Biopharmaceuticals and biosimilars in psoriasis: What the dermatologist needs to know

Bruce E. Strober, MD, PhD,a Katherine Armour, MD,b Ricardo Romiti, MD,c Catherine Smith, MD,d Paul W. Tebbey, PhD,e Alan Menter, MD,f and Craig Leonardi, MDg

Farmington, Connecticut; Victoria, Australia; São Paulo, Brazil; London, United Kingdom; Dallas, Texas; St Louis, Missouri

The entry of biosimilar forms of biopharmaceutical therapies for the treatment of psoriasis and other immune-mediated disorders has provoked considerable interest. Although dermatologists are accustomed to the use of a wide range of generic topical agents, recognition of key differences between original agent (ie, the name brand) and the generic or biosimilar agent is necessary to support optimal therapy management and patient care. In this review we have summarized the current state of the art related to the impending introduction of biosimilars into dermatology. Biosimilars represent important interventions that are less expensive and hence offer the potential to deliver benefit to large numbers of patients who may not currently be able to access these therapies. But the development of biosimilars is not equivalent to that of small molecule generic therapies because of differences in molecular structure and processes of manufacture. The planned regulatory guidelines and path to approval may not encompass all of these potentially important differences and this may have clinical relevance to the prescriber and patient. Consequently, we have identified a series of key issues that should be considered to support the full potential of biosimilars for the treatment of psoriasis; ie, that of increased access to appropriate therapy for the psoriasis population worldwide. (J Am Acad Dermatol 2012;66:317-22.)

Key words: bioequivalence; biologics; biopharmaceuticals; biosimilars; follow-on biologics; generics; pharmacokinetics; psoriasis.

Dermatologists are accustomed to prescribing generic topical agents such as corticosteroids and vitamin D analogs interchangeably as these formulations contain the same active ingredients as name brands. In contrast, the implications of using different formulations of systemic agents (eg, cyclosporine) are well acknowledged because of variations in bioavailability. Biosimilars represent additional complexity because of the specific nature of the molecules in question,

Janssen-Cilag, and is a member of the IPC. Dr Tebbey is or has served as a consultant or employee for IPC, Baxter Healthcare, Incyte Corp, Johnson and Johnson, and Wyeth-Pfizer. Dr Menter has served as a consultant, investigator, speaker, or advisory board member for Abbott, Allergan, Amgen, Astellas, Asubio, Celgene, Centocor-Ortho Biotech, DUSA, Eli Lilly, Galderma, Genentech, Novartis, Novo Nordisk, Pfizer, Promius, Stiefel, Syntix Biosystems, Warner Chilcott, and Wyeth-Pfizer, and is also a founding board member of IPC. Dr Leonardi is a consultant for Abbott, Amgen, Centocor-Ortho Biotech, and Pfizer; has been an investigator for Abbott, Amgen, Celgene, Centocor-Ortho Biotech, Genentech, Eli Lilly, Genzyme, Pfizer, Incyte, Schering-Plough, Novartis, Novo Nordisk, Vascular Biogenics, and Wyeth-Pfizer; and is a founding board member of IPC.

Accepted for publication August 31, 2011.
Reprint requests: Bruce E. Strober, MD, PhD, Department of Dermatology, University of Connecticut School of Medicine, 21 S Rd, 2nd Floor, Farmington, CT 06032. E-mail: strober@uchc.edu.
0190-9622/$36.00
© 2011 by the American Academy of Dermatology, Inc.
doi:10.1016/j.jaad.2011.08.034
Abbreviations used:

- EMA: European Medicines Agency
- EPO: erythropoietin
- FDA: Food and Drug Administration
- TNF: tumor necrosis factor

and as a consequence of the manufacturing process that introduces subtle yet significant changes to the active ingredient. The purpose of this review is to summarize the issues associated with the introduction of biosimilar agents into dermatology for the treatment of psoriasis.

STANDARD GENERIC DRUGS

Today there are more than 600 generic drugs in use in the United States and European Union.1,2 These generic versions of marketed drugs have been approved on the basis of establishing bioequivalence and pharmaceutical equivalence to the original brand-name drug.3 Two medicinal products containing the same active substance are considered bioequivalent if the bioavailability of both lies within acceptable predefined limits after administration of the same molar dose. This abbreviated approval process permits replacement of large, extensive human clinical trials with smaller bioequivalence studies designed to assess only pharmacokinetics or pharmacodynamics. The introduction of small molecule generic drugs has resulted in broader use of medicines along with substantial health care cost savings.

DIFFERENTIAL CHARACTERISTICS OF SMALL MOLECULES VERSUS BIOPHARMACEUTICALS

Small molecule drugs (ie, low molecular—weight organic compounds) and their generic equivalents are based on medicinal chemistry and are chemically synthesized and purified. Their use in the clinic is dictated by a postulated mechanism of action delineated by in vitro assays. Extensive and lengthy toxicology studies are usually required to support regulatory filings because the compounds are not developed to target specific elements of disease processes. The conventional methods used to make small molecule drugs generate highly purified products that can be readily and identically reproduced in different laboratories. Consequently, the active ingredient dictates the clinical outcome. This is why for small molecules, generally speaking, bioequivalence does correlate with therapeutic equivalence and why the approval of small molecule drugs is independent of the production process or site of manufacture.3 In this category there are small molecule agents such as acitretin and hydrocortisone that are commonly used by dermatologists for the treatment of psoriasis. Whereas cyclosporine is a small molecule, there are noted differences in bioavailability that warrant closer patient monitoring and therapy management. All of these structures are carbohydrate moieties ranging in molecular size from a molecular weight (in daltons) of 326 for acitretin, 362 for hydrocortisone, to 1202 for cyclosporine.

In contrast, biopharmaceuticals are biopolymers of organic molecules that are manufactured in living systems, such as animal or plant cells. These newer therapeutic tools are derived from a combination of understanding the fundamental biology of disease and advances in the technological engineering of proteins that target specific elements of cell processes. Such technology was first reported by the Nobel Prize winners Kohler and Milstein4 in 1975. Their discovery permitted the mass production of monoclonal antibodies as a consequence of the fusion of antibody-producing splenocytes to immortal myeloma cell lines. Today, biologic drugs include antibodies (protein structures that bind to specific receptors or cytokines), recombinant proteins (proteins that substitute for naturally occurring molecules such as hormones, cytokines, and enzymes), and vaccines (protein decoys that elicit a therapeutic immune response to specific pathogens or cancer antigens).5 Biologic drugs exhibit great variability in structure, which leads to divergence in function and therapeutic benefits. Relative to the small single amino acid threonine (molecular weight = 113) biologic therapies consist of complex polymers of amino acids that vary in size and sequence. Examples in dermatology include growth factors such as interferon-gamma; receptor:antibody fusion proteins such as etanercept; the human monoclonal antibody, adalimumab6-9; and the chimeric monoclonal antibody, infliximab. Function is based not only on the amino acid number and sequence but also on posttranslational modifications (eg, glycosylation) that are added by virtue of manufacture in living systems. Etanercept and adalimumab are therapies approved for the treatment of moderate to severe plaque psoriasis. Their structures are based on monoclonal antibodies and their concomitant technology; but they nevertheless differ in size (molecular weights of 150 and 148 kilodaltons, respectively) and in their capacity to bind to their target ligand, tumor necrosis factor (TNF).7,9 These differences manifest in both their binding affinity and the form of TNF that can be bound, features that can impact clinical outcome.10 Most biologic lead candidates are efficacious based on their selective
mechanisms of action, which is derived from a comprehensive understanding of the pathogenesis of disease. Because the nature of the biologic drug is inexorably linked to its process of manufacture, unlike the small molecule therapeutics, the regulatory path to approval also takes into consideration the process and facility for synthesis.

MANUFACTURING OF BIOSIMILARS

The goal of manufacturing therapeutic monoclonal antibodies is the production of high yields while maintaining biologic activity. The process used to manufacture a biologic entity determines the characteristics of the final product. Variation between a biologic and its biosimilar counterpart may derive from the protein sequence (cloning technology), expression system (selection of host cell, screening, and selection methodology), expansion (growth media, bioreactor conditions), recovery system (filtration, centrifugation), purification (chromatography binding and elution conditions), and constitution of final product (stabilizers).

Each step of the manufacturing process provides an opportunity to change the characteristics of the biosimilars relative to the original biologic. Regardless of the genetic source of the antibodies (eg, recombinant DNA, virus-encoded DNA, human plasma), impurities from the production process must be removed. These impurities include substances that were in the culture medium, cellular or microbial debris, DNA used as a template for the product, viral proteins or nucleic acids, enzymes, proteins, and salts used in the purification process. Purified protein is concentrated and transferred into formulation buffer by a process called ultrafiltration wherein large molecules are retained while small molecules are allowed to pass through a filter. Characteristics of the final product are determined by the number and sequence of purification steps, which are critical for maximizing yield and maintaining biological activity. Additional factors influencing resultant function are stability of the protein and process validation, which establishes assurances to support consistent product specifications, quality characteristics, and product purity. All of these factors can vary between lots of the same protein within the same manufacturing facility.

The TNF-alfa antagonists (eg, adalimumab, etanercept, and infliximab) comprise the most commonly used biologic agents for the treatment of moderate to severe psoriasis. Although all 3 drugs target TNF-alfa, the process of manufacturing for each drug differs. This feature may impact each drug’s relative affinity for TNF-alfa, reversibility of binding, dosing mode (intravenous vs subcutaneous), dosing intervals, and immunogenicity. These differences may lead to lack or loss of efficacy or variable toxicity potentially requiring a switch from one biologic to support the maintenance of clinical effect.

There are multiple examples wherein slight deviations in manufacturing process might result in an alteration of the clinical characteristics of the therapeutic molecule. Erythropoietin (EPO) is a complex protein that regulates the maturation of erythroid-progenitor cells into red blood cells. The product originally manufactured by Amgen (Thousand Oaks, CA) and approved for use under the brand name of Epogen for the treatment of anemia was subsequently licensed to Ortho Biotech (Bridgewater, NJ), under the trade name of Eprex. An increase in the incidence of pure red-cell aplasia was attributed to anti-EPO antibodies that targeted endogenous EPO, thus neutralizing the biological activity of both therapeutic and endogenous EPO. Retrospective analyses concluded that more than 90% of these adverse events were associated with Eprex, not Epogen. The differential rates of pure red-cell aplasia are thought to have been derived from a combination of a buffer formulation change and the use of different syringes resulting in the release of rubber stopper leachables, which increased the immunogenicity of the therapeutic protein.

In the neurology setting, Avonex (interferon beta-1a), indicated for relapsing and remitting multiple sclerosis, experienced various manufacturing facility alterations. Initially manufactured in Laupheim, Germany by Bioferon, the therapy was commercialized by Biogen (Weston, MA). Because of financial challenges, Bioferon ceased production, which forced Biogen to develop an independent manufacturing process. This involved a change in facility and a change in the production cell line. The Food and Drug Administration (FDA) approved the Biogen-manufactured Avonex based on sufficient similarity in various assays comparing physicochemical testing (eg, structural peptide mapping) and bioassays (eg, antiproliferation and major histocompatibility complex class I expression). In postapproval analysis, the immunogenicity of the new product was found to be significantly decreased relative to its originator, which serves to highlight the potential differences that might arise with apparently similar biopharmaceuticals.

Dermatology also experienced this phenomenon. Efalizumab (Raptiva) was FDA approved for the treatment of moderate to severe psoriasis in 2003. It is a humanized monoclonal antibody that binds to CD11a and prevents T-cell activation. During the
phase III program, there was a change in production from Xoma’s manufacturing facility in Berkeley, CA to that of the partnering company, Genentech in San Francisco, CA. Variations were noticed in the pharmacokinetic properties of the newly manufactured Genentech product relative to the original Xoma counterpart. In response, the FDA mandated a repeat of the phase III trials to evaluate safety and efficacy, thereby delaying FDA approval of efalizumab by 2 years.

**REGULATORY STATUS OF BIOSIMILARS**

The criteria for regulatory approval of biosimilars is likely to be an intensely debated topic over the next few years as government agencies strive to find an appropriate path forward. The FDA is in the process of establishing criteria to approve biosimilars for use in the United States including a focus on the inherent variations in structure and potential contaminants compared with the original biologic.\(^{16,18}\) But under continued discussion is whether biosimilar applications will require supporting clinical trials.\(^{19}\) The European Medicines Agency (EMA) has concluded that biosimilars need only be similar, and not identical to, the original biologic and has provided scientific guidelines on assessment of quality, along with the nonclinical and clinical standards that will be required.\(^{20,21}\) Similar to EMA, the Australian Therapeutic Goods Administration recognizes the difficulty in extrapolating the bioequivalence concepts used to approve small molecule drugs to those of biosimilars; and recent legislation in Brazil differentiates immunobiologics from small molecule pharmaceuticals.\(^{22,23}\)

Whereas these evolving regulatory guidelines will define the data needed for approval, it remains to be seen to what level the data sets will support the use of biosimilars by practitioners in the clinic.

**PERSPECTIVES ON BIOSIMILARS IN DERMATOLOGY**

There are currently 5 biologic therapies that are broadly approved for the treatment of moderate to severe psoriasis (Table I). The patent expirations for each of these innovator biologic agents take effect as early as October 2012 (etanercept) to September 2023 (ustekinumab). As a result of the potential revenue size, each is likely to stimulate the introduction of multiple biosimilar copies with companies already actively pursuing etanercept biosimilars. Regarding the US Medicare program alone, the introduction of biosimilars across the health care industry in the United States will likely result in important cost savings of $9 billion to $12 billion over the next 10 years.\(^{24}\)

The dermatologist requires a thorough understanding of the issues associated with biosimilars to facilitate interpretation of the clinical impact of different treatments. The introduction of biosimilars to dermatology may provide substantial benefits that are reflective of those seen with the use of generic small molecule drugs. Economic advantages transfer the cost savings of biosimilars to patients, which could improve access and adherence to treatment. Moreover, biosimilars could formulate a pathway that benefits those with psoriasis in developing countries. However, several important issues remain to be addressed regarding the substitution of biosimilars for currently approved biologic therapies. Not least is that biosimilars, although approved as safe and efficacious agents, will nevertheless be inherently different from the innovator products. Therefore, a substitution from innovator to biosimilar must be considered as a change in the clinical treatment of the patient. The data supporting any biosimilar must be sufficiently comprehensive to support their clinical adoption and use. At issue in this regard is the concept of extrapolation of clinical data from one therapeutic indication to another. In this scenario, a biosimilar might attain regulatory approval based on supporting information collected in rheumatoid arthritis, which results in a broad approval of the biosimilar to other indications such as psoriasis and psoriatic arthritis. The currently available TNF biologics for the treatment of psoriasis (adalimumab, etanercept, and infliximab) display differential efficacy in psoriasis compared with related diseases such as psoriatic arthritis, rheumatoid arthritis, and Crohn’s disease.\(^{25}\)

In addition, given the immunogenic nature of biologic drugs,\(^{11}\) testing for antidrug antibodies will be important in clinical trials of biosimilars.\(^{26}\)

Biosimilars conceptually hold considerable promise of low cost and broader patient accessibility that is especially important for the treatment of a chronic lifelong disease with a high prevalence, such as psoriasis. To support this potential, a relevant body of information may help form the solution to mitigating potential concerns related to the initial trial and use of biosimilars in dermatology. Patients may be switched from a branded biologic drug to a biosimilar agent only with rigorous therapeutic rationale. Beyond the initial switch patients on biosimilars should be monitored through time to generate a database that facilitates comparison of the biosimilar agents to the original innovator therapies, thus minimizing exposure to greater risks or uncertainties. It is important to recognize that inherent differences exist between biopharmaceuticals based on molecular structure. Thus, bioequivalence
may not equate to therapeutic equivalence, a key distinguishing factor relative to generic small molecule substitute agents commonly in use. That individual biologic agents are distinct in their protein sequence, folding, and glycosylation patterns impacts form, function, and immunogenicity.\(^2\) Consequently, the availability of data that deliver comprehensive therapeutic benefit-risk information seems to be a prerequisite to their broad adoption. Furthermore, such data sets should be relevant per indication, given that there are differences between the benefit-risk profiles of innovator biologics even of the same class; therefore biosimilars should not receive class labeling in the absence of indication-specific data.

To make effective comparisons in the clinic, biosimilar therapies should be easily distinguishable from their biopharmaceutical counterparts in terms of naming, classification, and packaging. For example, the use of different nonproprietary names for biosimilars would seem paramount to facilitate the tracking of risk:benefit profiles postapproval. To support their effectiveness, dermatologists should play a role in long-term pharmacovigilance of biosimilars, which can be accomplished through postmarketing surveillance and registries, many of which are already in place for biologic agents internationally.\(^2\) Vigilance will be essential in the physician-patient continuum to ensure that biosimilars are not interchanged without the full knowledge of the prescribing dermatologist and to ensure that the patient fully understands the implications.

Consideration should also be given to the impact of interchangeability on prescribing practices. Interchangeability relates to the substitution of a therapy subsequent to the prescription, ie, at the pharmacy. The resultant therapy that is ultimately given to the patient needs to be monitored to correlate actual therapy with patient outcomes. Thus, rigorous postapproval registries and pharmacovigilance programs will be important to delineate

### Table I. Biologic therapies for psoriasis

<table>
<thead>
<tr>
<th>Product</th>
<th>Description</th>
<th>Indications</th>
<th>FDA approval*</th>
<th>Psoriasis indication (FDA)*</th>
<th>US patent expiration(^y)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etanercept</td>
<td>Dimeric fusion protein of extracellular ligand-binding portion of p75 TNF receptor linked to Fc portion of human IgG1</td>
<td>Rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, plaque psoriasis</td>
<td>May 27, 1999</td>
<td>May 3, 2004</td>
<td>Oct 23, 2012</td>
</tr>
<tr>
<td>Ustekinumab</td>
<td>Human IgG1k monoclonal antibody against p40 subunit of IL-12 and IL-23 cytokines</td>
<td>Plaque psoriasis</td>
<td>Sept 25, 2009</td>
<td>Sept 25, 2009</td>
<td>Sept 25, 2023 est</td>
</tr>
</tbody>
</table>

\(^{\text{est}}\), Estimated; \(\text{Fc}\), fragment, crystallizable; \(\text{FDA}\), Food and Drug Administration; \(\text{IL}\), interleukin; \(\text{LFA}\), leukocyte function antigen; \(\text{TNF}\), tumor necrosis factor.


\(\text{US patent expiration estimated as 14 y from date of initial approval based on biologic precedents in class.}\)
between specific therapies. Patient safety cannot be compromised to facilitate increased access to cost-effective biosimilar therapies.

The authors thank Julia R. Gage for editorial writing assistance.

REFERENCES

19. Gingery D. FDA looks to middle ground at biologics hearing. Skin Allergy News 2010;41:38.