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The rise of biosimilars: Balancing innovation with affordable biologic alternatives

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Abstract--Background: Biologics have transformed the management of immune-mediated inflammatory conditions, such as rheumatoid arthritis (RA) and inflammatory bowel disease (IBD). The introduction of biosimilars—biologic medications that are highly similar and interchangeable with approved originators—has the potential to enhance market competition and improve patient access to necessary therapies. Aim of Work: This review aims to highlight the importance of collaboration among stakeholders to optimize the benefits of biosimilars and expedite their availability to patients while ensuring safety, quality, and effectiveness. Methods: The review analyzes regulatory frameworks, market dynamics, and pharmacoeconomic assessments regarding the introduction of biosimilars. It emphasizes the role of effective communication between physicians and patients, as well as the necessity for consistent treatment recommendations and reimbursement policies. Results: The findings indicate that collaboration between regulators and developers is essential to ensure

the quality and safety of biosimilars. Updating pharmacoeconomic assessments and payer policies is crucial to prevent nonmedical barriers to access. Enhanced understanding of biosimilars by patients is vital to reduce nocebo effects, while well-informed physicians can guide patients effectively through treatment transitions. Conclusion: To maintain a sustainable biosimilar market and healthcare systems, stakeholders must prioritize collaboration, operations efficiency, and information exchange. This approach will facilitate access to effective therapies for patients, improving outcomes in the treatment of RA and IBD.

Keywords---Biologics, Biosimilars, Rheumatoid Arthritis, Inflammatory Bowel Disease, Stakeholder Collaboration.

Introduction

Biosimilars are biologic medications that are essentially identical to the original biologics (reference products [RPs]) that have previously been approved by regulatory authorities, with no significant variations in terms of clinical effectiveness. Regulatory proteins (RPs) have shown effectiveness in several medical conditions and have significantly transformed the management of immune-mediated inflammatory disorders (IMIDs), such as rheumatic illnesses like rheumatoid arthritis (RA) and inflammatory bowel disease (IBD) [1-3]. The European Medicines Agency (EMA) and the United States (US) Food and Drug Administration (FDA) have granted licenses to many biosimilars for the treatment of rheumatoid arthritis (RA) and inflammatory bowel disease (IBD) (Fig. 1). Additionally, there are around 240 biosimilar candidates now being developed for various illnesses [4]. The use of biosimilars is expanding worldwide, with clinical exposure already surpassing 700 million patient-days [5]. Additionally, there is a rising trend of adopting biosimilars [6-8]. In 2017, infliximab and etanercept biosimilars accounted for 79% and 54% of the UK market share, respectively [7].

Biosimilars, due to their lower cost compared to reference products (RPs), may stimulate market competition, leading to budget sustainability and enhancing patient accessibility to biologic therapies. Recent projections indicate that biosimilars might lead to significant cost reductions worldwide. One estimate is that the USA could potentially lower direct expenditure on biologics by \$US54 billion from 2017 to 2026 due to the availability of biosimilars [9]. Within the European Economic Area, the presence of biosimilar competition has already led to a decrease in the average costs listed for biologics and an increase in patient availability [10]. The accumulation of empirical data from biosimilars [11-13] is bolstering their clinical use and enhancing trust in their efficacy. Nevertheless, a significant number of patients continue to get treatment using reference products (RPs), perhaps due to persistent apprehensions among physicians and patients about biosimilars.

Aim of Work

This article aims to use our extensive and varied expertise to provide a concise overview of our different and up-to-date viewpoints on the future of biosimilars in immune-mediated inflammatory diseases (IMIDs), with a specific emphasis on rheumatoid arthritis (RA) and inflammatory bowel disease (IBD). In addition, we analyze the barriers that hinder the broad use of biosimilars and propose strategies to optimize the advantages of biosimilars for healthcare systems and patients in the long run.

Perspectives from regulators and pharmacologists: The rigorous and efficient development of biosimilars

The regulatory clearance of biosimilars relies on the comprehensive body of evidence that demonstrates the comparability between the proposed biosimilar and the reference product [14]. Prior to biosimilar production, it is necessary to establish the specified quality characteristics of the reference product (RP), including its structural, functional, and other analytical aspects. In order to determine the quality target product profile of the proposed biosimilar, it is necessary to assess the range of variation for any feature that directly affects its effectiveness or safety. This may be done by carefully measuring numerous medication batches, which are considered essential quality attributes. [15-17] For instance, the essential characteristics that determine the quality of infliximab, which is the reference product for the biosimilar CT-P13, are numerous and encompass aspects such as the structure (both primary and higher-order structures, as well as glycosylation profiles), biological function (including receptor-binding affinity and cytotoxicity), content (specifically protein concentration), and impurities (such as host cell protein or DNA) [15].

The manufacturing procedures for biosimilars must be reverse engineered due to the lack of publicly accessible information on the reference products (RPs). The choice of the expression system, including the cell line and expression construct, is a crucial decision. This selection may impact the translational and post-translational alterations of biosimilars, as well as define the quantity and characteristics of impurities and contaminants in the final product [18]. The cell culture and product purification methods need to be systematically improved until the product achieves the desired characteristics [15, 17]. Subsequently, it is necessary to verify and meticulously regulate manufacturing procedures to guarantee the consistent production of a biosimilar candidate with the specified characteristics [15].

The process of demonstrating biosimilarity requires a systematic approach, following a sequence of steps that go from analytical analysis, to nonclinical investigations, and finally to clinical trials. This strategy is advocated by regulatory authorities such as the EMA and FDA [19, 20]. The majority of the effort in biosimilar development is dedicated to analytical analyses [21, 22]. By utilizing a combination of advanced methodologies that are independent and complementary, it is possible to accurately determine the level of similarity in critical quality attributes between the proposed biosimilar and the reference

product (RP) [14, 23]. Unfortunately, existing approaches are insufficient in providing comprehensive information on biosimilarity at the nonclinical stage. For instance, there is a lack of techniques to study how variations in post-translational modifications, like glycosylation, can affect the three-dimensional structure and function of proteins [24]. However, advancements in fields like mass spectrometry may potentially address these concerns in the future [25].

In nonclinical assessments, any differences that are found must be shown to have no clinical significance. The amount and kind of clinical evidence needed for approval will depend on the doubts that still exist over the similarity of the biosimilar [20]. Unlike clinical studies for novel medications, biosimilar clinical trials are specifically intended to determine the equivalence of pharmacokinetics and effectiveness between the proposed biosimilar and the reference product (RP). Additionally, these trials aim to show that the biosimilar and RP have comparable pharmacodynamic, immunogenicity, and safety profiles [14, 17]. The EMA guidelines, which align with FDA principles, typically advise that biosimilar trials incorporate a direct comparison of pharmacokinetics and pharmacodynamics, followed by at least one sufficiently powered, randomized, parallel-group, head-to-head comparison of effectiveness and safety [14, 19, 20]. Typically, equivalence studies, as opposed to noninferiority studies, are necessary to demonstrate that the proposed product is neither inferior nor superior to the reference product. Noninferiority trials may be appropriate in some situations, particularly when the RP dosage is nearing saturation of the target [20]. In order to determine the equivalence or noninferiority margins for the RP, it is necessary to take into account the variability in historical data. These margins represent the tolerable changes in effectiveness from a clinical standpoint [26, 27]. The sample size should be sufficient to identify significant differences of clinical importance between biosimilar and reference product (RP), and it may be lower in a noninferiority trial compared to an equivalence study [20]. Equivalence or noninferiority studies favor per-protocol analysis over superiority trials because it is more cautious and conservative compared to intention-to-treat analysis [28, 29].

The participants selected for a clinical trial evaluating the effectiveness of a biosimilar should typically have the same medical condition(s) as those for which the reference product is authorized. Additionally, they should be the most responsive to any possible variations between the two medications [19, 20]. Nevertheless, psoriasis serves as a valuable disease model for identifying potential variations in the clinical effectiveness and immunogenicity of adalimumab biosimilars compared to the reference product (RP). However, ongoing pivotal studies tend to focus more on patients with rheumatoid arthritis (RA), which may be attributed to the larger patient population and the potential commercial significance of RA [30]. The presence of high and unpredictable placebo response rates in ulcerative colitis (UC) might complicate the selection of this indication for biosimilar studies. The selection of endpoints in biosimilar clinical trials should be suitable and sufficiently responsive to identify any possible disparities between the reference product (RP) and the proposed biosimilar. The evaluation of CT-P13 in IMiDs involved the assessment of multiple endpoints in the PLANETRA equivalence study. These endpoints included the Disease Activity Score in 28 joints (DAS28) based on C-reactive protein (CRP), as well as the response rates

according to the American College of Rheumatology and European League Against Rheumatism (EULAR) criteria. The results showed that CT-P13 and the reference infliximab were highly similar in terms of these endpoints at week 30 [31-33]. The postmarketing phase III PLANETCD study compared CT-P13 and reference infliximab in patients with Crohn's disease (CD). The study used a primary endpoint based on the Crohn's Disease Activity Index [34]. In contrast, two cohort studies comparing these agents in patients with either CD or UC used composite primary endpoints. These endpoints included death, CD-related surgery, all-cause hospitalization, and reimbursement for other biologics [35, 36]. The PLANETCD research used the sensitive goals of endoscopic remission/mucosal healing as a tertiary effectiveness objective. These endpoints have previously been evaluated in prospective observational studies of CT-P13 therapy in patients with UC [37-39]. An essential aspect of evaluating the safety and effectiveness of biosimilars is the assessment of immunogenicity, as outlined in the recommendations provided by the FDA and EMA [20, 40]. Anti-drug antibodies (ADAs) may impact the effectiveness of biologic treatments by altering how they are processed in the body, or they might have negative effects on safety, leading to responses during infusion and serum sickness. These repercussions have been shown in studies [41, 42]. Immunogenicity risk is influenced by several variables, one of which is post-translational changes such as glycosylation, as mentioned in a recent study [43]. Despite the fact that glycosylation is a frequent point of difference between biosimilars and reference products (RPs), there have been no inconsistencies in terms of immunogenicity for any biosimilar authorized by the European Medicines Agency (EMA) [43]. The development and validation of immunogenicity assays must adhere to a strict methodology, in accordance with the comprehensive regulatory guidelines [44, 45]. When evaluating the applicability of an assay, it is important to compare alternative technologies, as was done with CT-P13 [46]. Nevertheless, there is ongoing discussion about the most effective way to design assays, and the use of different assays has resulted in significant differences in reported immunogenicity. This has made it difficult to compare studies with each other. For example, a systematic review of infliximab treatment revealed that the percentage of patients testing positive for ADA ranged from 0% to 65.3% in different reports.

Immunogenicity tests may be complex due to challenges encountered. Additionally, selecting suitable pharmacodynamic markers for some biologics might be problematic due to uncertainties in their mode of action. For instance, the intricate nature of tumor necrosis factor (TNF) signaling has resulted in a limited understanding of how TNF inhibitors work, especially in the context of inflammatory bowel disease (IBD) [47]. This is in contrast to the well-established understanding of how rituximab effectively depletes cluster of differentiation 20-positive (CD20+) B cells in rheumatoid arthritis (RA) [48]. Multiple pharmacodynamic indicators should be used in clinical trials that evaluate TNF inhibitors. The selection of targets, assay types, and techniques should be determined on a case-by-case basis. In rheumatoid arthritis (RA), it may be necessary to use a method that combines the assessment of biomarkers that indicate immunological and inflammatory processes. These biomarkers include rheumatoid factor and anticyclic citrullinated peptide, as well as CRP (C-reactive protein) and erythrocyte sedimentation rate [49].

The regulatory agency recommendations for biosimilar development are generally in agreement scientifically and suggest a sequential approach to conducting analytical, nonclinical, and clinical trials. However, there are differences in the specific needs and interpretations of data across different agencies [50, 51]. For instance, the FDA mandates a minimum of one clinical pharmacokinetic study that includes the version of the reference product (RP) authorized in the United States. In contrast, Swissmedic, the regulatory agency in Switzerland, favors comparability studies that utilize the RP from Switzerland. Additionally, Health Canada offers supplementary instructions to developers who choose a non-Canadian RP. [20, 52, 53] Regulatory authorities may also mandate studies that provide evidence for the extension of clinical data to patients from diverse ethnic backgrounds. In order for the Japanese regulatory authority to assess the effectiveness and safety of CT-P13, a drug used to treat rheumatoid arthritis, they conducted a study that compared its pharmacokinetics, effectiveness, and safety to that of the reference drug infliximab. This study was performed on Japanese patients with rheumatoid arthritis. Additionally, they conducted an extension study to evaluate the long-term safety of CT-P13 and its safety when patients switched from using the reference drug. Geographical differences in regulatory requirements may cause some doctors to be hesitant in completely embracing biosimilars in their clinical practice. This hesitation is further influenced by worries about extrapolating indications, as shown in the case of IBD [3].

Regulatory authorities advise biosimilar makers to synchronize their development plans with the particular requirements of each agency and engage in ongoing talks with the agencies throughout the development process of each biosimilar [54]. This is done to reduce inefficiencies and avoid delays. An effective biosimilar development strategy should include techniques to adequately monitor the clinical safety of the product and avoid any possible shortages in medication supply following its approval [55]. Efficient oversight of the biosimilar supply chain is crucial to prevent shortages of products, which might jeopardize patient safety and clinical results, and may arise from manufacturing problems, supply delays, or other interruptions [55]. When applying for biosimilar approval, the EMA mandates the inclusion of a risk management strategy and pharmacovigilance system. These should include the identification of hazards and the monitoring procedures unique to the RP [19]. In the United States, the FDA has the authority to require the establishment of a risk assessment and mitigation plan for authorized biosimilars, comparable to any other medicine [56].

Biosimilar developers should be aware of potential future modifications in approval paths, as regulatory agencies strive to simplify and expedite the development and review procedures for medical goods, such as via the implementation of the US 21st Century Cures Act [57].

Pharmacoeconomists in light of biosimilars

Biologics incur substantial expenses for the treatment of both rheumatoid arthritis (RA) and inflammatory bowel disease (IBD), resulting in restricted patient accessibility due to their high pricing. Nevertheless, the expiry of patents for biologics has facilitated the creation of more affordable biosimilars, resulting in heightened competition in the market and subsequent decreases in prices [7].

Initial pharmacoeconomic evaluations in patients with rheumatoid arthritis (RA) indicated that TNF inhibitors were not cost-effective compared to conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) for patients who were either new to treatment or had an inadequate response to csDMARDs [58]. Nevertheless, these assessments were conducted prior to the introduction of biosimilars onto the market, so failing to account for the influence of biosimilars on price competition and the resulting decrease in treatment expenses and increased availability for patients [59]. Biosimilars, market competition, and price reductions enhance the cost-effectiveness of biologic treatment in rheumatoid arthritis (RA). Available evidence in the field of IBD indicates that biosimilars have the capacity to provide financial benefits and enhance patient availability to biologics. Furthermore, it is anticipated that cost-effectiveness studies would be regularly revised. Researchers are currently investigating the cost-effectiveness of early biologic treatment in inflammatory bowel disease (IBD) [60]. A model based on data from the CALM trial in Crohn's disease (CD) demonstrated that "tight control," which involves using biomarkers to guide adalimumab treatment, was more cost-effective than standard clinical management over 2- and 5-year periods. The cost-effectiveness of this approach improved over time [60].

The use of biosimilars may also result in indirect economic advantages, which are often overlooked in cost-effectiveness evaluations [61]. Early therapy with disease-modifying antirheumatic drugs (DMARDs) or biologics may significantly enhance worker productivity in rheumatoid arthritis (RA), resulting in economic advantages for both people and society. Future cost-effectiveness evaluations should strive for maximum accuracy by integrating the most relevant information and being continuously updated. It has been acknowledged that it is important to reassess economic analyses after the availability of cancer biosimilars [62]. Erroneous price data may result in adverse cost-effectiveness assessments, which might limit patient access to therapy.

According to budget impact estimates, the adoption of biosimilars is expected to result in substantial cost savings, lower the cost of treating illnesses, and improve patient access to these medications [63]. According to one research, the implementation of CT-P13 in six European nations might result in a total savings of €15.3 million over a period of 3 years. This savings could increase to €20.8 million if 80% of patients already receiving infliximab also transition to CT-P13 [63]. The potential budget increases resulting from expanding patient access to biologics and providing additional services for patients must be carefully considered in light of the cost savings. In the analysis mentioned earlier, the cost savings achieved through the uptake of CT-P13 could be allocated to treat an additional 1200-1800 patients over a span of 3 years. In some countries, cost reductions may also facilitate early availability of biologics [64]. Redirecting cost savings towards new services might enable the use of therapeutic drug monitoring (TDM) to enhance the effectiveness of TNF inhibitor medication and provide tailored care for patients with inflammatory bowel disease (IBD) [65]. TDM entails the quantification of drug and ADA concentrations. The development of ADA is often linked to diminished primary effectiveness and a decline in response to IBD therapy [50]. Factors such as medication clearance and body weight may be used to anticipate the occurrence of ADA formation [66]. Implementing proactive TDM may have positive effects on long-term results [15,67]. Nevertheless, the TAXIT

and TAILORIX studies did not see any advantage in terms of clinical remission rates. However, it is worth noting that the high frequency of dosage intensification in the TAILORIX clinical care group could account for this outcome [68]. At now, proactive therapeutic drug monitoring (TDM) is only done in a small group of patients with inflammatory bowel disease (IBD) who are taking TNF inhibitors. It is not often advised unless it is expected to have an influence on clinical care. However, cost-effectiveness evaluations have shown that proactive TDM has advantages. Furthermore, the enhanced cost-effectiveness of biosimilars compared to biologics should support the integration of these drugs into clinical trials.

The actual cost reductions resulting from the use of biosimilars align with the previously estimated predictions. During the 2017-2018 fiscal year, the UK National Health Service achieved a cost savings of £324 million by transitioning to biosimilars or generics for eleven medications. A significant portion of these savings, amounting to about £100 million, was attributed to the adoption of infliximab biosimilars [69]. Similarly, a study examining rheumatology specialties in the UK from 2014 to 2017 found that the introduction of infliximab and etanercept biosimilars resulted in a savings of £38.8 million over a span of 2 years. This was due to the increased usage of biosimilars and the subsequent drop in the price of reference products [70]. Biosimilar availability in Scandinavian nations has resulted in substantial cost reductions and increased patient access to biologics, even though these countries already have high use rates [10, 65]. Since 2014, the majority of newly diagnosed IBD patients in Norway have been treated with biosimilar infliximab. Additionally, patients who were previously receiving infliximab maintenance therapy have now transitioned to using biosimilar infliximab. This change has resulted in increased patient access to treatment and reduced healthcare costs. Norway, Poland, and the UK have partially implemented a need to convert to biosimilar infliximab for induction and maintenance treatment of inflammatory bowel disease (IBD). France has set a goal of achieving 80% biosimilar penetration by 2022, which includes moving patients already treated with reference products [71].

There is no evidence indicating any safety or effectiveness problems when switching from RP to a biosimilar in cases of IBD or RA, as supported by many studies [12, 34]. For instance, in patients with Crohn's disease who had not been previously treated with biologic medications, the safety and effectiveness of reference infliximab and CT-P13 were comparable over a period of 54 weeks. This was seen whether patients received reference infliximab continuously, CT-P13 continuously, or switched to the other medication at week 30 [34]. Moreover, there was no significant disparity in the percentage of patients testing positive for ADA across the groups; the percentage of patients testing positive for neutralizing antibodies was likewise comparable [34]. Nevertheless, there is a scarcity of data on the economic consequences and use of healthcare resources associated with nonmedical switching. This was emphasized in a recent comprehensive analysis of published studies, which revealed a paucity of research using real-world estimates and noted methodological deficiencies in other studies. The presence of any additional expenses associated with the transfer of patients might hinder the adoption of biosimilars. The data from the DANBIO registry, which includes patients with inflammatory rheumatic disease, showed that switching from the

reference infliximab to CT-P13 only led to slight changes in the use of outpatient healthcare resources [11].

However, a recent study discovered that the small cost savings provided by biosimilar etanercept were not enough to warrant the extra effort required to actively switch patients from the reference product in certain Swedish counties [72]. There is a growing amount of data on single switches, but as far as we know, there have been no published studies that have looked at cross-switching (between two biosimilars) or multiple/repeated changes in RA or IBD. These studies would examine the effectiveness, safety, and cost implications of such switches [73]. Nevertheless, there is growing evidence in psoriasis that repeated switching between reference adalimumab and GP2017 (up to four switches) or between reference etanercept and GP2015 (up to three switches) does not have any detectable influence on efficacy, safety, or immunogenicity. However, future research should carefully evaluate the many interactions and connections in patients with different immune-mediated inflammatory diseases (IMIDs); the economic consequences related to the use of medications also need to be addressed.

Patients' Viewpoint: Enhanced Information Exchange Could Promote Increased Adoption of Biosimilars

In order for biosimilars to be adopted successfully, patients must comprehend the reasoning behind and have any apprehensions addressed about the initiation or transition to biosimilars. The European Crohn's and Colitis Organisation (ECCO) strongly supports the idea that patients should have complete information in order to make educated decisions based on evidence, and that this communication should take into account the patient's level of health literacy. ECCO emphasizes the importance of healthcare professionals (HCPs) in conveying the concrete advantages of the biosimilar product to patients. Additionally, ECCO recognizes the significant contribution that nurses may make in this process [73]. Nevertheless, the level of patient knowledge and comprehension of biosimilars is inconsistent. In a European study conducted between 2014 and 2015, it was discovered that about 36% of the 1059 patients with IBD were aware of biosimilars. Similarly, a survey conducted in Belgium in 2016 indicated that 49% of patients with RA were acquainted with biosimilars [74]. In a 2017 study conducted in the UK, it was shown that 66% of patients with rheumatoid arthritis (RA) and 80% of patients with ankylosing spondylitis (AS) who were getting reference products (RPs) or biosimilars had a clear understanding of what biosimilars are [72]. Among European patients with Inflammatory Bowel Disease (IBD) who were aware of biosimilars, the most prevalent worries were related to safety and effectiveness, with 47% and 39% of respondents expressing these issues, respectively. Approximately one-quarter of the participants did not have any particular concerns [74]. In addition, individuals with autoimmune disorders have voiced worries that nonmedical switching might have an impact on treatment results [54].

Patients may encounter placebo effects, which refer to the deterioration or exacerbation of symptoms caused by a negative mindset towards a particular treatment. These effects are only noticeable to the patient and can have an impact

on their quality of life, adherence to treatment, and the potential cost savings associated with biosimilars. Among a group of 100 patients diagnosed with rheumatoid arthritis (RA), ankylosing spondylitis (AS), or psoriatic arthritis, a significant majority of 89% agreed to move from the original infliximab medication to CT-P13, a nonmedical alternative [75]. Nevertheless, a significant portion of patients (28%) expressed a desire to go back to the original infliximab, with 44% of them seeing no deterioration in disease activity. This indicates that unfavorable opinions of biosimilars had an impact on the rate at which patients continued using them. A separate analysis of 125 patients diagnosed with either inflammatory bowel disease (IBD) or rheumatic disease revealed that 12.8% of them exhibited a nocebo response after being switched from the original medication (RP) to a biosimilar version of infliximab [76]. In the DANBIO registry, the primary reasons for reverting back to the original etanercept medication from the biosimilar version were subjective in nature [13]. The occurrence of nocebo reactions to biosimilars may be attributed to a combination of several patient-related characteristics and psychological processes, which are impacted by both the information given to patients and the treatment setting [74]. Perceptions of biosimilars may be influenced by patients' shared experiences, media attention, and the results of online searches, which can contribute to the occurrence of nocebo effects. Taking into account the presence of nocebo effects in the communication between patients and healthcare professionals may assist in reducing the negative impact of the nocebo effect and enhancing results [74]. Healthcare professionals (HCPs) may reduce the negative effects caused by biosimilars by being knowledgeable and self-assured. They can do this by promoting open and informed discussions with patients, leading to shared decision making [77]. Positive framing, informed permission within a specific context, and cohesive communication strategies may help mitigate the negative consequences of nocebo [72]. Although consumers are increasingly relying on online health information, a study revealed that the perceived quality of physicians had a stronger influence on treatment compliance compared to the perceived quality of internet health information [78]. This highlights the need of effective communication between healthcare professionals and patients. Furthermore, it is acknowledged that educational resources created by medical societies or government entities, in collaboration with patient groups, might be essential in facilitating patient education on biosimilars, particularly in the field of cancer.

Developers' Viewpoint: Novel Strategies to Enhance Value

Developers should address concerns about clinical outcomes and long-term performance of biosimilars by producing, publishing, and disseminating data that is suitable for stakeholders such as doctors, patients, and payers. This data should go beyond what is necessary for regulatory approval [79]. Engaging in educational initiatives and disseminating data via reputable medical publications might enhance doctors' confidence and knowledge with biosimilars [50]. An evidence-based strategy was effective in addressing doctors' concerns about indication extrapolation and transitioning from reference infliximab to CT-P13 for the treatment of IBD. This may have had a role in influencing ECCO's stance on biosimilars. Further examination of clinical data, in accordance with medical society criteria, may be carried out to provide further support for the use of

biosimilars. The extension stages of the CT-P13 PLANETRA and PLANETAS trials provided effectiveness analyses in various patient subgroups and analysis populations, as well as the use of alternative statistical procedures to handle missing data [74]. In order to facilitate comprehension for various stakeholders, like as patients and payers, publications may be translated into local languages or data can be efficiently conveyed via lay summaries.

With the increasing availability of biosimilars, the market will see intensified competition, leading to a decrease in pricing [7]. In order to ensure the sustainability of the biosimilar market, it is important for developers and payers to coordinate their pricing and market access strategies. This will help to strike a balance between the investments made by developers and a fair price, while also promoting healthy competition. In order to ensure long-term sustainability, companies must strive for efficiency not just in manufacturing, but also across the whole process, including research and development as well as distribution. Significantly, the capacity to extend the clinical use of biosimilars to other indications reduces expenses related to medication development and regulatory clearance [17]. The benefits of biosimilar development may be further enhanced by using novel strategies, such as the creation of medication formulations that are more convenient or have a longer duration of action, as shown by RP manufacturers [7]. Currently, infliximab biosimilars are given to patients by intravenous administration. However, there is ongoing research of a subcutaneous formulation of CT-P13, which might provide patients with enhanced convenience [70]. The future success and sustainability of a developer in the competitive biosimilars market will depend on their ability to provide value to their product and their commitment to an evidence-based strategy.

Conclusions

Biosimilar adoption may result in cost savings, which can then be used to enhance patient accessibility to biologic therapies for those requiring them. However, in order to optimize the benefits derived from the use of biosimilars, it is imperative that each party involved fulfills their respective obligations with utmost efficiency. The introduction of biosimilars has necessitated regulators to implement new frameworks. However, the continuous evolution in their scientific approach to biosimilar regulation has been instrumental in reducing the time and expenditure needed for biosimilar approval. This allows for the expedited delivery of biosimilars to patients, while maintaining the integrity of safety and effectiveness requirements. Payers should reassess pharmacoeconomic evaluations to accurately capture the effects of biosimilar market entrance, in order to alleviate nonmedical obstacles to biologic therapy for patients. Physicians should enhance their comprehension of biosimilars, bolstering their assurance in prescribing biosimilars in accordance with treatment and healthcare payer recommendations to optimize cost savings. Both patients and clinicians need to acknowledge the possibility of placebo effects. Enhancing physician communication techniques is necessary to mitigate the negative impacts of placebo phenomena on clinical results and treatment cessation, enhance patient satisfaction, and fully exploit the cost-saving benefits of biosimilars.

Developers must exhibit efficiency in order to reduce costs and maintain competitiveness in terms of pricing, all while ensuring that product quality, supply sustainability, and pharmacovigilance systems are not compromised. For a product to remain competitive in a market with numerous authorized biosimilars, it may need to include more innovation. Developers should conscientiously provide data to fulfill the demands of every stakeholder. Ultimately, the successful development of biosimilars requires effective collaboration among all parties involved, ensuring that patients may benefit from biologic treatment while also maintaining the long-term viability of the healthcare system.

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Crohn's disease

Ulcerative colitis

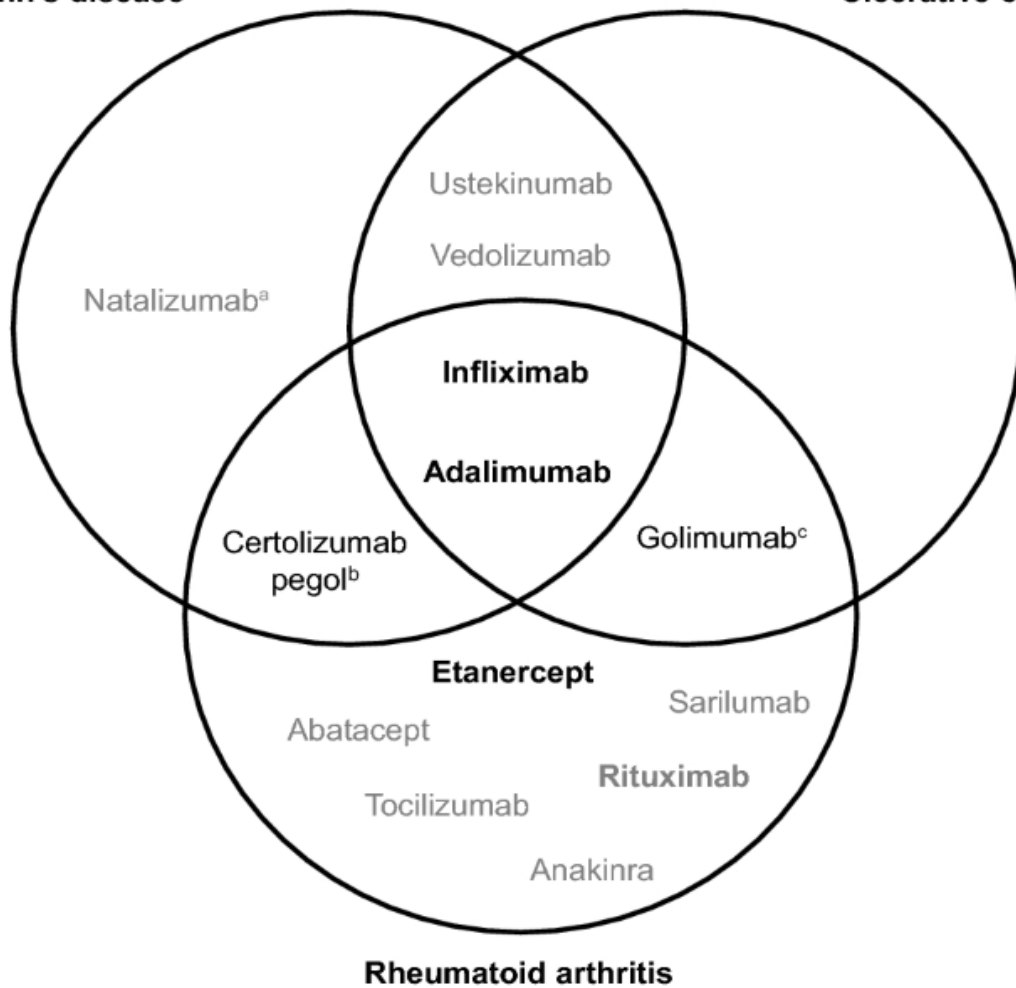


Figure 1. Biological drugs approved by the FDA and/or EMA for the treatment of rheumatoid arthritis (RA) and/or inflammatory bowel disease (IBD)