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Original Article

Bayesian statistics and clinical trial designs for human cells and tissue products for regulatory approval

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ABSTRACT

Introduction: In order to obtain premarket approval for medical products derived from human cells or tissues in the United States (US), the European Union (EU), and Japan, data from clinical trials are typically required to evaluate product efficacy and safety. Clinical investigators or study sponsors often face challenges when designing clinical trials on human cells and tissue products with the goal of obtaining premarket approval owing to the unique characteristics of products in this category. The methods used to administer, infuse and transplant these products vary more widely than the methods used for pharmaceuticals. In addition, final product quality may vary depending on the product source, i.e., patients or donors. These products are generally intended to treat intractable and rare diseases or injuries; therefore, it may not be possible to collect a sufficient number of cases and enrollment may be a long process. Moreover, since the technology for product development in this category is relatively new, knowledge and experience from previous studies are limited.
Methods: The key elements for the design of clinical trials to determine product efficacy were identified by examining clinical trial designs for approving products. Review reports for approved products from regulatory authorities in the US and Japan as well as the European public assessment reports in the EU were analyzed.
Results: For one product approved in the US, Dermagraft®, Bayesian statistics were used to evaluate product efficacy, instead of traditional (frequentist) statistics. Based on the statistical guidance for clinical trials recently issued by the US Food and Drug Administration, statistical analyses including Bayesian statistics are key elements in the design of clinical trials for products based on human cells and tissues. New regulations regarding human cells and tissue products have recently been implemented in Japan, including conditional and time-limited approval for regenerative medicine products. In these cases, Bayesian statistics are a promising alternative approach to support product development.
Conclusions: Our results emphasize the benefit of considering cogitating statistical methods, such as Bayesian statistics, when designing clinical trials for regulatory purposes.

1. Introduction

Medical products derived from human cells and tissues are unambiguously distinct from chemically synthesized drugs and medical devices, and are regulated separately by the authorities; they are categorized as “human cells, tissues, and cellular and tissue-based products (HCT/Ps)” in the United States (US) [1], “advanced therapy medicinal products (ATMPs)” in the European Union (EU) [2], and “regenerative medicine products” in Japan [3,4].

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When clinical investigators or study sponsors conduct clinical trials on human cells and tissue products with the goal of obtaining premarket approval, they often face challenges, particularly when assessing product efficacy, owing to unique characteristics of products in the category. There is wider variation in the methods used to administer, infuse and transplant these products than in those for pharmaceuticals. In addition, the quality of the final product may vary depending on the source, i.e., patients or donors. These products are generally intended to treat intractable and rare diseases or injuries; therefore, it may not be possible to collect a sufficient number of cases and study enrollment may be very slow. These features of cells and tissue products that may impact clinical study design were summarized in a guidance of the US Food and Drug Administration (FDA) [5]. Moreover, since the technology used for products in the category is relatively new, knowledge and experience from previous studies are limited.

In an analysis of the study designs of clinical trials on human cells and tissue products approved in the US, the EU, and Japan, we found that Dermagraft®, which utilizes allogeneic cells, was approved in the US based on pivotal study data that was analyzed using Bayesian statistics. In this pivotal study, an interim analysis, which is considered an adaptive design, was utilized, and these statistical approaches were important for the acceptance of the clinical efficacy of the product.

Bayesian statistics are an alternative to traditional statistics, i.e., frequentist statistics, and have recently been employed in clinical trials to evaluate pharmaceuticals, not only in Phase III studies, but also in Phase I and II studies [6]. In some cases, Bayesian statistics can be used to reduce the sample size and to apply mid-course adjustments to a trial design, or to stop a trial, shortening the study duration [7]. Moreover, Bayesian statistics have been regarded as a useful statistical method for clinical trials since the middle of the last decade because the approach is ideally suited to adapting to information accrued during a trial, potentially allowing for smaller and more informative trials [8]. In the pivotal Dermagraft® study, an interim analysis was utilized in the decision to stop the study when a targeted number of cases was reached, and to determine the necessity for additional enrollment. The purpose of an interim analysis is to stop a trial early if a sufficient difference between groups is obtained to conclude that an intervention is effective or harmful [9]. Early stopping may allow subjects in the placebo arm as well as those not in the trial to receive a beneficial treatment sooner. In contrast, when severe side effects are encountered, early stopping of the trial may prevent unnecessary harm. Early stopping may also save money and facilitate the rapid reporting and translation of results to clinical practice [9].

The FDA recently issued a guidance to the study design of clinical trials for medical devices, named “Guidance for the Use of Bayesian Statistics in Medical Device Clinical Trials” [7]. Although some additional conditions are required to utilize Bayesian statistics; 1) prior information should be discussed with the FDA prior to the initiation of a study, and 2) indications of the device may be impacted by modifications at the interim analysis, the Bayesian framework has several unique advantages over its frequentist counterpart. Traditional statistical methods only use information from previous studies at the design stage. In contrast, Bayesian statistics formally incorporate prior information gathered before, during, and outside of the trial [10]. Furthermore, many clinical trials are conducted over an extended period of time, and it is desirable to frequently monitor the interim results of such trials in order to promote more rapid decisions when sufficient evidence is obtained. Bayesian methods allow for more frequent monitoring and interim decision making during trials [10]. Based on the concept outlined in the FDA guidance as well as the successful example, Bayesian statistics should be considered in the design of studies to evaluate human cells and tissue products.

No such guidance documents for statistical methods used in clinical trials have been introduced by regulatory authorities in the EU and Japan; this initiative is unique to the US. Statistical inferences are based on mathematical models of experiments, including clinical trials. Moreover, in Japan, new regulations for human cells and tissue products were introduced in 2014, in which conditional and time-limited approval pathways specific to the product category are included [4].

In the current study, we performed a comparative investigation of the guidance documents for statistical methods for clinical trials in the US, the EU, and Japan, and summarized of a unique case in which Bayesian statistics and an interim analysis were successfully applied during a trial design.

2. Methods

Guidance documents describing statistical methods for clinical trials were obtained from appropriate regulatory websites in the US [11], the EU [12], and Japan [13]. Approval information for human cells and tissue products was obtained from the websites of the relevant regulatory authorities in the US (Biologics [14], Premarket approval (PMA) [15], Humanitarian Device Exemption (HDE) [16]), the EU [17], and Japan [18] at the end of June, 2016. According to the definitions and research methods used in previous studies [19,20], products utilizing either autologous or allogeneic human cells or tissues were selected from review reports in the US and Japan and from European public assessment reports in the EU. The study design for each product was identified from the clinical data section in each report. Individual review reports or European public assessment reports of the products approved in the US, the EU, and Japan were obtained from the following sources: the FDA websites for Carticel™ [21], Epicel® [22], Provenge® [23], Laviv® [24], Dermagraft-TC™ [25], Apligraf™/Garftskin [26], Composite Cultured Skin [27], Orcel™ [28], Dermagraft® [29], Gintuit [30], Hemacord [31], HPC/Cord blood [32], Ducord [33], Allocord [34], HPC/Cord blood [35], and HPC cord blood [36]; European Medical Agency (EMA) websites for ChondroCelect® [37], MACI [38], Provenge [39], and Holoclar [40]; and Pharmaceuticals and Medical Devices Agency (PMDA) websites for JACC [41], JACE [42], Temcell® HS Inj. [43] and HeartSheet® [44]. Information related to clinical trials for the approved products, such as that described at ClinicalTrials.gov [45], was also analyzed.

3. Results

3.1. Guidance on clinical trial design

In the US, several guidance documents related to clinical trial design for medical devices and human cells and tissue products have recently been issued by the FDA. “Guidance for the Use of Bayesian Statistics in Medical Device Clinical Trials” was issued by the Center for Devices and Radiological Health (CDRH) and the Center for Biologics Evaluation and Research (CBER) of the FDA on February 5, 2010 [7]. This guidance document clarifies the utilization of Bayesian statistics, and includes a strong recommendation for consultation with the FDA when planning a study protocol. It is specifically applicable to medical device clinical trials, including products derived from human cells and tissues. CDRH and CBER also issued the draft guidance document “Adaptive Designs for Medical Device Clinical Studies” on May 18, 2015 [46]. This document addresses adaptive designs for medical device clinical trials and is applicable to pre-market medical device submission,