Universidade de Lisboa

Faculdade de Farmácia

Biosimilars in the Treatment of Inflammatory Bowel Disease:

Current Trends and Future Perspectives

Inês da Silva Alves Gomes

Mestrado Integrado em Ciências Farmacêuticas

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Resumo

O aumento crescente da incidência da Doença Inflamatória Intestinal (DII), particularmente na população mais jovem e ativa, constitui um desafio claro na gestão e prevenção desta doença crónica. Ainda que com uma etiologia de carácter idiopático, não deixa de apresentar diversos focos terapêuticos, que permitem desenvolver abordagens inovadoras e direcionadas. A terapêutica biológica encontra-se na vanguarda do tratamento de doenças crónicas auto-imunes, nomeadamente a DII, com vantagens evidentes no que toca à comodidade dos regimes terapêuticos, bem como nos resultados clínicos promissores. No entanto, trata-se de uma abordagem terapêutica dispendiosa, que põe em causa a sustentabilidade dos sistemas de saúde e o acesso à medicação por parte dos doentes.

Com base numa revisão científica extensa, os biossimilares surgem como uma solução a este problema. Tratando-se de moléculas obtidas por biotecnologia, à semelhança dos seus parentes biológicos, asseguram a efetividade da terapêutica biológica na gestão da DII, com encargos financeiros consideravelmente inferiores. Atualmente, existem diversos medicamentos biológicos aprovados para o tratamento da Doença de Crohn e Colite Ulcerosa, nomeadamente o Infliximab, Adalimumab, Golimumab, Certolizumab, entre outros, servindo de base para o potencial desenvolvimento dos respetivos biossimilares. No entanto, à data, apenas o Infliximab e Adalimumab têm biossimilares disponíveis no mercado. A sua eficácia, segurança, imunogenicidade, entre outros parâmetros, foram comprovadas em ensaios clínicos de fase III e IV, de carácter essencialmente comparativo, o que permitiu também inferir acerca da possibilidade de alternar entre um biológico e o seu biossimilar durante o regime terapêutico dos doentes.

É importante reforçar o impacto farmacoeconómico do desenvolvimento de biossimilares, tanto no setor, como para os próprios doentes. Ainda que a oferta biossimilar para o tratamento da DII seja limitada a duas moléculas biológicas, vários têm sido os estudos realizados no sentido de avaliar a vantagem económica que esses biossimilares apresentam. A partir dos estudos compilados nesta monografia, é possível depreender que a introdução primária de um biossimilar no regime terapêutico de um doente com DII, ou até a substituição de um biológico pelo seu biossimilar, contribui para uma maior sustentabilidade dos sistemas de saúde e permite tratar mais doentes, devido ao acesso facilitado ao medicamento.

Palavras-chave: DII, biológico, biossimilar, eficácia, imunogenicidade, farmacoeconomia.

Abstract

The increasing incidence of Inflammatory Bowel Disease (IBD), particularly in the younger and more active population, constitutes a clear challenge in the management and prevention of this chronic disease. Despite having an idiopathic etiology, it still presents several therapeutic targets, allowing the development of innovative and targeted approaches. Biological therapy is at the forefront of the treatment of chronic autoimmune diseases, namely IBD, with clear advantages regarding the convenience of the therapy regimen itself, as well as promising clinical results. However, it is an expensive therapeutic approach, which questions the sustainability of health care systems and patients' access to medication.

Based on an extensive scientific review, biosimilars emerge as a solution to this problem. Because they are molecules obtained by biotechnology, like their biological relatives, they ensure the effectiveness of biological therapy in the management of IBD, with considerably lower financial costs. Currently, there are several biological medicines approved for the treatment of Crohn's Disease and Ulcerative Colitis, namely Infliximab, Adalimumab, Golimumab, Certolizumab, among others, serving as a starting point for the potential development of their respective biosimilars. However, to date, only Infliximab and Adalimumab have biosimilars available on the market. Their efficacy, safety, immunogenicity, among other parameters, were proven in phase III and IV clinical trials, of an essentially comparative character, which also allowed to infer about the possibility of switching between a biological and its biosimilar during the therapeutic regimen of the patients.

It is important to reinforce the pharmacoeconomic impact of the development of biosimilars, both for health care systems and for the patients themselves. Although the biosimilar offer for the treatment of IBD is limited to two biological molecules, several studies have been carried out to evaluate the economic advantage that these biosimilars present. From the studies compiled in this monograph, it is possible to conclude that the primary introduction of a biosimilar in the therapeutic regimen of an IBD patient, or even the replacement of a biological medicine by its biosimilar, contributes to a greater sustainability of health care systems and allows more patients to be treated, due to easier access to the medication.

Key-words: IBD, biological, biosimilar, efficacy, immunogenicity, pharmacoeconomics.

Acknowledgments

''And, when you want something, all the universe conspires in helping you to achieve it.''

-Paulo Coelho, *The Alchemist*

Upon reaching the end of a 5-year journey, I cannot help but thank a very special group of people who allowed this journey to become easier and more rewarding, and to whom I dedicate this monograph. I would like to thank my family most of all, for the unconditional support from day one, the joint celebration of successes and the support when motivation and courage failed. To my friends, Gonçalo Freitas, Alexandra Sousa, Igor Correia, Joana Perez, Francisca Mourinha and Catarina Mourão I thank you for the memories, for the complicity and for having made these 5 years the best years of my life. Without you, it would not have been the same. You are proof that, when we really want something, the universe conspires in our favor.

To the friendships I made while running for the Student's Association, I also extend my heartfelt appreciation, for being the proof that even in the face of adversity, something wonderful can arise.

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Abbreviations

$\alpha_4\beta_7$ – Alpha4-Beta7 Integrin

ADAs – Anti Drug Antibodies

APC – Antigen Presenting Cell

APOGEN – Associação Portuguesa de Medicamentos Genéricos e Biossimilares/Portuguese Association of Generic and Biosimilar Medicines

BMWP – Biosimilar Medicinal Working Party

BWP – Biologics Working Party

CD – Crohn's Disease

CDAI – Crohn's Disease Activity Index

CHMP – Committee for Medicinal Products for Human Use

CRP – C-Reactive Protein

ECCO – European Crohn's and Colitis Organization

EEA – European Economic Area

EMA – European Medicines Agency

EPAR – European Public Assessment Report

FDA – Food and Drug Administration

GMP – Good Manufacturing Practices

HBI – Harvey-Bradshaw Index

IBD – Inflammatory Bowel Disease

IFN-γ - Interferon gamma

IL – Interleukin

IV – Intravenous

JCV – John Cunningham Virus

MAdCAM-1 – Mucosal Addressin Cell Adhesion Molecule 1

NICE – National Institute for Health and Care Excellence

NK – Natural Killer

PASI – Psoriasis Area Severity Index

PASS – Post-Authorization Safety Studies

PD – Pharmacodynamics

PK – Pharmacokinetics

PML – Progressive Multifocal Leukoencephalopathy

pMS – partial Mayo Score

PRAC – Pharmacovigilance Risk Assessment Committee

QALY – Quality-Adjusted Life Year

RMP – Risk Management Plan

SC – Subcutaneous

TDM – Therapeutic Drug Monitoring

TGF – Transforming Growth Factor

T_h – T helper cell

TLR – Toll-Like Receptor

TNF – Tumor Necrosis Factor

UC – Ulcerative Colitis

WHO – World Health Organization

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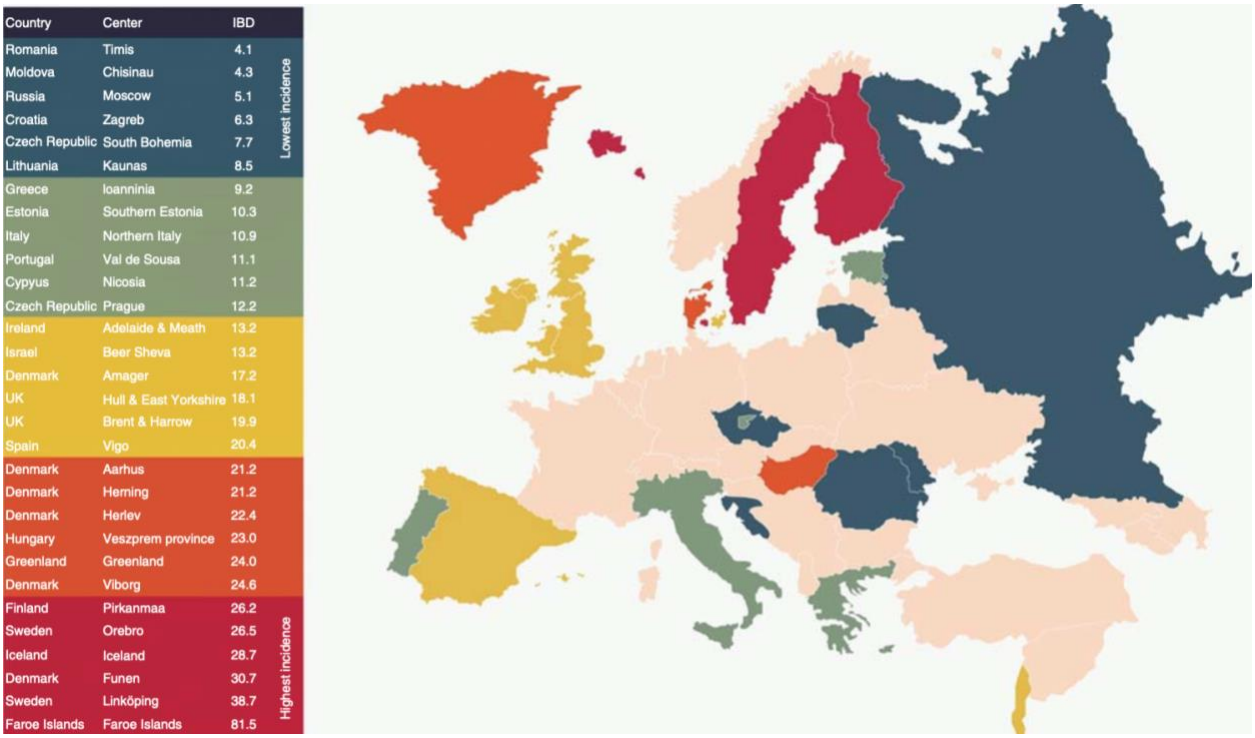
1. Introduction

1.1. Inflammatory Bowel Disease

Inflammatory Bowel Diseases (IBD) are a group of chronic, idiopathic, inflammatory diseases of the gastrointestinal tract. This group of illnesses includes 2 forms – Crohn's Disease (CD) and Ulcerative Colitis (UC) – which share some similarities, but differ in many clinical and pathophysiological aspects (1). Symptoms are similar to a certain extent, including diarrhea alternating with periods of constipation, abdominal pain and weight loss. However, some symptoms are disease specific, being that intestinal stenosis and fistula formation are more common in CD whereas blood loss in the stool, progressive loss of peristaltic function and complications such as toxic megacolon and intestinal perforation are more common in UC (1). Both CD and UC can progress to cancer, with progression to colorectal cancer more common in patients with UC (1).

1.1.1. Epidemiology



Country	Center	IBD	
Romania	Timis	4.1	Lowest incidence
Moldova	Chisinau	4.3	
Russia	Moscow	5.1	
Croatia	Zagreb	6.3	
Czech Republic	South Bohemia	7.7	
Lithuania	Kaunas	8.5	
Greece	Ioanninia	9.2	
Estonia	Southern Estonia	10.3	
Italy	Northern Italy	10.9	
Portugal	Val de Sousa	11.1	
Cypyus	Nicosia	11.2	
Czech Republic	Prague	12.2	
Ireland	Adelaide & Meath	13.2	
Israel	Beer Sheva	13.2	
Denmark	Amager	17.2	
UK	Hull & East Yorkshire	18.1	
UK	Brent & Harrow	19.9	
Spain	Vigo	20.4	
Denmark	Aarhus	21.2	
Denmark	Herning	21.2	
Denmark	Herlev	22.4	
Hungary	Veszprem province	23.0	
Greenland	Greenland	24.0	
Denmark	Viborg	24.6	
Finland	Pirkanmaa	26.2	Highest incidence
Sweden	Orebro	26.5	
Iceland	Iceland	28.7	
Denmark	Funen	30.7	
Sweden	Linköping	38.7	
Faroe Islands	Faroe Islands	81.5	

Figure 1 – Incidence rates (per 100,000) of IBD cases aged 15 or older in Europe in 2010. Adapted (2).

IBD affects about 5 million people worldwide, namely in industrialized countries, with about 1.4 million cases in North America (3,4) and 3 million in Northern Europe (5,6). The prevalence of UC varies from 2,4 to 294 cases for every 100 000 people (7), whereas CD varies from 1,5 (8) to 213 (9) cases for every 100 000 people. Furthermore, CD is more commonly diagnosed in women (10–13), whereas for UC there is no significant gender difference (14). UC patients are usually diagnosed between 30 and 40 years of age. When it comes to CD, the diagnosis occurs between the ages of 20 and 30 (5). The incidence rates of IBD cases in people with 15 years of age, or older, in Europe during 2010 are shown in Figure 1.

1.1.2. Pathophysiology

The pathophysiological mechanisms of this group of diseases are not entirely defined, as the etiology has many variants and there are several hypotheses that allow a general explanation for the occurrence of inflammation. Some of them are represented in Figure 2.

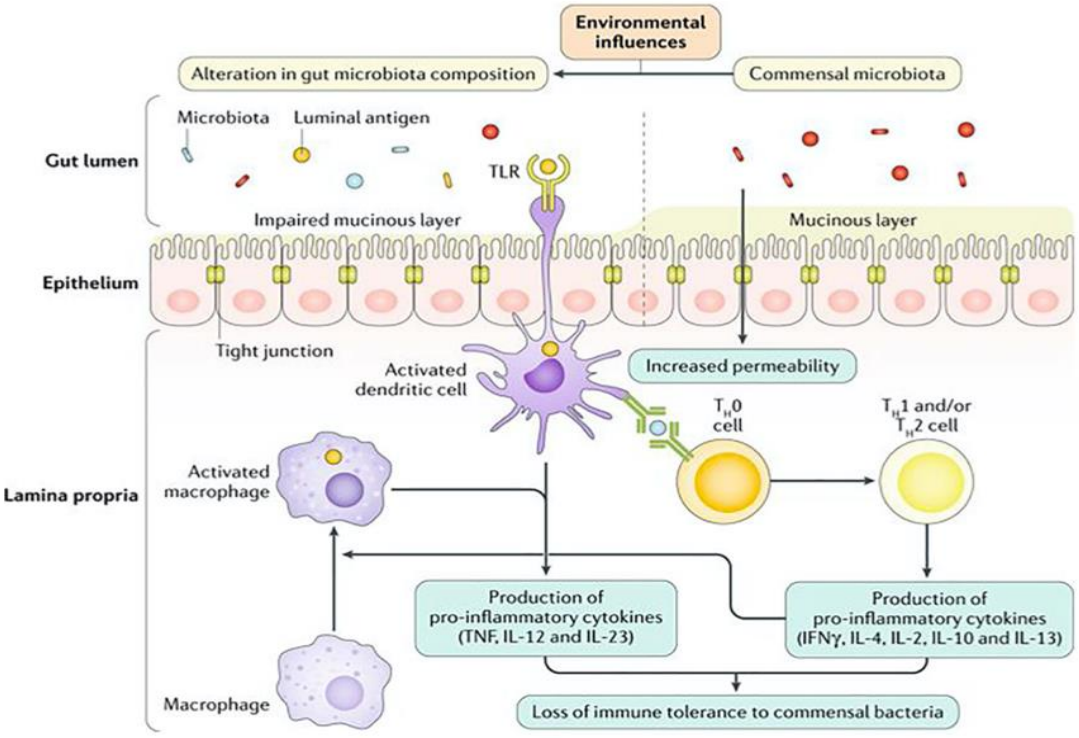


Figure 2 – Inflammatory Cascade of Inflammatory Bowel Disease. (Caption: TNF - Tumor Necrosis Factor; IL – Interleukin; IFNγ – Interferon gamma; T_H cell – T helper cell). Adapted (15).

Amongst the factors that seem to be related to the development of IBD, the following stand out:

- **Genetic Factors:** Genetic alterations may be associated with clinical aspects of intestinal inflammation, with genetics having a marked role in susceptibility to inflammation (1). The emergence of these diseases is then more common when there is a family history associated with them (16). The occurrence of IBD in first degree family members is about 40% (17).

- **Intestinal Microbiota:** Intestinal microbiota is associated with the maintenance and activation of the inflammatory process, by providing one or more antigens or stimulating factors that are capable of promoting an immune response (1). As such, it is possible that by-products from the microbiota (that act as antigens) promote inflammation in the presence of an ineffective or damaged mucous barrier (18). Because there is a reaction against antigens that can be considered *self* (19), since they are present in the intestine during the individual's life, the body develops an autoimmune reaction to them, and therefore IBD can be considered an autoimmune disease (1). However, not all elements of the intestinal microbiota are etiologically related to IBD, namely a group of microorganisms called probiotics, which play an important role in controlling inflammation (20). Scientific evidence suggests that they act by inducing suppressing cytokines (1). Patients with IBD tend to have a deficit of ‘’good bacteria’’, and evidence of this is supported, for example, by the decrease in the number of anaerobic bacteria and *Lactobacillus* in patients with active IBD (21).

- **Effector T-Cells vs Regulatory T-Cells:** In general, inflammation is considered to occur due to two pathways: 1) exacerbated effector T cell function; 2) deficient function of regulatory T cells (1). In the first assumption, there is an overexpression of proinflammatory cytokines, such as tumor necrosis factor (TNF), IL-12 and IFN-γ (22,23). In the second assumption, the deficient function of T cells is essentially due to the underexpression of regulatory cytokines, such as IL-10 (24) and the transformation growth factor (TGF-β) (25).

- **Pathways of Inflammation:** Inflammation of the intestinal mucosa is, in general, mediated by one of two pathways: 1) exacerbated T_H1 cell response, associated, as previously mentioned, with increased secretion of IL-12, IFN-γ and TNF; 2) exacerbated T_H2 cell response, associated with increased secretion of IL-4, IL-5 and IL-13 (26).

- **Intestinal Epithelium:** The cells of the epithelial mucosa are able to recognize microorganisms or substances produced by them, through the expression of Toll-Like Receptors (TLRs) (27). As such, under certain conditions, epithelial cells can react to these agents by producing cytokines, chemokines and other pro or anti-inflammatory substances (28,29), working as a barrier. Because of this, it is assumed that the epithelium plays an essential role in the physical separation of the potentially harmful microbiota and the reactive cells of the immune system (1).

- **Innate Immunity:** The occurrence of IBD may also be due to genetic abnormalities in innate immunity, involving the function of Antigen Presenting Cells (APCs), Macrophages and Natural Killer cells (NK) (1).

1.2. Biological Medicines

With the advance of modern medicine, it is imperative to develop innovative therapies aimed at controlling chronic diseases, such as IBD, giving the patient the best possible quality of life. Biological medicines are at the forefront of this new therapeutic scope. A biological medicine is a molecule of great complexity that is obtained artificially through living systems. Compared to the molecules that make up medicines of chemical origin, biological medicines are about 200 to 1000 times larger in size, and the production process is much more complex, due to the high complexity of the molecules (30,31). The complexity scale of a biological medicine is depicted in Figure 3. The production process involves several steps, starting with the selection of the gene that encodes for the protein of interest that is intended to be produced (31). This gene is then introduced into a host cell, the growth of which is monitored, allowing the cell to use its protein synthesis mechanism to convert the gene in question, into the protein to be obtained. This protein constitutes the biological medicine, but at this stage it is found in insufficient quantities to have any therapeutic effect. As such, it is necessary to stimulate cell multiplication and growth, in a medium optimized for this purpose, in order to obtain optimal amounts of protein (31). The final step is the isolation of the protein from the respective producing cell, with several purification methods (31). Due to their high molecular size and fragile molecular structure, they are generally administered parenterally (32).

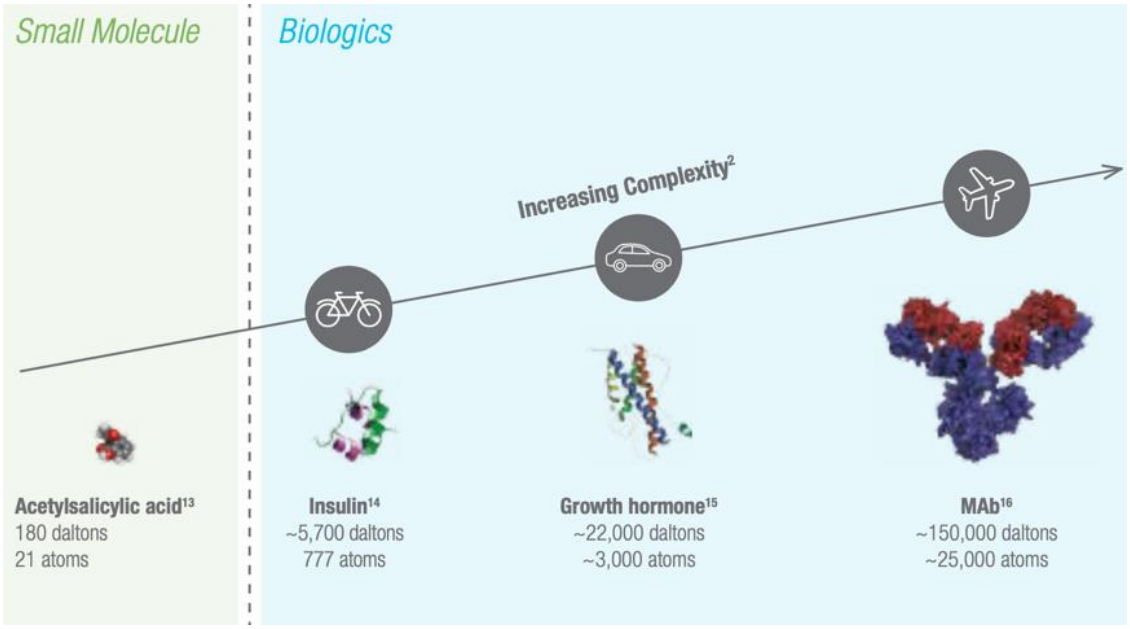


Figure 3 – Layout of the complexity scale of a biological medicine. (Caption: MAb – Monoclonal Antibody). Adapted (33).

Regarding the use of biologicals in the treatment of IBD, monoclonal antibodies are the most used, and there are currently several subtypes of monoclonal antibodies available as therapeutic options for the control of IBD, with Anti-TNF agents being the primary choice (34).

Nevertheless, the use of biological medicines has extremely high monetary costs, due to the complexity of the molecules and the sophistication of their production process, which limits their access (35), so the commitment to the development of biosimilars has grown exponentially. As well as biological medicinal products, biosimilars are produced through the use of living organisms or their by-products, utilizing Biotechnology (36). However, they are introduced to the market at considerably lower prices. As such, the use of biosimilars in the treatment of IBD is a way to promote the reduction of health care costs and facilitate patients' access to biological therapy, without compromising clinical results, with regard to treatment effectiveness, safety and immunogenicity.

2. Objectives

This monograph provides an overview of the world of biosimilar medicines and how its recent, however exciting, introduction in the pharmaceutical market can benefit the treatment of IBD.

Furthermore, this review clarifies the regulatory requirements for the marketing authorization of biosimilars, describes the currently authorized biosimilars for the treatment of IBD and suggests, based on a pharmacoeconomic analysis, applications for the possible savings in order to increase the health gains of IBD patients, while ensuring more sustainable health care systems.

3. Methods

Several browsers for scientific publications were used, namely *PubMed* (pubmed.ncbi.nlm.nih.gov) generously provided by the National Library of Medicine (NLM), *ScienceDirect* (www.sciencedirect.com) managed by Elsevier, and Google Scholar (scholar.google.com).

The criteria for the article selection went through filtering the search according to more recent publications, namely articles published between 2015 and 2020, with some of the selected articles having been published prior to that period. The research was done mostly in English and key terms such as the following were used: biosimilars in the treatment of IBD; biologics; anti TNF; immunogenicity; interchangeability; pharmacoeconomic analysis of biosimilars in IBD; and so on.

Finally, in addition to the aforementioned research platforms, much of the information was also obtained from websites and documents provided by important health entities, namely the European Medicines Agency (EMA), the U.S. Food and Drug Administration (FDA), the World Health Organization (WHO), the National Institute for Health and Care Excellence (NICE), the Portuguese Association of Generic and Biosimilar Medicines (APOGEN) and the European Crohn's and Colitis Organization (ECCO). This was crucial to access the standards and scientific guidelines that regulate the subject under study, allowing this review to be built based on legal and current foundations and references.

4. Biological Medicines for Inflammatory Bowel Disease

When it comes to IBD and biological therapy, the therapeutic arsenal resides in Monoclonal Antibodies. This type of antibody comes from a single type of clone of a single mother cell (B lymphocyte) and is obtained through the multiplication of hybridomas, which constitute a fusion between a B lymphocyte (where the antibody of interest is produced) and Myeloma cells (37). The antibody then binds to a single type of antigen (37).

The increasing use of this therapeutic class in the treatment of IBD has a clear benefit in clinical results and in improving patients' lifestyle (34). Its therapeutic benefit is optimized with its early introduction into the therapeutic regimen of patients and with continuous use as a maintenance regimen (34). Table 1 illustrates some of the monoclonal antibodies approved for the treatment of IBD, as well as their induction and maintenance regimens.

Table 1 – Examples of monoclonal antibodies approved for the treatment of IBD. Adapted (34).

Biological	Commercial Name	Administration Route	Approved for	Mechanism of Action	Induction Regimen	Maintenance Dose
Infliximab ([1]Biosimilars)	'Remicade' 'Inflectra'[1] 'Remsima'[1]	IV	CD e UC	Anti-TNF	5 mg/kg at weeks 0, 2 and 6	5 mg/kg
Adalimumab	'Humira'	SC	CD e UC	Anti-TNF	160 mg - week 0 80 mg - week 2	40 mg
Golimumab	'Simponi'	SC	UC	Anti-TNF	200 mg - week 0 100 mg - week 2	50 mg if <80kg 100 mg if >80kg
Vedolizumab	'Entyvio'	IV	CD e UC	Anti-integrin	300 mg at weeks 0, 2 and 6	300 mg
Ustekinumab	'Stelara'	IV (induction) SC (maintenance)	CD	Anti-IL-12 and IL-23	week 0: 260 mg if <55kg 390 mg if 55-85kg 520 mg if >85kg	90 mg

The following molecules constitute the biological medicines currently used in the treatment of IBD, with particular emphasis on monoclonal antibodies. Figure 4 outlines the different mechanisms of action of monoclonal antibodies in the treatment of IBD.

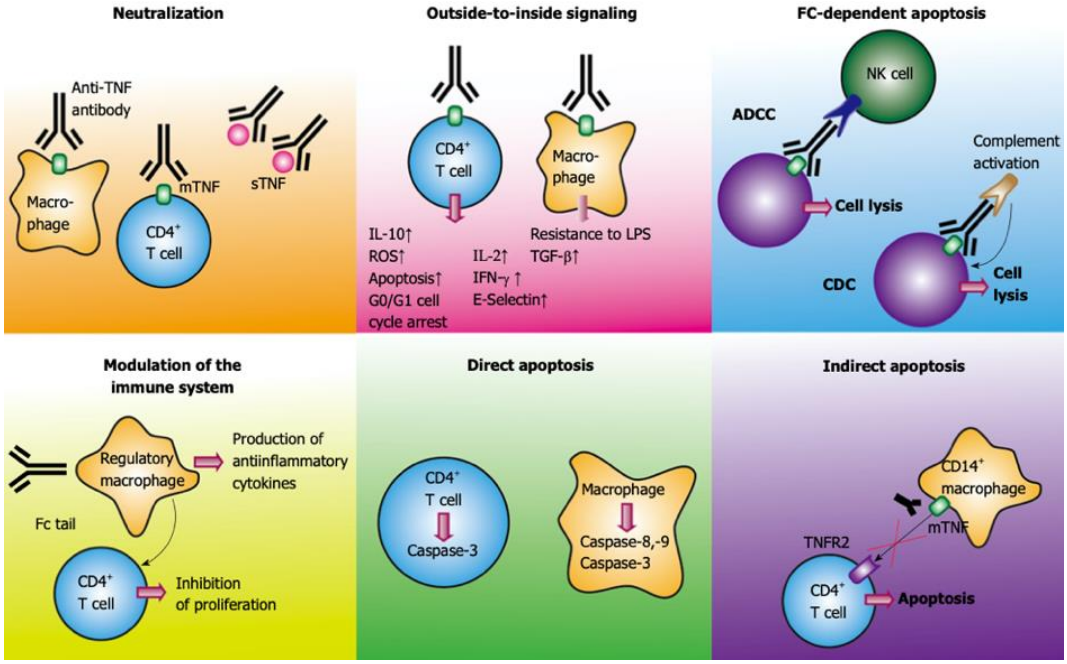


Figure 4 – Different mechanisms of action of monoclonal antibodies in IBD. (Caption: TNF - Tumor Necrosis Factor; mTNF - transmembrane TNF; sTNF - soluble TNF; TNFR - TNF receptor; IL – Interleukin; ROS – Reactive Oxygen Species; IFNγ - Interferon gamma; TGF-β - Transforming Growth Factor beta; NK cell - Natural Killer cell; ADCC - Antibody-Dependent Cell Cytotoxicity; CD - Crohn's Disease; CDC - Complement Dependent Cytotoxicity; LPS - Lipopolysaccharide). Adapted (38).

a) Infliximab - Remicade®

Infliximab is a chimeric monoclonal antibody, consisting of 75% of human sequences, with a high specificity and affinity for TNFα (39,40). Its mechanism of action is characterized by the formation of stable complexes with soluble (monomeric and trimeric) and transmembrane forms of TNFα (41). The ability of this agent to bind to the transmembrane forms of TNFα results in the lysis of monocytes and macrophages, by a process mediated by antibodies and the complement cascade (42–44). It is administered intravenously, starting with an induction regimen at weeks 0, 2 and 6, followed by a remission maintenance regimen with administrations every 8 weeks, at an average dose of 5 mg per kg of body weight (45).

b) Adalimumab - Humira®

Adalimumab is a humanized G1 immunoglobulin monoclonal antibody approved for the treatment of UC and CD (38,46). It is administered subcutaneously, and can be administered by the patient himself, starting with a dose of 160 mg at week 0 of treatment and 80 mg in the second week, followed by a maintenance regimen with administration of 40 mg every 2 weeks (38). Like infliximab, it exerts its action by several mechanisms, namely binding to soluble and transmembrane forms of TNFα, complement fixation, antibody-mediated cytotoxicity and induction of apoptosis in leukocytes (47).

c) Golimumab - Simponi®

Within the group of monoclonal antibodies against TNFα, we can also find Golimumab, which was approved for the treatment of UC in 2015 by the National Institute for Health and Care Excellence (NICE) (34). It is a humanized G1 immunoglobulin monoclonal antibody, with high affinity and ability to bind to TNFα, which allows for a less frequent administration schedule than other agents of the same therapeutic class (48). It is administered subcutaneously, with a half-life of between 2 to 3 weeks (49,50). Despite being the most recently approved anti-TNFα agent for the treatment of UC, its use faces a barrier as there are no randomized trials for its use in the treatment of CD (51). The initial induction dose is 200 mg followed by the administration of 100 mg every 2 weeks, with the maintenance of remission being ensured by the administration of 50 mg (if the body weight is less than 80 kg) or 100 mg (if the body weight exceeds 80 kg) every 4 weeks (38).

d) Certolizumab - Cimzia®

Although included in the anti-TNFα monoclonal antibody category, Certolizumab differs from other agents in the same class, since it is a humanized Fab fragment glycolated with polyethylene, approved for the treatment of CD (52) in the United States and Switzerland (53), and not yet approved by the European Medicines Agency (EMA) (38). Since it is only the Fab fragment of an

antibody, it is not recognized by Fc receptors (38), which differs from the mechanism of action of other anti-TNFα agents. Like adalimumab and golimumab, it is also administered subcutaneously with a 400 mg induction regimen at weeks 0, 2 and 4 and a 400 mg maintenance regimen every 4 weeks (38). It has the ability to bind to soluble and transmembrane forms of TNFα, however, it is not able to induce complement fixation, antibody-mediated cytotoxicity or leukocyte apoptosis mechanisms (47).

e) Etrolizumab – rhuMAb β_7®

It is a biological anti-adhesion molecule, which binds to the alpha4-beta7 integrin ($\alpha_4\beta_7$) (15,54). This integrin binds to an adhesion molecule expressed in the intestinal vasculature, called mucosal vascular addressin cell adhesion molecule 1 (MAdCAM-1), which mediates the chemotaxis of leukocytes to the intestinal epithelium (55). Etrolizumab also has the ability to bind to $\alpha\varepsilon\beta_7$ integrin heterodimers (15), blocking the binding of this integrin to E-cadherin, preventing the adhesion of epithelial T lymphocytes to epithelial cells (56). This is explained by the fact that $\alpha\varepsilon\beta_7$ integrin is expressed by only 1-2% of circulating lymphocytes, while being present in 90% of intraepithelial lymphocytes and intestinal dendritic cells (57,58). It constitutes a therapeutic alternative to patients with IBD refractory to anti-TNF agents and an alternative to vedolizumab, due to its greater specificity (15).

f) Natalizumab - Tysabri®

It is a monoclonal antibody, also anti-adhesion, that binds nonspecifically to integrins $\alpha_4\beta_7$ and $\alpha_4\beta_1$, the latter expressed by lymphocytes in nervous tissue (15). By blocking the action of these integrins, Natalizumab modulates lymphocyte chemotaxis in the inflammatory process (59). However, it is not a first-line therapy, due to the high risk of developing Progressive Multifocal Leukoencephalopathy (PML), an opportunistic brain infection derived from the reactivation of the John Cunningham virus (JCV) (15,60,61).

g) Vedolizumab - Entyvio®

Like etrolizumab, it is an anti-adhesion humanized monoclonal antibody. It specifically binds to alpha-4-beta-7 ($\alpha_4\beta_7$) integrins expressed by specific intestinal lymphocytes, namely gut-homing IL17 T_H lymphocytes (34,62). This mechanism prevents the migration of these integrins to the intestinal parenchyma, consequently preventing inflammation (34). The fact that it is a molecule with specificity for the integrins produced by lymphocytes with predominant action in the intestine, it reduces the risk of PML (62).

h) Abrilumab – AMG 181®

This anti-adhesion monoclonal antibody has a mechanism of action quite similar to that of vedolizumab, inhibiting only $\alpha_4\beta_7$ integrin, however, unlike natalizumab and vedolizumab, whose route of administration is intravenous, Abrilumab is administered subcutaneously, with a superior bioavailability and half-life (15).

i) Risankizumab - Skyrizi®

Still regarding monoclonal antibodies, there has been an investment on the search for other pro-inflammatory targets, such as interleukins. In this context, Risankizumab is a humanized monoclonal antibody that antagonizes the action of IL-23 by binding to its p19 subunit (63). It has the advantage of not interfering with the IL-12 pathway, which is extremely important for the regulation of infectious and neoplastic processes (64). Although already approved for the treatment of moderate to severe plaque psoriasis, risankizumab is still undergoing clinical trials for the treatment of IBD. The results obtained so far seem to be promising, indicating that risankizumab is capable of inducing remission of Crohn's Disease in 31% of patients refractory to anti-TNF therapy, at week 12 of treatment (65).

j) Ustekinumab - Stelara®

Like risankizumab, Ustekinumab is a monoclonal antibody that exerts its action at the level of specific interleukins. In this case, it blocks the action of IL-12 and IL-23 by binding to their p40 subunits (15). Unlike risankizumab, ustekinumab is already an approved therapy for the treatment of moderate to severe Crohn's Disease (15). IL-23 is important in inducing and regulating the function of T_h17 effector cells (66,67), stimulating the secretion of various pro-inflammatory molecules such as IL-17^a, IL-17F, IL-22, IL-26, TNFα and IFNγ (68). IL-12, produced by phagocytic and dendritic cells in response to stimuli from pathogenic microorganisms, is essential in cell-mediated immunity as it activates Natural Killer (NK) cells and T lymphocytes, namely T_h1 lymphocytes, and is also important in mechanisms of hypersensitivity and activation of macrophages (69,70).

5. Biosimilars

According to the EMA, a biosimilar is defined as ‘’a biological medicinal product that contains a version of the active substance of an already authorized original biological medicinal product in the EEA’’ in which ‘’similarity to the reference medicinal product in terms of quality characteristics, biological activity, safety and efficacy based on a comprehensive comparability exercise need to be established’’ (71).

As the name implies, biosimilars are very similar to their original reference biological product, although they should not be referred to as a generic version of that original biological product. Biosimilarity implies that there is no meaningful clinical difference when it comes to safety, purity and potency between the original product and the biosimilar (72). The term ‘’Generic Drug’’ cannot be applied to biosimilars because, as their production cycle involves living organisms, it’s impossible to ensure that two drugs obtained from the same organism are completely identical, due to several unique post-translational modifications (73).

In order to be considered a biosimilar, a biopharmaceutical needs to check the biosimilarity criteria inherent to its approval, regarding equivalent pharmacokinetics (PK) and pharmacodynamics (PD) as well as similar efficacy, immunogenicity and safety (35).

5.1. Development of a Biosimilar, Approval and Regulation

Figure 5 – Development stages of a biosimilar medicine (Caption: PK – Pharmacokinetics; PD – Pharmacodynamics). Adapted (36).

The process of developing a biosimilar differs from the one used for biological products. Its development is a process that takes around 5 to 10 years and is essentially comparative, involving clinical and non-clinical stages and quality comparability. These stages are summarized in Figure 5. The development process and road to approval of a biosimilar are depicted in Figure 6.

The **first stage of development** covers quality, focusing on physico-chemical and biological comparability between the biosimilar and the original biological medicinal product, in order to ensure the purity of the biosimilar (36). If necessary, changes can be made to the manufacturing process so that the final product is as similar as possible to the original, and respects the criteria required by the EMA when submitting the documentation necessary to obtain the marketing authorization (36).

The **second stage of development** involves comparative non-clinical (pre-clinical) studies, similar to what happens with biological medicines. This stage essentially involves *in vitro* analytical and pharmacotoxicological studies, which are carried out primarily. The need to carry out *in vivo* studies is analyzed later on (36). If *in vivo* studies are required to evaluate the PK/PD of the biosimilar, their design should be based on the principles of the 3R: Replacement, Reduction, Refinement, with replacement indicating the need for ‘’the substitution for conscious living higher animals of insentient material’’, reduction meaning the need of reducing the ‘’numbers of animals used to obtain information of a given amount and precision’’ and refinement indicating

the obligation of decreasing ‘’the incidence or severity of inhumane procedures applied to those animals which still have to be used’’ (74). This stage supports the comparability studies carried out in the first stage.

Finally, the **third stage of development** involves conducting comparative clinical studies. These studies are not carried out to the same extent as clinical studies carried out in the development of a new biological product, because they are not intended to demonstrate efficacy and safety (since these have already been demonstrated in the studies carried out for the reference medicine), but rather demonstrate the existence of a comparable clinical effect between the biosimilar and the biological reference medicine (36). If there is a high level of comparability between the biosimilar and the reference biological medicine, then the clinical experience, safety and efficacy profiles associated with the reference medicine can be extrapolated, as they are relevant to the biosimilar. If this comparability exists between the safety and efficacy profiles of the biosimilar medicine and the original biological reference medicine, it avoids the need to carry out tests on humans, reducing the costs of the development process of the biosimilar medicine (36).

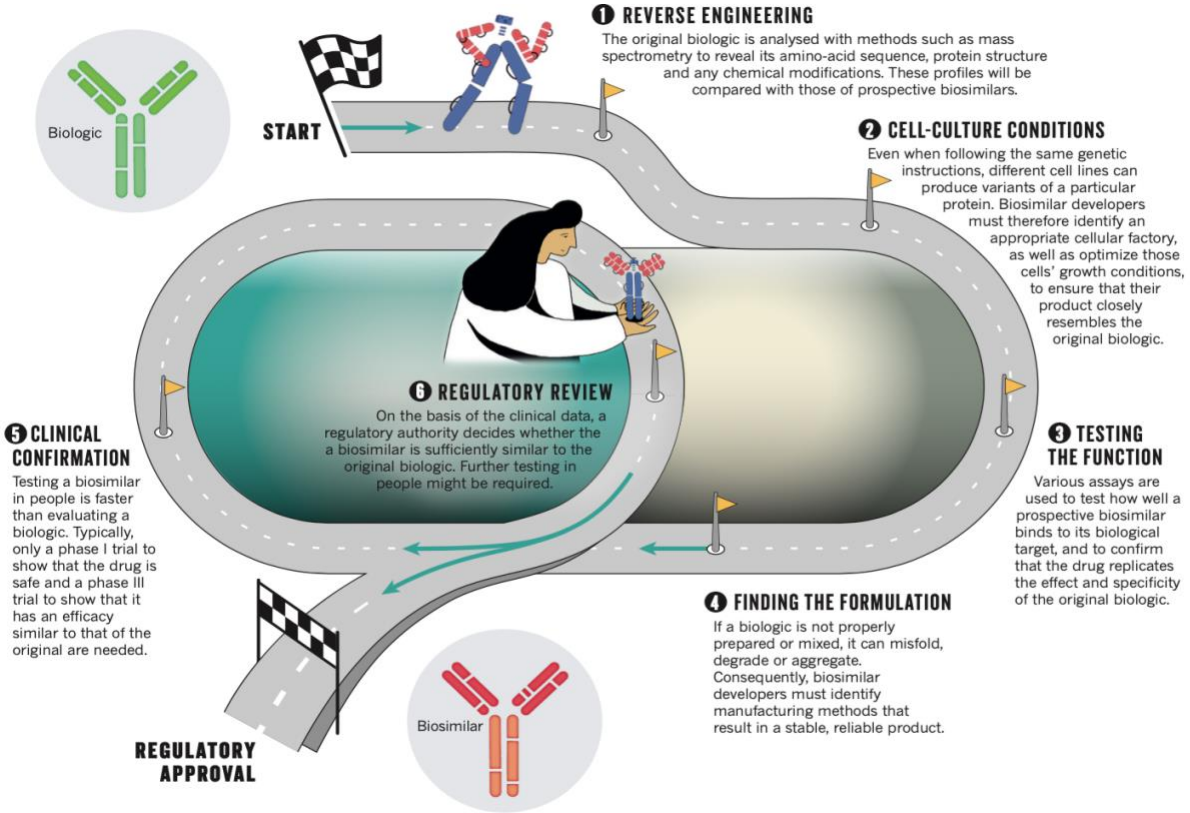


Figure 6 – Development process and road to approval of a biosimilar. Adapted (75).

The development process must be in accordance to the Good Manufacturing Practices (GMP). In order to ensure the correct implementation of these practices, the EMA coordinates inspections that are carried out by the regulatory authorities of the respective countries of the European Union (EU) (36).

5.1.1. Extrapolation from one therapeutic indication to another

The current version of the Committee for Medicinal Products for Human Use (CHMP) guidelines regarding biosimilars on clinical and non-clinical issues indicates that ‘’when biosimilar comparability has been demonstrated in one indication, extrapolation of clinical data to other indications of the reference product could be acceptable, but needs to be scientifically justified’’ (76).

This extrapolation is based on the data acquired from the three stages of development mentioned earlier. However, there are a few exceptions where additional data is required in order to allow extrapolation, such as:

- ‘’the active substance of the reference product interacts with several receptors that may have a different impact in the tested and non-tested therapeutic indications’’ (76);
- ‘’the active substance itself has more than one active site and the sites may have a different impact in different therapeutic indications’’ (76);
- ‘’the studied therapeutic indication is not relevant for the others in terms of efficacy or safety, i.e. it is not sensitive for differences in all relevant aspects of efficacy and safety’’ (76).

When it comes to extrapolation, immunogenicity shouldn’t be included since it depends on different variables, such as co-medication, dosing regimen, route of administration, and so on (76); It should be addressed during Pharmacovigilance activities and post-authorization Risk-Management plans (36,76).

5.1.2. Marketing Authorization Application

The marketing authorization application for a biosimilar (and all biotechnology-derived products) should be submitted to the EMA and evaluated by the Centralized Procedure, valid in all EU Member States, Iceland, Norway and Liechtenstein (36).

The registration dossier for a biosimilar medicine that is submitted contains information based on requirements laid down by the appropriate scientific guidelines established by the EMA, CHMP, BWP (Biologics Working Party) and BMWP (Biosimilar Medicinal Working Party) (36).

5.1.3. Pharmacovigilance

Regardless of the way they are produced, either by chemical synthesis or using biotechnology, any medicine must be subjected to pharmacovigilance, since the data collected during clinical trials that take place during the development process are not sufficient to identify and characterize all the possible adverse effects that may arise from the administration of that medicine, particularly the rarer adverse effects.

As for new medicines, the company responsible for the development of a biosimilar is required to develop and present a Risk Management Plan (RMP), as well as a description of the pharmacovigilance program, being approved by the EMA, needing to be in accordance with current European Union legislation and current pharmacovigilance guidelines (36,76). Regarding biosimilar medicines, the risk management plan is based on the safety profile of the reference medicine (36). The RMP is subsequently published in the European Public Assessment Report (EPAR) and must be updated throughout the life cycle of the biosimilar medicine (36). From the moment the biosimilar is commercialized, regular reports must be made in order to analyze the safety data available for that biosimilar, and can take a more complex form, namely Post-Authorization Safety Studies (PASS) coordinated by EMA's Pharmacovigilance Risk Assessment Committee (PRAC) (36,77). The PASS are designed to characterize/confirm the safety profile of the medicine, assess its benefit-risk and ensure the effectiveness of risk management measures (77).

5.2. Biosimilars approved for the treatment of Inflammatory Bowel Disease

Regarding biosimilars indicated for the treatment of IBD, the offer is limited, for the time being, to monoclonal antibodies, in particular anti-TNFα monoclonal antibodies. Above, the 4 main monoclonal anti-TNFα antibodies currently used in the treatment of IBD were mentioned. Currently, only Infliximab (Remicade®) and Adalimumab (Humira®) have biosimilars approved for the treatment of IBD. Biosimilars approved by the EMA and/or FDA for the treatment of IBD are summarized in Table 2.

Table 2 – Biosimilars approved by the EMA and/or FDA. Adapted (78).

Brand Name (molecule	INN (with suffix)	Regulatory Agencies	Manufacturer / marketing	Authorization date
Inflectra® (CT-P13)	Infliximab Infliximab-dyyb	EMA FDA	Pfizer Europe MA EEIG Celltrion Inc	Sept 2013 April 2016
Remsima® (CT-P13)	Infliximab	EMA	Celltrion Healthcare Hungary Kft	Sept 2013
Flixabi® (SB-2)	Infliximab	EMA	Samsung Bioepis UK Ltd (SBUK)	May 2016
Renflexis® (SB-2)	Infliximab-abda	FDA	Samsung Bioepis Co Ltd	May 2017
Ixifi® (GP1111)	Infliximab-qbtx	FDA	Pfizer Inc	Dec 2017
Zessly® (PF-06438179)	Infliximab	EMA	Sandoz GmbH	May 2018
Hulio® (FKB327)	Adalimumab	EMA	Mylan S.A.S.	Sept 2018
Idacio® Kromeya® (MSB11022)	Adalimumab	EMA	Fresenius Kabi Deutschland	Apr 2019
Amgevita® Amjevita® (ABP 501)	Adalimumab Adalimumab-atto	EMA FDA	Amgen Europe b.V. Amgen Inc.	Mar 2017 Sept 2016
Hyrimoz® (GP2017)	Adalimumab Adalimumab-adaz	EMA FDA	Sandoz GmbH Novartis	Jul 2018 Oct 2018
Cyltezo® (BI 695501)	Adalimumab-adbm	FDA	Boehringer Ingelheim	Aug 2017
Imraldi® Hadlima® (SB-5)	Adalimumab Adalimumab-bwwd	EMA FDA	Samsung Bioepis NL B.V. Samsung Bioepis Co Ltd.	Aug 2017 Mar 2019

(Caption: EMA – European Medicines Agency; FDA – U.S. Food and Drug Administration; INN – International Nonproprietary Name).

5.2.1. Infliximab Biosimilars

CT-P13 was the first Infliximab biosimilar to be approved, in 2013 by the EMA and in 2016 by the FDA (78,79). In addition to this, there are three other biosimilars of infliximab, two of which, Ixifi® (GP1111) and Renflexis® (SB-2), have only yet been approved by the FDA (78).

a) CT-P13 - Inflectra®, Remsima®

It is marketed under two different names, Inflectra®, marketed by Pfizer, and Remsima®, marketed by Celltrion (78), being the most studied biosimilar for the treatment of IBD (80).

The similarity of its efficacy, safety profile and immunogenicity have been proven in *in vitro* clinical studies, based on physico-chemical characteristics and with an essentially comparative component. The clinical studies performed consisted of double-blind randomized trials, whose subjects were patients with ankylosing spondylitis and rheumatoid arthritis. These studies made it possible to confirm the biosimilarity between CT-P13 and infliximab, demonstrating that there were no significant differences regarding the efficacy, safety profile, immunogenicity and pharmacokinetics of CT-P13 compared to its reference biological medicine (81–83).

Meyer et al. (84) conducted a cohort equivalence study with the objective of comparing the efficacy and safety profile of CT-P13 in patients with CD who did not respond to infliximab therapy, with approximately 2500 patients in each arm of the study. In short, this study confirmed the similarity of CT-P13 with infliximab in terms of the safety profile, with an equivalence margin established to be, at most, 10% of the absolute difference, constituting a more rigid parameter than that which it is generally required by regulatory agencies (84,85). The validity of this study is further corroborated by the fact that the sample of patients was about 4 to 5 times greater than that required to detect a difference of about 10% between the two groups under study (84).

Ye et al. (86) conducted a non-inferiority phase III randomized double-blind study in order to establish the efficacy of CT-P13 in 220 patients with CD unresponsive to infliximab therapy, as well as to evaluate endoscopic results, inflammatory markers, pharmacokinetics, safety, immunogenicity and also scientifically corroborate the validity of extrapolation for CT-P13. Patients received 5 mg/kg of CT-P13 or infliximab and disease progression was evaluated using the Crohn's Disease Activity Index (CDAI), during a 54 week follow-up period. This study allowed to

demonstrate the absence of significant differences regarding the efficacy of CT-P13 vs infliximab, as well as a similar variation in the values of C-reactive protein (CRP) and calproptectin, with a decrease in both parameters until week 6 with subsequent stabilization, both in patients being treated with CT-P13 and in patients being treated with infliximab (86). The profile of adverse effects and immunogenicity has also been shown to be similar for both the biosimilar and the reference biological medicine (86).

Two other non-inferiority phase IV studies, NOR-SWITCH (80,87) and SECURE (88), with 52 and 16 week follow-up periods, respectively, allowed to demonstrate that there were no significant differences in the worsening of the disease when under treatment with CT-P13 vs with infliximab and that the serum concentrations were similar in treatment with CT-P13 compared to infliximab. In both trials, the non-inferiority margin was set at 15% and patients received the same dosage of either the biosimilar or infliximab (i.e. 5 mg/kg every 7 to 9 weeks).

All four trials mentioned above are summarized in Table 3.

Table 3 – Comparative studies between Infliximab and CT-P13 in IBD. Adapted (85).

Trial	Design	Population	Follow-Up Period	Primary Endpoint
NOR-SWITCH	Non-inferiority Phase 4 Prospective Randomized Double-Blind	486 patients	52 weeks	Disease worsening at week 52: IFX vs CT-P13: 53 (26%) vs 61 (30%)
SECURE	Non-inferiority Phase 4 Prospective Open-label	88 patients	16 weeks	Change in serum concentration of IFX between baseline and 16 weeks for UC and CD separately: UC: 110,1%; CD: 107,6%
Meyer et al.	Equivalence Observational	3112 patients	24 months	Composite endpoint including all causes of IFX failure, either due to inadequate efficay or toxicity.
Ye et al.	Non-inferiority Phase 3 Randomized Double-blind	220 patients	54 weeks	CDAI-70 response at week 6: IFX: 81/109 patients; CT-P13: 77/111 patients

(Caption: IFX – Infliximab; CDAI – Crohn's Disease Activity Index).

b) SB-2 - Flixabi®, Renflexis®

Both Flixabi® and Renflexis® are marketed by Samsung Biopesis, however only Flixabi® was approved by the EMA in 2016 (78). Renflexis® was approved by the FDA in 2017 (78).

There is still little post-marketing information regarding SB-2, however, a long-term observational prospective cohort study was carried out, which was based on replacing the IBD treatment with infliximab with the biosimilar SB-2, in a total of 148 patients (89). There was similarity in clinical efficacy, pharmacokinetics and safety profile between SB-2 and infliximab, during a follow-up period of 18 months (89). Disease activity was assessed using the Harvey-Bradshaw Index (HBI; a simplified version of the CDAI) for CD, and the partial Mayo Score (pMS) for UC, with no significant changes in disease activity post-replacement with SB-2 (89). In addition, CRP, serum monoclonal antibody concentration and anti-drug antibodies (ADAs) (which constitute an indicator of immunogenicity) were measured before all biosimilar administrations, with no significant clinical differences in any of these parameters (89).

Another cohort study was carried out to confirm the similarity between SB-2 and infliximab, in which 276 patients were divided into 5 groups: non-responsive to infliximab or other anti-TNFs, non-responsive to infliximab and previously exposed to other anti TNFs, patients who replaced infliximab treatment with SB-2, patients who replaced SB-2 treatment with CT-P13 and patients who underwent multiple substitutions (90). In short, the similarity of efficacy and safety between SB-2, its reference biological medicine and the biosimilar CT-P13 was confirmed once again. Also the occurrence of adverse effects and their degree of severity was similar for the 3 molecules under study, however there was a higher incidence of serious adverse effects in the group of patients not responsive to infliximab and previously exposed to other anti-TNFs (90). The authors offer a hypothetical explanation for this result, namely that a previous treatment with an anti-TNF agent is suggestive of a more serious and refractory manifestation of the disease, leading to a greater likelihood that patients will develop more serious adverse effects (90).

c) PF-06438179/GP1111 - Zessly®

PF-06438179 is one of the three infliximab biosimilars approved in the EU, having been approved by the EMA in 2018 and is marketed by Sandoz (78).

Coehn et al. (91) carried out a randomized double-blind phase III study, which evaluated the efficacy, safety and immunogenicity of PF-06438179 in patients with moderate to severe rheumatoid arthritis who switched from infliximab therapy to this biosimilar, or who remained in a treatment regimen with PF-06438179. Patients received an intravenous 3mg/kg dose of either infliximab or PF-06438179 at weeks 0, 2 and 6, and then every 8 weeks, for a total of 78 weeks. The treatment dose could be increased to 5 mg/kg in patients with an inadequate response at week 14. The results demonstrated that there were no significant clinical differences regarding efficacy, safety and immunogenicity of PF-06438179 compared to its reference biological (91). Bioequivalence and similarity were also corroborated with regard to pharmacokinetics, structural characteristics and biological function, supporting the evidence of biosimilarity between infliximab and PF-06438179 and the validity of the extrapolation of the eligible indications for which infliximab was approved (91,92).

5.2.2. Adalimumab Biosimilars

Since 2017, six biosimilars of Adalimumab have been approved for the treatment of IBD, five of which have been approved by both the FDA and the EMA and one approved only by the FDA (BI-695501 - Cyltezo®) (78,93).

a) ABP 501 - Amgevita®

Marketed by Amgen, ABP 501 was the first biosimilar of adalimumab to be approved, in 2016 by the FDA and in 2017 by the EMA (78,93). Like its biological reference medicine, it is administered subcutaneously, and its pharmacokinetic similarity has been proven in a phase I clinical study, after healthy subjects received a subcutaneous injection of a single dose of 40 mg (94). In accordance with the scientific guidelines referred to above, comparative studies were also carried out, confirming the similarity between ABP 501 and adalimumab with regard to physico-chemical properties and biological activity (95,96).

Clinical efficacy, safety and immunogenicity were tested in phase III clinical trials in patients with psoriasis and rheumatoid arthritis, in groups of 350 and 526 patients, respectively (97,98). Both groups showed a moderate to severe manifestation of their disease (97,98). In the study with

psoriasis patients, the effectiveness of ABP 501 was measured by the percentage of improvement in the Psoriasis Area Severity Index (PASI) during the first 16 weeks of treatment. Patients who reached a PASI of 50 in the 16th week, continued the study until 52 weeks of treatment (97,99). Both the development of antibodies against the biosimilar (immunogenicity) and the reported adverse effects were similar to those found for adalimumab (93,99). In the study with patients with rheumatoid arthritis, similar results were confirmed over a 24-week study period (98).

b) SB5 - Imraldi®

SB5 was the second biosimilar of adalimumab to be approved, in 2017 by the EMA and in 2019 by the FDA (marketed under the name Hadlima®) (78).

As with the development of ABP 501, the clinical efficacy, safety and immunogenicity of SB5 compared to adalimumab was also determined in a phase III clinical trial comprised of 544 patients with rheumatoid arthritis, who received a 40 mg subcutaneous injection of either SB5 or adalimumab every other week, with a follow-up period of 24 weeks (100). The same incidence rates of serious adverse effects, reactions at the injection site and infections resulting from immunosuppressive treatment were demonstrated (100). Its pharmacokinetic similarity was demonstrated in a comparative study in 188 healthy volunteers (101).

A phase III transition study was also carried out in which, at the 24th week of treatment, patients who were undergoing treatment with adalimumab were randomized to continue with the original or switch to SB5, and patients who had already started treatment with the biosimilar continued the same regimen (102). After 52 weeks of study, it was concluded that the clinical efficacy was similar in all groups, as well as the safety and development profile of ADAs against adalimumab/SB5 (93,102).

c) GP2017 - Hyrimoz®, Halimatoz®, Hefiya®

GP2017 was approved by the EMA and FDA in 2018, being marketed by Novartis both in the EU and USA (78).

As mentioned for the two previous biosimilars, GP2017 was also subjected to phase I comparability studies in 318 healthy subjects, in which its similarity to adalimumab was proven, with regard to clinical efficacy, tolerability, safety and immunogenicity (103). Its effectiveness was also demonstrated in a phase III clinical trial with psoriasis patients, who were randomly assigned the biosimilar GP2017 or adalimumab (104). Patients received a subcutaneous injection of 80 mg of adalimumab or GP2017 at week 0, and then a 40 mg injection every other week, for a total of 51 weeks (104). At the 16th week of treatment, patients who were responding were randomized to continue with the established regimen until the 35th week of treatment or to switch to GP2017 or adalimumab (104). After 16 weeks, the similarity of clinical efficacy was verified through the analysis of the PASI score, and it was also found that there were no significant differences in the serum concentration of both monoclonal antibodies, their safety profiles or adverse effects (104).

d) FKB327 - Hulio®

Approved in 2018 by the EMA, and marketed by Mylan, FKB327 is another biosimilar of adalimumab approved for the treatment of IBD (78).

Its clinical efficacy was established to be similar to that of adalimumab in a comparative study comprising 180 healthy subjects, after a subcutaneous injection of a single dose of 40 mg, which corresponds to the maintenance dose (105). A phase III clinical study was also carried out in 730 patients with severe to moderate rheumatoid arthritis, in conditions similar to those described for the phase III studies carried out in the aforementioned biosimilars (106,107). This study also demonstrated the similarity between FKB327 and adalimumab in terms of safety, clinical efficacy, immunogenicity and pharmacokinetics (106,107).

e) MSB11022 - Idacio®, Kromeya®

MSB11022 was approved in 2019 only by the EMA as a biosimilar of adalimumab for the treatment of IBD, being marketed by Fresenius Kabi (78).

A phase I study, conducted in 213 healthy subjects who received a single dose of 40 mg, demonstrated the bioequivalence between MSB11022 and adalimumab (108). In addition, a

comparative analysis was also carried out between the two molecules, proving the similarity between them, at a physico-chemical and functional level (109). Similar to GP2017, MSB11022 was subjected to a phase III study with 443 patients with moderate to severe psoriasis, who were randomly assigned adalimumab or MSB11022 (110). Through the analysis of the PASI score, it was possible to determine equivalent efficacy between the two molecules after 16 weeks of treatment and the patients who responded to the treatment continued it until they reached the 52 weeks mark (110). At this point, patients who were assigned MSB11022 at the start of treatment remained on this regimen, and patients who were assigned adalimumab were randomized to continue on the same regimen or switch to the biosimilar (110). At the end of the 52 weeks, an equivalent serum concentration was found in all study groups, with similar safety and immunogenicity profiles between the two molecules being observed after 66 weeks of treatment (110).

5.2.3. Extrapolation

As mentioned before, when similarity between a biosimilar and its reference biological medicine is demonstrated, the EMA has to approve the extrapolation to the other indications of the reference biological product, when there is appropriate scientific justification (76). The extrapolation to other indications in the case of Adalimumab and Infliximab biosimilars was based on their TNFα binding mechanism, which is common to all diseases mediated by inflammatory processes and which was included in the comparative study carried out by the EMA (76,79).

5.3. Switching from a Biological to its Biosimilar

5.3.1. Switching

When biosimilarity between a biosimilar and its biological reference medicine is demonstrated, it becomes possible to replace the treatment with a biological medicine with its biosimilar, without compromising efficacy, safety and immunogenicity. However, for this substitution to be possible, it must be supported by scientific evidence, namely through clinical phase IV non-inferiority studies.

One of these studies, NOR-SWITCH (87), carried out in Norway, aimed to evaluate the safety and efficacy of replacing Infliximab with its biosimilar, CT-P13, in 486 patients with several autoimmune diseases, including CD, UC, spondyloarthritis, rheumatoid arthritis, psoriatic arthritis and psoriasis, whose primary endpoint under study was the worsening of the disease during a 52-week follow-up period. Patients were randomized to continue treatment with infliximab or to switch to biosimilar CT-P13, and at the end of the 52-week follow-up, there was disease worsening in 26% of patients on infliximab compared to about 30% of patients on CT-P13 (adjusted treatment difference of -4.4%, 95% confidence interval). Thus, as the difference detected between the two groups was below the pre-established cutoff (15%), the researchers concluded that CT-P13 was not inferior to infliximab. Regarding patients with CD, disease worsening was detected in 21.2% of patients on infliximab and in 36.5% of patients on CT-P13 (adjusted risk difference of -14.3%). As for patients with UC, disease worsening was detected in 9.1% and 11.9% of patients, respectively (adjusted risk difference of -2.6%). As for the detected adverse effects, with regard to serious adverse effects, there was a frequency of about 10% in the group being treated with infliximab and 9% in the group being treated with the biosimilar. With regard to adverse effects that lead to therapy discontinuation, the percentages in both groups were approximately the same. In summary, the study concluded that there is no inferiority of the biosimilar CT-P13 compared to infliximab, in terms of efficacy, safety and immunogenicity, making it safe to switch from infliximab to its biosimilar, in all its approved indications.

Other studies were carried out, based on the same objective, in order to prove that the replacement of infliximab with one of its biosimilars is possible with no efficacy or safety concerns (111).

However, for Adalimumab and its biosimilars, there is still not as much source of information to support the same conclusion regarding the possibility of switching (79). Nevertheless, as it was seen in the pre and post clinical studies necessary to demonstrate the similarity between adalimumab and its biosimilars during the development and approval processes, there are no significant differences in terms of structure, efficacy, safety or pharmacokinetics between adalimumab and its biosimilars, although these studies were essentially conducted in patients with diseases other than IBD (particularly rheumatoid arthritis and psoriasis) (97,100,102,104,106,107,112,113).

In any case, the replacement of a biological medicine with its biosimilar should only be done after careful assessment of the clinical situation, and under medical advice.

If a decision is made to switch from a biological medicine to a biosimilar, there are guidelines established by the NICE which suggest the following steps to allow a successful introduction of the biosimilar (114):

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 EMA licensing process 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 and explore gain-share agreements;
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 metrics to be collected during and after the introduction of biosimilars;
7. Submit data to national audits and registries.

5.3.2. Interchangeability

The Portuguese Association of Generic and Biosimilar Medicines (APOGEN) defines interchangeability as the substitution of a medicine for another that is equivalent to it, in a given clinical context, with the agreement of the prescribing physician (36). A medicine is considered to be interchangeable if it can be administered instead of another clinically equivalent product (36). Regulatory scientific data, published through the EPAR, should guide prescribing physicians' decisions on interchangeability (36). However, there is no consensus on an official definition of interchangeability, with the World Health Organization (WHO) considering an interchangeable product as "any pharmaceutical product ... which is therapeutically equivalent to a comparator product" (115). The EMA, on the other hand, does not have its own definition of interchangeability, but argues that this definition should be established at a national level (116). The FDA determines that interchangeability can only be established in studies that comprise a minimum of 3 switches, with each switch being subject to at least two exposure periods for each medicine (117).

According to statements established by the European Crohn's and Colitis Organization (ECCO) during a consensus meeting held in Vienna, Austria, in October 2016, there is a lack of

clinical and scientific evidence regarding reverse switching (switching from a biosimilar to the original biological medicine), multiple switching and cross-switching (switching from one biosimilar to another) (118).

5.3.3. The Nocebo Effect

Pouillon et al. (119) defines the nocebo effect as the negative effect of a pharmacological or non-pharmacological treatment, induced by the patient's expectations, with no direct relationship to the physiological action of the medication. This constitutes an obstacle to the introduction of biosimilars in clinical practice and the subsequent switching of a reference biological for its biosimilar, making it difficult for patients to adhere to therapy, which in turn results in loss of therapeutic efficacy and undermines the cost-benefit associated with the use of biosimilars. Figure 7 depicts the impact of the nocebo effect regarding treatment outcomes in IBD. This is particularly relevant in patients with IBD, as they are more prone to experience functional symptoms (symptoms that have no apparent physical cause, but that are related to alterations in the nervous system) (120).

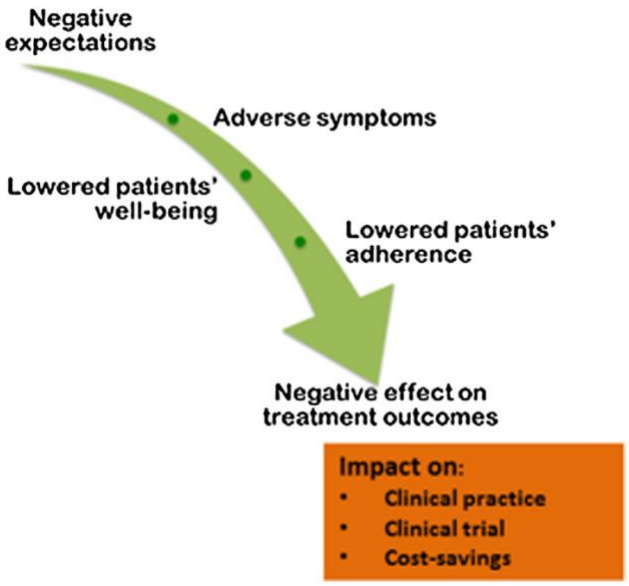


Figure 7 – The impact of the nocebo effect in treatment outcomes of biosimilar-treated IBD patients. Adapted (121).

It is also necessary to take into account that some patients develop secondary loss of response to anti- TNFα agents, a fact that has been documented in patients with IBD even before the emergence of biosimilars. This loss of response should not be associated with the introduction of biosimilars in the therapeutic regimen or the switch of a biological reference medicine for its biosimilar (85). It should also be noted that the annual loss of response to Infliximab is 13% per patient-year, and 20% per patient-year in the case of Adalimumab, which is also not associated with the practice of switching (122).

In this context, in 2018, the European ‘’NOCE-BIO Consensus Group’’ stated that all health-care professionals involved in the therapeutic path of patients with IBD should be aware of the nocebo effect and adopt strategies towards minimizing it (123). These strategies are based on key points, namely the role of each agent involved in the clinical course of a patient with IBD. Both the different agents and their roles in minimizing the nocebo effect are shown in table 4.

Table 4 – Key points to reduce the nocebo effect during biosimilar treatment in IBD. Adapted (121).

Group	Key roles to reduce the nocebo effect during biosimilar treatment
Physicians	• Biosimilar switch should be a clinical decision based on scientific evidence, taken by the physician and shared with the patient, who must be fully aware of this treatment choice; • Minimize lack of knowledge about the effectiveness and safety of biosimilars.
IBD nurses	• Provide personalized and accessible information about biosimilars and the nocebo effect; • Minimize lack of knowledge about the effectiveness and safety of biosimilars; • Nurses should be trained to communicate with patients and to get acquainted with positive framing.
Psychologists	• Implement an effective health-care provider-patient communication strategy; • Support psychological difficulties experienced by biosimilar-treated patients, directing them towards possible therapeutic approaches to deal with de nocebo effect, if needed.
Pharmacists	• Support the assessment of analytical, economical and clinical data, including pharmacovigilance data, to demonstrate the efficacy and safety of biosimilars; • Increase their knowledge about biosimilars and the rules of interchangeability; • Participate in the development of supporting material for other health-care providers, in order to promote their introduction of biosimilars into the health-care systems.
IBD patients	• Hear data about effectiveness and safety of biosimilars, rather than data concerning health management; • Request their direct caregivers to be informed about biosimilars; • Request their general practitioners to be informed about biosimilars.

It is also important to note that, although the main motivation for replacing a biological medicine with its biosimilar is the economic component, the basis for communication between health-care professionals and IBD patients should be the clarification of the concept of biosimilarity and the data on the efficacy and safety of biosimilar medicines, in an accessible and concise language. This is essential, since one of the fears detected in patients, which contributes on a large scale to the development of the nocebo effect, is that the main focus is only the economic sphere, neglecting aspects such as the effectiveness and safety of the therapy (121).

5.4. Pharmacoeconomic Analysis

Associated with the progressive increase in the incidence of IBD in the world (124), the high cost of biological therapies constitutes an obstacle to patients' access to these same therapies (85).

With the continuous introduction of new biological agents, with various therapeutic indications, namely the treatment of IBD, direct medical costs increase exponentially, proving to be particularly impeditive in countries with a medium-low gross national product (73).

Yu et al. (125) conducted a study of the market and cost of biological therapies in the treatment of IBD in the USA over a 9-year period (between 2006 and 2015) using a database of about 400,000 IBD patients. This study concluded that the percentage of patients with CD using biologics increased from 21.8% to 43.8%, while in the population with UC the percentage increased from 5.1% to 16.2%. Furthermore, the share of costs for these biologics increased from 72.9% to 85.7% over an 8-year period.

The introduction of biosimilars is a way to promote the reduction of health costs and thus facilitate access to biological therapy, without compromising clinical results. The initial introduction of biosimilars in the market, aimed at the treatment of IBD, predicted a reduction in the cost of biological therapy by about 15% to 35% (126). This has not only been seen, but the percentages have shown to be even more promising. In Norway, in the first year of commercialization of the Infliximab biosimilar, CT-P13, an incentive of 39% discount was offered compared to the price of infliximab (126). In the following year this percentage rose to 69% and, as a result, the market share of CT-P13 in Norway increased from 20% to 30%, in the 2 year-period (126).

According to a 2016 report carried out by the IMS Institute for Healthcare Informatics (127), it was predicted that, by 2020, 28% of the value of the global pharmaceutical market would correspond to biological agents. Still within the scope of this study, it was concluded that the use of biosimilars would allow savings of around 50€ billion in the five main EU markets (Germany, France, Italy, UK and Spain) and in the USA, reaching the 100€ billion mark.

This reduction in the cost of IBD therapy then becomes a central and essential focus for the possibility of treating more patients, without loss of therapeutic quality.

The ECCO carried out a series of surveys between 2013 and 2016, after the introduction of the first infliximab biosimilar in the market, in order to ascertain, among the respondents, the advantages associated with the introduction of biosimilars in the pharmaceutical market and in the therapeutic regimen of IBD patients. According to the information taken from these surveys, 90% of respondents considered that the biggest advantage associated with biosimilars was cost savings (128,129).

Brodszky et al. (130) conducted an analysis of the budgetary impact of the infliximab biosimilar, CT-P13, in Bulgaria, Czech Republic, Hungary, Poland, Romania and Slovakia, based on a 25% reduction in the price of the biological agent. The study ran for 3 years and was based on two scenarios: in the first, switching was not allowed, meaning that only patients initiating biological therapy received treatment with CT-P13; in the second, the analysis was performed on a sample in which 80% of IBD patients underwent treatment with CT-P13, including switching situations. In summary, it was found that in the first scenario the initiation of treatment with the biosimilar allowed savings of around 8€ million, while in the second scenario, which included patients who had started therapy with infliximab but switched to its biosimilar, savings amounted to 17€ million. The amount of money saved would be sufficient to treat between 700 and 1500 new IBD patients.

Another very interesting budget impact analysis was carried out by Jha et al. (131), in which the introduction of CT-P13 in therapeutic regimens was analyzed in patients with autoimmune diseases (including IBD) in Germany, the United Kingdom, Italy, the Netherlands and Belgium. The study assumed that CT-P13 would be 10% to 30% cheaper than infliximab, and based on this premise, it was found that, in the case of IBD, there was an increase in cost savings of about 12€ million to 36€ million in the case of CD, and 5€ million to 15€ million in the case of UC. This resulted in the possibility of treating between 1200 to 4700 additional IBD patients in the five countries under study, for 1 year.

With regard to cost-effectiveness studies, two studies were also carried out in nine European countries, where several biological agents used in the treatment of IBD were compared, namely CD, including infliximab, its biosimilar CT-P13, Adalimumab and Vedolizumab. One of these studies was carried out by Baji et al. (132) and demonstrated that CT-P13 was the most cost-effective agent, with cost-effectiveness ratios between 34,684€/QALY (quality-adjusted life year) and 72,551€/QALY in the countries under study (Belgium, France, Germany, Hungary, Italy, The Netherlands, Spain, Sweden, UK). The other study, coordinated by Rencz et al. (133) concluded that, in comparison with conventional therapies, CT-P13 demonstrated the best incremental cost-utility ratios, ranging from 34,580€/QALY in Hungary to 77,062€/QALY in Sweden. This means that, for each life-year gained (adjusted to quality of life parameters), CT-P13 requires the lowest monetary expenditure, in comparison with the other biological agents under study.

By analyzing all these results, the possibility of investing in specialized education of health care professionals about IBD becomes evident, but more importantly, it's clear that the access of biological agents to more IBD patients becomes easier, allowing them to initiate biological therapy at an earlier stage of the disease (73). Also, these cost savings could be directed to more specialized services, namely Therapeutic Drug Monitoring (TDM) (it involves the measurement of the biologic agent and ADA levels; the latter, if high, usually indicates loss of primary efficacy and possible loss of response to treatment), which could optimize biological therapy by allowing a more personalized therapeutic approach to each IBD patient, with beneficial long-term outcomes (134–136).

6. Future Perspectives

The objective of IBD therapy is to change the natural course of the disease, in order to improve the quality of life of patients and avoid permanent damage (137). This implies a quick and incisive approach upon diagnosis, directly resulting in better prognosis and allowing the achievement of optimistic endpoints regarding the remission of the disease. The treatment of IBD is optimized when biological agents are introduced as soon as possible, aiming at specific inflammatory targets, with a window in which the effectiveness of these agents, namely anti-TNF, is enhanced (138).

As already mentioned in previous topics, the use of biosimilars has numerous advantages, namely economic ones, facilitating the access of patients and the sustainability of health care systems, without compromising clinical efficacy and safety. In addition, the introduction of biosimilars in clinical practice constitutes an incentive to innovate and develop biosimilars from other biological agents, and to solve gaps and fears associated with the use of biosimilars (78). Because of this, in recent years there has been a growing investment in the development of new biosimilars for the treatment of IBD, not only for anti-TNF agents in their known administration routes, but also for new formulations for administration by alternative routes that are more convenient for the patient (139–141).

Table 5 illustrates the biosimilars under development with possible application in the treatment of IBD. In addition to Infliximab and Adalimumab, already pioneers with regard to biosimilars available on the market, biosimilars of the other two anti-TNF agents, Golimumab and Certolizumab, are also being developed, thus increasing the therapeutic arsenal in refractory patients, while reducing health care costs. For the time being, infliximab's biosimilar, BOW015, is licensed only in India.

Table 5 – Biosimilars under development for possible use in Inflammatory Bowel Disease. Adapted (78).

Molecule		Manufacturer	Current Status
Infliximab	BOW015	Epirus Biopharmaceuticals	Phase III study
	NI-071	Nichi-Iko Pharmaceuticals	Phase III study
	STI-002	Mab Tech / Sorrento Therapeutics	Pre-clinical
Adalimumab	CHS-1420	Coherus	Phase III study
	M923	Momenta/Baxalta	Phase III study
	LBAL	LG life Sciences / Mochida Pharmaceuticals	Pre-clinical
	MYL-1401A	Mylan Inc.	Pre-clinical
	PF-06410293	Pfizer Inc.	Phase III study
	BCD-057	Biocad	Pre-clinical
	ONS-3010	Oncobiologics	Pre-clinical
Golimumab	BOW100	Epirus Biopharmaceuticals	Pre-clinical
Certolizumab	PF-6688	Pfenex	Pre-clinical
	Xcimanze	Xbrane	Pre-clinical

However, these therapies are not flawless and have some disadvantages, namely the absence of primary response in about 30% of IBD patients and secondary loss of response (there is a primary response, but then it starts to decrease) in a considerable number of patients (142,143). In addition, they are accompanied by some potentially serious adverse effects resulting from the immunosuppressive effect they exert, namely reactivation of opportunistic infections, emergence of malignancies, development of ADAs, among others (144).

This drives the need to invest in the development of new biological agents, and their biosimilars, with equal or greater effectiveness and with the least possible adverse effects (144). Some of these innovative biological agents, serving as a starting point for the development of new biosimilars, include: Interleukin (IL) inhibitors, namely IL-12 and IL-23 (e.g. Ustekinumab); Antisense oligonucleotides (e.g. GED-0301/Mongersen); Anti-integrin inhibitors, among others (145). Some of the new biological agents under development, that could become reference products for the development of new biosimilars, are summarized in table 6.

Table 6 – New biologics under development for the treatment of IBD. Adapted (144).

Biological	Mechanism of action	Current Status
Bertilimumab	Chemokine CCL11 inhibitor	Phase II (UC and CD)
Bimekizumab	IL-17 inhibitor	Phase II (UC)
E6011	Chemokine CXCL1 inhibitor	Phase I/II (CD)
FFP104	CD40 antigen inhibitor	Phase II (UC)
Foralumab	CD3 antigen inhibitor	Phase II (CD)
KHK4083	OX40 receptor antagonist	Phase II (UC)
Mirikizumab	IL-23 inhibitor	Phase II (CD and UC)
PF04236921	IL-6 inhibitor	Phase II (CD)
SHP 647	$\alpha_4\beta_7$ integrin antagonist	Phase II (CD) and Phase III (UC)

(Caption: CCL – C-C motif chemokine ligand; CD – cluster of differentiation; CXCL – C-X3-C motif ligand; IL – Interleukin; OX40 – CD134).

Another important aspect that the pharmaceutical sector should focus on is the fact that, currently, there is not much specific information regarding the exclusive use of biosimilars in patients with IBD (73). As a general rule, the comparative studies necessary to prove the similarity between a biological agent and its potential biosimilar, are carried out on study samples from patients with other autoimmune diseases, namely rheumatoid arthritis and psoriasis. To combat the stigma associated with the concern of using molecules that are similar (not totally equal) to the original biologicals, for the same indication, it is imperative that more comparative clinical phase III and IV studies be done directly in patients with IBD.

Furthermore, the gap in clinical and scientific evidence regarding the benefits and risks of multiple switching, reverse switching and cross-switching between biosimilars in IBD patients is yet to be filled (73). This implies that concrete and standard regulatory and legislative criteria are established, in order to allow the harmonization of the nomenclature of new biosimilars (facilitating their recognition and regulation), clarify the standards and directives that govern the interchangeability (and its variants) of biological products, and their respective biosimilars, and fundamentally allow adequate pharmacovigilance (78).

We cannot talk about future perspectives without talking about patents. For a biological medicine, the period of exclusivity in the United States is 12 years (4 years data exclusivity and 8 years market exclusivity), during which time applications for biosimilars of that biological medicine can be submitted, however, the FDA cannot grant marketing authorization (146,147). As for the EU, the period of exclusivity is the same for chemical and biological medicines, establishing itself at 10 years (8 years data exclusivity and 2 years market exclusivity, with the possibility of 1 year extension) (146,147).

In this context, the aforementioned biosimilars that are in the process of being approved or still under development, have been proposed with essentially anti-TNF monoclonal antibodies as a reference. However, there are biological medicines approved for the treatment of IBD whose patent exclusivity period is coming to an end, opening the door for other companies to start the process of developing new biosimilars. An example of this is the case of Ustekinumab (Stelara®), a monoclonal antibody that acts by antagonizing IL-12 and IL-23, which set of patents is expected to expire in 2023 in the United States, and in 2024 in some European countries due to a patent term extension (148). In the remaining countries, the deadline ends in 2021 (148). As such, several companies are dedicating themselves to the development of ustekinumab biosimilars (149).

Table 7 shows some of the biologicals previously mentioned, some of which already have biosimilars, while the rest do not yet have biosimilars or have biosimilars under development. The information on the expiry of the respective patents allows us to infer which biologicals could be used as a reference for new biosimilars, contributing to the sustainability of health care systems and facilitated access by patients.

Table 7 – Estimated patent expiry dates for biologics used in the treatment of IBD. Adapted (147).

Biological	Mechanism of action	Approval date		Patent expiry date	
		EU	USA	EU	USA
Infliximab	Anti TNFα	13th Aug 1999	24th Aug 1998	13th Feb 2015	4th Sep 2018
Adalimumab	Anti TNFα	8th Sep 2003	31st Dec 2002	Oct 2018	Dec 2022
Certolizumab	Anti TNFα	1st Oct 2009	22nd Apr 2008	5th July 2021	13th Feb 2024
Golimumab	Anti TNFα	1st Oct 2009	24th Apr 2009	Oct 2024	Feb 2024
Vedolizumab	Blocks $\alpha_4\beta_7$ integrin	22nd May 2014	20th May 2014	Data not available	24th Jul 2017
Ustekinumab	Anti IL-12 and IL-23	16th Jan 2006	25th Sep 2009	Jan 2024	Sep 2023
Natalizumab	Blocks $\alpha_4\beta_7$ and $\alpha_4\beta_1$ integrins	27th Jun 2006	23rd Nov 2004	Aug 2015	Mar 2015

7. Conclusion

With the increasing incidence of IBD in the world's population, namely in younger age groups, there is a need to develop innovative therapies, with fewer adverse effects, allowing IBD to become manageable with little to zero impact on the patient's quality of life. Hence biosimilars emerge, standing out for their innovation and clinical efficacy, inherited from their reference biologicals, and for the financial sustainability they offer to health care systems.

Nowadays, the offer of biosimilars is limited only to those that arose from Infliximab and Adalimumab, which constitute the first line in biological treatment of IBD. However, the arsenal of biological medicines for the treatment of IBD is vast and growing, paving the way for the development of new biosimilars that may further cement the sustainability of health care systems, the therapeutic regimen of patients and increase therapeutic alternatives in refractory regimens.

Furthermore, the obvious and significant economic advantage biosimilars bring to the table allows biological therapy to reach more IBD patients, with an earlier and therefore more effective therapeutic approach. In addition to this, there is also the possibility of making a considerable investment when it comes to offering specific IBD training to health care professionals in charge of the clinical course of IBD patients. This investment also translates into a greater adherence to therapy by patients, breaking the stigma associated with the use of biosimilar medicines and their clinical effectiveness.

The use of biosimilar medicines presents itself as the future of the treatment of chronic illnesses, namely IBD, however there are still some gaps to fill. As such, investment in this area is essential, including obtaining more information from clinical trials conducted directly in IBD patients and a continuous and current pharmacoeconomic analysis. With the optimization of this therapeutic area, a group of illnesses once considered to be extremely debilitating, with a great impact on the physical and psychological well-being of patients, becomes bearable, allowing patients to have a better quality of life.

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