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Transplant of Tissue-Engineered Artificial Autologous Human Skin in Andalusia: An Example of Coordination and Institutional Collaboration.

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Abstract
A new model of tissue-engineered artificial autologous human skin developed in Andalusia is currently being transplanted into patients suffering from large burns within the Andalusian Public Healthcare System. This product is considered an advanced therapy medicinal product (ATMP) in Europe, and its clinical use implies meeting transplant and medicinal product legal requirements, being the Guidelines of Good Manufacturing Practice for ATMPs of particular importance. The preclinical research and clinical translation of the product have represented a technical, regulatory, and organizational challenge, which has taken 10 years since the first preclinical experiments were designed. Twelve patients with large burns, including 3 pediatric patients, have hitherto received artificial autologous skin grafts with an overall survival rate of 75% and positive clinical, homeostatic, and histologic results. Achieving such a milestone within our Healthcare System was possible through a multidisciplinary approach and the joint efforts of multiple publicly funded institutions and units under the coordination of the Andalusian Initiative for Advanced Therapies. In this article, we present the organizational model set up to facilitate collaboration and logistics among the professionals involved, totaling more than 80 people. The similarities between the tissue-engineered artificial autologous human skin transplant and other organ and tissue transplants, in terms of logistic requirements, reveal how regional and hospital transplant coordination have played a crucial role.

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Contents

Introduction

Andalusia, a pioneer in the development and clinical translation of advanced therapy medicinal products (ATMPs) [1], currently offers treatment for patients with large burns through the transplantation of a novel model of tissue-engineered artificial autologous human skin (AAHS) developed in Andalusia. This AAHS is considered an ATMP, a term coined in Europe, which refers to a special category of biological medicinal products that encompasses 4 types: somatic cell therapy, gene therapy, tissue engineering, and combined ATMPs. These products are regulated by general legislation for medicines and specific legislation for ATMPs. When based on cells, tissues, blood, or blood components of human origin, depending on the type of starting material used, they are also subject to

the same European directives for cell and tissue transplant or for blood and its components (related to the activities of donation, procurement or collection, testing, and traceability) [2,3]. The clinical translation of this type of medicinal product represents a major challenge mainly due to the technical complexity of the product itself, the labyrinthine regulatory framework, and the logistic requirements. The purpose of this article is to explain the organizational model implemented by the Andalusian Initiative for Advanced Therapies (AIAT) to foster collaboration among the multiple institutions and facilitate coordination of all the units involved in the logistic chain and transplant procedure. AIAT is a publicly funded organization created by the Regional Government of Andalusia to promote activities of research, development, and innovation in the field of advanced therapies by forging alliances with universities, scientific institutions, health care centers, patient associations, small and medium enterprises, and the pharmaceutical industry [4]. AIAT provides comprehensive support, which begins by offering regulatory assessment to gather the preclinical evidence required to start a clinical trial. This support also includes assessment for adapting the manufacturing process to comply with Good Manufacturing Practice (GMP) regulation as well as the design, setting up, and monitoring of clinical trials; assuming the sponsor's responsibilities; and the search for strategic associates. AIAT designed and promoted the creation of a network of GMP laboratories. This network belongs to the Andalusian Public Healthcare System (APHS) and is coordinated by AIAT, which also coordinates the provision of regenerative medicine treatments within the APHS.

1. Methods

The Andalusian AAHS consists of a combination of dermal fibroblasts, keratinocytes, and a biological fibrin-agarose scaffold under a patented procedure [5] that was tested in animal models. The preclinical development of this tissue-engineered AAHS was carried out by the tissue engineering group of the University of Granada, receiving support from several professionals belonging to different units of the APHS [6]. In order to translate this bioengineered skin to the clinical setting, and following approval from the ethics committee for the use of human-donated skin samples, the first step taken was the adaptation, optimization, and scaling up of the manufacturing process including its validation to comply with the Guidelines on GMP specific for ATMPs [7]. The process starts with a skin biopsy from the patient (9 cm^2) to isolate dermal fibroblasts and keratinocytes, which are later expanded using different culture medium and procedures. Fibroblasts are embedded into the fibrin-agarose scaffold, and keratinocytes are seeded on the surface 24 hours later. After several days in culture, the AAHS is nanostructured by means of a dehydration process to increase its resistance and flexibility, allowing its surgical suture. Once the manufacturing process was validated, authorization from the Spanish Medicine Agency was obtained to manufacture this GMP-compliant AAHS at the cell production and tissue engineering unit, part of AIAT's GMP Network, located at the University Hospital Virgen de las Nieves in Granada. Prior to AAHS transplantation into patients with large burns at the burn unit of the University Hospital Virgen del Rocio in Seville, further authorization was required from the Spanish Medicine Agency for its clinical use, and the necessary logistic chain was implemented. Because of the extremely demanding logistic nature of these "living" products, AIAT established a coordination protocol for all human teams involved in the activities required, comprising harvesting the skin biopsy, shipping the biopsy to the GMP laboratory, manufacturing and quality control of the AAHS, shipping the AAHS to the transplant center, transplant procedure, and pharmacovigilance (Fig. 1). Efficacy of the treatment is being evaluated through a prospective study carried out on these patients. Clinical evolution, homeostatic parameters (temperature, pH, and transepidermal water loss[TEWL]), and histologic analysis of the skin are periodically monitored until 90 days after transplantation.

2. Results

The development and clinical translation of our tissue-engineered AAHS have taken 10 years since the preclinical in vitro and in vivo experiments were designed. The organizational model implemented in Andalusia made it possible for the first patient with a large burn to be transplanted in June 2016, and 12 patients with large burns, including 3 pediatric patients, have received artificial autologous skin grafts in Andalusia to date. The average total body surface burnt in the 9 adult patients (7 men and 2 women) was 71% (range, 61%-80%). The average age in the adult group was 26 years (range, 18-45 years). The age and percentage of body surface burnt in the 3 pediatric patients (1 boy and 2 girls) were 3 years and 30%, 9 years and 60%, and 19 months and 40%, respectively. A total of 83,088 cm^2 GMP-compliant AAHS was transplanted into these 12 patients. Three patients died due to the severity of injuries, and 9 patients were discharged from the hospital following significant clinical improvement (75% survival rate). Results of clinical evolution, homeostatic parameters (temperature, pH, and TEWL), and histologic analysis of the skin after transplantation are beyond the scope of this article, although we can report positive results such as TEWL, which was normalized at 3 months after AAHS transplant in almost all surviving patients.

3. Discussion

The number of scientific publications in the field of advanced therapies has dramatically increased over the last years; nevertheless, only a few ATMPs are currently available to patients, especially in the case of tissue-engineered products [8]. Some explanatory factors include the fact that frequently tissue-engineered products are initially developed in academia, where most scientists are not familiar with the intricacies of the regulatory requirements. Moreover, optimization, scaling up, and validation of the manufacturing process complying

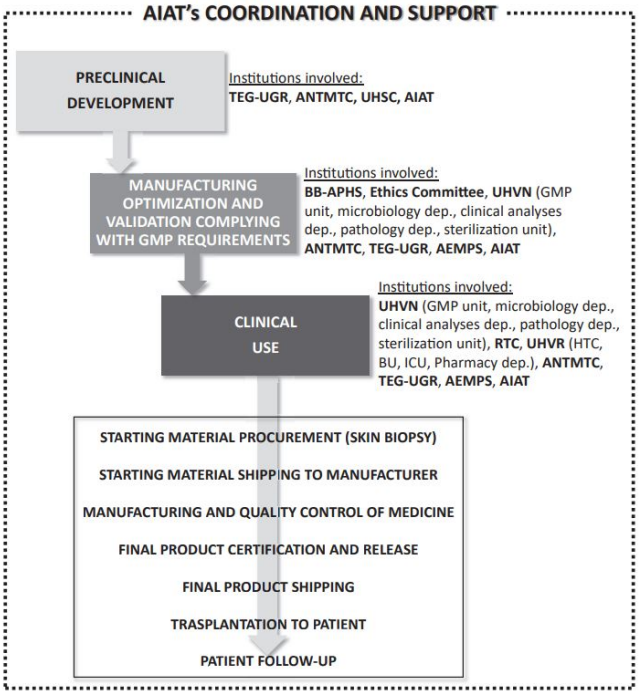

Figure 1. Steps in the development and clinical use of the tissue engineered artificial autologous human skin in Andalusia and institutions involved under the coordination and support of the Andalusian Initiative for Advanced Therapies (AIAT). AEMPS, Agencia Española de Medicamentos y Productos Sanitarios (Spanish Medicine Agency); ANTMTC, Andalusian Network of Transfusion Medicine, Tissues, and Cells; BB-APHS, Biobank of the Andalusian Public Healthcare System; BU, burn unit; GMP, good manufacturing practice; HTC, hospital transplant coordination; ICU, intensive care unit; RTC, regional transplant coordination; TEG-UGR, Tissue Engineering Group University of Granada; UHSC, University Hospital San Cecilio; UHVN, University Hospital Virgen de las Nieves; UHVR, University Hospital Virgen del Rocío .

with the GMP specific for ATMPs can be challenging, particularly in the case of complex products such as our AAHS. Finally, the critically demanding logistic chain, similar to other organ and tissue transplants, needs to work accurately, requiring stringent coordination. The treatment of 12 patients with large burns in Andalusia with our GMP-compliant AAHS represents a landmark achievement made possible through a multidisciplinary approach and the joint efforts of multiple institutions, all of them publicly funded in our case. Beyond scientific excellence and high professionalism, other factors have clearly contributed. The role played by AIAT, with a team of experts in scientific, technical, and regulatory aspects related to ATMP research, tissue donation, ATMP manufacturing, and clinical use, has been decisive in supporting the clinical translation and coordination. Furthermore, Spain is the world leader in organ donation rates, with Andalusia at the front due to the existence of a successful network of transplant coordinators whose involvement has been crucial.

4. Conclusions

The transplant of the AAHS, developed in Andalusia within the framework of AIAT, represents an example of successful translation of research in a short period of time, considering the scientific, technical, and regulatory complexity of ATMP development. The translation into clinics has been possible thanks to the unstinting collaboration and precise coordination of multiple institutions and has been significant for patients with large burns with no therapeutic alternatives available. The similarity between tissue-engineered medicinal products and organ and tissue transplants highlights the need for a coordinated procedure among different units and departments and the crucial role that regional transplant organizations and hospital transplant coordination units can play in the ATMPs field.

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Competing interests

All authors declare there is not any financial or personal relationship with organizations that could potentially be perceived as influencing the described research.

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