint Accreditation Committee of ISCT-Europe and EBMT) has played an instrumental role since its establishment in 1998 [13]. Operating on standardized procedures, the JACIE accreditation system has attracted nearly 400 different centers seeking accreditation. The positive impact of accreditation on hematopoietic transplant outcomes, the predominant focus of JACIE-accredited centers, has been substantiated, underscoring the correlation between new center accreditation and enhancements in patient survival and reduction of procedural mortality [14,15]. Therefore, the implementation of quality management standards is strongly advocated, with the aim of refining processes and mitigating potential, possibly concealed, risks that might impact upon survival rates.

Accessibility to Commercial Products Across Countries and Reimbursement

A recent study has demonstrated that access to approved ATMP shows considerable variation among countries, including Ireland, United Kingdom, France, Germany, The Netherlands and Spain due to differences in reimbursement decisions [16]. For instance, Germany’s greater reimbursement through the public health system contrasts with the absence of reimbursement for several ATMPs approved by the European Medicines Agency (EMA) in Ireland. Furthermore, some countries, such as the UK, France and Spain, allocate limited reimbursement within their public health systems, resulting in constrained access linked to specific clinical conditions within the approved indications [16].

Some countries such as Spain and Italy have embraced the concept of “outcome-based reimbursement” for ATMPs, an approach in which complete payment for the product is linked to the patient’s outcome at a defined timepoint [17]. Fostering uniformity in ATMP access across Europe is pivotal, necessitating reimbursement approaches that ensure equitable access for all patients requiring these treatments. EUnetHTA, an international network for Health Technology Assessment across Europe, considered the EBMT registry as useful registry for post-launch evidence generation and might also be able to assist in national reimbursement programs [18]. This will become relevant upon the implementation on the January 1, 2025, of the incoming centralized health technology assessment and joint clinical assessment [19]. The follow-up and collection of post-treatment data are essential to assess long-term safety, as demonstrated by the need to better understand some complications such as the cases of T-cell lymphomas originating in a low percentage of patients treated with CAR–T-cell therapy, as recently

highlighted by ISCT, EBMT and the American Society for Transplantation and Cellular Therapy [20].

Development of Academic Products and Point-of-Care Manufacturing

Despite industry endeavors to implement autologous CAR-T therapy access, a series of barriers continue to impede progress, including intricate logistics (involving intercontinental cell shipments), slot reservation and manufacturing complications and bureaucratic delays [21]. A recent analysis has examined the accessibility to CAR–T-cell therapy of patients with diffuse large B-cell lymphoma (DLBCL) in Germany, France, Italy and Spain in 2020. A significant proportion (ranging from 58% to 83%) of patients with refractory or relapsed DLBCL falling within the EMA approved-label population and (between 29% and 71%) of those patients deemed clinically eligible did not ultimately receive commercially approved CAR–T-cell products [22]. Moreover, in countries such as Spain, the mean time from EMA approval to the authorization of price and reimbursement for orphan drugs, a category to which most ATMPs belong, averages approximately 18 months. Notably, nearly one-third of the approved orphan drugs do not ultimately secure reimbursement, with one half of them being indicated for diseases lacking any therapeutic alternative [23]. A recent analysis focused on the Spanish context indicated that, as of May 2023, a mere 20% of EMA-approved ATMPs were reimbursed by the public national health system [24].

To enhance patient access to advanced therapies, particularly in scenarios in which limitations of commercial products are significant, and where there is minimal commercial interest, the European legislation offers a mechanism to increase accessibility through the establishment of cell-manufacturing facilities within accredited healthcare centers, under the provision of hospital exemption [25–27]. Hospital exemption was established in the European ATMP regulation EC1394/2007 (Article 28) [28] to allow production of ATMPs outside the centralized marketing authorization path and has enabled access to several ATMPs treatments to patients without therapeutic alternatives in Europe. The experience of the Hospital Clinic of Barcelona with the ARI program has demonstrated the capacity of European-accredited healthcare centers to produce ATMPs (in this case CAR-T cells) with clinical results comparable with commercial products [29], increase patient accessibility by personalizing and shortening times, all at a lower reimbursement cost compared with commercial options, while ensuring compliance with the regulations set forth by the corresponding national regulatory agency [30,31]. Although there may be differences between the final manufacturing costs of academic ATMPs depending on local factors (e.g., personnel or maintenance costs of the facilities), most likely overall the price of academic products may be below the costs of the commercial ones. It will be interesting to follow the evolution of the pilot program launched by the EMA to guide and support academic centers in the development of ATMPs through a centralized development and approval process, the Spanish program just mentioned being the first of those selected in this initiative [32]. Furthermore, the results of a phase 2 randomized non-inferiority clinical trial currently recruiting patients in The Netherlands (HOVON-161 trial) merit keen interest. This study compares a point-of-care manufactured CAR-T (ARI-0001) against a commercial counterpart (axi-cel) in patients with relapsed or refractory DLBCL [33], and its findings may hold significance for the field. The future will also show whether academic pharma can keep pace with the many new commercial products entering the market, as multicenter trials to compare novel academic products with other approved products are costly. Therefore, early development and niche indications will be the most important areas for CAR-T cells produced in academic centers.

Nonetheless, within the intricate landscape of ATMP development, early collaboration among all stakeholders stands as an imperative cornerstone. Notably, the significance of public–private partnerships emerges as a key instrument in propelling the advancement of novel cell and gene therapy products within Europe [34]. The establishment of consortia or networks that cover the entire spectrum of ATMP development from inception to approval for a defined indication and inclusive of *in vitro, in vivo* and early-stage clinical trials is imperative. This collaborative framework invariably involves the early involvement of biotechnological or pharmaceutical companies that may potentially assume or share intellectual property ownership and drive subsequent product development through marketing authorization. Simultaneously, regulatory agencies must also collaborate from the embryonic stages of development [35]. Illustrative models of this approach are exemplified by initiatives such as the Spanish Cell Therapy Network (formerly TerCel, now renamed as TERAV) [36] or the Dutch Oncode Accelerator Program [37] or DARE-NL consortium [38]. With so many exciting national initiatives, the GoCART coalition [39], a joint initiative of the EBMT and the European Hematology Association, is an opportunity to combine these efforts from a European perspective.

Regulatory Challenges and Revision of the European ATMPs Legislation

The European legislation on advanced therapies, now about 20 years old [28], is currently under review. Its introduction meant a significant change for academic networks conducting research in cell therapy, gene therapy and tissue engineering, as some products subjected to “substantial manipulation” or applied to a function other than their physiological one, transitioned from the regulatory field of organ and tissue transplantation to the pharmaceutical legislation. This provided a focused approach expanding the regulatory knowledge and experience on ATMPs. Nevertheless, this may have had some impact on the number of approvals. Furthermore, a few holders of approved products have subsequently withdrawn them, mainly for regulatory and strategic reasons [24].

The concept of Hospital Exemption, as elaborated upon extensively in previous sections, warrants a reevaluation within the framework of the new legislation. The objective here is not to curtail its use but rather to standardize the quality criteria that underpin the access to ATMPs through this mechanism. This involves harmonizing the preclinical and clinical evidence supporting these therapies. Additionally, it is imperative that data pertaining to treatments and patient follow-up conducted under hospital exemption be mandatory and accessible within the registries established for this precise purpose [26]. The impending European legislation governing ATMPs should be thoughtfully aligned to the overarching objective of streamlining patient access to these treatments. This consideration is particularly critical in instances where these treatments represent patients’ sole or final recourse to potentially beneficial interventions. An international registry, such as the Cellular Therapy Registry of the EBMT, could be a suitable platform to report on all hospital exemption programs, to allow third-party monitoring of such programs in terms of safety and efficacy.

Patient’s Awareness, Unproven Therapies and Fraud

Concurrently with the development of gene and cell therapy as we know it today, based on the deployment of ATMPs developed through clinical trials and administered exclusively after regulatory agency authorizations, certain practitioners and clinics embarked upon the deployment of unproven gene and cell therapy treatments. In response, the ISCT, the EMA Committee for Advanced Therapies and allied entities have exerted rigorous efforts to both discern and condemn these practices. In a proactive stride, they have extended support to patients and patient associations, furnishing guidance on

the identification and differentiation of such deceptive activities [40,41].

Education and Workforce Development

The rapid expansion of the ATMP field has engendered a surge in growth, accompanied by hurdles inherent to the biological complexity of these products—spanning the spectrum from preclinical development to commercialization. This complexity encompasses diverse aspects such as the acquisition of starting materials, manufacturing processes (which are progressively advancing through the integration of automated production and bioreactors), logistical problems and regulatory challenges. Consequently, the imminent surge in demand for specialized professionals within this area is anticipated to be substantial in the forthcoming years, as underscored by the ISCT Europe Committee's recent work [42]. Within this context, conventional training programs offered by universities, research institutions or governmental bodies typically fall short in terms of their alignment with the training requisites and practical insights currently essential for academic institutions, biotechnology enterprises, major pharmaceutical companies and regulatory authorities—entities that will invariably require this expertise in the years to come. Last, access to certain specialized training environment might be significantly different and distributed unequally across and even within countries, endangering fair education possibilities for the new generation of academics and practitioners, given the complexity of technologies used for novel cellular therapies [43]. This is precisely where the scientific societies must play a pivotal role in augmenting and fostering the gene and cell therapy workforce. Notably, initiatives that have borne fruit are already underway through entities such as ISCT or EBMT, among others, highlighting their proactive contributions in this domain [42].

Final Comments

The field of gene and cell therapy research and its translation through the development and use of ATMPs has heralded a paradigm shift in the therapeutic landscape of medicine and will continue to do so in the coming years. Over the course of the last two decades, this field has been punctuated by a blend of accomplishments and setbacks. While the past two decades saw the emergence of only a handful of products, the current trajectory exhibits an unprecedented surge in momentum, conditioned by cellular immunotherapy and gene editing techniques.

In the years ahead, there will be notable challenges to confront. This ISCT and EBMT working group has briefly outlined some of these issues in the current article, focusing on the situation in Europe (Figure 1). Yet, it's clear that the progress and success of this field will depend greatly on the involvement of scientific societies like ISCT and EBMT, as well as other key players such as academic institutions, pharmaceutical and biotechnological companies, regulatory bodies and patient groups, among others. Together, these stakeholders will play a crucial role in achieving the main goal: to make these groundbreaking treatments available to patients, which have the potential to change the course of diseases they are designed to address.

Declaration of Competing Interest

FSG, JV, DF, JJZ and MG are members of the International Society for Cellular Therapy (ISCT-EU) Executive Committee. AR, CC, SC, HD, NG, CH, JHEK, BN, TR, ISG, JAS and AS are members of European Society for Blood and Marrow Transplantation (EBMT) executive committee or working groups representatives. FSG has received research support from Novartis, Gilead. Honoraria from Novartis, Gilead, Pfizer, BMS-Celgene and Pierre-Fabré. CC has received honoraria (personal and institutional) and travel support from Bellicum Pharmaceuticals, BMS, Jazz Pharmaceuticals, Kite / Gilead, Novartis and Sanofi SA as a compensation for speaker's bureau and advisory boards. JK was shareholder of Gadeta and is inventor on multiple patents dealing with engineered immune cells, and has received research support from Novartis, Milteny Biotech and Gadeta. JAS has received consultancy honoraria from Kiadis, Medac, Vertex and Jazz. AS has received research support from Takeda and honoraria from Takeda, BMS/Celgene, MSD, Novartis, Gilead Kite, Sanofi, Pierre Fabre, Janssen and Jazz Pharmaceuticals. All other authors have no commercial, proprietary or financial interest in the products or companies described in this article.

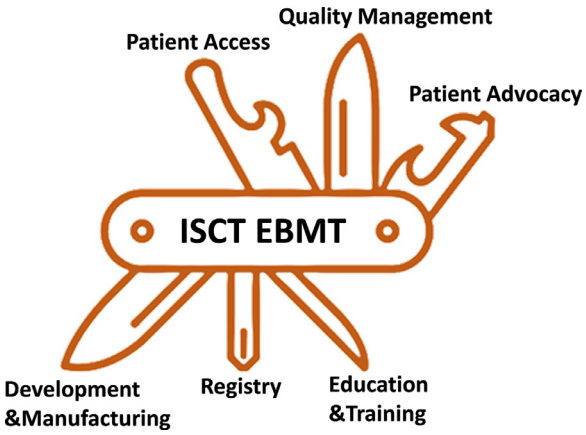

Figure 1. Collaborative efforts between scientific societies hold the potential to navigate the challenges in cell and gene therapy. The International Society for Cell & Gene Therapy (ISCT) and the European Society for Blood and Marrow Transplantation (EBMT) share a vision on the future of this rapidly evolving field, providing ideas for a sustainable growth to ensure patient access to innovative medicines. (Color version of figure is available online.)

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Author Contributions

Conception and design of the study: FSG and AS. Acquisition of data: all authors. Analysis and interpretation of data: all authors. Drafting or revising the manuscript: all authors. All authors have approved the final article.

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