Biosimilars

Jerry Bagel MD
Psoriasis Treatment Center of Central New Jersey
East Windsor, NJ

Biologic agents are complex protein monoclonal antibodies such as adalimumab and ustekinumab, and genetically engineered recombinant fusion proteins such as etanercept. These agents have added greatly to the therapeutic armamentarium in treating moderate to severe psoriasis. Patients with severe psoriasis are at an increased risk for depression, diabetes, and cardiovascular disease.[1] Unfortunately, these biologic agents access to patients with moderate to severe psoriasis are often limited because of their cost. A National Psoriasis Foundation (NPF) 2007 study reveled that over 50% of patients with moderate to severe psoriasis in the United States of America are treated only with topical therapy.[2] Armstrong et al reviewing an NPF survey from 2003-2011 determined that 25% of patients with moderate to severe psoriasis were not receiving any treatment.[3] Treatment with biologic agents have not only proven to be extremely efficacious in the treatment of psoriasis, they have also shown to improve quality of life and decrease depression and anxiety. Unfortunately, access is often limited due their excessive cost, which inhibits a large percentage of psoriasis patients from receiving biologic treatment. The recent and future expiry of data protection or patents for the first biologic agents has opened the door to developing biological products similar to these products.

In March 2010, the FDA was given explicit authority to review and approve biosimilars.[4] The FDA includes consideration of public information on previously approved biologic agents as a critical element in the approval of a biosimilar, providing the biosimilar is considered highly similar to the original reference drug. This allows biosimilar development not to based on their safety and efficacy, but rather on chemical and biologic similarities to the proprietary drug.

Utilizing molecular, analytical, toxicology, physiochemical, and pharmacodymic knowledge from the reference product also known as originator ie, adalimumab, ustekinumab, infliximab, etenercept, there could be an abbreviated pathway in the development of biosimilars and hence decrease their costs. It cost between 800 million-1.2 billion dollars to develop a new biologic agent. The cost of developing a biosimilar, depending upon whether a Phase III trial will be mandated by the FDA, is between 75-300 million dollars. Unfortunately, whereas most generic medicines, which are small molecules, are 30% of the cost of the brand name, biosimilars may still cost 70% of the originator price.

There is a difference between generics as we know them and biosimilars. Small molecule generics are efficiently approved by the FDA if they show blood levels ie, bioavailability of 75% or more relative to the parent compound. It is relatively easy to determine through analytic chemistry that the generic medicine is a molecular equivalent to the originator, and subsequently to determine blood levels. In the case of biosimilars, blood levels are not the only criteria. Biologic agents vary based upon the cell type, the recombinant DNA technique, the medium, and the process that is utilized for its production. Proteins can vary in amino acid modifications, glycosylation variants, and tertiary and quaternary structure alterations. Even if the amino acid sequence of two proteins are identical, post-translational modifications, three-dimensional structures and aggregation may alter the behavior of a protein drug. A slight variation in any of these parameters could result in slightly different epitope, or a different glycosylation. These minor changes can result in a different biologic molecule with different affinities to binding sites, and a different immunogenic profile.[5] Post translational modifications also include deamination, oxidation which can alter protein structure and cause aggregation which can cause immunogenicity. Amino acid isomerization is another form of post-translational modification ie, aspartic acid, can isomerize to iso-Aspartic acid possibly resulting in immunogenicity. Fortunately, technologic advances utilizing functional assays and genetic expression have helped in assessing differences. These analytical methods have been necessary to determine current differences in the manufacturing processes for some biologics, ie, batch to batch.

Analytical techniques, functional assays, as well as genetic expression techniques have been utilized to evaluate batch to batch differences from the originator and can also help determine differences between the originator and biosimilar.[6]

Primary structure medications secondary to amino acid modifications or glycosylation variants can be evaluated via mass spectroscopy and NMR spectroscopy. In regards to tertiary and quaternary structure the two main techniques for evaluating protein structure are X-ray crystallography and NMR. However, they are impractical because for X-ray crystallography the protein must be crystallized and NMR tends to be too time consuming. Since many aspects of tertiary and quaternary structure are determined by disulphide bonds, knowing their location and verifying their correct position utilizing enzymatic digests and comparing them to the originator can help verify similarity. Ion mobility spectrometry (IMS) evaluates the protein confirmation in gas phase and can also help compare it to the originator.[7]

Biosimilar developers do not have access to either the originator company's proprietary data or manufacturing process, and therefore need to develop their own processes to develop a biosimilar as chemically close as possible to the originator. As mentioned the question of quality attributes, strength and purity are especially important in the context of manufacturing process changes that occur in the production

of biologic agents. The reason for these process changes could be process improvements, scale changes, site transfers, or simply new batches.

Most biologic agents are glycoproteins, and even a well-controlled product may consist of proteins with the same amino acid sequences with many different glycosylated compositions. A correspondence in Nature Biotechnology by Schiestl et al[8] compared the different pre- and post-change batches of Enbrel Utilizing glycan mapping, cation exchange chromatography (CEX), and antibody-dependent cellular cytotoxicity in vitro bioactivity (ADCC) revealed a highly consistent profile for batches until the end of 2009. After 2009 major differences were found in the glycosylation profile. Enbrel continued to remain on the market with unaltered labels implying that the observed changes did not result in an altered clinical profile and was acceptable by health authorities.

Immunogenicity however is a concern, and evaluation of small differences in glycoprotein structures resulting in immunogenicity will have to be evaluated. Unfortunately, analytical data or animal data cannot predict immune responses in humans. Weise et al, American Society of Hematology 10/31/12.[9]

Another concern is the potential of protein biopharmaceuticals to form aggregates. Monomer proteins can form dimers, either reversible or irreversible, and particles may contain up to trillions of monomeric units. Aggregation cannot only decrease efficacy by reducing dosing concentration of drug, but they can also give rise to adverse toxicological and immunological responses. Size exclusion chromatography (SEC) is a simplistic low cost approach to characterize protein aggregates. Orthogonal analytical methods such as field flow fractionation can provide an additional level of assurance that SEC lacks.

The properties of a biologic agent that elicits an immunologic response are poorly understood and cannot be predicted from in vitro or in vivo (animal) testing, or even from the epitope or analytic chemistry of the molecule. Only clinical trials can provide this information. Analytical methods will continue to make rapid progress, however their capabilities and limitations need to be understood. The costs of the development of these technologies would have to be shared by smaller biotech companies that could not afford the high cost of these methods. Hence, post-marketing studies to detect immunogenicity may be required.

The burden of proof initially will be determining that the physicochemical and biological characteristics of the biosimilar are equivalent to the originator. The more analytical testing ie, chromatography, capillary electrophoresis, antibody affinity, pharmacodynic, genetic markers that show equivalency the more likely that the biosimilar is identical to the originator, and therefore will not require large and costly Phase III trial.

CT-P13 is a biosimilar infliximab that was compared to to innovator infliximab in in-vitro analytical studies. Similar infrared spectroscopy, tumor necrosis factor alpha neutralizing potency, and complement dependent cytotoxicity were noted. Subsequently, two clinical trials compared CT-P13 to infliximab in ankylosing spondylitis and in combination with methotrexate in treating rheumatoid arthritis. Results were similar between the two cohorts.[10] At weeks 14 and 30 ACR 20, 50, and 70 were similar between CT-P13 and Infliximab, and in the AS group the clinical responses were also similar. Antibody responses at week 24 were 27% for CT-P13 and 23% for the infliximab monotherapy in AS 50% of both the CT-P13 and innovator had antibodies at week 30. Since Inflixiamb is licensed for treatment in Crohn's disease and ulcerative colitis, psoriasis, and psoriatic arthritis studies are useful to support CT-P13 for treatment of these diseases.

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On June 28, 2013 the EMA (European Medicine Agency) recommended that CT-P13 be granted marketing authorization for the treatment of rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis, and Crohn's disease and ulcerative colitis. In the USA the patent for innovator infliximab does not expire until September 2018. Its patent expiration in the European Union is not until August 2014, and it will not be marketed until after that date.[10] Its launch however, in eastern and central Europe where patents are not in effect, is expected in 2013.

Demonstration of equivalence would mean the biosimilar have the same dose and frequency of administration as the originator.[11] An important question is whether, for example, a biosimilar of an antibody to TNF alpha in rheumatoid arthritis be extrapolated to their use in psoriasis. Another relevant question is will the prescriber know if the proprietary drug is given to the patient or will the pharmacist on their own initiative be able to give the patient a biosimilar without contacting the physician?

The oversight of biosimilars in Europe is based on similarity to a reference monoclonal antibody in terms of safety and

efficacy profile is established via analytical and cellular data, not through efficacy data ie, not through clinical trials. Having said all this, the biotech industry may be erecting barriers to slow biosimilars into the marketplace. The name brand companies through name brand recognition may promote that with 30 years of experience their manufacturing processes are most trustworthy even if they decide to produce biosimilars. If they are truly comparable to the originator products, biosimilars offer the possibility of decreasing cost and offering more patient therapeutic benefits. The question to be answered is whether the analytical techniques employed can elucidate a comparable efficacy/safety profile to the originator.

In conclusion, many psoriasis sufferers do not have access to effective therapies because of high cost. Reducing the cost of biologics should increase patient access. As technology advances, analytic techniques should help provide an effective method to predict efficacy and safety of biosimilars prior to human use. Should biosimilars show comparable analysis to the originator insurance companies will likely enforce the use of biosimilars prior to approval of proprietary biologics.

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AUTHOR CORRESPONDENCE

Jerry Bagel MD
E-mail:..... dreamacres@aol.com