ANNENBERG CENTER FOR HEALTH SCIENCES
AT EISENHOWER
Imparting knowledge. Improving patient care.

RESEARCH perspectives

Biosimilars—Advances in Research and Development

A CME Activity

Overview

Steven R. Feldman, MD, PhD, summarizes the latest information on the advances in biosimilar research and development, while providing clinical implications of recent clinical data and ongoing trials involving biosimilars in relation to the data for their reference biological product. The goal of this program is to raise awareness about biosimilars, and discuss recent data, which may provide more trust in the use of biosimilars and ultimately prove beneficial to patients.

Content Areas:

- Glycosylated biopharmaceuticals reviewed
- Totality-of-the-evidence approach
- GP2015, a proposed etanercept biosimilar
- CT-P13, an infliximab biosimilar
- GP2017, an adilimumab biosimilar
- Unanswered questions about biosimilars

Faculty

Steven R. Feldman, MD, PhD
Professor of Dermatology, Pathology and Public Health Sciences
Department of Dermatology
Wake Forest University School of Medicine
Winston-Salem, North Carolina

Table of Contents

Supported by an independent medical education grant from Sandoz, Inc., a Novartis Division.

Participate in interactive questions, download activity slides, and obtain your CME credit online.
https://www.annenberg.net/Biosimilars-Advances-CME

CE/CME Information

Target Audience
This activity was developed for rheumatologists, dermatologists, gastroenterologists, and other health care professionals who have an interest in biosimilars.

Learning Objectives
At the conclusion of this activity, participants should be better able to:

- Summarize the latest advances in biosimilar research and development
- Interpret the clinical implications of recent clinical data and ongoing trials involving biosimilars in relation to the data for their reference biological product
- Incorporate recent evidence-based research into clinical practice

Accreditation and Certification
The Annenberg Center for Health Sciences at Eisenhower is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

The Annenberg Center for Health Sciences at Eisenhower designates this enduring material for a maximum of 1.5 *AMA PRA Category 1 Credits*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Disclosure Statement
In accordance with the Accreditation Council for Continuing Medical Education Standards, parallel documents from other accrediting bodies, and Annenberg Center for Health Sciences policy, the following disclosures have been made:

Steven R. Feldman, MD

Grant Support	AbbVie, Celgene, Galderma, Janssen, Novartis
Consultant	AbbVie, Advance Medical, Caremark, Celgene, Galderma, Gerson Lehrman Group, Guidepoint Global, Janssen, Kikaku, Leo Pharma, Lilly, Merck, Mylan, Novartis, Pfizer, Qurient, Sanofi, Sienna, Sun Pharma, Suncare Research, Valeant, Xenoport
Speaker's Bureau	AbbVie, Celgene, Janssen, Leo Pharma, Lilly, Novartis, Taro
Significant Shareholder	Causa Technologies, Medical Quality Enhancement Corporation
Founder/ Technology Officer	Causa Technologies
Royalties	Informa, UpToDate, Xlibris

The faculty for this activity has disclosed that there will be discussion about the use of products for non-FDA approved indications.

Additional content planners
The following have no significant relationship to disclose:

Coy Alden Flowers, MD (peer reviewer)

Victoria Anderson, BA (medical writer)

Annenberg Center for Health Sciences
John Bayliss, VP, Business Development, spouse is an employee of Amgen, Inc; all other staff at the Annenberg Center for Health Sciences at Eisenhower have no relevant commercial relationships to disclose.

The ideas and opinions presented in this educational activity are those of the faculty and do not necessarily reflect the views of the Annenberg Center and/or its agents. As in all educational activities, we encourage practitioners to use their own judgment in treating and addressing the needs of each individual patient, taking into account that patient's unique clinical situation. The Annenberg Center disclaims all liability and cannot be held responsible for any problems that may arise from participating in this activity or following treatment recommendations presented.

This activity is an online enduring material. Successful completion is achieved by reading and/or viewing the material, reflecting on its implications in your practice, and completing the assessment component.

The estimated time to complete the activity is 1.5 hours.

Our Policy on Privacy
Annenberg Center for Health Sciences respects your privacy. We don't share information you give us, or have the need to share this information in the normal course of providing the services and information you may request. If there should be a need or request to share this information, we will do so only with your explicit permission. See Privacy Statement and other information at http://www.annenberg.net/privacy-policy/

Contact Information
or help or questions about this activity please contact Continuing Education:
ce@annenberg.net

1. Introduction

Steven R. Feldman, MD, PhD

Biologic medications have revolutionized the treatment of serious arthritic, skin, and gastrointestinal illnesses, but they are costly products. As these drugs lose patent protection, biosimilar products are being brought to market. Biologics are too large and complex to duplicate. Should we trust biosimilars?

Hi. I'm Dr. Steve Feldman, professor of dermatology at the Wake Forest Baptist Medical Center in Winston-Salem, North Carolina. This program tries to answer this question by reviewing and commenting on recently published research data for rheumatologists, dermatologists, gastroenterologists, as well as other health care providers who currently use or may consider the use of biosimilars. In our review of recent literature, we will summarize the latest research on the more recent advances in biosimilars research and development, while providing clinical implications of recent clinical data and ongoing trials involving biosimilars in relation to the data for their referenced biologic product.

There are common misconceptions among providers with regards to the scientific evidence behind the use of biosimilars. Clinicians need to understand what a biosimilar *is,* and what it is not. And they need to be clear about safety and evidence among biosimilars in relation to the origin product. Biosimilars are designed to be similar to the originator biologic, and that they undergo vigorous tests to demonstrate this similarity. This program addresses issues of confidence using biosimilars across various diseases, including switching, and provides valuable clinical information showing biosimilars perform similarly to the innovator product. Raising awareness about biosimilars can help generate trust in biosimilars among health care professionals, and may ultimately prove beneficial to patients.

2. Acceptable changes in quality attributes of glycosylated biopharmaceuticals

Schiestl M, et al

Hello. This is Dr. Steven Feldman, professor of dermatology at the Wake Forest Baptist Medical Center in Winston-Salem, North Carolina. I'll be discussing the publication, Acceptable Changes in Quality Attributes of Glycosylated Biopharmaceuticals, by Martin Schiestl and colleagues. This study report was published in *Nature Biotechnology.*

I selected this article because it provides more transparency anchoring the debate about acceptable changes in quality attributes. Data revealed physicochemical differences in each of the glycosylated recombinant therapeutic proteins in this study. This article highlights several different factors that may account for changes in quality attributes. Manufacturers are required to demonstrate the process change does not alter the clinical safety or efficacy of the biologic product based on principles of the comparability exercise regulated in guidelines.

Let's look at the methods.

Three major-marketed glycosylated biopharmaceuticals were reviewed, analyzing the quality profiles of darbepoetin alfa, rituximab, and etanercept. The data revealed substantial alterations of the glycosylation profile for all tested products, most probably caused by changes in the manufacturing processes. The observed changes, however, in these studies predicted the reference medicine, and therefore its approved biosimilar, do not alter the clinical profile, and therefore are acceptable by the health authorities.

Here are my thoughts and analysis of this study.

This study provides a critical understanding of biologics, without which we cannot begin to understand biosimilars. Biologics are such complex glycoproteins that nobody can duplicate them. Many people hear that and think biosimilars cannot be trusted. But the principle that biologics are too complicated to duplicate means that even the innovator varies from batch to batch, as demonstrated in this study. Knowing we have accepted some degree of variation all along makes the idea of biosimilars a whole lot easier to digest. We'll have far, far more data showing that the biosimilar is similar to the innovator product than we have had showing the different batches of the product are similar.

These findings make me realize that when I thought I was prescribing an innovator biologic that was a unique protein, I was actually prescribing a mixture of things that varied over time. That doesn't bother me or change my management in any way because innovator biologics work and have worked great, consistently, wonderfully, despite whatever variation there has been. The results of this study make me very comfortable with the idea of using biosimilars, especially as those biosimilars will be tested to ensure that they are similar and perform similarly to innovator biologics.

This study is not informative, though, about all innovator biologics. Data on only 3 were provided. While this study is informative about the variation in the drugs, it is not informative about what clinical implications those variations have. Based on the clinical performance in my experience, I doubt the variation is meaningful, not clinically anyway. Moreover, the study does not tell us anything about the role of patient adherence and drug handling. I suspect the variation in how well patients care for and use the medication, once they receive it, dramatically swamps any differences in the batch-to-batch or innovator-to-biosimilar variation.

3. The totality-of-the-evidence approach to the development and assessment of GP2015, a proposed etanercept biosimilar

Strand V, et al.

Hello. This is Dr. Steve Feldman, professor of dermatology at the Wake Forest Baptist Medical Center in Winston-Salem, North Carolina. I'll be discussing the publication, The Totality-of-the-Evidence Approach to the Development and Assessment of GP2015, a Proposed Etanercept Biosimilar, by Dr. Strand and colleagues. This study report was published in *Current Medical Research and Opinion.* I selected this article to discuss the totality-of-the-evidence concept.

Physicians may be unfamiliar with the totality-of-the-evidence concept. The goal of this review is to describe the inherent variability that is natural to biologics in using the proposed etanercept tumor necrosis alpha inhibitor biosimilar GP2015, as an example, to provide details on the type and extent of analytical, preclinical, and clinical data considered by regulatory authorities with respect to the approval of biosimilars. Physicians have been trained to look at clinical data, primarily, when making choices about which drug to use. For biosimilars, however, physicians need to be aware of the complete data package; the analytics, preclinical, and clinical data, that is considered by regulatory agencies when concluding whether a proposed biosimilar is approvable, or not, as a biosimilar. The totality-of-the-evidence includes all analyses and performed trials used to approve the product and justify use of the biosimilar in all indications for which the reference medicine is approved. This article is an overview of the stages of the in-depth process of developing a biosimilar from its reference medicine, in this case to etanercept.

Biosimilar development involves a number of stages. The initial stage examines multiple batches of the referenced medicine—and they are characterized to understand structural and functional attributes—and determine the variability of post-translational modifications over time and from batch to batch. Data then set the development target and boundaries of acceptable variability of the biosimilar.

Stage 2 involves target-directed development of a manufacturing process for the biosimilar molecule. The final stage includes confirmation of high similarity, comparing structural and functional level to determine whether the biosimilar molecule is essentially the same as the reference molecule. Then preclinical properties, toxicology, tolerability and nonhuman pharmacology are compared using relevant in vitro and in vivo models.

Final phase 3 confirmatory clinical efficacy and safety trial is conducted in a relevant population to allow detection of clinically meaningful differences between the biosimilar and reference medicine, should such differences exist. These analytical data serve as a foundation of the overall comparability exercise in the totality-of-the evidence concept. Discussion of confirmatory study is to use a clinical indication, primary endpoint study duration that has the best chance of detecting differences in efficacy or safety between the biosimilar and reference product, if such differences exist.

Biosimilars also offer an opportunity to learn more about biologic medicines in general. For example, how changes in the critical quality attributes of a biologic correlate with clinically relevant outcomes.

Let me share my thoughts about this study and analysis of it.

This study highlights the tremendous extent to which biosimilars are studied to assure that they will function in the same way as the innovator biologic. Biologics are very complicated molecules. No one can create perfect copies. But we can make sure they are highly similar. So similar that we would not expect the biosimilar to perform any differently than the innovator product. I expect the detailed description this manuscript offers of the studies done on biosimilars will help assure doctors and patients that they can expect the same extraordinary life-changing benefits from biosimilars that we have seen from the innovator biologics that the biosimilars are trying to copy. I expect we will see, pending any legal challenges, rapid uptake in the use of biosimilars driven by payers and largely accepted by the medical and patient communities. Because biologic medications are too difficult to perfectly copy, there will always be some degree of uncertainty, even with the innovator products. That degree of uncertainty has not bothered us since the introduction of innovator products. It may be that the greatest uncertainties that remain are largely practical legal issues of bringing the biosimilars to market.

4. The PROSIT-BIO cohort: A prospective observational study of patients with inflammatory bowel disease treated with infliximab biosimilar

Fiorino G, et al.

Hello. This is Dr. Steve Feldman, professor of dermatology at the Wake Forest Baptist Medical Center here in Winston-Salem, North Carolina. I'll be discussing the publication, The PROSIT-BIO Cohort: A Prospective Observational Study of Patients With Inflammatory Bowel Disease Treated With Infliximab Biosimilar, by Dr. Fiorino and colleagues. This study was published in *Inflammatory Bowel Diseases.* I selected this article to discuss because of the large cohort of patients in a multicenter study using CT-P13, the first infliximab biosimilar evaluated by the European Medicines Agency, the EMA.

Previously, little information was available on the safety and efficacy of infliximab biosimilar CT-P13 in patients with inflammatory bowel disease, specifically with ulcerative colitis and Crohn's disease. CT-P13 became the first monoclonal antibody approved through the EMA's biosimilar regulatory pathway for rheumatoid arthritis, ankylosing spondylitis, adult and pediatric Crohn's disease, ulcerative colitis, psoriatic arthritis, and psoriasis. This study addresses the issue of confidence using infliximab biosimilar in inflammatory bowel disease and switching from the originator. Concerns included different dosing of infliximab 5 mg per kilogram in IBD, as well as the use of concomitant immunosuppressive medication.

Before beginning my analysis, let's hear about some of the study's highlights from the lead author's perspective.

What do you feel are the 3 most important highlights or findings of this study?

The most important summary points are: 547 patients using CT-P13, 97 of whom were switched from infliximab, were followed for a mean of 4.3 plus or minus 2.8 months. The rate, 12.2%, and characteristics of serious adverse events (SAEs), was in line with previous experience with infliximab. The occurrence of infusion reactions and drug withdrawal for SAEs was 7% and 8.2%, respectively. The whole efficacy in terms of induction and/or maintenance of remission and response was approximately 90% at 24 weeks. The rate of primary failure was 8.1%, and loss of response, 18.6%, was in line with previous experience with infliximab.

What impact do you think this study will have on the utilization of the biosimilar infliximab in patients with IBD?

This experience has increased the confidence in the use of the first infliximab biosimilar in real-world practice, although long-term data and more information after the switch are awaited.

This was a multicenter study from 31 referral centers studying patients previously diagnosed either as ulcerative colitis, 234 of them, or Crohn's disease, 313, to review the efficacy of biosimilar CT-P13 on patients who received treatment for at least 8 weeks. The study included 311 patients who were naïve to antitumor necrosis factor alpha agents, 139 who had a previous exposure to biologics, and the remaining 97 were switched to CT-P13 after a mean of 18 plus or minus 14 infusions of infliximab reference product.

Here were the study's key findings. After 2061 infusions, 66 serious adverse events were reported (12.1%), 38 (6.9%) of them were infusion-related reactions. Infusion reactions were significantly more frequent in patients pre-exposed to infliximab than to other antitumor necrosis factor alpha inhibitors. The incidence ratio is equal to 2.82, with a 95% confidence interval of 1.05 to 7.9. Efficacy in terms of induction and/or maintenance of remission and response was high, with efficacy at 24 weeks, approximately 90%. For this specific study, efficacy

estimations at weeks 8, 16, and 24 were as follows: 95.7%, 86.4%, and 73.7% for naïve patients; 97.2%, 85.2%, and 62.2% for pre-exposed patients; and 94.5%, 90.8%, and 78.9% for switched patients. Although no direct comparison was performed, preliminary data on efficacy and safety of CT-P13 were in line with those of infliximab. Outcomes of the suggested studies all show CT-P13 to be effective and safe treating IBD in real clinical practice.

Here are my thoughts and analysis of this study.
The biosimilars are designed to be similar to the originator biologic. Biosimilars undergo a large battery of tests to demonstrate this similarity. The testing includes in vitro tests showing how similar the drugs are, including how well the drug binds to its target, and in vivo testing showing that the pharmacology of the biosimilar is similar to the originator. Given the similarity of the biosimilar to the innovator, and the lack of magic in medicine, we should expect biosimilars to perform similarly to the innovator drug.

The main finding of this study is that, as expected, the biosimilar gave similar clinical outcomes. This study is not going to suddenly change a lot of people's treatment outcomes, because even though the biosimilar works, patients who could be effectively treated with biosimilar infliximab could be treated with the originator. I doubt restrictions on use imposed by payers would be changed by the availability of a biosimilar. This study may make doctors and patients more comfortable with the idea of using a biosimilar. Insurers may use this data to encourage greater use of biosimilars if doing so provides a cost savings. While this study does not rule out the possibility of small differences between the biologic and the innovator, we need to realize there may be small differences even between different batches of the innovator product. This study is not informative about whether today's innovator infliximab works the same as the infliximab that was used in clinical trials over a decade ago.

5. Efficacy and safety of CT-P13 (biosimilar infliximab) in patients with rheumatoid arthritis: comparison between switching from reference infliximab to CT-P13 and continuing CT-P13 in the PLANETRA extension study

Yoo D-H, et al.

Hi. This is Dr. Steve Feldman, professor of dermatology at the Wake Forest Baptist Medical Center in Winston-Salem, North Carolina. I'll be discussing the publication, Efficacy and Safety of CT-P13 (Biosimilar Infliximab) in Patients With Rheumatoid Arthritis: Comparison Between Switching From Reference Infliximab to CT-P13 and Continuing CT-P13 in the PLANETRA Extension Study, by Dr. Yoo and colleagues. This study report was published in *Annals of the Rheumatic Diseases.*

I selected this article because it focuses on the comparison of efficacy and safety between switching from reference infliximab to CT-P13, and continuing CT-P13 in the significant PLANETRA Extension Study, focusing on patients with rheumatic diseases, specifically rheumatoid arthritis. Three hundred two of 455 patients who completed the PLANETRA study enrolled in this extension study. This study is important because one of the most common uses of infliximab is for patients with rheumatoid arthritis. This study provides valuable information showing that biosimilar infliximab performs, as expected, similar to the innovator infliximab product. Moreover, switching from innovator infliximab to biosimilar infliximab had no apparent effect on treatment outcome.

This was a multinational open-label extension study that recruited patients with rheumatoid arthritis who had completed the 54-week randomized parallel group study comparing CT-P13 with the reference product. There were 302 subjects. 158 received CT-P13. They were the maintenance group. And 144 received the reference product. They are the switch group.

The study studied switching from infliximab reference product to biosimilars CT-P13, or continuing CT-P13 in patients with rheumatoid arthritis for an additional 6 infusions. CT-P13 was given a dose of 3 mg per kilogram and was administered intravenously every 8 weeks from weeks 62 to 102. Efficacy assessments were made at baseline and at weeks 14, 30, 54, 78, and 102. Efficacy endpoints included the proportion of patients meeting American College of Rheumatology, that's ACR-20, ACR-50 and ACR-70 criteria.

Here were the key findings.

In the switch group, there were no notable differences in ACR response rates between weeks 54, the last reference product treatment, and week 102, 48 weeks after the last reference product infusion. In the maintenance group, the responses to CT-P13 observed in the main study were sustained during the extension study. The study demonstrated that in patients with rheumatoid arthritis receiving methotrexate, switching from reference product to CT-P13 was not associated with any detrimental effects on efficacy, immunogenicity, or safety. This study demonstrated CT-P13 remained efficacious and well tolerated during a 2-year treatment period. Data support the long-term efficacy of CT-P13 in patients with rheumatoid arthritis.

Here are my thoughts and analysis of this study.

One key point of this study is that patients on infliximab biosimilar seem to do, as expected, as well as patients on infliximab. But this study goes even further, showing that patients who switch from the reference infliximab to the biosimilar infliximab also do well. One of the big concerns with biosimilars is

the potential that they could be more immunogenic than the innovator product. Such immunogenicity might be more apparent when switches occur between the innovator and the biosimilar. This study gives us confidence that the CT-P13 biosimilar of infliximab does not have any unusual immunogenicity and that switching between it and the reference infliximab product is unlikely to affect patient treatment outcomes. As we look to the future, this study gives us confidence that biosimilar infliximab is appropriate for use in patients who are currently doing well on reference infliximab. This study gives us great information on switches between the biosimilar and the innovator. When multiple biosimilars become available, however, we'll have the issue of switches between those different biosimilar products. This study does not tell us whether those studies will cause any problem, though it seems unlikely they would.

5. Efficacy and safety of CT-P13 (biosimilar infliximab) in patients with rheumatoid arthritis: comparison between switching from reference infliximab to CT-P13 and continuing CT-P13 in the PLANETRA extension study

6. Key design considerations on comparative clinical efficacy studies for biosimilars: adalimumab as an example

Lai Z, La Noce A.

Hello. This is Dr. Steve Feldman, professor of dermatology at Wake Forest Baptist Medical Center in Winston-Salem, North Carolina. I'll be discussing the publication, Key Design Considerations on Comparative Clinical Efficacy Studies for Biosimilars, Adalimumab as an Example, by Dr. Lai and colleagues. This study report was published in *Rheumatic and Musculoskeletal Diseases.* I selected this article because it provides a review of 9 phase 3 global clinical efficacy studies to highlight key study design considerations of proposed biosimilars.

This study uses adalimumab as an example to highlight design elements that may deserve special attention, including therapeutic indications (and for our discussion, plaque psoriasis, specifically), target patient population, background therapy, blinding stratification, transition design—which is a switch from originator to biosimilar product—primary dependent variable, choice of equivalence vs noninferiority design, selection of equivalence margin, and alternative statistical considerations. An equivalence design is thought to be more rigorous, demonstrating biosimilarity of a biosimilar vs the branded product. This review will help clinicians understand regulatory requirements for biosimilar development and design of pivotal clinical trials to demonstrate comparative efficacy and safety for biosimilars vs branded products, when considering prescribing biosimilars for rheumatic diseases.

Before beginning my analysis, let's hear about some of the study's highlights from the lead author's perspective.

What do you feel are the 3 most important highlights or findings of the study?

To demonstrate biosimilarity, and not efficacy and safety de novo, phase 3 comparative clinical studies for biosimilars have some design features (equivalence or non inferiority design, switch from the reference product to a biosimilar or vice versa) distinct from those for novel biological products.

Key study design elements vary among the 9 phase 3 studies for 8 adalimumab biosimilars, in terms of the disease indications, target patient population, background therapy, disease activity, transition design, primary endpoint, equivalence margins, etc. While each biosimilar is compared with the reference product in these studies, due to the differences in study design, it may be difficult to compare the different biosimilars with each other. Even if the reference product has been approved for multiple indications, pivotal phase 3 studies to demonstrate comparative efficacy and safety for biosimilars are usually carried out in 1 disease indication and extrapolated to other indications. For example, out of the 8 adalimumab biosimilars that were (or are) evaluated in phase 3 comparative studies with the reference product, 4 were evaluated only in rheumatoid arthritis, 3 only in plaque psoriasis, and 1 in both rheumatoid arthritis and psoriasis.

What impact do you think this study will have on the utilization of proposed adalimumab biosimilars in patients with plaque psoriasis?

By understanding the different phase 3 study design approaches taken with 8 adalimumab biosimilars, either approved or in development, the study's findings will hopefully:

1) help clinicians evaluating the comparative efficacy and safety data for the adalimumab biosimilars; and

2) facilitate their discussions with patients on switching to or initiating adalimumab biosimilar for the treatment of plaque psoriasis.

Here are the methods of this study.

A psoriasis 2013 phase 3 clinical trial with 448 subjects for GP2017, a biosimilar for adalimumab, permitted enrollment of patients who received prior biologic therapies. The primary endpoint was a 75% reduction in the Psoriasis Area and Severity Index. We call that a PASI-75, at week 16 in patients with plaque psoriasis. Psoriasis studies indicated that treatment assignment, weight, and age are the most influential factors for mean percent change in PASI score at week 16. Efficacy is decreased mainly in patients with body weight greater than 90 kg or with body mass index (BMI) > 30 kilograms per meter squared. The most significant decrease in efficacy occurs in patients with body weight > 140 kg. Data show it might be worthwhile to consider weight or BMI as a stratification factor with the biosimilar adalimumab or to exclude extremely obese patients, because obesity tends to be more frequent in patients with psoriasis. Of the 5 indications approved for adalimumab, the greatest placebo-adjusted response rate was found in psoriasis, 61% to 64%. Psoriasis may represent a more sensitive disease model to detect any potential difference in immunogenicity of the biosimilar vs branded adalimumab. Ongoing consultation during the development of the biosimilar product is necessary to make adjustments, as necessary, based on preclinical and clinical data, because the totality of evidence is used for regulatory approval.

Here are my thoughts and analysis of this study.

To get a biosimilar approved, they must show it is similar to the innovator biologic. You can do all kinds of preclinical tests to show that products are similar, but to alleviate any residual uncertainty that the drugs will perform similarly, a single clinical trial can be done. That trial should be done with patients who have the condition that would be most sensitive for identifying the difference between products. This study makes the case that for tumor necrosis factor inhibitors, psoriasis would be the best condition to study. Psoriasis is easily measured, and because psoriasis is often treated with the biologic in isolation—as opposed to rheumatoid arthritis or psoriatic arthritis in which concomitant methotrexate is often used—there should be good sensitivity for detecting immunogenicity.

The results of this study won't have any immediate impact because we don't have an adalimumab biosimilar on the market in the United States. In the future, this study should give us great confidence that adalimumab biosimilars can have similar actions as the innovator products. I think many people believe a lot of questions remain unanswered. Here are a few. Will doctors be comfortable prescribing a biosimilar that is not identical to the original drug? Will we accept patients being switched from originator to biosimilar without our knowledge? Will we be satisfied if biosimilars are tested in patients with rheumatoid arthritis and not psoriasis? Will we be comfortable with potential differences in immunogenicity, safety, and efficacy? Will we be comfortable with the biosimilar using the same generic name that the originator drug uses? I think these questions are easily answered knowing that different branches of the innovator product vary too.

So, **will doctors be comfortable prescribing a biosimilar that's not identical to the original drug?** We have been comfortable giving patients different batches of the innovator, and they're not identical.

Will we accept patients being switched from the originator to a biosimilar without our knowledge? Patients have been switching between different batches of the innovator without our knowledge.

Will we be satisfied if biosimilars are tested in patients with rheumatoid arthritis and not psoriasis? The current batches of innovator have not been compared to the original batch in any clinical trial, so if we are comfortable with no trial at all, we ought to be comfortable with a rheumatoid arthritis trial.

Will we be comfortable with potential differences in immunogenicity, safety, and efficacy? We have been comfortable with potential differences in immunogenicity, safety, and efficacy between different batches of the innovator, and we'll have more data on biosimilars showing that there aren't differences in immunogenicity, safety, and efficacy.

Finally, will we be comfortable with the biosimilar using the generic name that the originator drug uses? We have been comfortable with different batches of the innovator using the same generic name. I would be comfortable if well-tested biosimilars use that generic name, too.