IBD REVIEWS REVIEW ARTICLE

Biosimilar Monoclonal Antibodies: Considerations for Gastroenterologists

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Abstract

Background and primary objective: *The first biosimilar of the tumor necrosis factor-alpha inhibitor infliximab has been approved in multiple countries. Indication extrapolation was a key area in which regulatory decisions differed. This review provides an overview of biosimilarity, and discusses approaches to indication extrapolation, issues relating to immunogenicity, and clinical implications for gastroenterologists.* ***Procedures:*** *This was a narrative review of regulatory guidelines related to biosimilar products with a focus on indication extrapolation, immunogenicity, and clinical implications for gastroenterologists.* ***Discussion and conclusions:*** *Biosimilarity is established with comprehensive quality comparisons followed by comparative nonclinical and clinical studies. Differences identified during the quality comparison may have clinical implications and must be investigated. Although comparative analytical data provide the foundation for use of a biosimilar for the specific indication(s) tested, additional factors must be considered when determining the appropriateness of indication extrapolation. Current abbreviated regulatory processes are facing challenges about the indication extrapolation of complex biologics such as monoclonal antibodies, particularly when there are potential differences in disease pathogenesis and safety and immunogenicity profiles between the target populations/indications. Particularly relevant to gastroenterologists is whether clinical study data in rheumatologic diseases, taken together with the analytical and preclinical data, form an adequate basis for approval of a biosimilar in inflammatory bowel disease-related indications. The results of ongoing studies of biosimilar infliximab in patients with inflammatory bowel disease are anticipated to help to better inform clinical decisions regarding this product.* (IBD Rev. 2016;2:3-12)

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Introduction

The first biosimilar monoclonal antibody, a biosimilar of the tumor necrosis factor (TNF) alpha inhibitor infliximab, has been approved in several countries including European Union member states, multiple Latin American countries, Canada, Korea, and the USA[1-7]. As additional complex biological products approach patent expiration, it is anticipated that many new biosimilar products will require evaluation[8]. For the biosimilar infliximab, differences in the indications approved by various regulatory authorities raise important clinical considerations regarding indication extrapolation (IE). The publicly available clinical information for the biosimilar infliximab included a single phase III equivalence study versus the originator product in rheumatoid arthritis (RA) and a single phase I pharmacokinetic study in ankylosing spondylitis (AS)[1,9,10]. From these direct comparative patient data, regulatory authorities in Brazil, Europe, and Korea approved the biosimilar for all indications for which the originator monoclonal antibody had approval, including rheumatologic (RA, AS, psoriatic arthritis), dermatologic (plaque psoriasis), and gastrointestinal indications (Crohn's disease [CD], pediatric CD, ulcerative colitis [UC], and pediatric UC)[1,7,11]. In contrast, regulatory authorities in other countries were more conservative: in Chile, approval of biosimilar infliximab was for RA and AS only, while in Mexico, approval was restricted to rheumatologic and dermatologic indications[7,12]. In Canada, initial approval of biosimilar infliximab was for rheumatologic and dermatologic indications only, but this was later extended for inflammatory bowel disease (IBD) based on similarity in product quality, mechanism of action (MOA), disease pathophysiology, safety profile, dosage regimen, and on clinical experience with the originator product[2,11,13]. In the USA, the Food and Drug Administration (FDA) approved biosimilar infliximab for all eight indications for which the originator is approved with the exception of pediatric UC, which is anticipated after expiration of pediatric exclusivity in September 2018[14,15].

The ability to extrapolate from rheumatologic indications to gastrointestinal indications warrants closer examination[16]. This review will provide an overview of biosimilarity and will discuss approaches to indication extrapolation, issues relating to immunogenicity, and clinical implications for gastroenterologists.

What do biosimilarity and indication extrapolation mean?

Biosimilarity

Definitions of "biosimilar" or "biosimilarity" from various world health/regulatory organizations are summarized in table 1. The European Commission put forth a consensus information document that describes how biosimilar products are developed to be highly similar to the originator products in three key steps: quality comparability, nonclinical comparability and clinical comparability[17]. Quality encompasses physicochemical and biological comparability (e.g. molecular structure and functionality)[17]. Comprehensive analytical data from orthogonal, sensitive methods, including receptor binding studies and bioassays, are used for head-to-head comparisons of the biosimilar and the originator product[17]. Rigorous studies (nonclinical and clinical) directly comparing the biosimilar to the originator product are then required.

The World Health Organization (WHO) similarly describes a stepwise approach to the development of biologics, starting with comprehensive characterization and comparison of quality followed by head-to-head nonclinical and clinical studies[18]. The WHO guidelines emphasize that differences found between the biosimilar and the originator product at any step must be investigated, explained, and justified because they may signal the need for additional data[18]. Figure 1 provides a summary of the components of a comprehensive quality comparison of a biosimilar product with an originator compound, as described in the WHO guidance, including key challenges and

Table 1. Definitions of biosimilarity and criteria for indication extrapolation

Organization(s) (Country/Region)	Definition of biosimilarity	Criteria for indication extrapolation
EMA[19] and European Commission (EU)[17]	– A biosimilar is a biological medicinal product that contains a version of the active substance of an already authorized original biological medicinal product (reference medicinal product) in the European Economic Area. – Similarity to the reference medicinal product must be established in terms of quality characteristics, biological activity, safety, and efficacy based on a comprehensive comparability exercise.	– If biosimilarity has been demonstrated in one indication, extrapolation to other indications of the reference product could be acceptable with appropriate scientific justification. – Consider overall evidence of comparability provided from the comparability exercise and with adequate scientific justification. • Must include ≥ 1 clinical study in the most sensitive patient population measuring the most sensitive (i.e. most likely to show any differences between the biosimilar and the reference product) clinical endpoint(s). – If pivotal evidence for comparability is based on pharmacodynamic data, and for the claimed indications different mechanisms of action are relevant (or uncertainty exists), then applicants should provide relevant data to support extrapolation to all claimed clinical indications. – Biosimilar medicinal product applicants should also support such extrapolations with a comprehensive discussion of available literature including the involved antigen receptor(s) and mechanism(s) of action. – Only when quality, nonclinical and clinical comparability is achieved is the new medicinal product accepted as a biosimilar and is it justified for the biosimilar medicinal product to cross-refer to the clinical data obtained through the extensive experience of the reference product. This is described in the relevant scientific literature and in publicly accessible health authority documents. – Whether extrapolation to multiple indications is acceptable (or not) is decided on a case-by-case basis by the CHMP/EMA.
FDA (USA)[21,22]	– The biological product is highly similar to the reference product, notwithstanding minor differences in clinically inactive components. – 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.	– If requirements for licensure as a biosimilar are met based on data from a clinical study or studies sufficient to demonstrate safety, purity, and potency in an appropriate condition of use, the applicant may seek licensure of the proposed product for ≥ 1 additional conditions of use for which the reference product is licensed. – Sufficient scientific justification for extrapolating clinical data to support a determination of biosimilarity must be provided for each condition of use for which licensure is sought. – The scientific justification for extrapolation should address the following issues for the tested and extrapolated conditions of use*: • The MOA(s) in each condition of use for which licensure is sought; this may include: target/receptor(s) for each relevant activity/function of the product; binding, dose/concentration response, and pattern of molecular signaling upon engagement of target/receptor(s); relationships between product structure and target/receptor interactions; location and expression of the target/receptor(s). • The pharmacokinetics and biodistribution of the product in different patient populations (relevant pharmacodynamics measures may also provide important information on the MOA). • The immunogenicity of the product in different patient populations. • Differences in expected toxicities in each condition of use and patient population (including whether expected toxicities are related to the pharmacologic activity of the product or to off-target activities). • Any other factor that may affect the safety or efficacy of the product in each condition of use and patient population for which licensure is sought. – In choosing which condition of use to study that would permit subsequent extrapolation of clinical data to other conditions of use, the sponsor should consider choosing a condition of use that would be adequately sensitive to detect clinically meaningful differences between the two products.

(Continue)

Table 1. Definitions of biosimilarity and criteria for indication extrapolation *(Continued)*

Organization(s) (Country/Region)	Definition of biosimilarity	Criteria for indication extrapolation
WHO (International)[18] (Adapted by Panama, Costa Rica, and Guatemala)[7]	– "Similarity" is the absence of a relevant difference in the parameter of interest, and a similar biotherapeutic product (i.e. biosimilar) is a biotherapeutic product that is similar in terms of quality, safety, and efficacy to an already licensed reference biotherapeutic product.	– If similar efficacy and safety between the biosimilar and the reference product have been demonstrated for a particular clinical indication, extrapolation of these data to other indications (i.e. not studied in independent clinical studies with the biosimilar) may be possible if all of the following conditions are met: • A sensitive clinical test model has been used that is able to detect potential differences between the biosimilar and reference product. • The clinically relevant MOA and/or the involved receptors are the same for the different indications being considered†. • The safety and immunogenicity profiles of the biosimilar have been sufficiently characterized and there are no unique/additional safety issues expected for the extrapolated indications. • If the efficacy study used a non-inferiority design and demonstrated acceptable safety and efficacy of the biosimilar compared with the reference product, a convincing argument must be made that this finding can be applied to the extrapolated indications‡.
ANVISA (Brazil)[7]	– ("Biological medicine")	– Extrapolation of safety and efficacy data for other therapeutic indications of biological products registered by a comparability pathway will be established through specific guides. – Extrapolation of the indications will be possible after demonstrated comparability in terms of safety and efficacy between the products. – The clinical test model used to prove the safety and efficacy should be able to detect potential differences, if any, between the products. – The mechanism of action and receptor involved for the different required indications must be the same. – The safety and immunogenicity of biological products must be sufficiently demonstrated.
Mexico (COFEPRIS)[7]	– ("Biocomparable")	– No specific rules; evaluated on a case-by-case basis.

*Differences between conditions of use with respect to these factors do not necessarily preclude extrapolation. A scientific justification should address these differences in the context of the totality of the evidence supporting a demonstration of biosimilarity.
†If the MOA is different or not known, then a strong scientific rationale and additional data will be required[18].
‡For example, results from a non-inferiority trial in an indication where a low dose is used may be difficult to extrapolate to an indication where a higher dose is used, from both efficacy and safety points of view[18].
ANVISA: Agência Nacional de Vigilância Sanitária; CHMP: Committee for Medicinal Products for Human Use; COFEPRIS: Comisión Federal para la Protección contra Riesgos Sanitarios; EMA: European Medicines Agency; FDA: US Food and Drug Administration; MOA: mechanism of action.

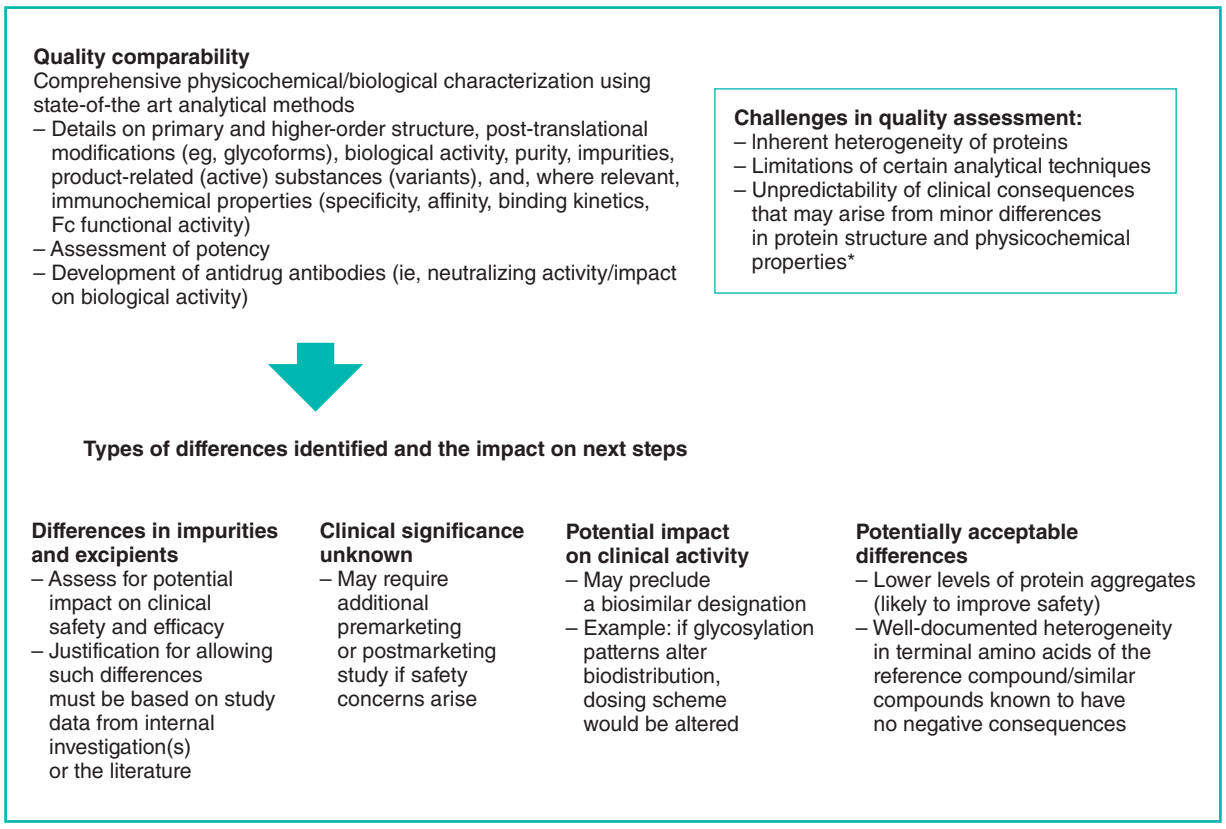

Figure 1. Overview of quality comparability of biosimilars, challenges, and types of differences *(WHO 2009 guidance)*[18]. *For example, the impact of oxidation of certain methionine residues varies among proteins and can range from no impact to substantial reduction in biological activity of the protein, or increased immunogenicity; if such differences are identified between a biosimilar and originator product, further evaluation would be needed. Fc: crystallizable fragment.

types of differences that may be identified[18]. Once analytical similarity is demonstrated, this can provide a rationale for reducing the amount of nonclinical and clinical data required to establish biosimilarity[18]. The WHO guidance favors a "case-by-case" approach for each class of products and identifies several factors that help determine the amount of data needed, including the biological product/product class, extent of characterization using state-of-the-art analytical methods, observed/potential differences between the biosimilar and originator product, and clinical experience with the product class (e.g. safety/immunogenicity concerns in a specific indication)[18]. Of note, the dosage form and route of administration of a biosimilar product must be the same as that of the originator product[18-20].

The FDA also suggests a stepwise approach similar to the other regulatory agencies, noting that approval will be based on the totality of the evidence[21]. The requested evidence includes analytical studies demonstrating similarity to the originator product "notwithstanding minor differences in clinically inactive components," animal studies (including toxicity), and comparative clinical study(ies) that "demonstrate [similarity in] safety, purity, and potency" in ≥ 1 indication approved for the originator product[21]. The type and extent of animal and clinical studies needed are influenced by the ability to detect differences between a biosimilar and an originator product using state-of-the-art assays[22]. Of note, the manufacturer of an originator product will have extensive knowledge/information about the product and aspects of the process such as the established controls and acceptance parameters, whereas the biosimilar manufacturer will be using a different process without direct knowledge of

what processes are in place for the reference product[22].

In Latin American countries, regulatory authorities are moving toward more established standardized pathways for approval of biosimilars; however, there is much variability between countries and in some instances the regulatory processes regarding biosimilars may not be as strict as those in the EU and USA[7,23]. The nomenclature used by local authorities also differs between countries; biosimilars are referred to as "biological medicines" in Brazil, whereas the term "biocomparables" is used in Mexico[7].

Indication extrapolation

Indication extrapolation refers to the approval of a biosimilar for treatment in indications for which it has not been clinically studied[1]. Important considerations and criteria for IE that have been identified by the European Medicines Agency (EMA), FDA, and WHO are summarized in table 1.

The scientific approach to indication extrapolation

A scientific approach to IE focuses on the MOA of the originator and the biosimilar products and potential differences between them, as well as potential differences in each of the indicated diseases being considered[24]. The MOA of anti-TNF monoclonal antibodies is not fully understood[24]. Nonetheless, at minimum, even in the absence of "residual uncertainty" in the analytical data, a biosimilar product should have an MOA that is the same as that of the originator product to the extent that it is known[24,25].

In the case of the first approved biosimilar infliximab, the key contributor to differences in the regulatory decision making was the concern raised by potential differences in the MOA in IBD-related indications versus the MOA in rheumatologic indications or the MOA in dermatologic indications[2,5,26]. The MOA of infliximab in IBD may involve crystallizable fragment (Fc)-mediated effector functions that are not, or at least not to the same extent, involved in the rheumatologic and dermatologic diseases for which the originator product is indicated[5,24]. During quality assessment, a difference in glycosylation in the Fc portion of the biosimilar monoclonal antibody molecule was observed; this change was thought to produce the difference in antibody-dependent cellular cytotoxicity (ADCC; an Fc effector-related function) observed in a sensitive in vitro assay[4].

The EMA based their decision to allow IE from rheumatologic to gastrointestinal conditions based on the totality of the evidence provided, including a subsequent in vitro test model that did not detect the difference[4]. The justification for discounting the difference in glycosylation in the Fc portion included that (i) although the original assay detecting a difference was more sensitive, the subsequent model was considered more clinically relevant; (ii) ADCC may be a secondary MOA; (iii) other analytical data suggested that the specific Fc gamma receptor IIIa (FcγRIIIa) may not significantly affect ADCC or monocyte/macrophage activity; and (iv) no published reports of anti-TNF monoclonal antibodies inducing ADCC in human patients were found[4,24]. Health Canada also considered the biosimilar manufacturer's rationale for discounting the difference in Fc glycosylation and subsequent effect on ADCC in the more sensitive assay; they reviewed the literature and concluded that ADCC could not be ruled out as an MOA in IBD[5]. The rationale for Health Canada's conclusion was that (i) another anti-TNF that lacks the ability to induce ADCC (certolizumab pegol) had minimal efficacy in patients with CD compared with other anti-TNFs, including infliximab, and (ii) there were notable differences in the safety profile of infliximab between the patient populations studied in the dossier (i.e. RA and AS) compared with the IBD patient population. Namely, the risk of hepatosplenic T-cell lymphoma may be "uniquely associated" with adolescent and young adult patients with IBD[5]. Thus, Health Canada determined that potential differences in MOA (i.e. ADCC may be an active MOA of

infliximab in IBD, but not in rheumatic disease), as well as pathophysiologic and safety profile differences between disease types, were of sufficient concern to prevent IE of biosimilar infliximab to IBD-related indications based on clinical data in rheumatic diseases[5].

The clinical approach to indication extrapolation

The clinical approach to IE focuses on selecting the most appropriate clinical model(s) to provide the greatest chance of detecting differences in efficacy and/or safety when comparing the biosimilar product to the originator product. The regulatory consensus is that clinical evaluation should be conducted in the most sensitive patient/disease population among the potential indications being considered[17,18,21,24]. Key components for establishing the sensitivity of the clinical test model include (i) the population type (i.e. in relationship to the treatment effect size), (ii) the endpoints being examined, (iii) the dosages used, and (iv) the time point(s) of assessments; specific details of these components have been reviewed in more detail elsewhere[24].

Notably, the most sensitive population for assessment of clinically meaningful differences in efficacy is not necessarily the most sensitive for assessing potential clinically meaningful differences in safety and/or immunogenicity[27].

The case of biosimilar infliximab illustrates the complexities inherent in IE for biosimilars. In natural killer cells from CD patients with genotypes V/V and V/F at amino acid residue 158, the biosimilar bound less strongly to FcγRIIIa compared with the originator product; in contrast, in cells with genotype F/F (wild-type), binding was comparable between the biosimilar and the originator product[4]. These differences in binding to FcγRIIIa among the genotypes observed at a cellular level may translate to differences in patient response to treatment[24]. Although it is impractical to have separate clinical studies in each type of patient population, identifying the most sensitive population(s) is needed for accurate clinical comparison of key parameters[24].

Immunogenicity

Antidrug antibodies (ADAs) do not typically form until 6-12 months after initiation of treatment with a biological product; therefore, to make an appropriate assessment regarding the immunogenicity profile of a biosimilar product, long-term (i.e. at minimum one year after treatment) comparative ADA data are needed for the indication being tested[18,24,28,29]. Critically, timing and incidence of ADA formation may differ between patient populations[30]. For example, in patients with RA, ADAs to infliximab were reported to rise from 13% after the initial two infusions to 30% at three months and 44% at six months (the rise in ADAs was associated with lower infliximab trough levels)[30,31]. In a study of patients with CD, 14% of patients developed ADAs over approximately one year (54 weeks) of treatment with infliximab. The differences in ADA rates observed with infliximab treatment in RA and CD populations imply that the immunogenicity potential of a biosimilar could also differ from the tested indication to other indications[24]. In addition, fully validated and highly sensitive assays are needed to accurately detect ADAs because methodologic issues (including nonspecific binding) may undermine the ability to make accurate assessments. In the CD study described above, ADA assessments were rendered inconclusive in almost half (46%) of patients because infliximab was detected in the serum samples and, because of limitations of the assay employed, could compete for detection of ADAs[24,31]. Further complicating the assessment of immunogenicity potential is concomitant use of immunosuppressant treatments that may be common with certain indications[24]. Factors that can complicate the assessment and extrapolation of immunogenicity data are summarized in table 2. When considering extrapolation of efficacy and safety data, it is important to investigate the immunogenicity of

Table 2. Factors complicating extrapolation of immunogenicity data

ADA formation may vary in different patient/disease populations[24]
Concomitant use of an immunosuppressant may impact ADA formation[35-37]
Immunogenicity may change with long-term exposure (induction of tolerance vs. increased ADAs)[24]
Methodologic issues with assays may lead to inadequate assessments[24,31]

ADA: antidrug antibody.

biosimilar products in the patients most likely to mount an immune response or to experience immune-related adverse events to better establish whether IE is feasible[18].

Clinical implications for gastroenterologists

In response to the approval of infliximab biosimilar monoclonal antibodies, the European Crohn's and Colitis Organisation (ECCO) has conducted web-based surveys of IBD specialists to assess their awareness of and readiness to use such biosimilar products[32,33]. The first such survey was conducted in 2013 (the year biosimilar infliximab was introduced) and a follow-up survey was conducted in 2015 (after the biosimilar had been available for two years)[32,33]. A total of 307 and 118 ECCO members responded to the 2013 and 2015 surveys, respectively[32,33]. While experience with the newly approved biosimilars could not be assessed in the 2013 survey, in the 2015 survey, most (82%) respondents reported that they had access to biosimilar products and over half (60%) had prescribed them in the past year[33].

Both surveys explored the views of respondents on IE. When given a hypothetical scenario of two randomized clinical trials (one each in rheumatology and CD patients) showing no difference between the biosimilar and originator products, approximately half (51%) of 2015 survey respondents agreed that the biosimilar should be approved for all originator indications, whereas only about one-fourth (24%) of 2013 survey respondents had concurred[33].

When considering one randomized clinical trial in CD patients that showed no differences between a biosimilar and an originator product, 35% of the 2015 survey respondents would use the biosimilar in other IBD indications (including off-label uses)[33]. Furthermore, 31% would use the biosimilar in CD and UC, 25% would use it only in CD, and 9% would wait for more evidence in IBD[33]. In comparison, among 2013 respondents, relatively few (16%) would use the biosimilar in CD and UC, about half (53%) would limit use to CD, and almost one-third (30%) would not use the biosimilar for either CD or UC without further evidence[32].

Based on the results of these two surveys, it appears that concerns and uncertainties regarding use of biosimilars, including on IE, were prevalent in gastroenterology clinical practices in 2013, but declined in subsequent years. While these findings reflect shifts in perceptions regarding biosimilars, it is important to note that participants in the original survey were not necessarily the same as those in the follow-up survey, and that the number of survey respondents was much lower in the follow-up survey; therefore, statistical comparisons cannot be made[33]. In addition, although confidence in use of biosimilars and acceptance of indication extrapolation appear to have increased, it should be noted that most IBD specialists remain opposed to automatic substitution of an originator with a biosimilar by non-physicians[32,33].

The 2013 ECCO position statement on the use of biosimilar medicines in the treatment of IBD generally advocates for "sound scientific

evidence" and a "patient first" approach as the chief drivers of clinical decisions[16]. While recognizing the potential cost savings associated with use of biosimilars, ECCO also recommends rigorous evaluation of efficacy and safety of the biosimilar compared with the appropriate originator product within the IBD patient population[16]. Among the key guiding principles is the concept that a biosimilar proven effective and safe for one indication may not necessarily be effective and safe for a second indication for which the originator product has been shown to be safe and effective[16]. Additionally, specific evidence from patients with IBD is recommended to establish efficacy and safety in this indication[16]. Particularly, the 2013 ECCO position statement notes that, for patients with IBD, decisions related to therapeutic equivalence and interchangeability of biosimilars must be considered carefully[16]. However, the British Society of Gastroenterology (BSG) in 2016 recommended that stable patients can be switched to infliximab biosimilar, although recommended against automatic substitution without the endorsement of the prescribing physician[34]. This decision was based on observational studies in IBD and the premise that physiologic differences between the originator and the biosimilar were not considered to be "clinically meaningful"[34].

Conclusions and recommendations

Biosimilarity is established with comprehensive quality comparisons followed by comparative nonclinical and clinical studies. Differences identified during the quality comparison may have clinical implications and must be investigated. The advent of biosimilar monoclonal antibodies raises important issues around IE. Although analytical data might provide the foundation for use of a biosimilar for the specific indication tested, additional factors must be considered when determining the appropriateness of IE[24]. The current abbreviated regulatory processes are facing challenges regarding IE of complex biologics, such as monoclonal antibodies, particularly when potentially different MOAs and possible differences in disease pathogenesis and safety profiles are involved in the indications being considered[24]. In addition, immunogenicity may differ between patient/disease populations and have implications for IE[24,30]. Of particular relevance to gastroenterologists is whether clinical study data in non-IBD indications, taken together with the analytical and preclinical data, form an adequate basis for approval of a biosimilar in IBD-related indications. In the case of the first approved biosimilar infliximab, there were differences in the decisions regarding IE among regulatory authorities. The current 2013 ECCO guidance examines this issue and recommends rigorous evaluation of comparative efficacy and safety within patients with IBD to establish that a biosimilar is effective and safe for this specific indication[16]. A key supportive argument for this approach is based on experience with currently licensed biological medicines[16]. The results of ongoing studies of biosimilar infliximab in patients with IBD are anticipated to help to better inform clinical decisions regarding this product.

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