

Monoclonal Antibodies in Treating Inflammatory Bowel Disease

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Contributor: Zvonimir Petric , Joao Goncalves , Paulo Paixao

Monoclonal antibodies (MAbs) have revolutionized the treatment of many chronic inflammatory diseases, including inflammatory bowel disease (IBD). IBD is a term that comprises two quite similar, yet distinctive, disorders—Crohn's disease (CD) and ulcerative colitis (UC). Two blockbuster MAbs, infliximab (IFX) and adalimumab (ADL), transformed the pharmacological approach of treating CD and UC. However, due to the complex interplay of pharmacology and immunology, MAbs face challenges related to their immunogenicity, effectiveness, and safety.

monoclonal antibodies

inflammatory bowel disease

anti-TNF- α agents

infliximab (IFX)

adalimumab (ADL)

1. Introduction

According to the definition, biologic therapy (biologic therapeutic) is a medicine that is made from living organisms (or its products), and is used for the treatment of diseases, as well as for disease prevention or diagnosis ^[1]. The definitions given by the regulatory agencies in the EU, the European Medicines Agency (EMA), and in the USA, the Food and Drug Administration (FDA), are more or less similar ^{[2][3]}. In 2020, the FDA rephrased its definition by adding that biological product actually refers to all proteins, including any alpha amino acid polymer greater than 40 amino acids ^[3]. This change, however, has regulatory repercussions without being generally relevant for the clinical practice.

Biopharmaceutical innovation and the implementation of biologic therapy have revolutionized the treatment options for many diseases, from the field of oncology to chronic and inflammatory autoimmune disorders, such as inflammatory bowel disease (IBD) and rheumatoid arthritis (RA), where prior pharmacological attempts with conventional therapy have often been unsuccessful. Hence, it is no surprise that, in the eyes of patients and clinicians, biologic therapeutics are perceived as a game-changing therapeutic modality.

Biologic therapeutics (also called biologics, biologic medicines, biological products, biologics-based medicines, biotherapeutics, biopharmaceuticals, etc.) are well-known as relatively complex molecules produced via a highly sophisticated biotechnological methodology; hence, their high price is unsurprising. Biologics are the fastest-growing therapeutic modality. In 2020, the biologics market was valued to be around EUR 278 billion, while it is expected to reach an astonishing EUR 465 by 2026, according to ^[4]. Moreover, among the best-selling drugs in 2020, the top-selling was adalimumab (Humira®). Among the top ten drugs, six were monoclonal antibodies (MAbs)

[5]. As the global market for biologics is obviously rising, it can be expected that such fast expansion in the coming years will pose big challenges for manufacturers and their production plans if they want to stay at the top in the ever-changing pharmaceutical landscape.

One of the most successful biologics is monoclonal antibodies (MAbs), also referred to as therapeutic antibodies in the case of their multi-indication use. The unique attribute of MAbs is their monospecificity, meaning that they recognize one particular antigenic determinant, i.e., an epitope, on a given molecule. Moreover, as antibodies are secreted by an individual hybridoma, they are completely identical immunoglobulin molecules, which show identical affinity to a target of medical interest, as well as identical physiochemical properties [6].

The nomenclature of MAbs was devised by the World Health Organization (WHO), and follows the International Nonproprietary Nomenclature (INN) (**Figure 1**), except in the case of muromonab (murine monoclonal antibody) [7].

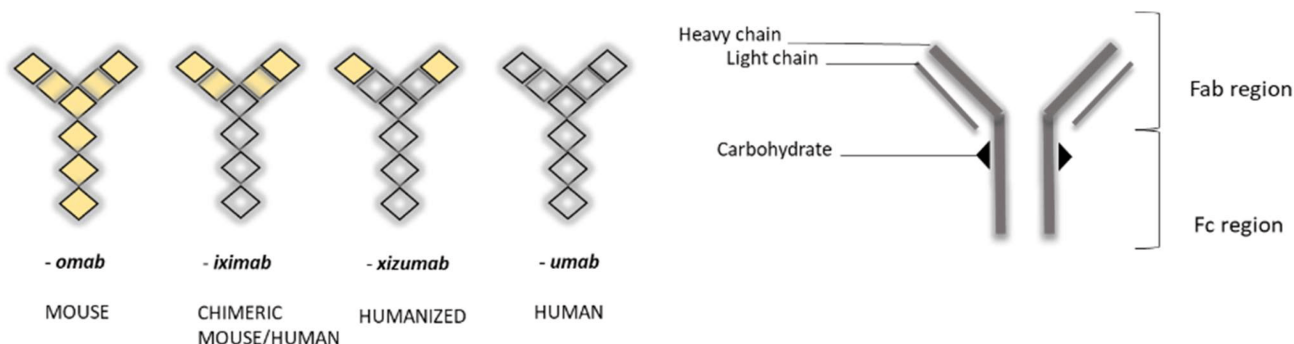


Figure 1. Schematic view of nomenclature for monoclonal antibodies (MAbs) (**left**) and general representation of their “Y” structure (**right**) [6]. Note the change in color, representing the differing humanization of antibodies.

In the biopharmaceutical and pharmacological sense, biologics greatly differ from conventional therapy, also known as small-molecule drugs (**Table 1**). The fundamental differences between these therapeutic modalities, such as their size, chemical structure, physicochemical and biophysical properties, stability, complexity, and specificity, determine the differences in the processes of absorption, distribution, metabolism, and elimination (acronym ADME), i.e., pharmacokinetics (PK), as well as pharmacodynamics (PD). In addition, these differences also influence the way that both therapeutic modalities are manufactured [8].

Table 1. General differences in small-molecule drugs vs. biologics [8][9].

Small-Molecule Drugs	Biologics
Low molecular weight (<0.5 kDa)	High molecular weight (>2–5 kDa)
Small size + lipophilicity allows passage across barriers	Due to its large size, penetration is not expected across barriers
Homogenous mixtures	Heterogeneous mixtures, with possible variants

Small-Molecule Drugs	Biologics
Well-defined structure	Structure may not be known (or not well-defined)
Physicochemically less complex	Physicochemically very complex
Easily synthesized	Made from live cells and organisms
Less critical steps in the manufacturing process	Many critical steps in the manufacturing process
Very well characterized (methodology is known)	Not easily characterized
Stable; heat stable	Not stable; heat sensitive
Administered orally	Usually administered parenterally (intravenously, intramuscularly)
Relatively short half-life; daily dosing regimen	Longer half-life (days to weeks); monthly dosing regimen
High risk for “off-target effects”	High selectivity and specificity for a target
Metabolism by liver enzymes—Cytochrome P450 (CYP)	Catabolism (degradation) and limited toxicity
Higher risk of drug interactions and toxicity due to CYP	Drug interactions are less common
Immunogenicity is not expected	Immunogenicity is a big challenge
Treatment is not expensive, i.e., lower costs of development	Treatment is very expensive, i.e., development costs are much higher
Longer development cycle	Shorter development cycle
Well-defined mechanisms of action	Pleiotropism in pharmacological effects
Rigid in terms of structure manipulation	Structure manipulation is possible and can offer an enhancement of pharmacological properties

Pharmacodynamics (PD) Related to MAbs

MAbs are 150 kDa immunoglobulin G (IgG) monoclonal antibodies, composed of two heavy chains and two light chains, which are linked by disulfide bonds, and which join to form a molecule resembling the letter “Y” (**Figure 1**). Tips of the “Y” (i.e., heavy + light chains) are called the variable region, while the stem portion of the “Y” (heavy + heavy chains) is called the constant region. Variable regions comprise an antigen-binding fragment (Fab), while constant regions comprise a fragment crystallizable (Fc) region. The Fab region binds to receptors on the cell’s surface, such as Fcγ receptors (FcγR) and neonatal Fc receptors (FcRn) [\[10\]](#)[\[11\]](#).

The general pharmacological function of MAbs, for example, antagonism against tumor necrosis factor-alpha (TNF-α) cytokines, is dependent on the selective binding of the antibody to the target of interest (antigen) through

variable regions. In addition to determining the antibody specificity of an antigen, variable regions also determine the potency of MAbs. On the other hand, the constant region impacts the functional effects of MAbs, such as its developability (i.e., biophysical properties), immunogenicity (i.e., ability to provoke an immune reaction), and effector functions (i.e., binding to receptors and PD). MAbs can also have post-translational modifications, such as amino acid and carbohydrate (glycosylation) modifications. Even a slight change in the constant (or variable) region can have a big and unpredictable impact on the clinical pharmacology of MAbs, meaning that both PK (ADME) and PD (efficacy, effectiveness, and safety) can be altered [\[10\]\[11\]](#).

As proteins, MAbs have a very low oral bioavailability, poor gastrointestinal stability, and poor lipophilicity, which makes them unsuitable for oral administration. Their apparent volume of distribution is considered to be relatively small and often limited to the circulatory tissue. In a steady state, typical values of the apparent volume of distribution (Vd) are within the range of 3.5–7 L, which indicates the limited distribution of MAbs to vascular and interstitial spaces [\[9\]](#).

The transfer of MAbs from plasma to interstitial space depends on the convective transport (as opposed to diffusion seen with small-molecule drugs), while the rate is determined by capillary permeability. Convection depends on the hydrostatic and osmotic pressure gradients between blood and tissue, but also on the vascular endothelium containing pores, which differ in amount and size. Some tissues may have a more “leaky” endothelium, while capillaries in the brain and their endothelial cells are actually impermeable, meaning that concentrations of MAbs in the brain are less than 1% relative to plasma concentrations [\[12\]](#).

It is also important to mention that MAbs administered via extravascular routes, i.e., intramuscularly (i.m.) or subcutaneously (s.c.), will have a rate of absorption dependent on the convective transport and lymph flow [\[13\]\[14\]](#). While the lymph volume can influence the apparent volume of distribution in a steady state [\[14\]](#), it can also be stated that the distribution of MAbs is relatively fast, while elimination (by either excretion or catabolism) is relatively slow [\[9\]\[13\]](#).

Due to their large size, MAbs are not eliminated by the kidneys in normal situations, while biliary excretion is also not considered to be relevant as the number of MAbs eliminated in this way is very small. Hence, the main elimination of MAbs is facilitated by proteolytic catabolism. Catabolism is mediated via lysosomal degradation (to amino acids) after the uptake of the antibody into cells by two mechanisms. The first uptake mechanism is pinocytosis, a form of unspecific fluid-phase endocytosis, which takes place on the vascular monolayer of endothelial cells. Pinocytosis is not limited to any particular organ or tissue, but instead occurs throughout the body where rich capillary beds are located, i.e., endothelial cells (liver, muscle tissue, skin, gastrointestinal tract, etc.) [\[12\]](#) [\[13\]\[15\]](#). The second uptake mechanism leading to MAb elimination is receptor-mediated endocytosis, where an MAb's Fc domain interacts with Fc cell receptors (FcγR), leading to endocytotic internalization, and the subsequent inactivation of MAbs (via lysosomal degradation). Various types of immune cells, such as monocytes, macrophages, natural killer (NK) cells, and dendritic cells, express FcγR on their surface membrane [\[12\]\[16\]](#). However, one additional interaction is related to receptor-mediated endocytosis, which implies the Fab-binding

domain of the antibody to its specific target, i.e., epitope. This is known as a specific clearance pathway of MABs, and is often referred to as target-mediated drug disposition (TMDD) [9][13][17].

TMDD is considered to be a PK, i.e., drug distribution, phenomenon. It has a lower elimination capacity compared to unspecific pinocytosis and, thus, can be saturable (contrary to an unspecific pinocytosis clearance mechanism that typically shows a linear behavior within the approved therapeutic dosage range). An in-depth explanation of TMDD is beyond the scope here; only its general relevance is presented. In short, TMDD occurs due to a very high affinity and very high binding specificity of the drug for its relatively low-capacity (i.e., low-density) pharmacological target. This phenomenon can be viewed as an example of how PD impacts PK (usually PK impacts PD), and as such, it is relevant to the disposition of biologics, contrary to common belief, as well as for some small-molecule drugs. TMDD could lead to the increased elimination of a drug due to the fact that the drug–target complex molecules can become endocytosed and degraded [13][18][19]. Hence, drugs cleared primarily via TMDD will show dose-dependent nonlinear elimination (even at therapeutic concentrations for some drugs), so TMDD can be considered as an important contributing factor for drug elimination. However, due to the generally high therapeutic concentrations of MABs used in the clinical setting, TMDD will not usually be the main factor that contributes to increased drug clearance, as there will be the sufficient fraction of a drug (unbound), compared to the fraction (bound, i.e., captured) on the target (receptor). As an example, antibodies against soluble antigens, e.g., tumor necrosis factor- α : TNF- α , infliximab (IFX), and adalimumab (ADL), are administered in a high dose and display linear elimination within that therapeutic range [9][13]. In conclusion, the rate of drug elimination mediated through TMDD will mainly depend on the drug dose, target capacity (density), drug affinity, binding specificity, and the rate of catabolism [13].

Other molecular aspects of pharmacology, which add an additional layer of complexity to the PKPD properties of MABs, are target turnover rate, changes in the patterns of glycosylation, off-target binding, immunogenicity (i.e., generation of anti-drug antibodies: ADAs) and the FcRn-mediated recycling of MABs. Due to immunogenicity, i.e., antibody–ADA immune complexes, one can also expect changes in antibody disposition, such as increased clearance and reduced half-life [9]. On the other hand, FcRn-mediated recycling serves as a salvage pathway for MABs, as it protects antibodies from lysosomal degradation and, thus, it partially counteracts the clearance process. Despite being a capacity-limited process (such as TMDD), FcRn-mediated recycling has a very important PKPD consequence, which is the prolongation of elimination half-life and, consequently, a longer duration of pharmacological effects [20]. Hence, FcRn-mediated recycling can be exploited as a prospective tool for improving the pharmacological properties of antibodies. On the other hand, blocking the FcRn activity was shown to be a good strategy for the treatment of myasthenia gravis. Currently, nipocalimab (anti-FcRn monoclonal antibody) is under clinical trials in adults (phase III) and children (phase II) [21][22]. Similarly, efgartigimod alfa (antibody Fc fragment) is currently expected to be approved in the EU for the treatment of generalized myasthenia gravis [23]. It is worth mentioning how the expression of Fc receptors in different pathologies can result in a variety of immunological responses, e.g., autoimmunity, inflammation, or allergies. Additionally, the therapeutic effectiveness of MABs is found to be related to the genetic variants of Fc receptors in individuals [24]. This also means that in IBD, the dysregulation of FcR signaling [25] could have a positive (or negative) influence on the clinical response. In order to be “druggable” enough, the MAb drug target should be easily available and tissue-specific, while, at the

same time, maintaining a low receptor turnover rate and low density. The latter properties offer less frequent dosing, or using a drug in lower amounts [26]. In addition to the previously described molecular PKPD complexities related to MAbs, there are also patient-related complexities, which cause interindividual variability in PK, in turn affecting PD. These differences are mostly related to age, pharmacogenetic profile (genetic polymorphisms), concomitant medications, immunogenicity (ADAs), and disease/health status [9][14]. Hence, as the knowledge on PKPD, inter-patient variability, and underlying pathology is still limited, it is important to bear in mind their joint influence on the pharmacological success of MAbs [14][17]. Therefore, clinicians often use biomarkers and clinical endpoints as a surrogate for pharmacological success. For example, in the case of IBD, the serum level of C-reactive protein (CRP), or a fecal calprotectin, and the status of mucosal healing are of great help in monitoring disease progression and evaluating the success of pharmacological intervention [9][27][28][29].

3. Inflammatory Bowel Disease (IBD)

IBD is an umbrella term, which is mainly used to describe a group of contrasting yet related intestinal disorders: Crohn's disease (CD) and ulcerative colitis (UC). Both disorders are characterized by non-infectious chronic relapsing episodes of inflammation of the gastrointestinal tract, probably caused by a dysregulation of immune response to the gut microbiome in genetically susceptible individuals [30][31]. As the etiology and pathophysiology of IBD is puzzling (**Figure 2**), so far, it has been established that genetic risk factors, environmental factors, lifestyle, mucosal immunity via the intestinal barrier, and the gut microbiome (intestinal dysbiosis) all play a role in the development of the disease. Despite the knowledge on the interplay of these factors, the health burden of IBD is still globally rising. In 2017, according to sources, the number of cases worldwide was 6.8 million, and currently, around 7 million people are living with IBD worldwide [32][33]. Additionally, the impact of such a burden on the health system in the next few years, especially if we consider the global trends in aging of the population, may become cumbersome.

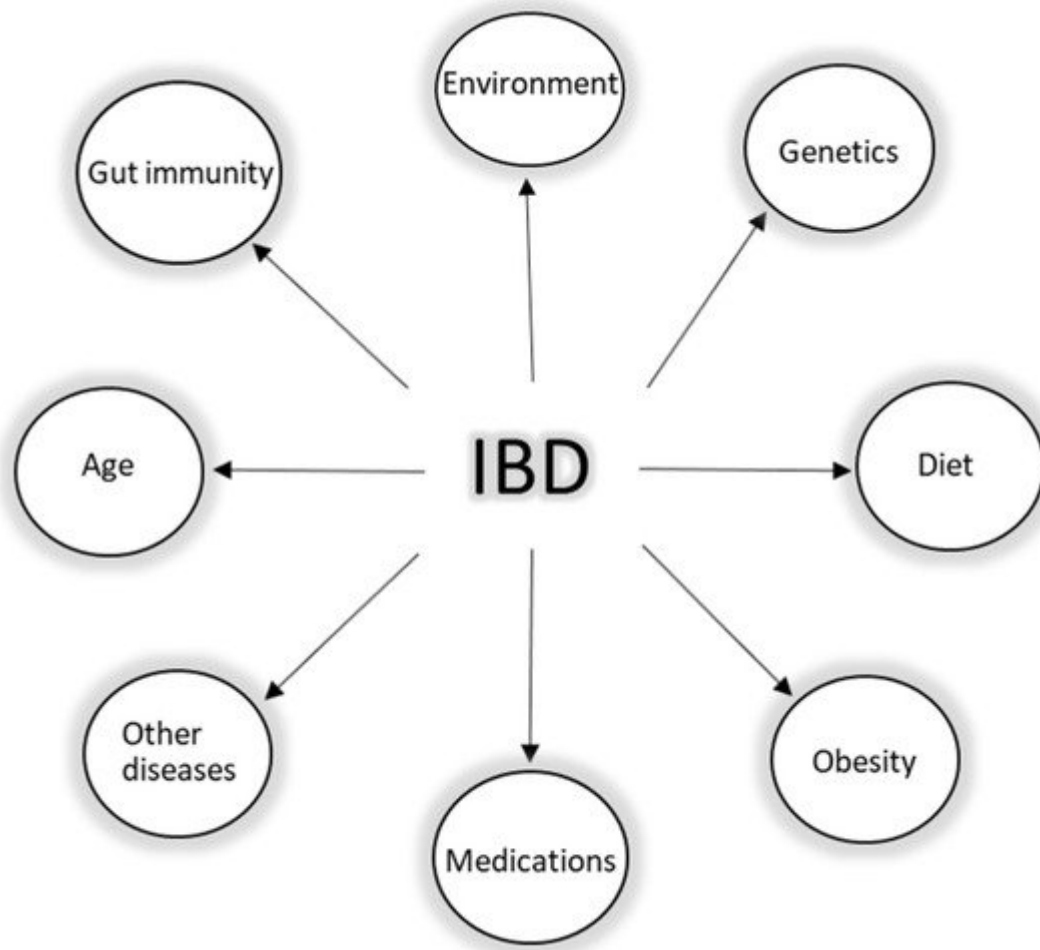


Figure 2. Factors influencing the etiology and pathophysiology of IBD [30][32][34].

The mortality from IBD can be considered to be relatively low, and the age of patients at the time of diagnosis is often relatively young, but at the same time, highly industrialized countries have a greater IBD burden when compared to countries in transition [35][36][37]. However, it is not yet certain if the countries in transition, when the prevalence of IBD is much higher than it is now, will be able to offer biologics to all patients. Instead, the solution may lie in biosimilars, which could be a viable cost-effective alternative to ease the health-economic burden [37].

Crohn's disease (CD) can occur anywhere in the gastrointestinal tract (GI), and the inflammation is transmural, i.e., all layers of the bowel may be affected. CD can be classified according to the disease location (terminal ileal—L1; colonic—L2; ileocolic—L3; or isolated upper GI—L4), or according to behavior (non-structuring and non-penetrating—B1; structuring—B2; penetrating—B3). Disease localization influences the presentation of the disease, but generally speaking, patients with CD suffer from diarrhea, often feel abdominal discomfort and pain, and experience substantial weight loss. If the disease affects the small bowel, it can result in the malabsorption of iron, cobalamin (vitamin B12), and bile acids. Rectal bleeding is not very common, except in the case of disease localization in that area. CD in the upper gastrointestinal tract can be manifested by aphthous ulcers, vomiting, and nausea. If CD is left untreated, most patients will develop complications of CD, such as perirectal abscesses, and anorectal and anal fistulas. Serious complications are also abdominal abscesses and colorectal cancer [38]. It is

worth stressing how common it is that diarrheas lead to the loss of potassium, magnesium, and other electrolytes (as well as various vitamins), which has a negative effect on many physiological processes, such as cardiac rhythm, gastric motility, and renal function. The clinical symptoms of such a scenario include muscle weakness, arrhythmias, increased insulin resistance, tremor, encephalopathy, and bone disorders [39].

Ulcerative colitis (UC), on the other hand, is characterized by continuous mucosal inflammation (with no patchiness), which starts in the rectum and can be extended to the rest of the large intestine, except for the small bowel. UC has various classifications such as the Montreal consensus (based on anatomical regions): ulcerative proctitis—E1; distal or left-sided UC—E2; and extensive UC—E3. The severity of the disease (or disease activity index: DAI) is classified by the Mayo Score based on four parameters (stool pattern, rectal bleeding, endoscopic findings, and the physician's assessment). UC is also associated with colorectal cancer, while a rare but potentially fatal complication of UC is toxic megacolon [38].

4. Short Immunological Background of IBD

In the healthy gut, Toll-like receptors (TLRs), as pathogen-sensitive innate immune receptors found on monocytes, macrophages, dendritic cells, and epithelial cells, help to maintain the intestinal epithelial barrier. This protective mechanism involves nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B), which triggers the expression of inflammatory molecules such as TNF- α and other chemokines. However, in patients with IBD, as barrier function is impaired, TLR signaling is hyperactivated and, consequently, the expression of TNF- α and IL-1, IL-2, IL-6, and IL-12 is elevated [34][40]. Currently, it is well-established that for the development of IBD, both innate and adaptive (or acquired) immune responses need to be engaged (**Figure 3**). The innate immune response includes the same cells in CD and UC. Hence, IBD studies show similar increases in macrophages and dendritic cells with the increase in pro-inflammatory cytokines such as TNF- α , a key player in IBD, and others, such as interleukin 1 (IL1), IL-12, and IL-6. On the contrary, the adaptive immune response has a completely different pathway in CD, compared to UC. The inflammation in CD is mediated via the T helper type 1 and T helper type 17 cell-mediated cytokine profile (Th1 and Th17). The inflammation in UC is mediated via natural killer T cells (NK cells) and T helper type 2 cell-mediated cytokine profile (Th2) (**Figure 3**) [34][40].

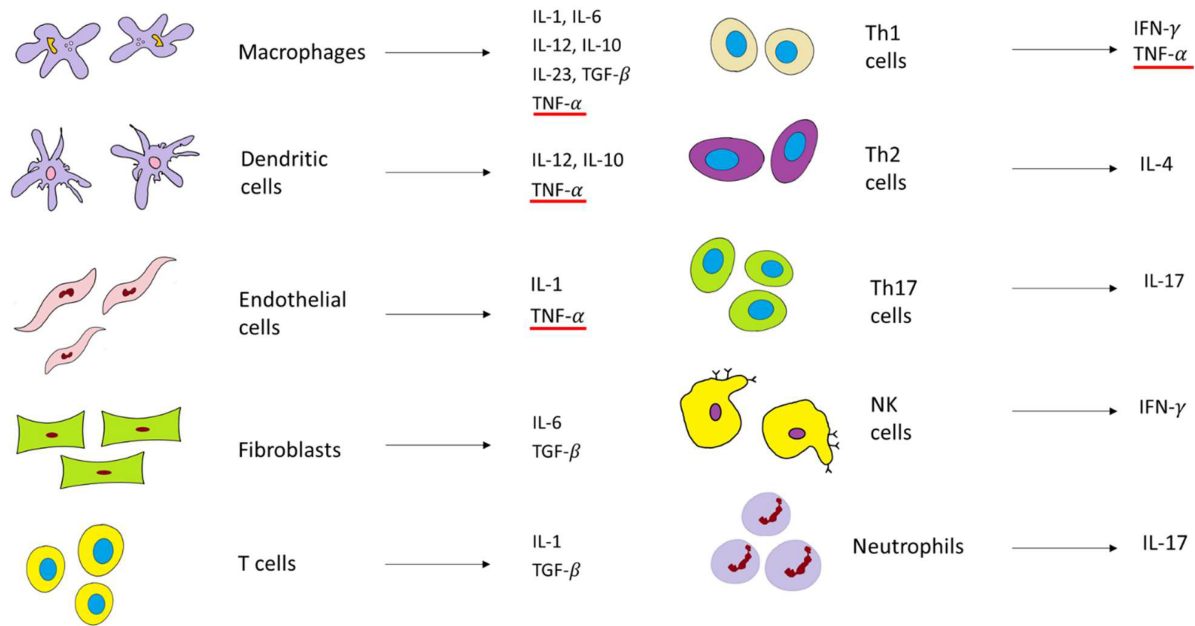


Figure 3. Main cells and cytokines involved in the immune response in IBD. The red line depicts TNF-α as the main proinflammatory cytokine of the inflammatory cascade [\[40\]](#).

5. Pharmacological Armamentarium of IBD: Targeting TNF-α with Anti-TNF-α Agents—IFX and ADL

Some of the main proinflammatory cytokines include TNF-α, IL-1, and IL-6 (**Figure 3**). TNF-α is considered to be at the top of the inflammatory cascade and acts as a key player in IBD pathogenesis [\[40\]](#). In healthy (physiological) conditions, as previously stated, TNF-α is a beneficial immune mediator that is responsible for maintaining balanced gut immune homeostasis. However, in the inflammatory state, TNF-α is produced relatively quickly (within one hour) compared to other proinflammatory cytokines. Moreover, TNF-α has a high potency, as it binds to the receptors with a very high affinity [\[41\]\[42\]](#). As it is a transmembrane protein (tm) and expressed on the cell surface, tmTNF-α (also known as mTNF-α) is cleaved by a metalloproteinase, which liberates another form of TNF known as soluble TNF-α (sTNF-α). sTNF-α can be found (and measured) as a homotrimer circulating in the blood. Both mTNF-α and sTNF-α are bound to transmembrane receptor molecules p55/p60 (also known as TNFR1) and p75/p80 (also known as TNFR2), which can also exist in their soluble forms. mTNF-α is a ligand for both these receptors, and their overexpression is additionally upregulated by interferons [\[43\]](#).

The binding of TNF-α to receptors forms TNF–TNFR complexes and leads to the overexpression of inflammatory cytokines, cell apoptosis, and necrosis, or alternatively, cell survival, depending on the signaling cascade. One interesting phenomenon related to TNF-α is the possibility of autoupregulation and the creation of a positive pro-inflammatory feedback loop, which further amplifies the inflammatory process [\[44\]](#). Therefore, the concept of the pharmacological targeting of this pleiotropic cytokine [\[45\]](#) was a revolutionary step in the early 1990s, when the first experiments confirmed the proof of concept [\[46\]\[47\]](#).

A few years later, the pharmacological armamentarium of IBD, in addition to conventional therapy, was supplemented by IFX, approved for medical use by the FDA in 1998, while the approval of ADL followed four years later. IFX is a chimeric (human–murine) monoclonal IgG1 anti-TNF- α antibody, while ADL is a fully human monoclonal IgG1 anti-TNF- α antibody (**Figure 4**) [48][49].

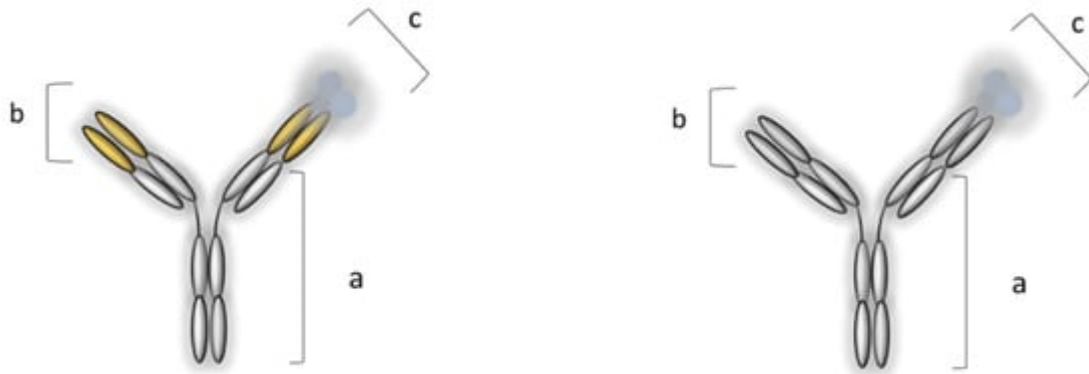


Figure 4. Monoclonal IgG1 anti-TNF- α antibodies (MAbs): infliximab, IFX (on the **left**), and adalimumab, ADL (on the **right**). **IFX**: (a) Human IgG1 constant region, (b) mouse antigen-binding variable region, and (c) homotrimer of TNF- α ; **ADL**: (a) human IgG1 constant region, (b) human antigen-binding variable region, and (c) homotrimer of TNF- α [6][50].

Both anti-TNF- α agents revolutionized the treatment of IBD and contributed to a paradigm shift in the pharmacological management of IBD (**Figure 5**).

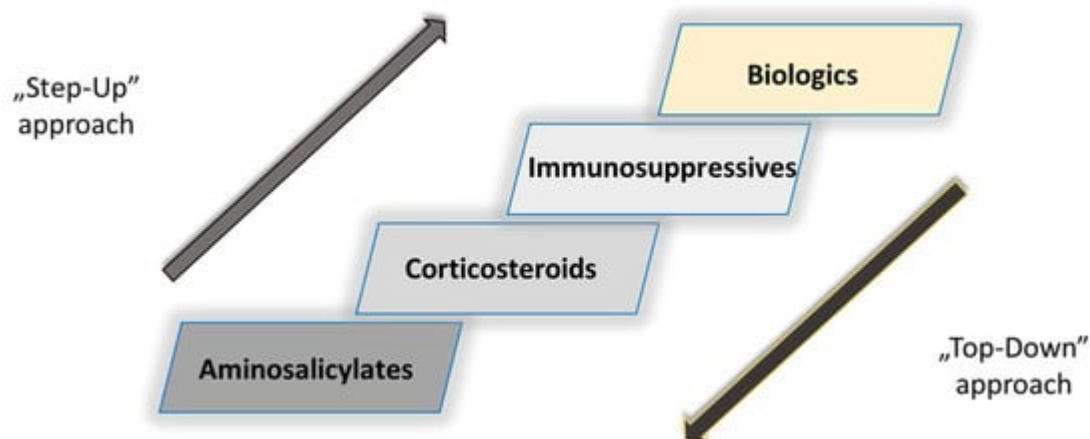


Figure 5. Pharmacological armamentarium of IBD and paradigm shift in the management of IBD [51].

The conventional treatment approach also known as “step-up” was replaced with the “top-down” approach (**Figure 5**). In other words, this is the concept of gradually introducing different pharmacological drug classes in the case of IBD progression, starting first with aminosaliclates (5-aminosalicylic acid and sulfasalazine), corticosteroids (prednisone) and immunosuppressives (azathioprine, 6-mercaptopurine), and as the last option, biologics (IFX and ADL), which eventually became first-choice drugs [51].

Therapeutic goals also shifted as clinical remission changed from being based on disease symptomatology only to an objective criterion, such as endoscopic mucosal healing, i.e., the regression and disappearance of endoscopic lesions, which is known as endoscopic remission [52]. Such a new approach of IBD treatment is named “treat-to-target approach” [53]. Its proposed benefits are reducing the disease burden at early stages of IBD and improving clinical outcome. However, in this approach, MABs should be applied tentatively, as some researchers suggest, because not all IBD patients will require immediate treatment with biologics as the first-line therapy. On the other hand, a 2-year open-label randomized EU trial [54] showed that even an early introduction of more potent treatments in CD (e.g., infliximab with azathioprine) resulted in a better outcome.

IFX (≈ 149 kDa; pharmacotherapeutic group—immunosuppressants; anatomical therapeutic chemical (ATC) code L04AB02) was introduced in Europe 23 years ago (Europe in 1999; USA in 1998) and was first approved for the treatment of CD (and later for UC). It was later approved for the treatment of conditions such as rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and psoriasis (a full list is shown in **Table 2**) [55]. Interestingly, the first clinical use of IFX was actually in a pediatric patient (12-year-old girl), whose symptoms of CD had not been relieved by conventional therapy at that time (prednisone, mesalazine, azathioprine, metronidazole, and enemas with salicylic acid). Initially, colonoscopy and tissue biopsy revealed severe inflammation and multiple aphthous lesions of the colon, as well as crypt abscesses with granuloma. Finally, after 2 years of discomfort, the patient received IFX, and immediately after the first dose, an improvement in her clinical symptoms was noticed [56].

Pharmacological studies showed that IFX binds and neutralizes both mTNF- α , expressed on immune cells (macrophages, T cells, dendritic cells, etc.) and sTNF- α , which in turn potentiates cell lysis via processes of antibody-dependent cellular cytotoxicity (ADCC), reverse signaling, and apoptosis [55]. In addition to ADCC, it is believed that IFX has one additional mechanism of action: complement-dependent cytotoxicity (CDC) [57]. However, in studies with peripheral blood mononuclear cells, IFX was not able to induce CDC [58]. Once the TNF- α is antagonized by IFX, effects that follow include the downregulation of proinflammatory cytokines, the reduced migration of immune cells (such as macrophages and T lymphocytes), and overall, a reduction in previously exaggerated immune response [48].

In some of the first clinical studies for CD [59], IFX showed a better clinical response compared with the placebo (41% vs. 12%, $p < 0.008$). Clinical remission was achieved in 33% of patients compared to the placebo (33% vs. 17%, $p < 0.005$), while 65% of patients had a primary endpoint reduction in the CDAI score (Crohn’s Disease Activity Index) of 70 points, compared to 17% who received the placebo ($p < 0.001$) [59]. The other two big studies of IFX in CD, namely, the ACCENT I [60] and SONIC trial [61], undoubtedly confirmed the superiority of IFX in terms of clinical response and remission and, as such, paved the way for IFX dosing in CD as we know it today. Therapy with IFX was shown to improve mucosal healing as a secondary endpoint in the SONIC trial measured on the CDEIS (Crohn’s Disease Endoscopic Index of Severity) scale [61].

In the ACT I and ACT II trials [62] in patients with UC, IFX was confirmed to be superior for treating the symptoms of disease, compared with the placebo. Clinical remission and mucosal healing were higher in the IFX group, and

additional follow-up studies showed that IFX was able to sustain its effectiveness [62]. IFX was also found to improve the healing of perianal fistulas, interestingly, via local administration into inflamed tissue [63].

Regarding the pharmacokinetics, IFX administered via intravenous infusion (i.v.) shows a low apparent volume of distribution, with a long elimination half-life (**Table 3**). The area under the plasma concentration–time curve (AUC) increases proportionally with the dose of IFX, which indicates linear pharmacokinetics for the studied dose [48][64][65][66]. Additionally, IFX during repeated infusions (10 mg/kg, Q8W) in Crohn's patients did not show signs of accumulation [67].

ADL ($\approx$ 148 kDa; pharmacotherapeutic group—immunosuppressants; anatomical therapeutic chemical (ATC) code L04AB04) is the first fully human monoclonal IgG1 anti-TNF- α antibody to be developed, and it was first introduced in the USA in 2002 (Europe in 2003) [68]. Initially, the FDA approved the drug for the treatment of moderate to severe rheumatoid arthritis. In 2007, ADL received approval for the treatment of CD, and later for UC. Some additional indications include juvenile idiopathic arthritis and uveitis (a full list is shown in **Table 2**) [68].

ADL binds and neutralizes both forms of TNF- α with high affinity, and shows a high similarity to IFX in terms of binding kinetic characteristics and general descriptive pharmacodynamic effects. Remaining drugs from classes of anti-TNF- α agents (etanercept, certolizumab, and golimumab) show different binding characteristics, which could explain why these drugs, despite being from the same class, exhibit different levels of effectiveness across indications [69].

In the CLASSIC I and CLASSIC II trials, ADL induced and maintained clinical remission in patients with CD [70]. Moreover, patients on ADL were up to two times more likely to maintain remission at week 56, compared to the placebo. The CHARM trial [71] confirmed the effectiveness of ADL in the maintenance of clinical remission in patients with CD (40% vs. 17% for placebo group, $p < 0.001$), and the better healing of fistulas (33% vs. 13% for placebo group, $p < 0.016$). The EXTEND trial [72] confirmed overall superiority based on the mucosal healing rate of patients with CD (24% vs. 0% for placebo group, $p < 0.001$). The ACCES trial [73] showed that the occurrence of fistula healing in CD was greater in anti-TNF- α -naïve patients treated with ADL compared to those treated previously with IFX (60% vs. 28% for IFX group, $p < 0.01$). ADL was also shown to induce and sustain corticosteroid-free remission in both groups. In the CHOICE trial [74], ADL was shown to be effective in patients with CD who were primary non-responders to IFX (besides being an effective first-line therapy for anti-TNF-naïve patients).

In the ULTRA I and ULTRA II trials [75], the effectiveness of ADL was evaluated in UC. Results showed that ADL was also superior to the placebo in the induction of remission, clinical remission response, and mucosal healing. In addition, in the ULTRA II trial, approximately 40% of patients had prior exposure to the anti-TNF- α agent, meaning that ADL is beneficial to both primary non-responders and those who initially had a response that was not sustained [75].

Results from comparison studies of IFX vs. ADL in UC suggested that IFX is more effective in the induction of remission, response, and mucosal healing at week 8, while at week 52, both drugs are equally effective as a maintenance therapy [76]. However, in a very recent publication from Lee et al. [77], in a first head-to-head comparison in UC patients, results suggested that both drugs have comparable remission rates at week 8 (47% vs. 56.7%, $p = 0.364$) and week 52 (39.8% vs. 50%, $p = 0.331$). Additionally, both drugs are suggested to have comparable clinical response rates at week 8 (86.7% vs. 76.7%, $p = 0.196$) and at week 52 (72.3% vs. 76.7%, $p = 0.642$). Additionally, there were no significant differences regarding unwanted outcomes either (hospitalizations, steroid prescriptions, switching to a secondary anti-TNF agent, or the rates of an adverse event). Finally, CRP levels greater than 5 mg/L were correlated as a significant predictive factor for a poor disease outcome [77].

Regarding the pharmacokinetics, ADL, although being administered subcutaneously (s.c.), shares disposition similarities with IFX, i.e., a relatively low apparent volume of distribution, long elimination half-life, and relatively low systemic clearance (Table 3) [78][79][80]. Despite having many similarities with IFX, ADL has some pharmacological differences (Table 3 and Table 4).

The general goals of anti-TNF- α therapy in IBD can be summarized as follows: (i) inducing sustained endoscopic mucosal healing/endoscopic remission (as the primary endpoint), (ii) maintaining deep clinical remission (i.e., corticosteroid-free remission), (iii) preventing and reducing related complications of IBD disease, and (iv) improving the quality of life of IBD patients [81].

Table 2. Indications and “off-label” use of infliximab (IFX) and adalimumab (ADL) [68][82].

IFX	ADL
Crohn's disease	Crohn's disease
Ulcerative colitis	Ulcerative colitis
Pediatric Crohn's disease	Pediatric Crohn's disease
Pediatric ulcerative colitis	Rheumatoid arthritis
Rheumatoid arthritis	Juvenile idiopathic arthritis
Ankylosing spondylitis	Polyarticular juvenile idiopathic arthritis
Psoriatic arthritis	Active enthesitis-related arthritis
Psoriasis	Psoriatic arthritis
	Plaque psoriasis
	Pediatric plaque psoriasis
	Axial spondyloarthritis
	Hidradenitis suppurativa
	Uveitis
	Pediatric uveitis
	Panuveitis
Behcet's disease	Behcet's disease
Pyoderma gangrenosum	Pyoderma gangrenosum
Hidradenitis suppurativa	Alopecia areata
Graft versus host disease	Pemphigus
Sjogren's syndrome	Sarcoidosis
	Wegener's granulomatosis

IFX	ADL
Uveitis Kawasaki disease [78][83] (in healthy subjects);	[64][83] (ADL) [68]
denotes the minimum post induction trough concentrations of patients with IBD suggested to be associated with an increased likelihood of mucosal healing at week 14 for IFX, and at week 4 for ADL [84].	

Anti-TNF- α Agent	Dose	Route	Cmax $\mu\text{g/mL}$	Ctrough * $\mu\text{g/mL}$	Tmax Days	Clearance mL/h	Half-Life Days	Vd L	F %	AUC $\mu\text{g} \cdot \text{h/mL}$
IFX	5 mg/kg	i.v.	126.2	>7	0.0875	11	14.1	4.8	100%	37 022
ADL	40 mg	s.c.	3.6	>7	7.9	16	14.5	7.9	64%	2167

i.v.—intravenous route; s.c.—subcutaneous route; Cmax—maximum plasma concentration; Tmax—time to reach maximum concentration; Vd—apparent volume of distribution; F—bioavailability; AUC—area under the curve.

Table 4. Differences in routes of administration and dosing of infliximab (IFX) and adalimumab (ADL) in CD and UC [68][82].

Biologics	Route	Induction Dose (CD and UC)	Maintenance Dose (CD and UC)
IFX	i.v.	5 mg/kg; Weeks: 0, 2, 6.	5–10 * mg/kg; Every 8 weeks.
ADL	s.c.	160 mg day 1, and 2; + 80 mg on day 15. or 80 mg Days: 1, 2, 15.	40 mg Every 2 weeks **. * Higher dose is recommended in the case of unsustained response to IFX ** Initial start on day 29

i.v.—intravenous route; s.c.—subcutaneous route; CD—Crohn's disease; UC—ulcerative colitis.

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