FEATURE

The Role of Biosimilar and Orphan Drugs in Treating Patients With Rheumatologic Disease

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Biosimilar drugs may offer affordable targeted therapies to patients across a spectrum of rheumatologic, oncologic, and gastrointestinal diseases, but they pose unique clinical trial design and licensing issues. Governments provide incentives for developing orphan drugs that would not otherwise be cost-effective to manufacture, allowing for the possibility of effective treatment options for rare diseases, including many rheumatologic conditions.

Jürgen Braun, MD, PhD, medical director of the Rheumazentrum Ruhrgebiet, Herne, Germany, defined biosimilars as products sufficiently similar to a biopharmacological product already approved by a regulatory agency [Kay J. *Arthritis Res Ther* 2011]. He stated that biologics revolutionized medicine, contributing significantly to better quality of life for patients with rheumatic diseases. Several points were addressed, which are summarized in this article.

BIOSIMILARS ARE NOT COMPARABLE TO GENERIC DRUGS

Biosimilars are unlike generic drugs, and they are much larger, more complex structures with 4 levels of protein folding. Cellular activity is dependent on correct glycosylation; differences in glycosylation could turn an immunomodulatory antibody into a cytotoxic antibody.

Prof. Braun emphasized that biosimilars are not identical to the reference drug, and a range of structural differences may exist [Woodcock J et al. *Nature Rev Drug Discovery* 2007], which are allowed when there are no clinically meaningful differences in safety, purity, and potency between products [Patient Protection and Affordable Care Act. Pub L No. 111-148, Section 7002 (2010)].

PATENT EXPIRATIONS AND ECONOMIC BENEFITS FOR MANUFACTURERS DRIVE BIOSIMILAR DEVELOPMENT

Patents for 5 of 9 biologic agents used in rheumatology will expire by 2015 in Europe and by 2019 in the United States. Incentives to manufacturers of biosimilars include 1-year exclusive marketing, which may be extended to 42 months [Patient Protection and Affordable Care Act. Pub L No. 111-148, Section 7001 (2010)].

Two new infliximab biosimilars were approved by the European Medicines Agency (EMA) in 2013 for use in rheumatology. Seven rituximab and etanercept biosimilars are being marketed in Mexico, India, and South America that do not have EMA or US Federal Drug Administration (FDA) approval [Scheinberg MA, Kay J. *Nat Rev Rheumatol* 2012]. Eight rituximab biosimilars plus 13 biosimilars of adalimumab, etanercept, and infliximab are in the pipeline and in various phases of clinical trials.

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CHANGES IN MANUFACTURE OF BIOPHARMACEUTICALS

Production changes have resulted in decreased [Rudick RA et al *Neurology* 1998] and increased immunogenicity [Bennet CL et al. *N Engl J Med* 2005]. Prof. Braun pointed out that postapproval manufacturing changes vary by jurisdiction, but the original manufacturer has detailed information pertaining to production changes that are not available to the biosimilar manufacturer [Schneider CK *J Ann Rheum Dis* 2013]. Due to production changes, infliximab and etanercept can today be regarded as biosimilars to the compounds approved 10 years ago.

EMA AND FDA GUIDANCE ON BIOSIMILAR STUDIES

EMA guidelines require biosimilar trials to demonstrate pharmacodynamic (PD) and pharmacokinetic (PK) comparability of monoclonal antibodies using *in vitro* studies; animal

studies may also be required [Committee for Medicinal Products for Human Use. *Guideline on Similar Biological Medicinal Products Containing Monoclonal Antibodies*. European Medicines Agency 2012]. At least one randomized clinical trial (RCT) with double-blind, parallel-group comparative design is sufficiently powered to demonstrate therapeutic equivalence plus the collection of long-term immunogenicity and safety data of biosimilar monoclonal antibodies.

US regulations take a "totality of evidence approach" wherein FDA scientists integrate information to make an overall assessment. According to FDA guidelines, a biosimilar agent need not be licensed for all routes of administration, all doses, or an indication for which the reference product has already obtained approval [US Department of Health and Human Services, FDA. *Guidance for Industry. Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009* Draft 2012]. Data from a clinical trial of a biosimilar for one disease may be extrapolated to support approval for additional indications that have been licensed for the reference. No recommendations are made for whether the trial design is noninferiority or equivalence or for the size and duration of the trial.

CLINICAL TRIAL DESIGN SUPPORTING NEW DRUG LICENSING AND BIOSIMILARS DIFFERS

Clinical trials of biosimilars must demonstrate equivalence to the reference within a prescribed margin; noninferiority trial design is not suitable. Biosimilar trials must use the same dose as the reference, thus eliminating the need for Phase 2 dose-ranging studies.

Remicade (infliximab) biosimilar CT-P13 began with *in vitro* comparability studies of the primary and secondary mechanism of action (MOA) to demonstrate comparable Fc binding. A Phase 1 double-blind, randomized, controlled trial (RCT) of CT-P13 versus Remicade® in ankylosing spondylitis followed; the primary endpoint was the ratio of geometric means of PK parameters of both agents at Weeks 22 and 30 [Park W et al. *J Ann Rheum Dis* 2013].

A Phase 3, double-blind RCT of CT-P13 versus Remicade® was then conducted with 606 patients with active rheumatoid arthritis; the primary end point was the proportion of patients achieving American College of Rheumatology (ACR20) response at Week 30, and secondary end points were the proportion of patients with ACR50 and ACR70 and the frequency of adverse events. All parameters were comparable among all time points [Yoo D et al. *J Ann Rheum Dis* 2013].

Differences in the pharmacodynamics of clinical response rates were, however, demonstrated at 4, 8, and 12 weeks in drugs that had identical response rates at 30 weeks, showing the need for more careful monitoring by incorporating more frequent, early time points [Kay J et al. *J Ann Rheum Dis* 2013].

EXTRAPOLATED DATA MAY BE USED TO SUPPORT BIOSIMILAR USE

Biosimilars may be used in diseases for which the reference drug has been approved after demonstrating comparable therapeutic effects. Ankylosing spondylitis, psoriatic arthritis, and Crohn's disease are treated with tumor necrosis factor inhibitors; extrapolated data could be used to allow biosimilars to treat these conditions.

Remsima, the first EMA-approved infliximab biosimilar, demonstrated impressive comparability with minor differences that the EMA determined were not clinically relevant. Nevertheless, postmarketing studies are required to confirm the efficacy and safety of the extrapolated indication.

CONCERNS REGARDING BIOSIMILAR USE FOR PATIENTS AND RHEUMATOLOGISTS: SWITCHING VERSUS SUBSTITUTION OF BIOSIMILARS MAY REQUIRE FURTHER TESTING

No guidance exists on switching, in which patients are transitioned to a biosimilar following initial treatment with reference, and substitution, in which the biosimilar is considered to be interchangeable; substitution could be made by the pharmacist without input from the prescriber.

Trials are needed to investigate the effects of a single switch versus repeated switching; switching to a biosimilar could adversely affect patients, and only one trial has been performed. Frequent switching should not be allowed because subtle differences introduced during processing could trigger an immune response.

It is likely that biosimilar availability will reduce the cost of targeted therapies for patients; Prof. Braun explained that the social contract mandates that the potential risk to the individual of switching to a biosimilar be weighed against the societal benefit of lower cost that extends care to more patients.

ORPHAN DRUGS IN RHEUMATOLOGIC DISEASES

Jonathan Kay, MD, University of Massachusetts Medical School, Boston, Massachusetts, USA, defined an orphan drug as one that is used to treat rare diseases having <200,000 people in the United States and <250,000 in the

European Union [FDA. http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/HowtoapplyforOrphanProductDesignation/ucm364750.htm. Accessed July 14, 2014; EMA. http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000034.jsp. Accessed July 14, 2014]. Rare diseases affect 5000 to 8000 people, and 80% have a genetic origin.

The Orphan Drug Act in the United States and Orphan Regulation in the European Union were necessitated by the small number of people with rare diseases that made drug development unattractive to drug companies. Therapeutics have not been developed for rare diseases because companies manufacturing an orphan drug have small sales revenue relative to the development cost.

ANTICIPATED FINANCIAL LOSSES CAUSED REGULATORY AGENCIES TO PROVIDE FINANCIAL INCENTIVES TO DRUG COMPANIES

Incentives for orphan drug development in the United States include tax credits for the cost of clinical research, annual federal grant funding for the costs of clinical testing, aid in designing clinical trials, 7 years of exclusive marketing protection following the development and approval of an orphan drug, and waiver of filing fees [FDA Consumer Health Information *Developing Orphan Products: FDA and Rare Disease Day* 2009].

The European Union also offers funded research grants, access to centralized marketing procedures, protocol assistance, 10 years of exclusive marketing following approval, reductions of 50% for marketing fees, and fee waiver of protocol assistance and preauthorization inspection fees [Hughes B et al. *Nat Rev Drug Discov* 2008].

Since 1983, the FDA has designated 3088 products as orphan drugs and approved 455 orphan drugs for use in rare diseases. The European Commission has designated >1000 drugs as orphan medicinal products and approved 104 orphan drugs for rare diseases [European Commission Public Health. http://ec.europa.eu/health/human-use/orphan-medicines/index_en.htm].

REQUIREMENTS FOR ORPHAN DRUG STATUS

Orphan drug designation may be requested for a previously unapproved drug or as a new use for a currently approved drug. Orphan drug status may be granted for the same drug and the same rare disease if the respective sponsors file separate applications [http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/Howtoapplyfor|OrphanProductDesignation/ucm356481.htm]. Obtaining orphan drug status does not alter standard regulatory requirements; safety and efficacy must be demonstrated in adequate well-controlled trials.

The EMA and FDA applications require documentation that the prevalence of the disease is below the statutory threshold and that the sponsor has no reasonable expectation that research and developments costs can be recovered by sales of the drug [http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/Howtoapply forOrphanProductDesignation/ucm124795.htm#]. Scientific need for the drug must be established, including a discussion on the medical plausibility of using the drug for the specific indication. Clinical trial data supporting the expected efficacy of the indication must be included, if it exists. When no human trial data exist, preclinical data in animal models testing the active moiety or molecular structure may be used. The application must include all data from *in vitro* studies, preclinical efficacy animal studies, clinical experience with the drug in the rare disease, and a summary of the worldwide regulatory status and marketing history of the drug.

Orphan drug incentives and benefits have resulted in many drugs being developed and approved for rare diseases that address the unmet need to treat patients with rheumatologic diseases of low prevalence. Dr. Kay underscored that treatment for many of these rare diseases would not be available without the intervention of the EU and US regulatory agencies.