Biosimilars in Rheumatoid Arthritis: What Does a Changing Treatment Landscape Mean for You and Your Patients?

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Activity Information

Activity Description and Educational Objectives
In this activity, an expert in rheumatoid arthritis discusses the role of biosimilars in the management of this disease.

Upon completion of this activity, participants should be better able to:
• Recognize similarities and differences of biosimilars relative to their biological reference agents based on structure, regulation, and clinical properties
• Identify current safety and efficacy data regarding the use of biosimilars in rheumatoid arthritis
• Apply biosimilars into the management of individual patients with rheumatoid arthritis in accordance with current evidence and expert recommendations

Target Audience
This activity has been designed to meet the educational needs of rheumatologists and other clinicians involved in the treatment of patients with rheumatoid arthritis.

Requirements for Successful Completion
In order to receive credit, participants must view the activity and complete the post-test and evaluation form. A score of 70% or higher is needed to obtain CME credit. There are no pre-requisites and there is no fee to participate in this activity or to receive CME credit. Statements of Credit are awarded upon successful completion of the post-test and evaluation form.

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Time to Complete: 30 minutes

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Leonard H. Calabrese, DO, does intend to discuss either non-FDA-approved or investigational use for the following products/devices: biosimilars under investigation in rheumatology.

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Biosimilars: A Foundational Overview

Dr. Calabrese: Hi. This is Dr. Len Calabrese from the Cleveland Clinic Lerner College of Medicine in Cleveland, Ohio. Welcome to this educational activity focused on the role of biosimilars in rheumatoid arthritis. After completing the activity, access the post-test and evaluation form by clicking the red “Get Certificate” button.

I really encourage you to download the slides, Practice Aids and any other features that you may be interested in. You can also share what you learn in this presentation with your colleagues. To post this presentation via Twitter, Facebook, LinkedIn, or e-mail, just select “Share This Presentation” from the menu in the upper left.

Biologic drugs have made a significant impact in the treatment of RA and other inflammatory diseases.

These therapies specifically target key modulators of the inflammatory response, such as pro-inflammatory cytokines, lymphocytes (eg, T or B cells), and cell surface receptors.

Although biologic therapies have demonstrated clinical efficacy, availability and patient access to these treatments may be limited, which can impact patient outcomes.

There’s a prevailing theme of this presentation and that is to provide these treatments to patients at lower cost, once patents come off of the original biopharmaceuticals. Biosimilars have now been developed; several biosimilars have been approved by regulatory agencies as of now to treat rheumatoid arthritis and other inflammatory conditions, and these are commercially available in many countries throughout the world.

Introducing Biosimilars: A Foundational Overview

Biosimilars have been developed to provide these treatments to patients at a lower cost, once patents for the originator biopharmaceutical have expired.

Several biosimilars have been approved by regulatory agencies to treat RA and other inflammatory diseases and are commercially available in many countries.

Biosimilarity

...“that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components” and that “there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product” (Section 351(i) of PHS Act)

Generic

Copy of a small-molecule (chemical) drug, which can be fully defined structurally and reproduced with an identical chemical structure.

A biosimilar cannot be identical to the originator biologic:
- Biologic drugs are made in living cells, and the proprietary manufacturing processes are specialized and never fully disclosed by the manufacturer of the originator


Biologic drugs have made a dramatic impact on rheumatoid arthritis and other immune-mediated inflammatory diseases. These therapies specifically target key modulators in the integrated immune response. It can be either cytokines or cellular elements.

And although biologic therapies have demonstrated profound efficacy, raising the bar for therapy, the availability and patient access to these therapies may be limited because they’re extremely expensive, and this can affect patient outcomes.

So, to start out, what is a biosimilar? Regulatory agencies have stated that the biologic product is highly similar to the reference product, notwithstanding minor differences in clinically inactive components. That means that it’s really not a carbon copy, but it’s highly similar. And there is some additional wording that talks about safety, purity, and potency of the product being variables that are important to compare and contrast. This is in contrast to generics, which are literally carbon copies of an originator compound.

So if we compare the biosimilar process, first of all, it is possible to start out with the same genetic sequence, because this is public domain. But after that, much of this process is proprietary. The biosimilar producer will not have the exact same vector to start out with the same genetic sequence, because this is proprietary. There will be different growth media, different incubators, different bioreactor conditions, all contributing to different elution, purification, and excipient addition. And finally, the packaging will be different.


The regulatory approval process of a biosimilar requires much, much more data than a generic small molecule. And here on this graph, we’re showing three different regulatory agencies, the FDA in the middle; EMA, the European equivalent; and the WHO, all kind of providing this high-altitude guidance as to what type of analytics must be done, what type of nonclinical in vivo studies, whether or not animals studies are needed, what type of clinical studies, and then, finally, extrapolation, which has to do with the approved indications for these drugs.


So, let’s look at how the process of creating a biologic looks like. It starts out by having source DNA that encodes the RNA to create a protein of a given biologic, an antibody, or an antireceptor of some sort. Then there is a long and laborious and very high-tech process of protein production, purification, and validation that actually goes into the packaging and production of a drug.


So if we compare the biosimilar process, first of all, it is possible to start out with the same genetic sequence, because this is public domain. But after that, much of this process is proprietary. The biosimilar producer will not have the exact same vector available. Even though they are grossly similar, they will be of different cell lines. And then in the manufacturing process, this all will be different, because this is proprietary. There will be different growth media, different incubators, different bioreactor conditions, all contributing to different elution, purification, and excipient addition. And finally, the packaging will be different.
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Physicochemical characterization

Biological characterization

Preclinical studies

Clinical studies

Pharmacovigilance

The Stepwise Development Approach for a Biosimilar

Phase 1

Phase 2/3

PK, PD, safety, and immunogenicity assessment

Efficacy, safety, and immunogenicity assessment

No clinically meaningful differences demonstrated

No clinically meaningful differences demonstrated


Summary of Stepwise Development

- Stepwise approach enables the biosimilar developer and regulatory agencies to:
  - Determine the extent of residual uncertainty of biosimilarity at each step of development
  - Identify additional relevant studies and analyses that may be needed to resolve this uncertainty

- “Totality of the evidence”
  - Application for regulatory approval for a potential biosimilar includes a comprehensive data package from all stages of development (ie, analytical and functional comparability, animal studies, and clinical data)

Now, this slide shows the stepwise development approach of a biosimilar. The largest step is the physicochemical characterization and the biologic characterization. Up toward the top is the clinical study, which is actually quite small compared to the ex vivo efforts that must go in to show this high degree of similarity. Now, finally, pharmacovigilance—that means once a drug is released into practice—there must be ongoing safety analysis.

If we look at the clinical studies, the originator compounds, you have to do large pivotal clinical trials on thousands of patients and demonstrate efficacy in each and every indication that you’re interested in seeking approval for your compound.

Biosimilars are different. Once it has been demonstrated that these are highly similar ex vivo, then clinical studies really only have to demonstrate similarities in pharmacokinetics, pharmacodynamics, safety, and noninferiority in terms of efficacy. So, much, much smaller trials. And since it costs over half a billion dollars for an originator to be approved, this is greatly foreshortened, and hopefully will save a lot of money.

Summary of Stepwise Development

So, to summarize, at this point in time, the stepwise approach that I’ve outlined shows that the emphasis is on the ex vivo similarity and the “totality of evidence” means that the application for regulatory approval for a potential biosimilar includes a comprehensive data package that includes analytics, functional comparability, plus/minus animal studies, and ultimately clinical data. Let’s drill into this a little bit.

Clinical Trial Designs for Biosimilars


Interpreting the Results From Superiority and Equivalence Trials

Superiority Trial

Equivalence Trial

Favors Drug 2

Favors Drug 1

Drugs Are Equivalent

Planned for magnitude of difference in trial for significance (Drug 1 vs Drug 2)

Drug 1 is superior

The difference was not statistically significant

-6

Drug 1 is equivalent to Drug 2

Failed to demonstrate that Drug 1 is equivalent to Drug 2


So, the clinical design for biosimilars is much different for clinical trial design for an originator compound. You have a new biologic. You want to demonstrate that it’s efficacious. It has to be compared to something. If it’s early disease, it might be compared to placebo. If it’s advanced disease, it might be compared to an established DMARD like methotrexate in rheumatoid arthritis, or it might go head to head with another biologic. You’re looking to demonstrate generally superiority over placebo. Biosimilars, on the other hand, all you’re trying to do is demonstrate that this is equivalent to the originator.
You can see the design on the left of a superiority trial, where the
degree of clinical improvement must be superior. On the opposite
side, the equivalence trial demonstrates that you establish a preset
window of therapeutic equivalence, and it must reside within
that window to be deemed equivalent. And we're not looking to
make this better, and we're not looking to make this worse. We're
looking statistically to achieve the endpoint of equivalence.

Noninferiority studies
- Evaluate whether a biosimilar is not clinically inferior to the
originator (thus, using only one margin)
- May be employed for assessment of biosimilars if the study
population and endpoint(s) are appropriate and sufficient
scientific justification is provided.

Current FDA Guidance

“A sponsor should provide adequate scientific justification for the
choice of study design, study population, study endpoint(s),
estimated effect size for the reference product, and margin(s)
(how much difference to rule out). Sponsors should discuss their
study proposal(s) and overall clinical development plan with FDA
before initiating the comparative clinical study(ies).”

Extrapolation of Indications for Biosimilars

- The FDA states that with sufficient scientific justification,
the potential exists for a biosimilar to be approved for
≥1 conditions of use for which the reference product is
approved based on extrapolation of data.

Extrapolation of efficacy and safety data to other
indications may be possible if:

- Biosimilarity has been clinically confirmed in a key indication
- A shared MOA for each indication has been shown between
the reference product and the biosimilar


So, the overall clinical design for biosimilars includes noninferiority
studies, which must show that the therapeutic endpoint is not
inferior to the originator.

A Closer Look at the Current Biosimilar Landscape in Rheumatoid Arthritis

Now, let’s take a closer look at the current biosimilar landscape in rheumatoid arthritis. This is a moving picture, a map of the world showing in the dark area that there are already approved biosimilars in much of the industrialized world. And particularly outside of the United States, they’re moving ahead at a more rapid rate with multiple biosimilars across multiple specialties, not just rheumatology. This is oncology and endocrinology and many other areas. And there are already biosimilar pathways being approved even in non-industrialized countries.

Dr. Calabrese: Share what you learn in this presentation with your colleagues. To post this presentation via Twitter, Facebook, LinkedIn, or e-mail, just select “Share This Presentation” from the menu in the upper left.

So, as of the time of this recording, we have three approved biosimilars in the rheumatology space. One is called CT-P13. The official FDA name would be the originator, infliximab, with a four-letter designation. That doesn’t mean anything, but it gives a unique status.

So this is infliximab-dyyb. So it was approved in April of 2016. Like infliximab, this TNF blocker is indicated for Crohn’s disease, pediatric Crohn’s disease, ulcerative colitis, rheumatoid arthritis, spondyloarthritis, psoriasis, and psoriatic arthritis. There were multiple randomized clinical trials. But if you actually look at the patient numbers—look at the Ns here—300, 174, and a small switch study of only 39 patients, [this pales in comparison to when a new biologic is needed]. The efficacy and safety were found to be noninferior, and in the safety bundle in particular, treatment-emergent adverse events were no more likely to be seen with a biosimilar, and especially immunogenicity, which has been a prevailing concern from a biologic perspective, was shown to be similar.
These are some additional ongoing registries and postmarketing studies which have added to the database of this biosimilar. In particular, the NOR-SWITCH study, which I’ll mention again, is a widely quoted study. The remainder of these registration studies are basically looking at ongoing treatment-emergent issues that may be of concern, and thus far none have been found.

And because it was noninferior in psoriasis, with an endpoint of a PASI-75, this is highly similar—not identical, but certainly noninferior by biostatistical standards—it was granted extrapolation for the other indications of etanercept. Also in this study, the safety was a major endpoint, and there was no difference in treatment-emergent adverse events leading to discontinuation.

A second approved biologic is a biosimilar etanercept-szsz. So it was approved in August of 2016. And similar to etanercept, it has broad approval in JIA, PsA, AS, and psoriasis, in addition to rheumatoid arthritis. There are three studies which examined basically [PK], safety, and immunogenicity—very small studies with just a few score of patients. And then a pivotal study—Study 302, with over 500 patients—done in psoriasis.

And because it was noninferior in psoriasis, with an endpoint of a PASI-75, this is highly similar—not identical, but certainly noninferior by biostatistical standards—it was granted extrapolation for the other indications of etanercept. Also in this study, the safety was a major endpoint, and there was no difference in treatment-emergent adverse events leading to discontinuation.

The third currently approved biosimilar was approved in September of 2016. This is biosimilar adalimumab, known as “atto.” It is a TNF blocker, which has broad approval indications of RA, JIA, psoriasis, spondyloarthritis, and a spectrum of spondyloarthropathy and inflammatory bowel disease.


This is a summary of the clinical database—again, a relatively small study of healthy subjects which established PK and immunogenicity. And then the comparator clinical trials, which looked at two diseases, RA and psoriasis, [with] varying doses based upon what is used with the originator compound.

And again, a summary of these data showed similar PK and the clinical studies next showed similar efficacy in rheumatoid arthritis after 6 months, similar efficacy in psoriasis after 1 year. And in these larger clinical studies, similar immunogenicity and similar safety. So, equivalent efficacy, safety, and immunogenicity, leading (via extrapolation) to approval.

ABP 501 Versus Adalimumab1-5

**Clinical Confirmation**
- **Similar efficacy**
  - RA 6-month study
  - PsO 1-year study
- **Similar safety**
  - RA – with MTX
  - PsO – without MTX
- **Similar immunogenicity**
  - RA and PsO
  - PsO includes transition to ABP 501


Finally, some practical considerations regarding this. There is some terminology that we need to understand. A lot of this is switching, substitution, interchangeability, and the rest of these, I think, have face validity, and you recognize cost and patient preference.

**NOR-SWITCH1**

<table>
<thead>
<tr>
<th>Patients With Disease Worsening By Condition, %</th>
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</thead>
<tbody>
<tr>
<td>All</td>
</tr>
<tr>
<td>RA</td>
</tr>
<tr>
<td>PsA</td>
</tr>
<tr>
<td>SpA</td>
</tr>
<tr>
<td>Infliximab (n = 241)</td>
</tr>
<tr>
<td>CT-P13 (n = 240)</td>
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</tbody>
</table>


I referred to the NOR-SWITCH study previously. This was a large study, 52 weeks of patients receiving infliximab. Halfway, they were randomized to stay on branded infliximab or switch to the biosimilar. And the primary outcome was disease worsening at 12 months, and then immunogenicity was a secondary endpoint. And as you can see, virtually no difference in efficacy or immunogenicity, and this has been used as one of the most impressive studies that at least a single switch is possible.
Where will biosimilar cost savings accrue? This is kind of a crystal ball at the present time. Most people are putting their money that it will be insurers, outpatient facilities, office settings—so they're physician-administered. Insurance companies will do well.

Patients? This remains to be seen. If I have a patient that tells me that there is a biosimilar that they have been told that they will get a rebate on if they switch to this, and there's no medical contraindications, I would be all for it. I have yet to see this in my practice at the present time.

<table>
<thead>
<tr>
<th>Setting</th>
<th>Self-Administered From Retail or Mail-Order Pharmacy</th>
<th>Physician-Administered Inpatient Facility Setting</th>
<th>Outpatient Facility Setting</th>
<th>Office Setting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insurers</td>
<td>++</td>
<td>+</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Facilities</td>
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<tr>
<td>Physicians</td>
<td>NA</td>
<td>NA</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>Patients</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>+</td>
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</table>

**Interchangeability**

**SEC. 7002. Approval Pathway for Biosimilar Biological Products**

(a) Licensure of biological products as biosimilar or interchangeable. —Section 351 of the Public Health Service Act (42 U.S.C. 262) is amended—

“The term 'interchangeable' or 'interchangeability,' in reference to a biological product that is shown to meet the standards described in subsection (k)(4), means that the biological product may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product.”

Lastly, interchangeability. Interchangeability means that a biosimilar can be substituted for the reference product by [someone] other than the clinician. That could be a pharmacist, it could be an insurance company. In other words, you lose control as a clinician of doing this. We all have concerns over this because down the pike here a few years, there may be four biosimilars for etanercept; what would be the consequences of switching from biosimilar 1 to biosimilar 3 to biosimilar 2 to biosimilar 4? We don't know.
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The Ongoing Issue of Interchangeability\(^1,2\)

- In January 2017, the FDA released draft guidance regarding biosimilar interchangeability, recommending that sponsors conduct ≥1 switching studies to demonstrate safety and efficacy in patients alternating between the 2 products.
- However, requirements will vary based on the nature of the proposed interchangeable product and may include, but need not be limited to, an evaluation of data and information generated to support a demonstration of a biological product’s biosimilarity.

Impact of Interchangeability on Prescribing Practice\(^1,2\)

- Currently, biosimilars are not interchangeable with traditional or generic medications.

If deemed interchangeable with original brands, branded scripts could be filled with biosimilars without the prescribing doctor’s approval, similar to generic versions of traditional medications.

This is much, much different, obviously, to generic drugs, where repeated switching back and forth has been clearly demonstrated to be both safe and effective.

Conclusions

- Biosimilars are not generic, but highly similar drugs with similar efficacy, safety, and immunogenicity.
- Approval process is generated on a “totality of evidence,” with an inverted trial design:
  - Ex vivo and analytics are more involved and relied upon than clinical pivotal studies.
- Biosimilars for RA have been recently approved and more will likely become available in the near future, impacting clinical decisions.

So, let me conclude by making a few points here. The first and foremost, biosimilars are not generic, but highly similar drugs with similar efficacy and toxicity. That’s what it requires to be a similar. This approval process is generated on something that we refer to as a totality of evidence, with an inverted trial design, where ex vivo and analytics are more involved and relied upon more than clinical pivotal studies. Biosimilars are here to stay, and the field is fast, and moving rapidly, and we as clinicians need to keep up on all of these data.

My takeaway points are, I am in favor of biosimilar use in my practice. I have not used any biosimilar at the present time. I am pretty convinced that single switching seems safe and effective. I am not sold that interchangeability has been demonstrated, and I am glad that there is a high bar for this. I am eager to see more data in this space and try to keep up with this.

So, finally, again, I’d like to thank you for your attention. I would encourage you to tell your colleagues about this program. Just select “Share This Presentation” from the menu in the upper left, and they’ll be able to join in this learning experience. Thank you.

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