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Biosimilars in ulcerative colitis: When and for who?

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ABSTRACT

The introduction of biological agents has revolutionized the management of ulcerative colitis (UC). Biosimilars are considered to be equivalent to the reference biologic products in terms of pharmacokinetic properties, clinical effectiveness and safety and have now been approved in inflammatory bowel diseases (IBD). CT-P13 was the first biosimilar to infliximab that obtained regulatory approval by the EMA and US FDA. Accumulating data on biosimilars led to an increased acceptance amongst practicing gastroenterologists and their use can be associated with a potential reduction in healthcare costs. This review discusses the current state of knowledge on biosimilar use in UC. Authors review the existing data on clinical efficacy, safety and immunogenicity of biosimilar infliximab and adalimumab agents. Emerging data suggests that switching from originator to biosimilar is safe for CT-P13 infliximab, however data on other biosimilars, multiple-switching, reverse-switching, or cross-switching between biosimilars is lacking. The pathway for interchangeability of biosimilars is different in the US and Europe and many aspects have yet to be clarified by federal regulators. Since the approval of the first biosimilar, the biosimilar concept seems to be successful and has led to an increased use of biosimilar drugs in the treatment of UC worldwide with a better access for patients to biologic. Real-world data from prospective observational studies for 'follow-on' biosimilars is needed to ensure that safety, efficacy and immunogenicity is comparable to the originator in IBD, and that switching from the originator or among biosimilars is a safe option.

1. Introduction

The introduction of biological agents has revolutionized the management of ulcerative colitis (UC) in the past decade. Based on the consensus statements of the European Crohn's and Colitis Organization (ECCO) and the American Gastroenterological Association (AGA), in patients with UC who fail to respond to corticosteroids or thiopurines or present steroid-dependent disease, anti-TNF therapy to induce complete corticosteroid-free remission is recommended [1,2]. Although biological drugs are effective, widespread application of these drugs became the most important cost driver of the management of Inflammatory Bowel Diseases (IBD), even exceeding hospitalization and surgery related expenses [3]. The global expenditure on biological treatments approaches almost unaffordable costs, while global access to these treatments is relatively low. Long-term expenditure may become unsustainable for payers and health care systems. Recent or impending expiry of patents for certain biologics has led to the development of biosimilar products. The growing number of biosimilar drugs offer more options for healthcare providers and patients and also better control of costs, partly by switching from the originator to biosimilar alternatives [4].

A biosimilar medicine ('biosimilar') – by the definition of the European Medicines Agency (EMA) – is a medicine highly similar to another biological medicine already marketed in the EU (the so-called 'reference medicine') [5]. A very similar definition is given by the US Food and Drug Administration (FDA), as well [6]. Biosimilars should not be referred to as generic medications. Biologic drugs are made in living cells, as such, no two biologic drugs are structurally identical due to unique post-translational changes. In accordance with regulatory frameworks laid out by the EMA and the FDA, development of biosimilars is subject to comprehensive comparability exercises in order to assure similarity of the biosimilar with the reference medicinal product (RMP) in terms of

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quality characteristics, efficacy and safety. The approval pathway of biosimilars involve a stepwise approach starting from non-clinical analyses (to prove in vitro physicochemical, structural, functional and toxicological similarities) and if there are still some minor differences between the products in some of the non-clinical attributes, outstanding discrepancies should be addressed by the clinical phase (phase I study to demonstrate equivalence in terms of pharmacokinetics, pharmacodynamics and safety, and/or phase III clinical study to demonstrate no meaningful differences with respect to efficacy, safety and immunogenicity). All results should be considered in the 'totality of evidence' approach confirming that these properties of the product in question are 'highly similar' to the RMP and there are no clinically meaningful differences [5–12]. If the biosimilar product is demonstrated to be highly similar to the RMP after comparative analyses in one of the licensed indications, it will be granted approval for all the approved indications of the reference product. This is known as 'indication extrapolation', which is one of the key regulatory properties of biosimilar development. Of note, this is not an automatic process, it has to be demonstrated that the main pathway of action of the molecule is similar across the different indications [6,7,9,10,11]. Data extrapolation across indications does not imply less reassurance of biosimilar efficacy and safety when supported by scientific justification but represents a process for saving time, resources and unnecessary experimental repetition [7,9,10,13,14]. Nevertheless, post-marketing studies and high level of pharmacovigilance are important [9,10].

Despite stringent approval processes by the EMA and US FDA, acceptance of biosimilars among physicians still encounter some resistance. This appears to be important mainly for the extrapolated therapeutic indications [15,16]. Reasons for this may derive also from the cited paradigm that biosimilars are 'similar but not identical', which is inevitable considering the nature and complexity of manufacturing techniques of biologic medicines, however upon approval, it is concluded that these potential differences have no clinically important effect on safety, efficacy and potentially immunogenicity. The aim of this review is to discuss existing data on clinical efficacy and safety of biosimilar anti-TNF agents, and to assess the current data and future perspectives of switching from originator to biosimilar products in UC patients.

2. Efficacy and safety of currently approved biosimilars in ulcerative colitis– the available evidence

2.1. The biosimilar landscape in IBD

CT-P13 biosimilar IFX (Inflectra®, Celltrion, Incheon, South Korea and Remsima®, Hospira, Incheon, South Korea) was the first biosimilar that was approved for use in all indications of the reference product and received marketing authorization from the EMA in 2013 and from the US FDA in 2016 [17,18]. Another biosimilar IFX SB2 (Flixabi®, Samsung Bioepis and Biogen, South Korea) has also been approved by the EMA (May 2016) and the US FDA (April 2017) for the same indications as the reference product [19].

ABP 501 is a biosimilar of adalimumab (Amjevita® Amgen Inc., USA; Amgevita® and Solymbic®, Amgen Europe, The Netherlands) and it was approved by US FDA in September 2016 and by the EMA in January 2017 [20,21]. BI 695501 biosimilar adalimumab (Cyltezo®, Boehringer Ingelheim, Germany) was approved by US FDA in August 2017 [22]. SB5 (Imraldi®, Samsung Bioepis and Biogen, South Korea/USA) have also been authorized by the EMA in June 2016, and waiting for US FDA approval [23].

Currently, many more biosimilars products to infliximab and adalimumab are in the development pipeline. Fig. 1.

2.2. Biosimilar infliximab – efficacy, safety and immunogenicity in naïve and switched patients

CT-P13 is the only biosimilar for which observational 'real-world' data in UC is currently available. Numerous studies — conducted in Hungary, Czech Republic, Norway, South Korea, Poland, and the Netherlands — have shown that CT-P13 is effective and

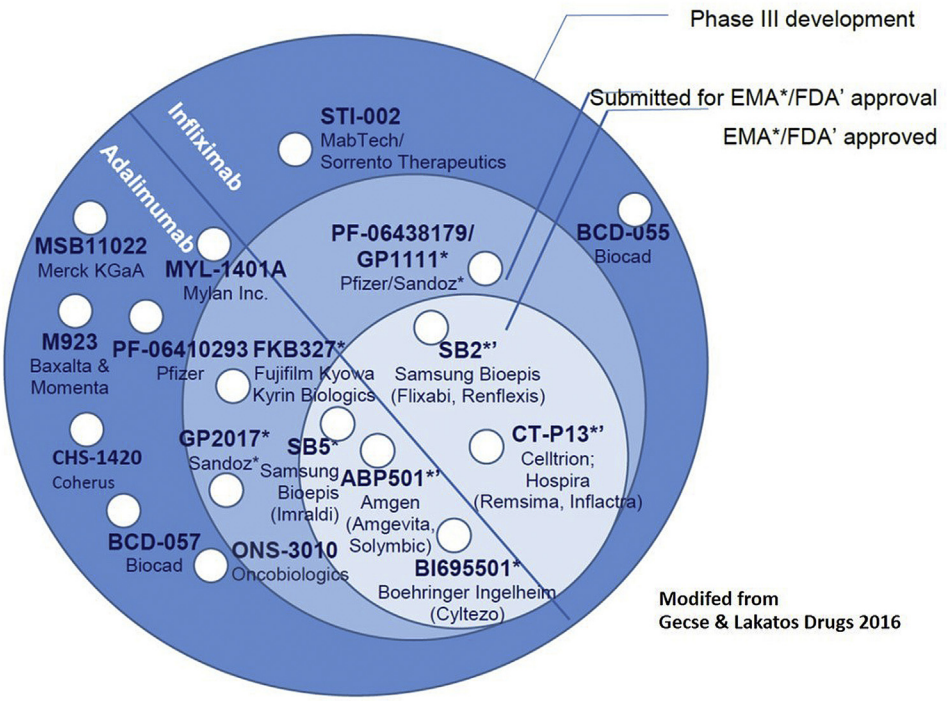

Fig. 1. The biosimilar 'horizon' – current developement state of biosimilars (Modified from: Gecse & Lakatos, Drugs, 2016) [57].

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