Inflammatory Bowel Disease Biological Treatments

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Inflammatory bowel disease (IBD) is a chronic disease that requires lifelong medication and whose incidence is increasing over the world. There is currently no cure for IBD, and the current therapeutic objective is to control the inflammatory process. Approximately one third of treated patients do not respond to treatment and refractoriness to treatment is common. Therefore, pharmacological treatments, such as monoclonal antibodies, are urgently needed, and new treatment guidelines are regularly published.

Keywords: action mechanism ; anti-integrins ; anti-TNF-α ; biologics ; Crohn's disease ; inflammatory bowel disease ; monoclonal antibodies ; ulcerative colitis

1. Introduction

Inflammatory bowel disease (IBD) is a chronic disease characterized by intestinal inflammation with a relapsing and remitting clinical course that generally requires lifelong medication and is associated with significant morbidity, hospitalization needs, and productivity losses [1]. Furthermore, the disease is progressive, with damage accumulation and treatment failure over time. Additionally, IBD is considered a systemic disease, with extra-intestinal manifestations and symptoms frequently affecting the joints, skin, eyes, and (although less often) the liver, pancreas, or lungs, which can also contribute to morbidity and reduced quality of life [2][3][4]. Importantly, incidences of the disease are increasing world-wide. The highest rates have been traditionally found in North America and Europe, but currently there is a worrying trend of increasing occurrence of the disease in previously low-incidence regions (e.g., Asia, South America…), which is likely associated with adoption of a westernized mode of life involving varied factors such as diet pollution, microbial exposure, sanitation [5][6][7], and possibly even psychological stress [8][9]. In addition, IBD is mainly diagnosed at a young age, so its prevalence is also high (1.6 million persons in US and 2.2 million persons in Europe) [10][11]. Not surprisingly, the costs associated with this disease are also high (1.7 million dollars per year in US and more than 2.5 million euro in Europe).

There are two main subtypes of IBD: Crohn's disease (CD) and ulcerative colitis (UC). These subtypes have different clinical presentation and histopathological findings [1]. However, some features are shared by both IBD types including clinical features (loss of weight and appetite, rectal bleeding, diarrhea, tenesmus, anemia), endoscopic features (erythema, loss of vascular pattern, erosions/ulcerations, spontaneous bleeding) and pathological features (crypt architecture distortion, higher in UC than in CD; crypt abscesses and shortening; infiltration of leukocytes into lamina propria) [1].

IBD is characterized by impairment of the epithelial and mucus layer barrier via disruption of tight junctions and inflamed lamina propria. This is associated with dysbiosis (altered gut microbiome composition), whose role as a causative factor or a consequence of mucosal inflammation is not yet clear [12][13]. Furthermore, the mucosal immune system constitutes the third most recognized component contributing to the complex underlying etiopathogenic mechanisms [14]. Indeed, pronounced infiltration of the lamina propria with a mix of neutrophils, macrophages, dendritic cells, and natural killer (NK) T cells is found in active IBD [15]. Increased Th1, Th2, Th9, Th17 and Th17.1 responses, as well as reduced Treg and Tr1 responses, have all been suggested to play a role in IBD pathophysiology, although it is highly unlikely that all of these responses are altered in each individual patient [16]. Thus, currently, the most accepted etiopathogenic theory is that IBD is caused by an impairment in immunological tolerance, resulting in an exacerbated immune reaction against intestinal microbiota in genetically susceptible individuals and thereby facilitating mucosal inflammation [13].

Biomarkers common to both UC and CD are fecal calprotectin (useful in screening IBD for endoscopic evaluation and clinical management of IBD) and fecal lactoferrin (used for assessing the course of disease activity and healing). These two intestinal inflammatory conditions share many genetic and environmental risk factors [1]. For example, it is recognized that antibiotics intake increases the risk of IBD, that psychological distress and sleep deprivation correlate with flare-ups, that depression and anxiety cause clinical recurrence, and that animal-based diet is harmful [1], although other contributing factors are more disease-specific [1][6].

Importantly, both types of IBD have been associated with an increased risk of developing colorectal cancer (CRC), primarily associated with the occurrence of chronic intestinal inflammation and extra-intestinal malignancies, which are related with both the chronic use of immunosuppressive therapies and an underlying inflammatory state [17][18]. The risk of developing CRC or extra-intestinal cancer increases with time since diagnosis (for example, the risk of developing CRC is high after six–eight years and increases linearly year by year) and the extension of inflammation [17][18][19]. However, recent studies [20] have presented robust data showing that this risk may not be as high as initially reported (i.e., for CRC it is now considered to be about two-fold), which might be attributed to different factors such as better screening strategies and colectomy implementation for high-grade dysplasia, on the one hand, and the potent immunosuppressive and/or chemopreventive properties of the drugs currently used, on the other [17]. However, as mentioned, immunosuppressive treatment may induce important side effects, including extra-intestinal cancer. Immunosuppressive agents may cause tumor formation through direct alteration of DNA, impairment of immune control of chronic infection by mutagenic viruses (Epstein-Barr virus, human papilloma virus), or a reduction of immunosurveillance of cancer or dysplastic cells [17]. Thus, in IBD patients, both too much inflammation and too much immunosuppression may be harmful, and these patients need to be carefully monitored to maintain the right balance among the two factors, through selection of the right treatment at each stage of the disease [17].

As a matter of fact, there is currently no cure for IBD, and the therapeutic objective is to control the inflammatory process. This is not easy, since multiple inflammatory pathways are concurrently activated in the intestinal mucosa and the pathogenic mechanisms sustaining inflammation in IBD are dynamic and change over time. Accordingly, treatment of patients needs to take into account the symptoms, inflammatory status and mechanism of action of the drug/s with most likely beneficial impact to adequately control the disease at each particular moment. Despite all of these efforts, approximately one third of treated patients do not respond to treatment (the proportion of primary non-responders may be as high as 30–50%), refractoriness to treatment is common (10% of patients treated with biologics become refractory) and safety issues (development of infectious, neoplastic or, other side effects) are also a major concern for both patients and clinicians [17][21][22]. Therefore, new pharmacological and non-pharmacological therapies [21][23][24][25][26], as well as optimization of the currently available therapeutic strategies [27] are urgently needed, and new treatment guidelines are regularly published [28][29].

Traditional treatments for IBD, such as aminosalicylates (sulfasalazine, mesalazine), corticosteroids (budesonide, prednisone), and some immunomodulators (thiopurines, i.e., azathioprine and 6-mercaptopurine; methotrexate), were introduced several decades ago (since the 1950s) and are still main-stream therapies [1][30]. These drugs have several advantages such as their relatively small size (<1000 Da), stable structure, reduced production cost, short half-life, (which is an advantage in cases where rapid elimination is needed), and oral route of administration [1]. Although they provide symptom improvement, they may also cause relevant adverse effects (including carcinogenesis, particularly thiopurines) due to their broad immunosuppressive, antimetabolic, or unknown mode of action, and some patients are refractory to these treatments.

More targeted or specific pharmacologic treatments for IBD interfere with two main pathways (namely cytokine signaling and immune cell trafficking) and are classified into biologics (monoclonal antibodies) and small molecule drugs [25]. These drugs have revolutionized the treatment of IBD (particularly that of its severe forms), and new entities are being evaluated and even incorporated to clinical practice relatively quickly.

Biological therapies were introduced in the late 1990s to induce and maintain remission (i.e., infliximab was introduced for treatment of CD and UC in 1999 and 2006, respectively). These therapies use monoclonal antibodies targeting tumor necrosis factor-α (TNF-α), integrins α4, and cytokine molecules such as the common p40 subunit of IL-12 and IL-23 [31]. Monoclonal antibodies are expensive and need to be administered intravenously or subcutaneously since proteolytic gastrointestinal enzymes can destroy them [32]. Following parenteral administration, proteolytic catabolism eventually occurs after the internalization of the antibody by phagocytes of the reticuloendothelial system [33]. Nevertheless, monoclonal antibodies display a long half-life, which facilitates adherence to treatment but may also be a disadvantage in face of an infection, surgery, or pregnancy. One of the principal concerns with biologics is the fact that they can fail since the immune system may recognize them as foreign bodies and block their efficacy over time. Thus, although biological drugs have helped many patients to achieve remission, on many occasions they lose their efficacy. Moreover, no single marker can be used as a prognostic indicator of response to any biologic treatment in IBD [34]. Therefore, new biologics [25] and new combinations of different biological drugs are currently being studied as a possible means to increase efficacy and safety of these treatments [27]. In addition, other therapies, namely targeted small molecule drugs [25], may be useful.

Targeted small molecule drugs include Jak inhibitors, modulators of sphingosine-1-phosphate receptors (lymphocyte trappers), phosphodiesterase inhibitors, and oligonucleotide-based therapeutics [25]. As with the traditional IBD treatments

mentioned above, these drugs are small chemical structures with a short half-life and a relatively low cost. These molecules have less potency and half-life than biologics, a generally less specific mechanism of action and, due to their broader diffusion (associated with their smaller size), a greater risk of unspecified side effects. However, an important advantage is their lack of immunogenicity [35].

2. Biological Therapies in IBD

As mentioned above, biological therapies use monoclonal antibodies. Monoclonal antibodies (mAbs) are immunoglobulins G (IgG), therapeutic proteins consisting of four polypeptide chains and two heavy and two light chains. There are two regions in the mAbs, the variable region (antigen-binding region, Fab) and the constant region (Fc). These mAbs are classified as murine antibodies with the suffix -omab; chimeric with the suffix -ximab; humanized with the suffix -zumab; and fully human with the suffix -umab [33] (**Table 1**).

Table 1. Main biologics (monoclonal antibodies) approved for IBD treatment.

Type of Antibody		Suffix	Anti-TNF-α	Anti-Integrin	Anti-Cytokine
	**Murine**	**-omab**			
	**Human**	**-umab**	**Adalimumab (CD, UC) Golimumab (UC)**		**Ustekinumab (CD, UC)**
	**Chimeric**	**-ximab**	**Infliximab (CD, UC)**		
	**Humanized**	**-zumab**	**Certolizumab pegol (CD)**	**Natalizumab (CD) Vedolizumab (CD, UC)**	

Abbreviations: CD, Crohn's disease; IBD, inflammatory bowel disease; TNF, tumor necrosis factor; UC, ulcerative colitis. Created in BioRender.

2.1. Anti-TNF-α Therapy

2.1.1. TNF-α

TNF-α is a pleiotropic cytokine involved in many biological activities, including cell proliferation, survival, and death. Although TNF-α is crucial for a normal immune response, when inappropriately or excessively produced it may be harmful and lead to diseases such as rheumatoid arthritis, psoriatic arthritis, psoriasis, noninfectious uveitis, and IBD, all of which are induced by the abnormal secretion of this cytokine. Thus, TNF-α has a key role in inflammation and the development and maintenance of chronic inflammatory diseases [36].

TNF-α is found in both a soluble and a transmembrane form. The transmembrane form is the initially synthetized precursor molecule and releases the soluble form after processing by the TNF-α converting enzyme (TACE), a membrane-bound disintegrin metalloproteinase. There are two receptors of TNF-α: TNFR1 (also termed TNFRSF1A, CD120a, and p55) and TNFR2 (also termed TNFRSF1B, CD120b, and p75). TNFR1 is expressed by all human tissues and is the key signaling receptor for TNF-α, whereas TNFR2 is generally expressed in immune cells and produces limited biological responses. Both soluble and transmembrane forms of TNF-α may activate TNFR1, but activities of the transmembrane form are relatively more TNFR2-dependent. Through complex intracellular pathways and molecular interactions, TNF-α causes cytotoxic and proinflammatory responses via TNFR1 and facilitates cell activation, migration, or proliferation via TNFR2 [36].

2.1.2. Anti-TNF-α Antibodies in Current IBD Therapy

Different anti-TNF-α antibodies have been developed and used for the treatment of IBD and other immune-mediated inflammatory diseases since 1998 [36]. Four of them are widely used in the treatment of IBD: infliximab, adalimumab, golimumab, and certolizumab pegol (**Table 1**).

Anti-TNF-α antibodies block soluble TNF-α, thus preventing pro-inflammatory signal transduction, leading to the apoptosis of T-cells [37] and the production of anti-inflammatory cytokines [38]. In general terms, it is assumed that antibodies against TNF-α inactivate this pro-inflammatory cytokine by direct neutralization [39]. Inhibition of the membrane-bound TNF/TNFR2 pathway is thus the basis to induce T-cell apoptosis [40] and the consequent inhibition of downstream pro-inflammatory signals. Nonetheless, and considering the complexity of TNF-α signaling, it is generally accepted that anti-TNF-α antibodies may display more complex effects in addition to the simple TNF blockade [41][42], as discussed below. Moreover, the affinity of the different antibodies to TNF-α and their cross-linking towards membrane-bound TNF-α has been found to be unequal between these drugs in several bioassays [43][44].

2.2. Anti-Integrin Therapy

In case of primary failure, it is recommended that IBD treatment is switched to a molecule with a different mechanism of action. Anti-integrin drugs prevent the traffic of inflammatory cells that mediate the inflammatory process in IBD. These drugs are important for those IBD patients who do not respond to an anti-TNF-α treatment. There are two anti-integrins currently available in the clinics, namely natalizumab and vedolizumab (**Table 1**).

Integrin is a leukocyte heterodimeric transmembrane receptor formed by two subunits, α and β, and it is divided into several groups depending on the structure of these subunits. Different populations of leukocytes express different integrins. Thus, α4β1 is found in most leukocytes, α4β7 is present in gastrointestinal lymphocytes and αEβ7 is expressed in intraepithelial T cells, dendritic cells, and regulatory T cells [45]. These integrins bind to vascular endothelial cell adhesion molecule-1 (VCAM-1) and mucosal addressin cell adhesion molecule-1 (MadCAM-1) on endothelial cells and to E-cadherin on mucosal epithelial cells [46]. The increase of the expression of cell adhesion molecules (CAMs) provokes the immigration of leukocytes to the intestinal mucosa and the recruitment of immune cells to the inflammation site, which is essential for the maintenance of inflammation [47]. In addition, integrins and their ligands may participate in the pathogenesis of extra-intestinal inflammatory manifestations of IBD [48][49]. Anti-integrin therapy blocks the interaction of integrin on the surface of circulating immune cells with endothelial CAMs, preventing the intestinal recruitment of lymphocytes to the inflammation site [50].

The anti-integrin drug natalizumab is a recombinant humanized IgG4 that targets the α4 subunit of the integrins α4β1 and α4β7 on leukocytes. This drug stops the migration of inflammatory cells across the cell layers and needs to be administered for a long term to achieve positive results [51]. In the very beginning, this drug was approved by the FDA for multiple sclerosis treatment and later for CD, but it is only used in moderate to severe cases of CD due to its adverse effects [47], particularly progressive multifocal leukoencephalopathy (which is associated with the blockade of α4β1 integrin/VCAM-1 interactions by this drug in the central nervous system) [49][52].

2.3. Anti-Cytokine Therapy

Ustekinumab is a fully humanized IgG1k mAb (**Table 1**) that binds the shared p40 subunit of cytokines IL12 and IL-23 preventing the binding of the cytokine to its receptor and reducing the activation of immune cells, thus reducing symptoms in active CD [51]. IL-12 consists of the heterodimer of p35 and p40 while IL-23 is made up of p19 and p40 subunits. In the presence of IL-12 and activated CD4+, T cell differentiates into a Th1 cell that increases interferon (IFN) γ production. IL-23 promotes the formation of Th17 cells [53]. The neutralization of IL-12 and IL-23 inhibits the cytokine production that is involved in the pathogenesis of CD, inducing remission in this disease [54][55]. The neutralization of IL-12 and IL-23 does not affect immune responses stimulated through other cytokines or cellular activities [54]. There is a precise specificity in the molecular interaction between ustekinumab and IL-12/23p40.

Ustekinumab shows clinical efficacy in psoriasis, psoriatic arthritis, and moderate to severe CD [53][56]. The incidence of the development of neutralizing antibodies is low and ustekinumab has a flexible dosage. The induction phase requires intravenous administration but during the maintenance phase the administration is subcutaneous, which is an advantage for the patient [57]. In most CD patients, remission is maintained after three years [58]. Furthermore, effectiveness of ustekinumab has also been demonstrated in UC [59]. This drug is now approved for both types of IBD [25].

2.4. New Biologics

New biologics or biologic-related therapies are currently under development in an attempt to overcome the drawbacks associated with the approved treatments [25].

For example, a new anti-TNF-α oral formulation (AVX-470) is being developed to achieve gut specificity which would increase patient safety as well as comfort. Interestingly, this is not a monoclonal, but a polyclonal anti-TNF-α antibody

derived from cow colostrum with less than 1% of antibodies specific for this key cytokine. However, it is considered a promising strategy due to the known safety of bovine milk-derived IgA and the fact that the antibodies are released in the small intestine and colon [25].

Etrolizumab, is a humanized monoclonal anti-β7 antibody that blocks both α4β7 and αEβ7. αEβ7 controls the epithelial retention of homed lymphocytes in intestinal inflammation [60]. Etrolizumab may internalize β7 and in that manner, the integrin is inhibited on the cell surface [61]. This antibody has not been approved for IBD treatment yet seems to be effective to induce remission in both UC and CD [60][62].

Many new agents targeting other cytokines, particularly IL-12/23 and IL-17 (downstream effector of IL-23), are also under deep evaluation in clinical trials. So far, the selective p19 inhibition through IL-23 (but not IL-12) has not proved to be advantageous in terms of its efficacy or safety [25]. Furthermore, inhibition of the IL-23 effector cytokine IL-17 aggravates the bowel inflammatory condition, possibly due to a role of IL-17 in epithelial barrier maintenance and regulation of gut colonization by segmented filamentous bacteria [63][64]. Thus, safety data on these options will be key to determine their right place (if any) in IBD treatment [25].

In addition to the mentioned monoclonal antibodies that inhibit α4 (natalizumab), β7 (etrolizumab) or both integrin subunits (vedolizumab), abrilumab (another anti-α4β7 monoclonal antibody), PF-00547659 (an anti-MadCAM-1 monoclonal antibody), and AJM300 (a small molecule integrin-α4 inhibitor) are being evaluated. The main advantage of these new adhesion inhibitors is their good safety profile, particularly for elderly and multi-morbid patients with malignancies in their history. However, broader studies are required to completely exclude possible relevant risks [25].

Other biologics inhibit IL-17, such as bimekizumab, or inhibit the p19 subunit of IL-23, such as mirikizumab, which reduces the activity of Th17 pathway. Bimekizumab inhibits IL-17A and IL-17F ligands, ixekizumab inhibits IL-17A ligand and brodalumab inhibits IL-17 receptor. These molecules have a safe profile and do not increase rates of infections or malignancy [27][65] but have not yet been approved for clinical use.

3. Conclusions

Nowadays, there are many available treatments for IBD, from conventional to biological or small molecules.

Biological treatments are very successful in the therapy of IBD. However, these treatments are still expensive and new patients with IBD must begin first with the traditional treatments without knowing if they will work for them. On the other hand, IBD has no cure, and even with these novel treatments, patients must frequently switch their medication and undergo colonoscopy. Moreover, many patients do not respond correctly to treatments and frequently surgery is their only option. Therefore, new treatments (both biological and small molecules) are constantly being tested.

Despite the efforts made in recent years to fill the gap in the mechanistic knowledge of biologicals, particularly regarding anti-TNF-α therapies, further studies are needed in order to better understand the action mechanism of these drugs, which will help understand how to improve efficacy and safety. These studies will hopefully pave the path to a personalized medicine.

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