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Original article

Non-clinical assessment design of autologous chondrocyte implantation products

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ABSTRACT

The aims of this study were to investigate the premarket assessment of autologous chondrocyte implantation (ACI) products especially regarding the non-clinical assessment by surveying the guidelines and review reports of authorized ACI products in detail and to provide information regarding the non-clinical assessment of the safety and efficacy for the future development of regenerative medicine products to design effective premarket assessment. The non-clinical assessment plays a role in justifying the testing of investigational products in humans. Effective non-clinical assessments minimize the risk of clinical trials and achieve prompt product development. In this study, we focused on authorized ACI products that remain in the body of patients for a long time and often contain extrinsic components such as animal tissue-derived collagen.

We summarized the details of the characteristics of each ACI product, non-clinical assessment design and related guidelines. To design effective non-clinical assessments, we discussed the evaluation method (particularly the validation of clinical assessment and mechanical property testing), the employed animal models, and the differences in the assessment of the safety and efficacy of the products.

Based on these investigations, we provide the details of satisfactory non-clinical assessment of ACI products and indicate the possibility of more effective non-clinical assessment of ACI products and other future regenerative medicine products.

1. Introduction

The clinical testing of novel human cell and tissue products such as regenerative medicinal products is generally based on non-clinical assessment programs that span the discovery-phase and proof-of-concept (POC) studies to definitive safety studies.

Non-clinical assessments play a role in justifying the testing of investigational products in humans and facilitate prompt product development. Non-clinical assessment should help facilitate the following: first, establish the scientific rationale of the proposed approach; second, identify, characterize, and minimize potential local and systemic toxicities; third, confirm a safe initial clinical starting dose, dose-escalation scheme and dosing regimen; and fourth, inform subject eligibility and clinical evaluation strategies [1].

Recently, we published the research paper on regulation of allogeneic human cells and tissue products [2] and on autologous

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human cells and tissue products [3]. However, there is no such detail of non-clinical assessment of autologous human cells and tissue products, especially of autologous chondrocyte implantation (ACI) products.

Four ACI products have been authorized in the United States (US), the European Union (EU) and Japan since 1997 until 2013. The ACI products remain inside the body of patients for a long time as implants. Therefore, the risks should be assessed and understood as much as possible, although redundant assessment is not desirable for the applicants and patients. For this reason, keeping the number of assessments low is important for ensuring that the assessments are safe and effective for patients.

In addition, the National Diet of Japan passed Revised Pharmaceutical Affairs Law in 2014. According to the revised law, a therapeutic product for regenerative medicine is defined as a product distinct from pharmaceuticals and medical devices, enabling regenerative medical products to be given a conditional, time-limited marketing authorization much earlier than that under the previous system [4] Conditional, time-limited marketing authorization system is expected that it makes quick patients' access to novel therapy, however, there were concerns that the clinical safety of a product was not sufficiently confirmed by the early authorization, so the more effective preclinical assessments that clearly confirm the proof of concept and address the adverse events would be required than in the previous system.

The aims of this study were to investigate the premarket assessment of ACI products especially regarding the non-clinical assessment by surveying the guidelines and review reports of authorized ACI products in detail and to provide effective information on the safety and efficacy for the future development of regenerative medicine products.

2. Methods

2.1. Guidelines for premarket assessment

This study included four ACI products approved in the US, the EU and Japan before April 2014.

To understand the requirements of the regulatory agencies in each nation, we surveyed the following guidelines of premarket assessment related to knee repair cartilage products: “Guidance for Industry Preparation of IDEs and INDs for Products Intended to Repair or Replace Knee Cartilage” [5] and “Guidance for FDA Reviewers and Sponsor Content and Review of Chemistry, Manufacturing, and Control (CMC) Information for Human Somatic Cell Therapy Investigational New Drug Applications (INDs)” [6] by the Food Drug Administration (FDA), “Guideline on human cell-based medicinal products (EMA/CHMP/410869/2006)” [7] and “Reflection paper on *in-vitro* cultured chondrocyte containing products for cartilage repair of the knee” (EMA/CAT/CPWP/568181/2009)” [8] by the European Medicines Agency (EMA), “The evaluation index of medical device in next generation (Evaluation index about regeneration of articular cartilage)” [9] and “Ensuring the safety and quality of human autologous cell-based or tissue-based pharmaceutical or medical device” [10] by the Ministry of Health Labour and Welfare (MHLW).

2.2. Authorized ACI products

To survey the details of non-clinical assessments of each product, we surveyed the review reports or public assessment reports for premarket assessment. The summary of the basis of approval of Carticel® [11], review report by JACC [12] and the European Public Assessment Reports (EPAR) on ChondroCelect™ [13] and MACI® [14] were obtained from the appropriate web sites of the FDA, the EMA and the Pharmaceuticals and Medical Device Agency (PMDA), respectively. The details of the assessments were surveyed regarding the type of assessment, the animal model and the duration and method of assessment. The type of assessment was classified as “Pharmacodynamics”, “Pharmacokinetics”, “Mechanical property” and “Validation of clinical evaluation” for pharmacology, and “Local toxicity”, “Systemic toxicity”, “Tumorigenicity” and “Genotoxicity” for toxicology. The abbreviation of this article is listed in Table 1.

3. Results

3.1. Characteristics of ACI products

The therapeutic indication for all products was cartilage defects of the knee. In addition, the indication was limited to the femoral condyle in the case of Carticel® and ChondroCelect™ especially. The recommended lesion size of each product was different: 1–5 cm^2, >4 cm^2 and 3–20 cm^2 in ChondroCelect™, JACC, MACI®, respectively. In the case of Carticel®, the recommended lesion size was not described. The cell numbers of each product are shown in Table 2. Regarding the product component, the ACI products contained an extrinsic component such as medium and/or a collagen component. The autologous chondrocytes of JACC were subjected to three-dimensional culture in authorized bovine dermis-derived atelocollagen to retain the implanted cells within the lesion. Similarly, MACI® contained a collagen component; the cells in MACI® were seeded onto a CE-marked porcine type I/III collagen membrane, and the membrane was secured into the lesion with porcine fibrin glue. On the other hand, the Carticel® and ChondroCelect™ contained only Dulbecco's modified Eagle's medium (DMEM) as an extrinsic component (Table 2).

3.2. History of regulatory action of ACI products

There have been several issuances of guidelines related to authorized ACI products.

The first issuance regarding ACI products was “Guidance on Applications for Products Comprised of Living Autologous Cells Manipulated Ex Vivo and Intended for Structural Repair or Reconstruction; Availability” [15] in May 1996 (Fig. 1 (a)) in the US. The

Table 1
The list of abbreviations.

Abbreviation	Description
ACI	Autologous Chondrocyte Implantation
CAT	Committee for Advanced Therapy
CBER	Center for Biologics Evaluation and Research
CDRH	Center for Devices and Radiological Health
CHMP	Committee for Medicinal Products for Human Use
CMC	Chemistry, Manufacturing, and Control
DMEM	Dulbecco's Modified Eagle's Medium
ECM	Extra Cellular Matrix
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
ICRS	International Cartilage Research Society
INDs	Investigational New Drug Applications
JP	Japan
MA	Massachusetts
MHLW	Ministry of Health Labour and Welfare
PMDA	Pharmaceuticals and Medical Device Agency
PF	Periosteal Flap
PF/AuCC	Periosteal Flap/Autologous Cultured Chondrocyte
POC	Proof-of-Concept
US	United States