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Viewpoint

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Belgian IBD Research Group [BIRD] Position Statement 2019 on the Use of Adalimumab Biosimilars in Inflammatory Bowel Diseases

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Abstract

The emergence of biosimilars is generally considered as an opportunity to guarantee accessibility to affordable treatments and to enhance financial sustainability of national health systems. Since 2017, five biosimilars of adalimumab were approved by the European Medicines Agency [EMA] for use in inflammatory bowel disease: ABP 510, SB5, GP2017, FKB327, and MSB11022. In this position statement, the available efficacy and safety data of the different adalimumab biosimilars in immune-mediated inflammatory diseases are summarised. Furthermore, the Belgian IBD research group [BIRD] formulates statements concerning the use of adalimumab biosimilars in inflammatory bowel disease.

Key Words: Adalimumab; biosimilars; inflammatory bowel disease; IBD

1. Introduction

Biosimilars are not a new concept in the field of inflammatory bowel disease [IBD]. Since the approval of the first infliximab biosimilar by the European Medicines Agency [EMA][1] in 2013, extensive data and experience concerning the use of infliximab biosimilars in immune-mediated inflammatory diseases are available. A biosimilar contains a version of the active substance of an already authorised biologic [called 'reference product'], but is not identical with it.[2] The European legislation has offered since 2006 a legal framework for biosimilars. The EMA requires that 'similarity to the reference medicinal product in terms of quality characteristics, biological activity, safety and efficacy based on a comprehensive comparability exercise needs to be established'.[2] The concept and methodology of the comparative investigations are further elaborated in the guidelines of the EMA.[2] Since 2017, five biosimilars of adalimumab were approved by the EMA for use in inflammatory bowel disease [IBD].[3–7] Following the BIRD recommendations in 2015[8] and the BIRD position statement on the use of infliximab biosimilars for IBD in 2017,[9] we now present a position paper in order to summarise the available efficacy and safety data of the adalimumab biosimilars. In the next section, the evidence on which the approval of the EMA was based is summarised for the five adalimumab biosimilars that are available for use in Belgium as of 2019 [Table 1]. The order in which the different molecules are discussed is based on the date of approval by the EMA. Of note, many more biosimilars are in development [www.gabionline.net].

2. Different Biosimilar Preparations for Adalimumab

2.1. ABP 501

ABP 501 [Amgevita®, Amgen] was the first adalimumab biosimilar that was approved by the EMA in 2017. Comparative analysis has

Table 1. Major characteristics and endpoints of the different EMA-approved adalimumab biosimilars available in Belgium.[3–7,13,15,17,20,22]

		ABP 501	SB5	GP2017	FKB 327	MSB11022
Brand name	Humira®	Amgevita®	Imraldi®	Hyrimoz®, Hefiya®, Halimatoz®	Hulio®	Idacio®, Kromeya®
Formulation	Mannitol, polysorbate 80, water for injections	Glacial acetic acid, sucrose, polysorbate 80, sodium hydroxide quantum	Sodium citrate dihydrate, citric acid monohydrate, L-histidine, L-histidine hydrochloride monohydrate, sorbitol,polysorbate 20	Adipic acid, citric acid monohydrate, sodium chloride, mannitol, polysorbate 80, sodium hydroxide, hydrochloric acid, water for injection	Monosodium glutamate, sorbitol, methionine, polysorbate 80, hydrochloric acid, water for injection	Sodium dihydrogen phosphate dihydrate, disodium phosphate dihydrate, mannitol, sodium chloride, citric acid monohydrate, sodium citrate, polysorbate 80, sodium hydroxide, water for injection
Volume [mL]	0.4	0.8	0.8	0.8	0.8	0.8
Needle size [gauge]	Syringe: 29 Pen: 29	Syringe: 29 Pen: 27	Syringe: 29 Pen: 29	Syringe: 27 Pen: 27	Syringe: 29 Pen: 29	Syringe: 29 Pen: 29
Study population in psoriasis RCT [number of patients]		Moderate-to-severe plaque psoriasis [350]	-	Moderate-to-severe chronic plaque psoriasis [465]	-	moderate-to-severe chronic plaque-type psoriasis [443]
Primary endpoint in psoriasis RCT		PASI score percent improvement from baseline to Week 16 [also 52-week follow-up]	-	Proportion of patients who achieved PASI 75 at Week 16 [also 51-week follow-up]	-	PASI 75 response rate after 16 weeks [also 52-week follow-up]
Study population in RA RCT [number of patients]		Moderate-to-severe active RA[4] [526]	Moderate-to-severe active RA[4] [544]	-	Moderate-to-severe active RA[4] [730]	-
Primary end point in RA RCT		20% improvement from baseline in ACR 20 at Week 24	20% improvement response rate on ACR 20 at Week 24 [also 52-week follow-up]	-	Response rate of ACR 20 at Week 24 [also 76-week follow-up]	-

RCT, randomized controlled trial; PASI, psoriasis area severity index; ACR, American College of Rheumatology response rate; RA, rheumatoid arthritis.

shown that ABP 501 and the originator adalimumab are highly similar molecules with respect to physicochemical properties[10] and biological activity.[11] Furthermore, a phase I study showed similar pharmacokinetics [PK] between ABP 501 and the adalimumab originator [both the US and the EU formulations] after a single 40 mg subcutaneous [SC] injection.[12] In a phase III trial in 350 patients with moderate-to-severe plaque psoriasis, ABP 501 demonstrated clinical similarity to the adalimumab originator from baseline to Week 16 of treatment, as measured by the percent improvement in Psoriasis Area Severity Score [PASI] response.[13] Patients who achieved PASI 50 at Week 16 continued on study until 52 weeks; patients who initially started the originator were rerandomised 1:1 to either continue the originator or to switch to ABP 510.[14] PASI 50/75/90/100 responses across the three groups were similar until the end of this maintenance study. Adverse events [AE] were balanced between treatment groups and similar to the known safety profile of the adalimumab originator. The frequencies of developing antidrug antibodies [ADAs] was balanced between each treatment group, including those patients who transitioned from the originator to ABP 501.[14] Another phase III study in 526 patients with moderate-to-severe active rheumatoid arthritis [RA] demonstrated similar clinical efficacy, safety, and immunogenicity between ABP 501 and the adalimumab originator during 24 weeks of follow-up.[15]

2.2. SB5

Pharmacokinetic similarity between SB5 [Imraldi®, Biogen] and the adalimumab originator [EU and US] was demonstrated in a PK study in healthy subjects.[16] Equivalent efficacy between SB5 and the adalimumab originator was shown in a phase III study, in 544 patients with moderate-to-severe active RA, with regard to the primary endpoint—American College of Rheumatology 20 response rate [ACR20] —and other efficacy endpoints at Week 24.[17] The safety profile of SB5 was also comparable to that of the originator, with similar incidence rates of treatment-emergent adverse events [TEAEs], serious infections, and injection site reactions, and with similar incidence of ADAs.[17] In a subsequent phase III transition study, patients in the originator group were rerandomised 1:1 at Week 24 to either continue with the originator or switch to SB5, and patients on SB5 continued this regimen.[18] Over the course of the study, ACR response rates were similar across all treatment groups up to Week 52, demonstrating maintained efficacy after transition from the originator to SB5. After transition, safety profiles across treatment groups were comparable, as was the incidence of ADAs. The authors stated that 'switching does not have negative effects in terms of reduced efficacy or increased AEs or immunogenicity', though the study was not designed for statistical comparisons of equivalence.[18]

2.3. GP2017

A phase I study in healthy subjects showed bioequivalence between GP2017 [Hyrimoz®, Halimatoz®, Hefiya®, Sandoz] and the adalimumab originator [EU and US], without clinically relevant differences in safety, tolerability, and immunogenicity.[19] In a 51-week double-blinded, phase III study in 465 patients with moderate-to-severe chronic plaque psoriasis, Blauvelt *et al.* randomly assigned patients to GP2017 or the originator.[20] Responders at Week 16 were rerandomised in a 2:1 ratio; they continued their originally assigned treatment until Week 35 or they received either GP2017 or the originator during three alternating 6-week periods. After 16 weeks of treatment, equivalent efficacy—assessed by the PASI 75—was shown between GP2017 and the originator. Furthermore, no relevant differences in mean trough serum drug concentrations and safety profile [overall and treatment-related AEs, serious or severe AEs] was shown over the 51-week period for all treatment groups. The authors stated that 'switching between adalimumab originator and GP2017, up to four times in a subset of patients, had no detectable impact on efficacy, safety or immunogenicity'.[20] On the other hand, it is important to mention that this study was not powered to assess treatment switching.

2.4. FKB327

A phase I study in healthy subjects demonstrated similar pharmacokinetics of FKB327 [Hulio®, Mylan] and the adalimumab originator [EU and US] after administration of a single dose of 40 mg.[21] Efficacy, safety, and immunogenicity of FKB327 were evaluated in a phase III study in 730 patients with moderate-to-severe active RA.[22] Patients in the FKB327 group and the originator group had comparable ACR20 response rates at Week 24 and similar mean serum trough concentration-time profiles.[22] The two groups were comparable with regard to the prevalence and titres of ADAs and the reporting of TEAEs.[22] In a following randomised open-label extension study, treatment responders were rerandomised to FKB327 or the originator.[23] Interim analysis at Week 30 showed comparable ACR20 response rates after continuous [FKB327–FKB327] and switched [FKB327–originator, originator–FKB327] treatment, without consistent differences in PK and ADAs profiles between treatment groups.[23]

2.5. MSB11022

A phase I study demonstrated bioequivalence between MSB11022 [Idacio®, Kromeya®, Fresenius Kabi] and the adalimumab originator in healthy volunteers.[24] In a comparative analysis at the physicochemical and functional levels, a high similarity of MSB11022 and the originator was shown as well.[25] In a phase III study, 443 patients with moderate-to-severe chronic plaque-type psoriasis were randomised to receive MSB11022 or the originator.[26] Equivalent efficacy [defined as PASI 75 response rate] was shown after 16 weeks of treatment. In the following extension study, responders [patients who achieved PASI 50] continued treatment up to Week 52.[26] Patients initially randomised to receive MSB11022 continued this treatment, and patients initially randomised to receive the adalimumab originator were rerandomised 1:1 to either continue the originator or switch to MSB11022. PASI response rates were comparable between the MSB11022, continued reference adalimumab, and switch arms. Furthermore, mean trough levels up to Week 52 were comparable across the three treatment groups. Over the course of the study, MSB11022 and the originator showed a comparable safety profile up to Week 66, with similar immunogenicity and no new safety signals observed.[26]

3. Extrapolation

During the past few years, some concerns have been raised about the use of biosimilars in indications that have not been formally investigated during the clinical development of the biosimilar, hampering their use in clinical practice.[27] Nonetheless, the scientific principle of extrapolation of data is not new for biosimilars; it has already been exercised for many years with changes in the manufacturing process for originator biologics, where often important changes were observed.[28] After similarity of the specific biosimilar has been properly proven, the EMA authorises the extrapolation to other indications of the reference product when there is appropriate scientific justification.[2] The basic concept supporting the extrapolation of data on ABP501, SB5, GP2017, FKB327, and MSB11022 lies in the mechanism of binding to tumour necrosis factor alpha [TNFα], which is

common for all immune-mediated inflammatory diseases and which was included in the comparability exercise by the EMA.[2,29] Since the emergence of the infliximab biosimilars, considerable clinical evidence from cohort studies and the NOR-SWITCH randomised controlled trial have been published.[29–33] Although these studies are not mandatory, they do support the use of biosimilars in an indication which was not evaluated in the pivotal trials.

4. Safety and immunogenicity

Immunogenicity, that is the generation of antibodies, is a specific concern in the use of biologics. Immunogenicity cannot be predicted by preclinical studies.[9] Immunogenicity is associated with enhancement of drug clearance, loss of response, and side effects such as hypersensitivity reactions.[9]

In Belgium, the federal medicinal agency [FAGG/AFMPS] has made a position statement on biosimilars and pharmacovigilance.[9] They recommend development of a risk management plan [RMP] for each new marketing authorisation of a biosimilar, including adequate pharmacovigilance with permanent follow-up of the safety of the medicinal product after authorisation. Furthermore, FAGG/AFMPS states that biosimilars cannot be approved if an increased risk for immunogenicity has been observed; immunogenicity testing of the biosimilar and the reference product should be conducted within the biosimilar comparability exercise by using the same assay format. Identification of the biologic product is very important when reporting adverse events. If the prescriber decides to move from one biologic to the other [originator/originator; originator/biosimilar; biosimilar/originator; or biosimilar-X/biosimilar-Y], adequate follow-up and accurate recording of the modification are necessary.[9]

Concerning the adalimumab biosimilars, no safety or immunogenicity data are currently available for IBD patients. However, in the aforementioned biosimilar trials in RA and psoriasis patients, the safety and incidence of ADAs were comparable between adalimumab biosimilars and the originator.[15,18,20,23,26] Of note, in these studies patients were followed for a rather short period [maximum 52 weeks], hence long-term observational studies are mandatory in evaluating the safety and occurrence of antibodies after 1 year of treatment.

5. Switching and Multiple Switching

There are currently no data concerning switching IBD patients from the adalimumab originator to a biosimilar. However, in the adalimumab biosimilar phase III studies in RA and psoriasis, a proportion of patients were switched after induction. In some trials, multiple switches were constructed [originator to biosimilar to originator, biosimilar to originator to biosimilar]. The published data showed no significant impact on efficacy, safety, or immunogenicity.[13,18,20,23,26] On the other hand, it is important to mention that these studies were not powered to assess treatment switching. As mentioned before, several randomised controlled trials in the field of infliximab biosimilars could not show differences in safety or efficacy between switched and naïve patients.[31–33] In their systematic literature review, Cohen *et al.* assessed clinical outcomes of switching reference products to biosimilars. They stated that: 'The extensive collected data suggest that switching from a reference product to a biosimilar is not inherently dangerous, and that patients, health care professionals, and the public should not assume that it is problematic'.[34] In their position update concerning the use of biosimilars in IBD, the Italian Group for the Study of Inflammatory Bowel Disease [IG-IBD] supports the concept of switching from adalimumab originator to an adalimumab biosimilar in IBD patients, based on the available preclinical and clinical studies.[29] Concerning switching between adalimumab biosimilars, currently no data are reported. Nonetheless, a thorough pharmacovigilance system for all biologics is important for monitoring rare safety events. This can increase confidence of patients and health care professionals in using biosimilars, leading to increased acceptance.[34] Furthermore, the potential of a nocebo effect needs to be taken into account, which could be a significant challenge in therapy with biosimilars. The nocebo effect is defined as a negative effect of a medical treatment that is induced by patients' expectations, and that is unrelated to the physiological action of the treatment.[35] The nocebo effect can alter IBD patients' outcomes by unnecessary cessation of biologic treatment, and could have a negative impact on the cost savings of biosimilars. The health care provider plays an important role in offering the appropriate information and education to the patient, not only about the concept of biosimilars, but also explicitly discussing the possibility of the nocebo effect.[35]

6. Substitution

Substitution, that is the passage of a specialty subject to a prescription to another specialty by the pharmacist, without consulting the physician, is not allowed in Belgium for biologics [including biosimilars], according a revised FAGG/AFMPS position statement on biosimilars and pharmacovigilance.[9,36] Furthermore, from a practical point of view, a change in injection device can impact on the correct administration of the drug and patient preference.[37]

7. Formulations

Adalimumab is administered via subcutaneous injection. The adalimumab biosimilar formulations differ in their excipients and administration devices, which could influence the choice of the physician when considering starting adalimumab in a case [Table 1]. The most common AE with the adalimumab originator in trials were injection site reactions, including erythema and/or itching, haemorrhage, related pain, and swelling.[38] In the past, a number of studies have been published on the possible role of buffers causing irritation or pain upon injection, especially subcutaneous [SC] injection. Most of these studies focused on erythropoietin. Zbacnik *et al.* concluded that these studies suggest that citrate could be problematic in terms of causing pain upon injection.[39] However, other factors are known to play a role in pain perception. Hence, a variety of factors [needle gauge, frequency of administration, administered volume, etc.] need to be considered when assessing pain upon injection, not simply the buffer composition.[39] The current formulation of the adalimumab originator differs from the one that was initially commercialised; it has fewer excipients [it contains no citrate any more], it has a smaller injection volume [0.4 mL instead of 0.8 mL], and the delivery systems have a smaller needle [29 vs 27 gauge]. Two phase II, randomised cross-over studies, in patients with RA, were consistently in favour of the current citrate-free 40 mg/0.4 mL formulation compared with the citrate-containing 40 mg/0.8 mL formulation of the adalimumab originator with regard to injection site-related pain. However, it is not clear which feature[s] of the 40 mg/0.4 mL formulation [composition, volume, and/or needle size] is most responsible for pain reduction.[38]

8. Challenges

The emergence of biosimilars is generally considered as a new opportunity to guarantee accessibility to affordable treatments and to

enhance financial sustainability of national health systems. However increasingly adopted in many European countries, Belgium has one of the lowest biosimilar uptake rates in Europe.[36] In Belgium, the price negotiations are set on a per case basis for each new biosimilar, in contrast to generics where a mandatory price reduction is fixed. For biologics, switching during treatment is only recommended under the supervision of a health care professional. As a result, biosimilar market penetration may depend on physician loyalty to the reference product and physician acceptance of the biosimilar.[36] Therefore it is important to educate stakeholders about biosimilars and to distribute appropriate information from independent institutions about their safety and efficacy.[40] Of course, the health care provider also himself plays an important role in educating the patient about the concept of biosimilars.

Biologic originator companies may offer a collection of support services such as reimbursement assistance for specialty therapies, patient follow-up and adherence services, and patient assistance programmes.[41] In order to stimulate the uptake of biosimilars, the government could, for example, offer a compensation to both the prescriber and the end-user of a biosimilar. These resources can then be invested in the management of patients at the IBD unit [e.g., support for IBD nurses, expanding the reimbursement of faecal calprotectin, therapeutic drug monitoring, vaccination, or early access to newer compounds such as darvadstrocel]. Currently there is no negotiation at all between the Belgian authorities and the health care professionals. If one would really like to change the current clinical practice [e.g., with an increased uptake of biosimilars], all stakeholders should be engaged from the start. This is something the Belgian authorities still need to understand.

9. Conclusions and BIRD Recommendations

Based on the current regulatory guidance from the EMA and the current literature about efficacy and safety of adalimumab biosimilars in immune-mediated inflammatory diseases, BIRD members agree on the following statements:

1. Extrapolation from randomized controlled trials [RCTs] in RA and psoriasis supports the use of biosimilars ABP 510, SB5, GP2017, FKB327, and MSB11022 in IBD [Crohn's disease and ulcerative colitis].
2. Initiation of patients with adalimumab according the reimbursement criteria of anti-TNFs in Belgium: ABP 510, SB5, GP2017, FKB327, and MSB11022 can be prescribed, since initiating therapy with these products appears today as safe and effective as initiating therapy with the reference product adalimumab.
3. Switching from originator adalimumab RP to ABP 510, SB5, GP2017,FKB327, or MSB11022 for patients who are in a stable clinical remission on adalimumab originator therapy is acceptable, since such switch appears today as safe and effective as treatment maintenance with the originator. At present, immunogenicity does not seem different after the switch of the reference product adalimumab to an adalimumab biosimilar.
4. Automatic substitution [dispensing one medicine instead of another equivalent and interchangeable medicine at the pharmacy level without consulting the prescriber] is not appropriate.
5. Pharmacovigilance is essential for any new biologic medicine, and patients prescribed with ABP 510, SB5, GP2017, FKB327, or MSB11022 should be followed in the long term.

Scientific societies such as BIRD welcome the biosimilars and encourage competition between reference products and biosimilars. The price reduction can contribute towards the general goal to further improve IBD patient care by increasing the uptake of biologic treatments. Moreover, a reduction of the budget spent thereby will facilitate reimbursement of new molecules in the field of IBD. However, currently the uptake of biosimilars for adalimumab, as has been the case for other molecules, is very low. Scientific societies such as BIRD are looking for better interactions with the government in order to have all stakeholders on board in pursuing lowering health care costs. In this way, more investments will be possible in quality of care of patients with IBD.

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Conflict of Interest

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Author Contributions

MS collected the data and wrote the paper, PB revised the draft and incorporated additional findings, MF revised the draft and incorporated additional findings, HP revised the draft and incorporated additional findings, FB revised the draft and incorporated additional findings. All authors reviewed and approved the final paper.

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