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REVIEW

Biosimilars to Antitumor Necrosis Factor Agents in Inflammatory Bowel Disease

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Eman Al Sulais[1]
Turki AlAmeel[2]

[1]Department of Medicine, Royal Commission Hospital, Jubail, Saudi Arabia; [2]Department of Medicine, King Fahad Specialist Hospital, Dammam, Saudi Arabia

Abstract: Anti- tumor Necrosis Factor (anti-TNF) agents are the backbone treatment of moderate to severe cases of inflammatory bowel disease. One of the main drawbacks of these agents is the high cost. The introduction of biosimilar products to anti-TNF agents is expected to lower the cost. Health care providers ought to be aware of the available data that addresses the safety and efficacy of biosimilars in IBD patients. This article outlines the current evidence-based data regarding the available biosimilar products, their safety, efficacy and how to deal with patients' concerns.

Keywords: biosimilars, inflammatory bowel disease, tumor necrosis factor inhibitors

Introduction

Inflammatory bowel disease (IBD), which encompasses ulcerative colitis (UC) and Crohn's disease (CD), is a chronic relapsing condition that primarily affects the gastrointestinal tract.[1,2] It results in a significant impact on the well-being of patients and overall healthcare expenditure.[3] The introduction of the tumor necrosis factor inhibitor (TNFi) infliximab as a therapeutic option for Crohn's disease marked a new era in 1998.[4] The subsequent approval of three more medications in this class made TNFi's the backbone for the management of moderate to severe cases of UC and CD.[5] Their use resulted in improved outcomes and lower requirements for surgical intervention.[6,7] Although concerns have been raised about the long-term safety of TNFi's,[8] they remain the preferred class of biologics in certain indications, such as perianal fistulizing CD or acute severe UC.[9,10] The high cost of these agents constitutes the main limiting step in accessing them for many patients. In a cohort study from the UK, TNFi's accounted for one-third and two-thirds of the costs of caring for patients with UC and CD, respectively, being significantly higher than the cost of surgery and hospitalization combined.[11] If the current trend continues, the proportion of patients using biologics is expected to increase over time, with a parallel increase in costs.

Biosimilars were introduced into the market in 2013. However, many clinicians remain doubtful about their safety and efficacy. An evidence-based approach would help gastroenterologists develop an informed opinion about the use of biosimilars in IBD.[12,13] This paper reviews the existing literature related to biosimilars in IBD. Aspects related to their efficacy, safety, and regulatory approval process are discussed. The patient's perspective, including the potential nocebo effect, is also addressed.

Correspondence: Eman Al Sulais
Department of Medicine, Royal Commission Hospital, P.O. Box 496, Jubail, Qatif 31911, Saudi Arabia
Email e.alslais@gmail.com

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How Does a Biosimilar Get Approved?

In contrast to generic medications, biosimilar regulations require comparative preclinical and clinical data. The aim of which is to avoid uncertainties regarding the level of characterization achievable, and the possible clinical consequences of differences in physical–chemical characteristics, such as the amount of impurities.[14,15]

Regulatory agencies require a Phase 1 (pharmacokinetic/pharmacodynamic) trial and at least one Phase 3 clinical (randomized controlled) trial to demonstrate the equivalent efficacy, safety, and immunogenicity of the biosimilar to those of the reference agent. The equivalence trial design needs to be conducted on patients with a disease for which the reference agent is licensed, whereas the pharmacokinetic/pharmacodynamic study may be conducted on healthy individuals.[16] Both equivalence and non-inferiority study designs are acceptable. Usually, a non-inferiority study design is appropriate for products with a wide safety margin, whereas an equivalence trial is conducted for products with a narrow safety margin. Equivalence trials provide a stronger rationale for the extrapolation of efficacy data to other indications.[17]

What are the Available Biosimilars?

For infliximab, three biosimilars are available: SB2 (FLIXABI®, Samsung Bioepis, Incheon, South Korea[18] and Biogen, Hillerød, Denmark), PF-06438179/GP1111 (ZESSLY®, Sandoz, Holzkirchen, Germany[19]), and CT-P13 (INFLECTRA®, Pfizer, New York, NY, USA;[20] REMSIMA®, Celltrion, Incheon, South Korea[21]). For adalimumab, the biosimilars are SB5 (IMRALDI®, Biogen, Hillerød, Denmark, and Samsung Bioepis, Incheon, South Korea[22]), ABP 501 (AMGEVITA®, Amgen, Thousand Oaks, CA, USA[23]), GP2017 (HYRIMOZ®, Sandoz, Holzkirchen, Germany[24]), BI 695501 (CYLTEZO®, Boehringer Ingelheim, Ingelheim am Rhein, Germany[25]), and FKB327 (HULIO®, Mylan, Canonsburg, PA, USA;[26] Fujifilm Kyowa Karin Biologics, Tokyo, Japan).[27]

Infliximab Biosimilars

CT-P13 was the first infliximab biosimilar to be approved. The original approvals in Europe in 2013 and the USA in 2016 were granted on the basis of submitted data from the applicants driven largely from rheumatology literature.[27] Two double-blind trials—phase 1 PLANETAS on ankylosing spondylitis and phase 3 PLANETRA on rheumatoid arthritis—demonstrated the bioequivalence of CT-P13 to the reference product (RP) infliximab.[28,29] The US Food and Drug Administration (FDA) approval of two other infliximab biosimilars (SB2 and PF-06438179) and the approvals of NI-071 in Japan and BOW015 in India were also based on studies on rheumatoid arthritis.[30,31] CT-P13 remains the most widely studied biosimilar for IBD.[32]

Is CT-P13 as Effective as the Reference Product in Patients with Inflammatory Bowel Disease?

Multiple studies on CT-P13 use in patients with IBD have been published (Table 1). A French equivalence study by Meyer et al[33] compared the effectiveness and safety of infliximab (RP) with CT-P13 in patients with infliximab-naive CD. The trial comprised approximately 2500 patients in each arm and was designed as a real-life, comparative, equivalence cohort study. Using a nationwide health administrative database, the researchers included all patients with CD who had received one or more doses of infliximab between March 1, 2015, and November 30, 2016. The primary outcome of the study was a composite endpoint of death, all-cause hospitalization except childbirth for 1 night, CD-related surgery, and documented use of ustekinumab, adalimumab, or vedolizumab. Patients were followed until the onset of a predefined outcome or censoring. Patients were censored at the study's end (June 30, 2017), at switch from RP to CT-P13 (or vice versa) plus 30 days, or at the discontinuation of infliximab. Only the first event was considered. The equivalence margin was set as 10% of the absolute difference. The primary outcome did not differ between the RP and CT-P13 groups (log-rank test, $P > 0.20$). The 6-, 12-, and 18-month cumulative incidence rates of the primary outcome were 29.6% (95% confidence interval (CI), 27.8 to 31.4), 43.1% (95% CI, 41.2 to 45.1), and 51.5% (95% CI, 49.6 to 53.4), respectively, in the RP group, and 28.6% (95% CI, 26.9 to 30.4), 41.6% (95% CI, 39.7 to 43.6), and 50.1% (95% CI, 48.1 to 52.0), respectively, in the CT-P13 group. In the multivariate analysis of the primary outcome, CT-P13 was equivalent to RP (hazard ratio, 0.92; 95% CI, 0.85 to 0.99). In terms of safety, the multivariable analysis did not demonstrate any significant differences between RP and CT-P13. The study by Meyer et al[33] drew important conclusions. First, it showed the bioequivalence of CT-P13 to the RP. The equivalence margin of 10% was stricter than what is required by regulatory agencies. Moreover, the sample size was 4 to 5

Table 1 Swtich Studies of Originator Infliximab to Biosimilar CT-P13 in Inflammatory Bowel Disease

Trial	Design	Population	Follow-Up Period	Primary Endpoint
NOR-SWITCH[32]	Non-inferiority Phase 4 Prospective Randomized Double-blind	486 patients IFX (n=241) CT-P13(n=245) CD: 78 (32%) 77 (32%) UC: 47 (20%) 46 (19%) SA: 45 (19%) 46 (19%) RA: 39 (16%) 38 (16%) PA: 14 (6%) 16 (7%) P: 18 (7%) 17 (7%)	52 weeks	Disease worsening at week 52: IFX Vs CTP3: 53 (26%) Vs.61 (30%)
SECURE[44]	Non-inferiority Phase 4 Prospective open-label	88 patients CD: 46 (52.3%) UC: 42 (47.7%)	16 weeks	Change in serum concentrations of IFX between baseline and 16 weeks for UC and CD Separately: (geometric mean ratio of CT-P13 compared with IFX): UC: 110.1% (90% CI 96.0–126.3) CD: 107.6% (97.4–118.8)
Meyer et al[35]	Equivalence Observational	3112 patients RP group: 1434 (46.1%) CT-P13 group: 1678 (53.9%)	24 months	Composite endpoint including all causes of infliximab failure, either due to inadequate efficacy or toxicity: IFX VS CT-P13 (log-rank test; P = 0.20)
Ye et al[39]	Non-inferiority Phase-3 Randomized Double-blind	220 patients	54 Weeks	Primary efficacy endpoint was CDAI-70 response at week 6: CTP3: 77/111 patients (69.4%, 95% CI 59.9 to 77.8) INX: 81/109 (74.3%, 65.1 to 82.2) Difference –4.9% [95% CI–16.9 to 7.3]

Abbreviations: IFX, infliximab; CD, Crohn's disease; UC, ulcerative colitis; SA, Spondylosing arthritis; RA, Rheumatoid arthritis; PA, psoriatic Arthritis; P, psoriasis.

times larger than what is required to detect a 10% to 15% difference between the two groups.[33]

Can We Switch from the Reference Product to CT-P13?

The NOR-SWITCH study was designed to address this very question. It was a prospective, 52-week, randomized, double-blind, non-inferiority Phase 4 trial that involved all six relevant diagnoses for which infliximab is approved. In total, 486 patients with CD, UC, spondyloarthritis, rheumatoid arthritis, psoriatic arthritis, and chronic plaque psoriasis, who were on stable treatment with infliximab (RP), were enrolled. The patients on stable treatment with reference infliximab for at least 6 months were randomized in a 1:1 ratio to either continue infliximab (RP) or switch to the CT-P13 regimen without a change in the dosage. The patients were recruited from 19 gastroenterology departments, 16 rheumatology departments, and 5 dermatology departments in 25 Norwegian hospitals. The per-protocol analysis included 155 patients with CD and 93 with UC. The primary endpoint was worsening of the disease during the 52-week follow-up period, defined as a consensus on disease worsening between the investigator and the patient and leading to a major change in treatment, or worsening of the disease-specific composite endpoint. The Harvey–Bradshaw Index and Partial Mayo Score were used for the patients with CD and UC, respectively. The fecal calprotectin level was a secondary endpoint for the patients with IBD. The non-inferiority margin was set at 15%. The authors of the NOR-SWITCH study concluded that there was no significant difference in the loss of response, safety, or immunogenicity between those who remained on originator infliximab for the duration of the study and those who were switched to CT-P13. Although the risk difference for the patients with CD slightly favored their remaining on the originator drug (risk difference, −14.3%; 95% CI, −29.3 to 0.7), whereas the patients with UC were noted to have a more balanced result (risk difference, −2.6%; 95% CI, −15.2 to 10.0), the study was not powered to show non-inferiority in individual diseases.[34] An open-label extension of the NOR-SWITCH study was recently published, in which patients on CT-P13 throughout the 78-week study period (maintenance group) were compared with those switched to CT-P13 at week 52 (switch group). The per-

protocol analysis showed disease worsening in 16.8% of the patients in the maintenance group versus 11.6% in the switch group, with an adjusted risk difference of 5.9% (95% CI, −1.1 to 12.9). Both groups had similar rates of adverse events and antidrug antibodies.[35] Despite the compelling results of the NOR-SWITCH study, it had important limitations.[36] First, the primary outcome in the patients with IBD was a symptom-based score. This is no longer acceptable for gaining regulatory approval of a biological agent for IBD. In CD, for example, the Harvey–Bradshaw Index relies heavily on the patient symptoms, with little use of objective measures, and correlates poorly with the biological evidence of the active disease, including endoscopic assessments and C-reactive protein levels. Conversely, it has the potential to overestimate the disease activity in patients with functional symptoms.[37] The lack of an objective confirmation of disease worsening—whether endoscopically, biochemically, or radiographically—is an important limitation of this study. Second, the non-inferiority margin was set at 15%, which is usually used in superiority studies to show a clinically important difference. The choice of a relatively large non-inferiority margin in a study that was underpowered to address a population with IBD specifically is a major limitation to accepting its conclusion.[38]

Some of these concerns were addressed by Ye et al[39] who published the results of the first clinical trial to confirm the non-inferior efficacy of CT-P13 relative to infliximab (RP) in biologically naive patients with active CD. In this multicenter, double-blind, phase 3 trial, patients were randomly assigned to receive CT-P13 and then CT-P13, CT-P13 and then infliximab, infliximab and then infliximab, or infliximab and then CT-P13, with the switch occurring at week 30. The primary endpoint was clinical improvement, defined as a decrease in the CD Activity Index by 70 points at week 6. In total, 220 patients were enrolled in the study and the non-inferiority margin was set at 20%. The clinical response rate was similar between the CT-P13 and infliximab (RP) groups (i.e., 69.4% vs 74.3%, respectively), where the difference of 4.9% established non-inferiority in the primary endpoint. Mucosal healing at week 54, as assessed by the simplified endoscopic score for CD that was read by a blinded centralized reader, was similar between the groups. There was no statistically significant difference between the treatment groups in terms of the week-54 production rate of antidrug antibodies, which were positive in 39.3% of the patients in the CT-P13–CT-P13 group, 32.7% in the CT-P13–infliximab group, 38.9% in the infliximab–infliximab group, and 54.5% in the infliximab–CT-P13 group. The study was criticized for setting a liberal non-inferiority margin of 20%. Moreover, the sample size was calculated for the primary endpoint of clinical improvement at week 6. Similar to the NOR-SWITCH study, it was underpowered to address secondary and tertiary points. In particular, the question was raised of whether switching between CT-P13 and infliximab (RP) can be performed after 30 weeks of treatment without a loss of efficacy. The results showed no statistically significant difference in the rates of immunogenicity or mucosal healing between the groups. Nonetheless, the 12% absolute difference in mucosal healing between the CT-P13–CT-P13 and infliximab–CT-P13 groups and the 21% absolute difference in immunogenicity between the CT-P13–CT-P13 and infliximab–CT-P13 groups could be clinically relevant.[40] Overall, the evidence supports the safety and efficacy of a one-time switch between the RP and the infliximab biosimilar.[30] This is in line with recommendations recently published in a consensus document by multidisciplinary experts.[41] It should be mentioned that data on the safety and efficacy of switching from one biosimilar to another of the same originator or of multiple switches among different molecules are lacking. Therefore, these options should be avoided in the absence of direct evidence of efficacy and safety.[27]

Is There an Increased Risk of Immunogenicity When Switching from the Reference Product to CT-P13?

Immunogenicity, whereby the development of antidrug antibodies leads to infusion reactions and rapid clearance of TNFi, is associated with loss of response to these agents in IBD. Different assays are being used to measure drug and antidrug antibody levels. The most commonly used assay types are the: enzyme-linked immunosorbent assay (ELISA), radio-immunoassay (RIA) and a fluid phase mobility shift assay. Nonetheless, standardization of these assays to measure anti-IFX or anti-ADA antibodies is lacking.[42]

One of the main concerns clinicians have about biosimilars is their potential for increased immunogenicity compared with that from RP. In an online survey among the European Crohn's and Colitis Organisation (ECCO) members in 2013, this was the concern expressed by 67%

of the respondents.[43] The SECURE trial, an open-label, multicenter, phase 4 non-inferiority study, addressed important points related to pharmacokinetics and immunogenicity in patients with IBD switching from RP to CT-P13. Patients with CD and UC, who were in clinical remission on infliximab RP, were switched to CT-P13 at the same dose. The primary outcome of the study was serum concentrations of infliximab between baseline and 16 weeks for UC and CD separately. Secondary endpoints included antidrug antibodies to infliximab at weeks 8 and 16 after switching to CT-P13. The non-inferiority margin was set at 15%. The per-protocol analysis was conducted on 88 patients, with almost equal distribution between UC and CD diagnoses. The median serum concentration for the patients with UC did not change between baseline and week 16, being 3.6 μg/mL at both time points. On the other hand, the median drug concentration was 3.5 μg/mL at baseline and 4.0 μg/mL at week 16 for the patients with CD. Therefore, in both populations, the serum concentrations of infliximab at 16 weeks after switching to CT-P13 were non-inferior to those on originator infliximab. There was no difference between the two groups in the formation of antidrug antibodies.[44] Conversely, once a patient develops antibodies to infliximab RP, cross-reaction with the biosimilar will occur as well. This was nicely demonstrated in an in vitro study of sera from patients with IBD and from healthy controls. Individuals who had negative antidrug antibodies to infliximab RP also tested also negative for anti-CT-P13 antibodies. In contrast, all sera from 69 patients with positive antidrug antibodies to infliximab RP showed cross-reactivity with CT-P13. The antibodies-to-infliximab titers against RP or CT-P13 were strongly correlated (r values between 0.92 and 0.99, $P < 0.001$). However, the antibodies to adalimumab in adalimumab-treated patients with IBD (n = 7) did not cross-react with either infliximab RP or CT-P13.[45] Therefore, it is generally agreed upon that any event related to the immunogenicity of a TNFi cannot be overcome by a biosimilar of the same molecule.[27]

Adalimumab Biosimilars

The European Union patents on adalimumab expired in October 2018.[27] Adalimumab biosimilars have received approval by the European Medicines Agency (EMA) and are in use in several countries. Similar to infliximab, equivalence trials on adalimumab biosimilars were conducted on patients with rheumatological diseases. A phase 3 trial of more than 500 patients with rheumatoid arthritis was conducted to compare adalimumab RP with SB5. The two arms were similar in their response rates, which was defined as the American College of Rheumatology Criteria of a greater than or equal to 20% improvement (ACR20) at week 24 in the per-protocol analysis. Both groups were comparable in other endpoints, including erythrocyte sedimentation rate, pharmacokinetic data, treatment-related adverse events, and antidrug antibody response. Subgroup analyses showed that both groups were comparable regardless of their antidrug antibody status.[46] A subsequent study looked at the same population to assess outcomes of switching from adalimumab RP to SB5. At week 24, the patients receiving adalimumab RP were re-randomized to continue with adalimumab RP (ADA/ADA group) or to switch to SB5 (ADA/SB5 group), whereas patients receiving SB5 continued with SB5 (SB5 group). At week 52, switching from adalimumab RP to SB5 had no treatment-related issues, such as increased adverse events, increased immunogenicity, or loss of efficacy.[47] To our knowledge, there are no published studies on the safety, efficacy, or immunogenicity of adalimumab biosimilars in patients with IBD. Nonetheless, since adalimumab RP is one of the top-selling monoclonal antibodies used for immune-mediated inflammatory diseases,[48] clinicians ought to consider the significant cost savings of switching to a less expensive form of the drug. It would be reasonable to extrapolate data from infliximab biosimilars in patients with IBD to adalimumab.

Can Biosimilars Be Used Interchangeably with the Reference Product in Patients with Inflammatory Bowel Disease?

Although interchangeability has not been studied in populations with IBD, one-time switching between the RP and a biosimilar has been addressed in the aforementioned studies. This implies that a biosimilar product may be substituted for the RP without the intervention of the healthcare provider who prescribed the RP.[49] The FDA mandates that interchangeability studies should have at least three switches, with each switch crossing over to the alternate product for at least two exposure periods with each drug.[50] The study should use either a non-inferiority or an equivalence design. The results of a phase 3 trial looking at interchangeability between adalimumab and GP2017 in patients with psoriasis were published in 2018. In a double-blind design, more than 500 patients

were included in the study and assigned to one of the following four arms: adalimumab RP throughout the study, GP2017 throughout the study, and two interchangeability arms allowing up to four switches. The authors found no impact of switching in terms of efficacy, safety, or immunogenicity.[51] However, until such high-quality data become available for patients with IBD, multiple switches between the RP and biosimilar are best avoided. Currently, there are no biosimilars for the treatment of IBD that have been designated by the FDA as interchangeable.[52] ECCO guidelines conclude that scientific and clinical evidence is lacking regarding reverse switching, multiple switching, and cross-switching among biosimilars in patients with IBD.[53]

Can We Extrapolate Data from a Trial on One Indication to Another?

Extrapolation in the context of biosimilars is the process of extending efficacy and safety data from one approved therapeutic indication for which the biosimilar has been clinically tested to other indications for which the RP is authorized.[51] Although extrapolation has been criticized by some authorities in the field of IBD,[54] the principle stands on solid arguments based on clinical and preclinical data.[55] It relies on the concept that TNFi's for the treatment of an immune-mediated disease, such as rheumatoid arthritis, psoriasis, and IBD, share the same mechanism of binding TNFα. Potential differences between the RP and biosimilars in relation to the Fc region can be addressed in a trial on one indication and extrapolated to other indications.[27] The ECCO position statement on biosimilars states that the biosimilarity is more sensitively characterized by in vitro assays than by a clinical trial.[56] Therefore, regulatory bodies, including the EMA, have stated that the extrapolation of clinical efficacy and safety data (which were not specifically studied during the clinical development of the biosimilar monoclonal antibody) to other indications to other indications of the reference monoclonal antibody is possible, based on the totality of evidence with adequate and relevant justification.[54]

Biosimilars and Cost Savings

The cost of monoclonal antibodies remains one of the major financial burdens to healthcare systems around the world. Biological treatment accounted for more than one-third of US spending on prescription drugs in 2015 and more than two-thirds of drug spending growth between 2010 and 2015.[57] The global market is forecast to reach US$131.33 billion by 2023.[55]

In addition to the increasing incidence of IBD in many parts of the world,[58] more patients are receiving biological treatment for the disease. In a market share study using a database of 415,405 patients with IBD over a 9-year period, the percentage of patients with UC using biologics increased from 5.1% to 16.2%. In the population with CD, the proportion of patients using biologics increased from 21.8% to 43.8% over the same 9-year period. The share of costs for these medications increased from 72.9% in 2007 to 85.7% in 2015.[59] The introduction of biosimilars was expected to reduce the cost of biologics by 15% to 35% compared with the price of the RP. However, in some instances, cost savings went even further. For example, the company launching CT-P13 offered a 39% discount compared with the price for the RP in the first year in Norway. In the following year, the price was reduced to a 69% discount compared with that of the RP. The market share of CT-P13 in that country increased from 20% to 30%.[60] Gastroenterologists ought to be mindful of the potential cost savings in prescribing biologics. This is particularly true if they have received funding from pharmaceutical companies for educational activities or consulting services. Continuing to argue for the use of the RP, despite the evidence showing non-inferiority of the biosimilar, may cast doubt on the clinician's impartiality. In a recent analysis of Medicare prescription databases in the USA, researchers found significant associations between industry payments and Medicare spending. For every $1 in payments to physicians, there was a $3.16 increase in spending for adalimumab (95% CI, $2.84 to $3.48; $P < 0.001$), and a $4.72 increase for certolizumab (95% CI, $3.65 to $5.80; $P < 0.001$).[61]

Biosimilars and the Nocebo Effect

The nocebo effect is an important obstacle in efforts to switch to biosimilars.[62] It is defined as a negative effect of a pharmacological treatment that is induced by the patient's expectations, with no direct relationship to the physiological action of the medication.[63] The issue is of particular importance in IBD compared with other immune-mediated illnesses. Patients with IBD are prone to have functional symptoms, and the prevalence of irritable bowel syndrome in this population is estimated to be 39%.[64] The development of such symptoms after a non-

medical switch to biosimilars may be mistakenly attributed to the medication, thus hampering attempts at cost saving through the use of biosimilars. One should also bear in mind that a certain percentage of patients will develop secondary failure to TNFi's. This had been documented in patients with IBD, even before the introduction of biosimilars. The annual risk of a loss of response to infliximab is 13% per patient-year, whereas that for adalimumab is 20% per patient-year.[67] This should not be mistakenly attributed to the decision to switch. Studies on the nocebo effect with biosimilars in IBD remain sparse. In an open-label Dutch study, 192 patients with rheumatoid arthritis agreed to transition to CT-P13. Over the 6 months of follow-up, one-quarter of these patients stopped treatment mainly because of an increase in the subjective features of the tender joint count and the patient's global assessment of disease activity, possibly explained by nocebo effects.[65] One would expect similar findings in the population with IBD. In a recent survey of patients with UC and CD, the majority had not heard of biosimilars, and those who had (38%) harbored doubts and concerns about their safety and efficacy. The majority of respondents expressed their desire to know whether they were receiving the reference drug or the biosimilar.[66] The patient's expectations of adverse events are likely to be influenced by negative media coverage and, perhaps more importantly, the negative beliefs of healthcare providers about a treatment.[67] Physicians, nurses, pharmacists, and other providers in charge of patients who are being treated with biosimilars need to be aware of the nocebo effect and to adopt strategies to minimize it.[68] In addition to sharing the decision-making with patients and obtaining an informed consent, such strategies should include positive framing. The focus should be on the common aspects between biosimilars and biological RPs with regard to their efficacy, safety, and immunogenicity, and on discussion of the advantage of the lower cost of the biosimilars.[69] Patients were found to be more likely to accept the switch if the decision was taken by their primary-care physician instead of a pharmacist.[70]

If a Decision Is Made to Switch to Biosimilars, How Should It Be Implemented?

The UK National Institute for Health and Care Excellence (NICE) guidelines suggest the following steps for the smooth introduction of biosimilars to a particular clinical practice.[71]

1. Identify clinical and pharmacy champions to take the lead in introducing biosimilars.
2. Consult all stakeholders (including patients) to ensure confidence in using biosimilars.
3. Provide information about the licensing processes of regulatory agencies for biosimilars, extrapolation and equivalence, and the manufacturing process (including intra-product manufacturing changes for both biological medicines and their biosimilars).
4. Identify the potential cost-saving and re-investment opportunities.
5. Seek formal approval at the local formulary committee once there is clinical consensus to include biosimilars on the formulary.
6. Collect baseline data and agree on the metrics to be collected during and after the introduction of biosimilars. Submit the data to national audits and registries.

Naming of Biosimilars

The U.S Food and Drug Administration's (FDA),[72] Australia's drug regulatory agency, the Therapeutic Good Administration (TGA),[73] and UK NICE stated that the biosimilars being prescribed to patients must be introduced by their brand names in order to help patients identify which drug they are using.[71] This is crucial so that in case adverse events occur, the patients will be able to report them to the correct product manufacturer.[71]

Conclusion

Biosimilars to anti-TNF agents have similar efficacy to the RP. Once a biosimilar has been shown to be equivalent to the RP in one indication, extrapolation to other indications—including IBD—is accepted by regulatory agencies. After approval and introduction to the market, the decision to switch should be based on an economic evaluation and taken in consultation with stakeholders, including the patients (Figure 1). Interestingly, the production of a new class of the biosimilars, called "biobetter" or "biosuperior" drugs is under way, with the aim being to improve one or more of the drug's properties through alteration of the manufacturing process.[74]

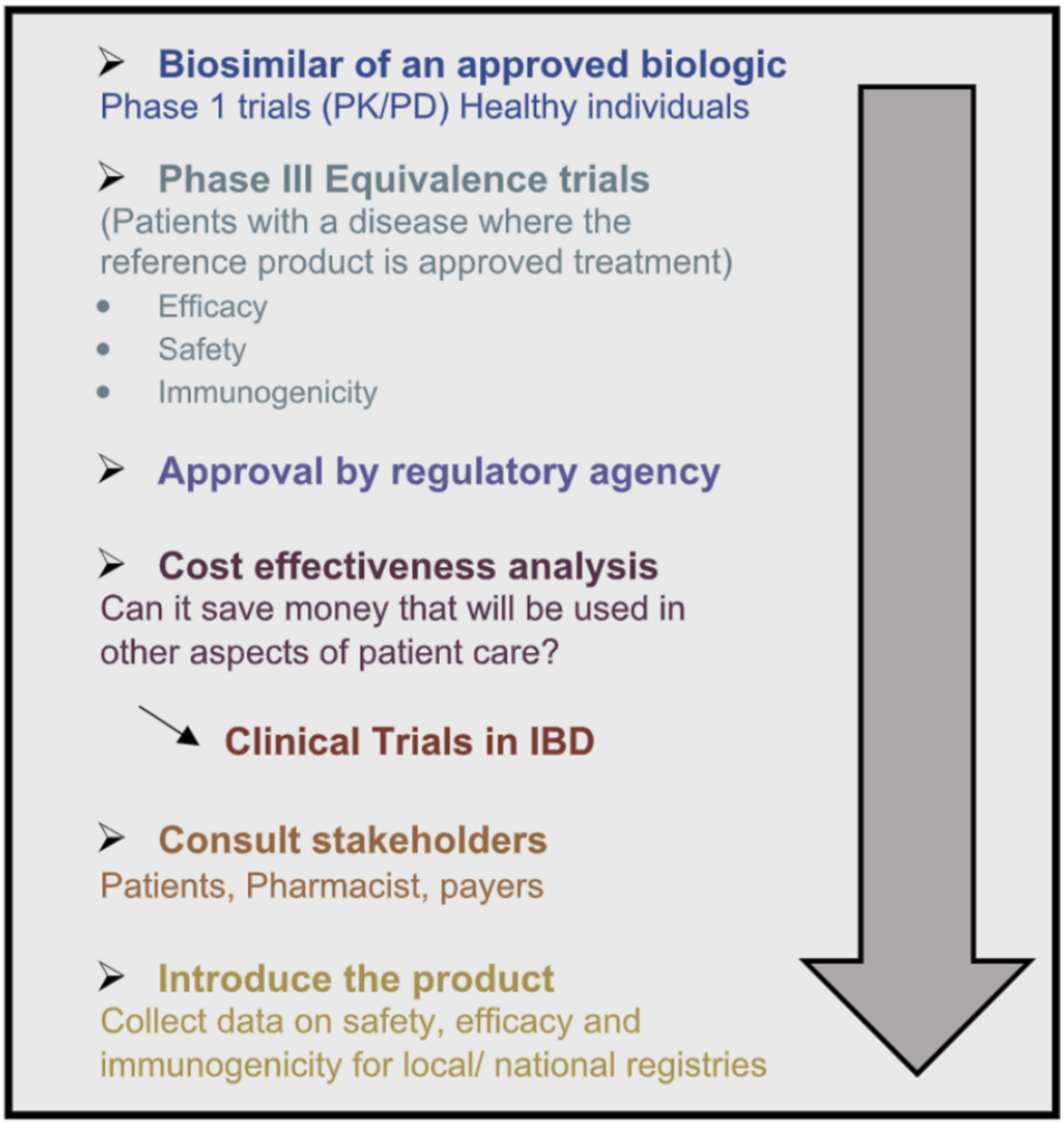

Figure 1 An approach to introducing a biosimilar to inflammatory bowel disease (IBD) practice.**Abbreviation:** PK/PD, pharmacokinetic/pharmacodynamic.

Although, approval of such class cannot be made using biosimilar pathway as these products do not fulfill the criteria of biosimilarity.

Disclosure

ES declares no conflicts of interest related to this study. TA has received consulting and speaker fees from Janssen, AbbVie, and Takeda.

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