Statistical Considerations in the Design of Biosimilar Cancer Clinical Trials

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(Received April 2011; accepted May 2011)

Abstract

When a patent of an innovative (brand-name) small-molecule drug expires, generic copies of the innovative drug may be marketed if their therapeutic equivalence to the innovative drug has been shown. The small-molecule drugs are considered therapeutically equivalent and can be used interchangeably if two drugs are shown to be pharmaceutically equivalent with identical active substance and bioequivalent with comparable pharmacokinetics in a crossover clinical trial. However, the therapeutic equivalence paradigm cannot be applied to biosimilars since the active ingredients of biosimilars are huge molecules with complex and heterogeneous structures, and these molecules are difficult to replicate in every detail. The European Medicine Agency (EMEA) has introduced a regulatory biosimilar pathway which mandates clinical trials to show therapeutic equivalence. In this paper, we discuss statistical considerations in the design and analysis of biosimilar cancer clinical trials.

Keywords: Biosimilar, bioequivalence, biologics, immunogenicity, equivalence.

1. Introduction

“Biosimilar” or “Follow-on biologics” are the terms used to describe medicines that are the equivalent of generic drugs, but for biologic therapies. There is an increasing interest in biosimilars from both generic manufacturers and biopharmaceutical companies as many biological products reach the market and subsequently lose their patent protection. When the patent of an innovative (brand-name) small-molecule drug expires, generic copies of the innovative drug may be marketed if their therapeutic equivalence to the innovative drug has been shown. However, the generic approach for small-molecule drugs cannot be applied to copies of biologics due to their complexity. Subtle changes in manufacturing processes, starting material and excipients may affect the efficacy and safety of biosimilars. Because it is impossible to show two biological products are identical, the term “biosimilars” was introduced in the Europe and “follow-on protein products” or “biogenerics” in the United States.

The Food and Drug Administration (2003) requires the evidence of average bioavailability through the conduct of bioavailability and bioequivalence studies for a generic product of small-molecule
drugs. Bioequivalence studies are generally conducted by comparing the in vivo rate and extent of drug absorption of a test drug and an innovative drug. In a standard in vivo bioequivalence study design for a small-molecule drug, a conventional two-treatment, two-period, two-sequence 2 × 2 randomized crossover design has been widely used. In this 2 × 2 crossover design, study subjects receive a single dose of both test and innovative drugs on separate occasions through random assignment to the two possible sequences of drug administration. Current FDA bioequivalence guidance requires one pivotal bioequivalence study, as well as recommends both fed and fasted bioequivalence studies for most products (even products whose labels say there is no food effect on absorption). Generic small-molecule drugs are considered to be therapeutically equivalent to an innovative drug if pharmaceutical equivalence (identical active substances) and bioequivalence (comparable pharmacokinetics) can be demonstrated. Formal clinical efficacy and safety studies are not required for the approval of generic drugs. However, the generic approach cannot be applied to biosimilar products due to the complexity of biological products.

In this paper we focus on the design of biosimilar cancer clinical trials. We will discuss the clinical trial design considerations such as crossover design versus parallel design, bioequivalence criteria, statistical analysis methods, sample size calculation, and choice of primary and secondary endpoints for pharmacokinetic studies and clinical studies. The rest of the paper is organized as follows. Section 2 presents statistical design considerations for the biosimilar cancer clinical trials, and Section 3 presents the statistical methods for the analysis of biosimilar cancer clinical trials. Finally, we conclude with a discussion.

2. Design Considerations for Biosimilar Cancer Clinical Trials

2.1. Parallel design vs. Crossover design

Biosimilars are not generic equivalents of the innovative drugs since active ingredients of biosimilars are not identical to those of the innovative drugs. The molecules of a biological drug are much larger and more heterogeneous, and have far more complex structures than the traditional chemical drug. Proteins are generally 100–1,000 times larger than small-molecules (Schellekens, 2004).

A crossover design has been widely used for a generic copies of small-molecule drugs due to a short half-life. Crossover trials have the advantage of potentially reducing variability since each subject acts as his or her own control. Required sample size will be much less in a crossover design than a comparable parallel design because the within-subject variability is usually smaller than the between-subject variability, and within-subject responses to treatment are usually positively correlated. A crossover trial was used to demonstrate bioequivalence of biosimilar filgrastim and Amen filgrastim (Waller et al., 2010a, 2010b; Lubenau et al., 2009).

A potential problem of a crossover design is the chance of carryover effect. Carryover effects can cause treatment by period interactions, which means that the treatment effect is not constant over time. Thus, a washout period is required so that the effect of the earlier treatment is not influencing the efficacy and safety for the next treatment. A sufficient length of washout period is needed to eliminate the possible carryover effects in a crossover design. The elimination half-life of a drug is the time it takes for a drug to lose half of its pharmacologic activity. The rate at which drugs are eliminated from plasma is commonly expressed as the half-life of the drug, which is the time required for the concentration of the drug in the plasma to decrease to 50% of its initial value. The plasma concentration decrease to 25%, 12.5%, 6.25% and just over 3% at 2, 3, 4 and 5 half-lives,