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Position Paper

Use of biosimilars in inflammatory bowel disease: a position update of the Italian Group for the Study of Inflammatory Bowel Disease (IG-IBD)

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ABSTRACT

The first infliximab biosimilar for the treatment of inflammatory bowel disease (IBD) was introduced in 2013, and today eight anti-TNF alpha biosimilars (three for infliximab and five for adalimumab) have been approved and licensed by the European Medicines Agency. Biosimilars present great potential in terms of cost saving and possible consequential reinvestment in the health care system. The increasing knowledge about the process of biosimilar development and use in IBD and the publication of many prospective clinical studies and real-life clinical experiences have progressively changed the point of view of IBD physicians. In the present position paper, the Italian Group for the Study of Inflammatory Bowel Disease present and discuss their updated statements and positions on this topic, with emphasis on the concepts of biosimilarity and extrapolation across indications, safety and immunogenicity, interchangeability and switching, automatic substitution, and, finally, patient education about biosimilars.

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1. Introduction

Biosimilars are biological medicinal products that are similar, but not identical, to an approved biological drug, called "originator" or "reference product" [1]. Like biological drugs, biosimilars are drugs obtained from biological sources (i.e. they are not synthesized), and thus can take on many biochemical forms, including vaccines, gene therapies and recombinant proteins such as growth factors and monoclonal antibodies. Because biological drugs are complex molecules made by living organisms that are naturally variable [2], biosimilars cannot be considered an exact copy of the originator, as instead synthetic chemical drugs are. Thus, the procedures (i.e. in the preclinical phase) for approval and use of biosimilars are more complex than those for the originators.

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Monoclonal antibodies (mAb) targeting tumor necrosis factor alpha (TNFα), namely infliximab, adalimumab, certolizumab pegol, and golimumab, are biological drugs used in the treatment of inflammatory bowel disease (IBD) and other immune-mediated inflammatory diseases. In particular, infliximab is an intravenously administered chimeric mAb (75% human and 25% murine sequences; IgG1κ) that was approved by the European Medicines Agency (EMA) in August 1999 [3]. Adalimumab is a subcutaneously administered human mAb (IgG1) that was approved by EMA in September 2003 [4]. The EU patents on the infliximab originator (Remicade®, J&J, USA [3]) expired in June 2013 or February 2015, depending on the country, and on the adalimumab originator (Humira®, Abbvie, USA [4]) in October 2018. Thus, three infliximab biosimilars and five adalimumab biosimilars have become available for the same indications as the originators. For infliximab, the biosimilars are: CT-P13 (Inflectra®, Pfizer, USA [5]; Remsima®, Celltrion, South Korea [6]), SB2 (Flixabi®, Samsung Bioepis, South Korea [7], and Biogen, Denmark), and PF-06438179/GP1111 (Zessly®, Sandoz, Germany [8]). For adalimumab, the biosimilars are: ABP 501 (Amgevita®, Solymbic®, Amgen, USA [9]), SB5 (Imraldi®, Biogen Denmark- Samsung Bioepis, South Korea [10]), FKB327 (Hulio®, Mylan, USA [11]; Fujifilm Kyowa Kyrin Biologics, Japan), GP2017 (Hyrimoz®, Sandoz, Germany [12]), and BI 695501 (Cyltezo®, Boehringer Ingelheim, Germany [13]). Other biosimilars of infliximab and adalimumab are expected to be approved in the near future [14].

Before the introduction of biosimilar mAbs in the EU market, several concerns had been raised about their use in clinical practice. An online survey conducted by the European Crohn's Colitis Organisation (ECCO) in 2013 showed that more than 60% of clinicians in Europe had little or no confidence in prescribing biosimilar mAb in clinical practice [15]. The main concerns were about the validity of extrapolating across indications, the potentially higher immunogenicity of biosimilar mAb than the originator, traceability, automatic substitution, and switching from the originator to a biosimilar. These concerns were common in the IBD community, and they were addressed and discussed in several position papers by national and international societies [16–20].

The introduction of the first infliximab biosimilar, the increased knowledge of biosimilars, and the publication of the first cohort studies [21–27] have progressively changed the point of view of IBD specialists. In fact, a follow-up of the above-mentioned ECCO survey revealed that in 2015 more than 80% of clinicians felt confident prescribing biosimilar mAb [28]. Such confidence was supported by three large prospective studies: The NOR-SWITCH randomized controlled trial [29] found no differences in efficacy, safety or immunogenicity between patients treated with infliximab and those who switched from the originator to CT-P13. The PROSIT-BIO observational study [30] and the PROSIT follow-up study [31] found that effectiveness, safety and immunogenicity in patients taking CT-P13 were similar to previously reported data for infliximab. Finally, a recently published, large comparative equivalence cohort study [32], using a French nationwide health administrative database, found no significant differences in terms of effectiveness and safety between Crohn's disease patients treated with infliximab originator and those treated with CT-P13.

Based on the increasing evidence, knowledge, and experience with biosimilars in IBD, a working group of the Italian Group for the Study of Inflammatory Bowel Disease (IG-IBD) decided to review the literature and to update the Italian position on the use of biosimilars in IBD patients [16]. Before publication, the updated statements were approved by IG-IBD members and by representatives of the national IBD patients' association (AMICI Onlus).

2. Biosimilarity and extrapolation across indications

2.1. Statement 1

A biosimilar mAb targeting the same molecule as the originator can be considered equivalent in terms of efficacy and safety when such equivalence is supported by in vitro assays and clinical studies. Extrapolation across indications is acceptable when a biosimilar mAb has been tested on one or more approved indications and has been approved and licensed by EMA.

The EMA defines a biosimilar of a mAb as a molecule that is highly similar to the reference product in terms of efficacy, safety and immunogenicity [33]. The approval process for biosimilar mAb in the EU is standardized and guarantees the quality of the product evaluated and licensed for market. The process requires robust preclinical evidence of biosimilarity, whereas clinical efficacy can be confirmed in a limited number of clinical trials conducted on the most "sensitive" indications for the reference product. To document any differences in biological activity between the biosimilar and the originator, data from comparative in vitro assays are required. These studies should demonstrate binding to target antigen(s), binding to representative isoforms of the relevant three Fc gamma receptors, Fab-associated functions (e.g. neutralization of a soluble ligand, receptor activation or blockade), and Fc-associated functions. Based on the in vitro data provided, EMA requests in vivo studies in those conditions where in vitro studies cannot investigate possible effects of the biosimilar drug [34]. Finally, the EMA requires that clinical studies be conducted in sensitive clinical models and study conditions, and the model should be relevant in terms of efficacy, safety, and sensitivity to demonstrate comparability in the indication(s) applied for [34].

After this comparability exercise and step-wise approach, EMA authorizes the extrapolation across indications from the most sensitive to all the other approved indications. Data on specific populations, such as children or the elderly, are not required for approval or extrapolation [34]. CT-P13 was approved for all indications based on two clinical trials, one on ankylosing spondylitis [35] and another on rheumatoid arthritis (RA) [36]. The same approach was used for SB2 with clinical trials on RA [37–39], for PF-06438179/GP1111 with a clinical trials on RA [40], for ABP 501 with clinical trials on RA and plaque psoriasis [41,42], for SB5 with clinical trials on RA [43,44], for BI 695501 with a clinical trial on RA [45], for GP2017 with clinical trials on RA and plaque psoriasis [46,47] and for FKB327 with clinical trials on RA [48,49].

Extrapolation has been strongly debated over the past years, and was one of the main concerns in the IBD community to accept biosimilars in their clinical practice. However, extrapolation is not a new concept, and it is based on solid arguments deriving from preclinical and clinical evidence [50]. The basic concept supporting the extrapolation of data on CT-P13, SB2, PF-06438179/GP1111, ABP 501, SB5, BI 695501, GP2017 and FKB327 lies in the mechanism of binding to TNFα, which is common for all immune-mediated diseases (e.g. RA, ankylosing spondylitis, IBD, and psoriasis); possible differences between originator and biosimilars related to Fc-region were carefully addressed and included in the comparability exercise [34]. Clinical data from several cohort studies [21–27,30–32] and the NOR-SWITCH randomized controlled trial [29] support the clinical value of extrapolation from other conditions to IBD. In particular, no significant differences in efficacy, effectiveness, safety or immunogenicity were found between IBD patients who were started with infliximab originator and those with CT-P13 [32] or between IBD patients who maintained treatment with infliximab originator and those who switched from infliximab originator to CT-P13 [29]. Therefore, the same approach should be adopted for the extrapolation of adalimumab biosimilars from other conditions

to IBD. The Italian Regulatory Agency (AIFA) approves this approach and considers it sufficient to demonstrate the quality of a licensed biosimilar so to be reimbursed by the National Healthcare System [51].

3. Safety and immunogenicity

3.1. Statement 2

Licensed biosimilars can be considered as safe as the originator. However, large observational studies are needed to monitor the long-term safety of biosimilars, and registries supported by all involved stakeholders should be developed.

3.2. Statement 3

Any event related to the immunogenicity of a mAb cannot be overcome by a biosimilar of the same molecule.

The safety profile of biosimilars has been the main outcome investigated since biosimilars have been launched on the market. Preliminary data from different countries did not show an increased rate of adverse events related to the use of infliximab biosimilars in IBD [21,23–24,26–27]. The NOR-SWITCH trial [29] also revealed no increased risk of adverse events, loss of response or infusion reactions in patients that switched from the originator to CT-P13.

The large "real-life" cohort of 547 IBD patients treated with a biosimilar, namely the PROSIT-BIO cohort [30], had as its primary outcome the safety of CT-P13, defined as the numbers of all adverse events, adverse events leading to discontinuation, and infusion reactions. This study found that the overall safety profile of CT-P13 was no different from what was expected for the reference product. Although 66 adverse events occurred in this study, there was no difference in their frequency or severity between the 313 infliximab-naïve patients treated with CT-P13, the 97 who switched from the originator to CT-P13, and the 139 who had been previously exposed to other anti-TNFα. However, infusion reactions were significantly more frequent in the patients previously exposed to anti-TNFα, with an incidence rate ratio (IRR) of 4.7 vs. naïve ($p < 0.001$) and 3.25 vs. switched ($p < 0.001$). This increased risk was greater in patients previously exposed to infliximab (IRR = 2.82; 95% CI, 1.05–7.9) than in those exposed to other anti-TNFα, indirectly demonstrating cross-reactivity between CT-P13 and the originator. Further expansion of the original PROSIT-BIO cohort confirmed the safety of CT-P13 in 810 IBD patients through a median follow-up of 327 days (IQR, 161-530) [31]. Infusion reactions leading to discontinuation were again significantly more frequent in patients pre-exposed to infliximab (10.7%) than in naïve patients (6.1%, $p = 0.04$ vs. pre-exposed) and in those who switched to CT-P13 (2.6%, $p = 0.008$ vs. pre-exposed). The rates of serious adverse events were 18.5, 74.0 and 48.5 per 100 person-years in the switched group, anti-TNFα naïve and anti-TNFα pre-exposed patients, respectively.

In the French comparative equivalence cohort study, 2551 patients with Crohn's disease were treated with infliximab originator and another 2499 patients were treated with CT-P13 [32]. Multivariate analyses did not reveal significant differences in serious infections (hazard ratio (HR) = 0.82; 95% CI, 0.61–1.11), tuberculosis (HR = 1.10; 95% CI, 0.36–3.34) or cancer (HR = 0.66; 95% CI, 0.33–1.32) between the two treatment groups.

Recently, a systematic review [52] of clinical studies about switching from biological originators to biosimilars (including 48 studies about switching from infliximab) found no differences in terms of safety and immunogenicity.

A recent in vitro study aimed to determine whether antibodies to infliximab cross-react among infliximab originator and two different infliximab biosimilars [53]. This study examined sera from 34 IBD patients who had been treated with the originator or with CT-P13, or had switched from the original to CT-P13, and had subsequently developed anti-infliximab antibodies. The patients' antibodies were found to recognize the originator, CT-P13 and SB2 equally well, irrespective of which molecule a patient had received in treatment. This finding of cross-reactivity suggests that the three molecules are similarly immunogenic. However, safety data for patients exposed to the two biosimilars are missing.

With regard to adalimumab biosimilars, no safety or immunogenicity data are available for IBD patients, but preclinical and clinical data from RA and psoriasis patients show that the safety and immunogenicity profiles do not differ among the five EMA-approved adalimumab biosimilars and the originator [9–13,41–49]. As is the case for infliximab biosimilars, large observational studies are needed to monitor the long-term safety and immunogenicity of these drugs, and the development of registries supported by all involved stakeholders should be encouraged.

4. Interchangeability and switching

4.1. Statement 4

Once biosimilarity has been confirmed, any biosimilar can be considered interchangeable with the reference product.

4.2. Statement 5

Switching from the originator to a biosimilar of the same molecule is acceptable.

Switching from one biosimilar to another of the same originator and multiple switches among different molecules should be avoided in the absence of direct evidence of efficacy and safety.

One of the main concerns since biosimilars have been licensed is the switching of patients from the originator to a biosimilar. In 2013, only 6% of surveyed clinicians considered the originator and the biosimilars interchangeable [15]. There is no agreement on the definition of interchangeability among regulatory agencies. The World Health Organization (WHO) considers interchangeable any "pharmaceutical product . . .which is therapeutically equivalent to a comparator product" [54]. EMA does not have its own definition of interchangeability, but states that the definition should be set at the national level [33]. The Italian Drug Agency (AIFA) adopts the WHO's definition [54]. Thus, in Italy, a biosimilar should be considered interchangeable with its own originator. This position has recently been stated and confirmed by AIFA [51].

According to a systematic review [52], switching from the infliximab originator to an infliximab biosimilar is supported by various studies, especially NOR-SWITCH [29]. This randomized controlled trial enrolled 482 patients already in treatment with infliximab originator for the maintenance of remission of various immune-mediated diseases including Crohn's disease (n = 155), ulcerative colitis (n = 93), spondyloarthritis, RA, psoriatic arthritis, and chronic plaque psoriasis. Patients were randomized to continue with infliximab originator or to be switched to CT-P13, and followed for 52 weeks. Disease worsening was observed in 53 patients (26.2%) in the infliximab originator group and 61 patients (29.6%) in the CT-P13 group, for an adjusted treatment difference of −4.4% (95% CI, −12.7% to 3.9%). Because this difference was below the pre-established cutoff of 15%, the study concluded that CT-P13 is noninferior to its originator. Among patients with Crohn's disease, worsening occurred in 21.2% and 36.5%, respectively (adjusted risk difference, −14.3%), and for those with ulcerative colitis disease worsening was seen in 9.1% and 11.9%, respectively (adjusted risk

difference, −2.6%). The frequencies of adverse events were similar between the infliximab originator group and the CT-P13 group: all adverse events, 68% vs. 66%; serious adverse events, 10% vs. 9%; and adverse events leading to discontinuation, 4% vs. 3%, respectively.

In the PROSIT-BIO study [30], a subset of 97 patients switched to CT-P13 after a mean of 18 infliximab infusions (SD = 14). No differences in safety or efficacy were observed between these switched patients and the 313 anti-TNFα naïve patients also treated with CT-P13. In the expanded PROSIT-BIO cohort [31], 155 patients switched to CT-P13 after a mean of 17 infliximab infusions (SD = 13). As in the original PROSIT cohort, no significant differences in safety or efficacy were found between switched and naïve patients. Finally, a prospective study of a Swedish cohort of 313 IBD patients switched from the originator to CT-P13 also found no increased risk of adverse events (including infusion reactions) or loss of response [55].

These data have been confirmed by several studies (reviewed in Ref. [52]), leading to the conclusion that switching between the infliximab originator and one of its biosimilars is acceptable and safe, without concerns about efficacy, safety or immunogenicity. With regard to adalimumab biosimilars currently approved by EMA, data on switching from the originator to a biosimilar in IBD patients are currently lacking. However, the different molecules have negligible differences in structure, and preclinical data show essentially the same biological effects as the originator and very similar pharmacological characteristics [9–13]. Moreover, clinical studies of switching in RA patients [43–46,48,49] and psoriasis patients [42,47] also found that the efficacy, safety and immunogenicity profiles do not differ among the five EMA-approved adalimumab biosimilars and the originator. The totality of evidence from preclinical and clinical studies thus supports the concept of switching from adalimumab originator to an adalimumab biosimilar also in IBD patients. In the absence of data from real-life experiences or large clinical studies, the switching of an IBD patient from adalimumab originator to an adalimumab biosimilar should only be done after a clinical evaluation. Other issues that should be considered, when choosing among available adalimumab formulations, are differences in terms of their excipients and administration devices (e.g. citrate versus citrate-free buffer, low-volume 80 mg versus 40 mg pen/syringe) [4,9–13], because they can potentially impact on patients' treatment adherence/persistence.

Clinical studies on the safety or efficacy of switching from one biosimilar to another of the same originator and multiple switch have not yet been reported. Thus the IG-IBD recommends against switching patients from one biosimilar to another biosimilar and multiple switch until clinical data supporting this practice become available. This position is consistent with that of the ECCO [56].

5. Automatic substitution

5.1. Statement 6

Automatic substitution must be avoided. The clinician alone is responsible for the prescription of a biological drug, and no pharmacist or other health care operator may assume this responsibility.

Automatic substitution is a practice that allows a pharmacist or other health care operator to replace a branded drug prescribed by a physician with a generic drug without consulting the prescribing specialist. This practice is common for synthesized drugs but is not applicable to biological drugs that are subject to different regulations, as stated by AIFA [35]. AIFA also states that the decision to prescribe the originator or a biosimilar must be left to the prescribing clinician, who should take into account the affordability of the prescription itself. Therefore, no other stakeholder is allowed to change the prescription of a biological drug made by a physician, and hospital policies should not limit the free prescription of these drugs. However, we recommend that the availability of certain biosimilars in a hospital be agreed upon between prescribing physicians and hospital administrators, with the purpose of maintaining costs incurred in the use of biological therapies.

6. Patient education about biosimilars

6.1. Statement 7

Patients' awareness about biosimilars should be fostered through education and the provision of up-to-date information, to let them make informed choices. Switching from an originator to a biosimilar should be done only after the patient has received appropriate information and has agreed.

As for any new medicinal product, biosimilars too have raised questions and concerns among patients. Their skepticism may be related to doubts about the effectiveness or safety of the products or about the way they are approved [57]. Therefore, a physician's proposal for therapy with a biosimilar, whether as a first drug or as replacement of an originator, may be viewed negatively by a patient, in particular if their knowledge about biosimilars is low. This reluctance could translate into low acceptance of biosimilar therapy and may even impair treatment outcomes (i.e. nocebo effect) [58]. A recent survey of patients with IBD, RA, psoriasis and certain cancers in the United States and European Union found low levels of awareness about biosimilars [59]. Moreover, the European Federation of Crohn's and Ulcerative Colitis Associations found that only 38% of 1181 surveyed IBD patients had heard of biosimilars, and many of them expressed concerns about these drugs' safety (46.5%) and efficacy (38.6%) [60]. These results suggest that patients should be provided reliable, up-to-date information to help them understand biosimilars and enable them to make informed choices about their treatment options.

7. Conclusions

This paper states the current position of the IG-IBD, a group of Italian physicians specialized in the management of IBD, on the use of biosimilars in Italy. Biosimilars represent a great opportunity for wisely saving money for the National Healthcare System and also create an opportunity for improving patient care, with reinvestment of the saved money (e.g. "gain-share"). When a biosimilar is approved by EMA according to the strict regulations applied to this drug class, we consider it equivalent to its originator. Switching from the originator to a biosimilar is acceptable, because this approach is safe, efficacious and leads to a significant cost reduction for the health care system and subsequently to the possibility of treating more patients. Careful pharmacovigilance should be done for biosimilars as for all biologics. Clinicians are fully responsible for the prescription of biosimilars, and these drugs cannot be automatically substituted by a pharmacist or other health care operator. Until supportive clinical evidence becomes available, cross-switching or multiple switching among biosimilars is not recommended. Finally, patients should be educated about biosimilars to improve their awareness of this drug class to enable them to make informed choices.

Conflicts of interest

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