Biosimilar Agents: Benefits, Emerging Therapies, and Their Safety

Executive Summary

Rheumatoid arthritis is a debilitating autoimmune disease characterized by painful joints and stiffness that can substantially decrease a patient's quality of life.[1-2] Biologic agents can be effective but are often cost prohibitive, reducing access and treatment adherence in some patient populations.[1, 3-4] Biosimilars can be more cost effective for many patients,[5] but their adoption into the clinic in other countries has been slow due to negative attitudes among clinicians.[6-7] Biosimilar agents are much newer to the United States, but early studies suggest that physicians possess a similar negative attitude that could impede their incorporation into the clinic.[3, 8] This negative perception is fueled by a lack of general knowledge about biosimilars, an unawareness of available and emerging agents, and a gap in understanding about their approval process.[8] Rheumatologists require more extensive education about biosimilars to increase adoption of the agents in the clinic and improve overall patient care. The proposed educational initiative will provide an expert-led review and evaluation of available and emerging biosimilar agents, their benefits to patients, and the rigors involved in their approval process. This information will help rheumatologists better understand biosimilar agents and how to implement them into patient care.

Practice Gaps and Learning Objectives

Background

Rheumatoid arthritis is a systemic autoimmune disease impacting over 1.3 million Americans and as much as 1% of the population worldwide.[1-2] The disease is characterized by joint pain and stiffness, and it can have a significant and negative impact on the quality of life in many patients.[1] In fact, pain associated with the disease may contribute to their higher likelihood of unemployment, particularly for patients that previously held physically demanding jobs.[9] Rheumatoid arthritis also puts patients at an increased risk of developing additional chronic diseases, like diabetes or heart disease.[9]

Biologics are one effective treatment for rheumatoid arthritis, particularly in patients that do not respond well to traditional disease modifying antirheumatic drugs.[10] However, the cost of biologic agents can be prohibitive to many patients, and introduction of biologic agents has led to an overall increase in the costs associated with treating rheumatoid arthritis. Studies have estimate that the direct costs per rheumatoid arthritis patients on biologics fall between $10,000 to $30,000 a year compared to only $3,000 a year with patients on more conventional treatments.[1]

Biosimilar agents are more cost effective and therefore could help improve treatment access and adherence for many rheumatoid arthritis patients.[1, 3-4] However, biosimilar agents are not exact copies of their biologic originators. Biologic agents are derived from living organisms and are consequently prone to complex posttranslational modifications

and other natural variations.[4, 11] These variations are often subtle and can even change between separate commercial batches of the same product, especially in monoclonal antibodies, fusion proteins, and other large and particularly complex molecules.[4,12] Creating an exact chemical copy of these extremely complex biologic agents is next to impossible. However, biotechnological advances have enabled replicas that while not exact, are extremely similar to the original biologic agents and have comparable efficacy and safety profiles.[4] Some experts predict that the introduction of these biosimilar agents could lead to a reduction in spending on biologics by as much as $44.2 billion from 2014 to 2024.[5] These biosimilar agents could therefore drastically reduce the cost of treatment for many patients while helping to improve access and overall treatment adherence.[1, 3-4]

Biosimilars have been available in South Korea since 2012 and the European Union since 2013 but were not available in the United States until much more recently after the expiration of several patents for major biologic agents. Additional patents for biologic agents are set to expire in the near future, paving the way for the widespread introduction of biosimilars.[3, 13-14] Infliximab-dyyb (CT-P13), a biosimilar of the monoclonal antibody (mAb) infliximab, was the first biosimilar introduced to the clinic for the treatment of rheumatoid arthritis in 2016.[13] Other agents are expected to receive FDA approval in the near future, including the adalimumab biosimilar adalimumab-atto (ABP 501)[15] and the etanercept biosimilar GP2015.[16] In fact, over 700 biosimilars are in the developmental pipeline wordwide,[16] underscoring the rapidly changing landscape of biosimilar agents.

However, physician acceptance and adoption of biosimilars in the clinic has been very slow throughout the rest of the world, in part due to a lack of general understanding about biosimilar agents, an inability to keep up-to-date with the rapidly changing treatment landscape, and a distrust of biosimilar agents and their approval process.[1,6,14,17] Early studies suggest physicians in the United States may exhibit a similar reluctance to incorporate biosimilar agents into their practice.[8] Rheumatologists are uniquely positioned to prescribe biosimilar agents to rheumatoid arthritis patients, and early education about general biosimilar concepts, available and emerging biosimilar agents, as well as information about the safety and approval process for biosimilars could improve their adoption in the clinic.

Practice Gap #1: Physicians are largely unfamiliar with general concepts and benefits associated with biosimilar agents.

Physicians in countries where biosimilars have been available for longer have a significant gap in their general understanding of the agents. One study that surveyed 222 rheumatologists across 11 countries in the European Union found that 97% of respondents claimed they were familiar or very familiar with biosimilars. However, follow-up questions revealed that less than half of physicians were able to correctly define a biosimilar.[6] Another study that surveyed 470 physicians in Europe revealed that

only 22% were familiar with biosimilars, 54% had a limited understanding, and 24% had never even heard of them.[18] Meanwhile, a separate survey of 81 rheumatologists in Canada found that 2/3 of physicians were unfamiliar with biosimilar agents.[4]

Since biosimilars are much newer to the United States, fewer studies have examined physician knowledge and attitudes about the agents. However, existing studies show a similar trend. One extensive survey of over 1200 physicians in different specialties throughout the United States found that a significant minority of rheumatologists was unfamiliar with biosimilar agents. For example, 15% of rheumatologists had either not heard the term "biosimilar" in their practice for over a month or were completely unfamiliar with the term.[8] Physicians also showed a general lack of knowledge about biologic and biosimilar agents. For example, 15.8% of rheumatologists were unable to correctly identify biologic agents from a list of drugs commonly used in their practice. This is especially concerning since respondents reported that they commonly prescribed biologic agents to their patients.[8] The study identified defining biologics, biosimilars, and biosimilarity as one of the major existing gaps in physician knowledge about the drugs.[8]

Rheumatologists may also not be fully aware of the benefits of biosimilar agents. For example, the same study found that 56.5% of rheumatologists had concerns about patient compliance or access to treatment with current biologic options.[8] However, 65.5% of the same rheumatologists were unwilling to prescribe biosimilar agents to either their new or existing patients.[8] Education about the potential cost benefits of biosimilar agents could help improve their adoption into the clinic since biosimilars are thought to make treatment less cost prohibitive and therefore may improve treatment access and adherence for many patient populations.[1, 3-4]

This collective evidence suggests that rheumatologists could largely benefit from general education and background about biosimilar agents and their benefits. Increased familiarity with general concepts could reduce negative perceptions surrounding the agents and improve patient care by helping physicians identify patient populations best suited to biosimilar treatments.

Learning Objective #1: Review biologic and biosimilar definitions, general biosimilar concepts, and the benefits associated with biosimilar treatment.

Practice Gap #2: Physicians may struggle with the rapidly shifting landscape of biologic treatments for rheumatoid arthritis.

The number of available biologic treatments for rheumatoid arthritis is rapidly growing. The patents for several major biologic agents have already expired and more patents are set to expire in the near future.[14] Biotechnological advances have meanwhile enabled the development of compounds that are near copies to major original biologics, like the originators infliximab, adalimumab, rituximab, and etanercept. These biosimilar agents possess similar efficacy and safety profiles to the originators[14] and could help to

dramatically reduce the cost of arthritis treatment for many patients.[3] Consequently, over 700 biosimilars are in the developmental pipeline wordwide,[16] and several of the most promising of these agents are already on the market in the United States or are currently in the pipeline for FDA approval.[3]

However, many physicians remain unaware of available and emerging biosimilar agents. In fact, a recent survey of over 1200 physicians across different specialties in the United States found that 55.5% of rheumatologist respondents were not aware that any biosimilars have been approved in the United States.[8] Continuing medical education about available and emerging biosimilar agents could help physicians navigate the quickly changing landscape of biologic treatments for rheumatoid arthritis.

For example, there are several thoroughly studied biosimilar agents of the monoclonal antibody infliximab. The biosimilar infliximab-dyyb (CT-P13) was the first monoclonal antibody biosimilar to receive FDA approval last year and represents the second biosimilar on the US market and the first with an indication for rheumatoid arthritis.[13] Extensive studies have shown that it has a comparable safety, efficacy, and immunogenicity profile to the originator.[3, 19-20] It has also been approved in South Korea since 2012 and the European Union since 2013, providing additional real-world support of its safety and efficacy.[3]

Infliximab biosimilars still in the pipeline for approval in the United States include PF-06438179 and SB2. Previous clinical studies with the biosimilar PF-06438179 show a similar safety, tolerability, and efficacy profile to the originator.[21] An ongoing phase 3 study is comparing the drug to the originator in patients with an inadequate response to methotrexate alone. Initial results are consistent with previous investigations and suggest a comparable efficacy between the biosimilar and the originator.[22] Ongoing studies on the biosimilar SB2 also suggest similar efficacy and safety outcomes to the originator.[23] The FDA recently agreed to review an application for SB2 in the treatment of rheumatoid arthritis and other conditions.[23] Conversely, the infliximab biosimilar BOW015 was recently discontinued despite initial evidence of similar safety outcomes to the originator.[23]

There are also a number of biosimilars in the pipeline for the monoclonal antibody originator adalimumab. One includes adalimumab-atto (ABP 501), which received a unanimous recommendation from the FDA's Arthritis Advisory Committee (AAC) for approval last year.[15] The committee also supported the use of the biosimilar for each of the originator's currently approved indications.[15] There are also several biosimilars in earlier stages of the pipeline. A recent update of on the ongoing phase 3 study for PF-06410293 reported that the drug has already met its primary objective by showing equivalent efficacy to the originator.[24] Meanwhile, GP2017 also recently demonstrated similar efficacy, safety, and immunogenicity to its originator in a phase 3 study.[25] Ongoing work with SB5 similarly indicates comparable results to the originator in trials, but less work has been done with the biosimilar ZRC-3197.[23]

There are also biosimilars in the pipeline for the originator rituximab. One prospective is the biosimilar PF-05280586, which is showing comparable profiles to the originator in structural, functional, nonclinical tolerability, pharmacokinetic, and toxicity studies as well as in clinical studies.[23, 26-27] Meanwhile, GP2013 also shows significant promise and has had similar profiles to the originator in preclinical and more recent clinical studies.[23,28] Similar results have also been seen for CT-P10,[23,29-30] while RTXM83 is still in early developmental phases.[23]

There are also available and emerging biosimilars for etanercept. Studies show the biosimilar GP2015 has bioequivalence to the originator, and the drug is currently under regulatory review by the FDA.[23, 28, 31-32] The drug received an unanimous recommendation for approval from the FDA's AAC last year and the committee also voted that presented evidence supported the use of the biosimilar for all the originator's currently approved indications [15,23,32] Similarly, phase 3 clinical studies with SB4 support a comparable safety profile to the originator.[33-34] Less work has been done with AVG01 and LBEC0101, though existing data also suggest comparable safety profiles to the originator. Initial clinical work in ENIA11 and HD203 also show similar profiles to entanercept.[23]

Given the new biosimilars on the market and the many emerging biosimilar options, continuing medical education could help physicians navigate a rapidly changing landscape. Indeed, 47.7% of respondents in the United States survey of physicians from different specialties expected continuing medical education to be an important source of reliable information about new biosimilars as they arrive on the market.[8]

Learning Objective #2: Discuss available and emerging biosimilar treatments.

Practice Gap #3: Physicians are unfamiliar with how biosimilars are approved by the FDA and therefore may distrust them.

Many physicians continue to distrust the efficacy and safety of biosimilar agents despite the rigors of the FDA approval process for the agents.[8] For example, in a pre-assessment for an online continuing medical educational activity, 25% of clinician respondents said they were only somewhat confident in the safety and efficacy data for infliximab-dyyb (CT-P13) and 19% said they were not confident in the data,[35] despite the fact that extensive research has been done on the safety and efficacy of the FDA-approved drug. Similarly, the aforementioned extensive study of over 1200 physicians in the United States revealed that 65.5% of rheumatologists disagreed that biosimilars would be safe and appropriate to prescribe to their new and existing patients.[8]

Part of the reason for this general distrust in the safety and efficacy of biosimilars may be a lack of understanding of the rigors involved in the FDA approval process. The same survey of physicians throughout the United States found that respondents across all

disciplines were largely unfamiliar with FDA requirements for the approval of biosimilars. For rheumatologist respondents, 41.5% did not know that biosimilars have to possess equivalent efficacy to the originator biologic and 44% did not understand that biosimilars have to be at least as safe as the originator counterpart to receive FDA approval.[8]

Respondents were also unfamiliar with core concepts involved in the approval process for biosimilar agents. For example, about half of respondents in the same study were unfamiliar with "totality of evidence," the process by which the FDA assesses and approves biosimilar agents.[8] In this approach, authorities base their decision on all available data. This could include characterization of the drug on a molecular and functional level, its immunogenicity, clinical studies, pharmacokinetics, and even nonclinical studies.[23] This concept may be unfamiliar to physicians because the approval process for different indications for the majority of drugs is not based on nonclinical or analytical data.[8] Similarly, only 12% of surveyed respondents were familiar with the concept of data extrapolation, or the process by which the FDA can use the totality of data to approve a biosimilar for other indications covered by the originator.[8] Likewise, survey respondents were unfamiliar with the FDA requirements for a biosimilar to be interchangeable with the originator. Over 42% of rheumatologists did not understand that studies had to demonstrate that a biosimilar was as safe and effective without any negative efficacy or safety impacts to be interchangeable.[8] Furthermore, over 75% of rheumatologists were not aware that pharmacists could dispense interchangeable biosimilar products in place of the originator or vice versa.[8] This is in direct opposition to a study where 74.6% of surveyed pharmacists reported they would be confident or very confident dispensing an interchangeable biosimilar for a biologic.[36]

Physicians throughout the United States may also recognize this knowledge gap and want to know more about biosimilar safety. When physicians in the United States survey were asked which topics they were interested in learning more about, 76% expressed an interest in the safety, efficacy, and potency of biosimilars, 38.9% expressed interest in better understanding the FDA approval process, and 48% wanted to know more about the extrapolation of indications.[8]

Similar statistics are seen in other parts of the world where biosimilars have been on the market for much longer. For example, one study that surveyed 222 rheumatologists across the European Union found that 65% of respondents had limited or no knowledge of how biologics were manufactured.[6] Similarly, a multi-country survey of 173 rheumatologists found that 53% of respondents listed inadequate safety data and 46% listed a lack of long-term data among the top reasons for not prescribing biosimilars to patients.[17] The unfamiliarity with regulations and manufacturing of biosimilars in countries where biosimilars have been approved and utilized by physicians for much longer highlights the importance of educating physicians in the United States early. Providing medical education about biosimilars, their regulations, and the approval process could help physicians feel more comfortable prescribing the medications as

more are introduced to the market. Education about the rigors of the FDA approval process may improve physician comfort with biosimilar agents and facilitate their incorporation into the clinic, ultimately improving patient access and adherence to treatment.

Learning Objective #3: Review the FDA approval process and requirements, including the concept of totality of evidence, the rationale for extrapolation of indications, and requirements of interchangeability.

Proposed Agenda

AGENDA

5 minutes	**Activity overview** **Pre-activity assessment**
10 minutes	**Introduction** --Introduction to biologic agents for rheumatoid arthritis --Introduction to biosimilar agents --Overview of the benefits of biosimilar agents
20 minutes	**Overview of Available and Emerging Biosimilar Agents** --Biosimilars of infliximab, adalimumab, rituximab, and etanercept
20 minutes	**Overview of Regulations and the Approval Process for Biosimilars** --Review the FDA approval and the concept of totality of evidence --Rationale for extrapolation of indications --Overview of Interchangeability
5 minutes	**Activity summary** **Post-activity assessment**

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