COMMENTARY

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

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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,

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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 Milstein[4] 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, adalimumab[6-9]; 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