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Inflammatory Bowel Disease: Current Treatment and Future Perspectives

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Abstract

Inflammatory bowel disease is a chronic and relapsing disorder on the gastrointestinal tract, which can be divided in ulcerative colitis and Chron's disease. Nowadays, it has been observed an exponential increase of new cases which turns this disease as a major health problem worldwide, where it is not a known cure. Indeed, the pharmacological approaches currently available only aims to induce and maintain remission in patients, with several side effects derived from long-term utilization. Therefore, there is a need to investigate and discover new possible therapeutic tools. Currently, there are several molecules under the process of research and development, but it can be also taken in account other strategies, such as the repurposing of drugs with a well-known medical indication and the adoption of natural products as promising therapies for the future. Therefore, this review aims to describe, summarize, and discuss new possible pharmacological tools and compare them to the current treatment applied, taking in account the data available on the literature, throughout non-clinical and clinical data.

Introduction

Inflammatory bowel Disease

Inflammatory Bowel Disease (IBD) is a chronic and relapsing inflammatory response localized in the gastrointestinal tract, which can be represented by two phenotypes, such as CD and UC [1-5]. Both conditions are characterized as debilitating conditions but not to be fatal [6]. There is not a known cure for this disease, although pharmacological treatment currently used can control its development and symptomology [1,6-8].

Clinical presentation of IBD presents a wide range of symptoms and signs that can be specific to the gastrointestinal tract, and others that are non-specific, which can be related to extraintestinal manifestations. As gastrointestinal signs and symptoms, it can be emphasized the diarrhea, abdominal pain/cramping, blood in feces and rectal urgency. On the other hand, as extraintestinal manifestations, there is fever, fatigue, anemia, weight loss, arthritis, ankylosing spondylitis, uveitis, iritis, pyoderma gangrenosum, sclerosing cholangitis and erythema nodosum [1,9-11].

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Both CD and UC share common clinical features, but can be distinguished by different pathophysiological aspects [1,12,13]. On one hand, CD is recognized as a transmural and discontinuous inflammations pattern that can involve any portion of the gastrointestinal tract, although it seems to affect mostly the perianal region and terminal ileum [1,3,6,14]. On the other hand, UC is characterized as an inflammatory response typically confined to the intestinal mucosa, localized in the large intestine, normally beginning at the rectum with the possibility of involving all the colon length posteriorly [1,3,15,16]. Taking in account the differences between both phenotypes, it is predictable that the damage done in intestinal tissue, when the disease is active, may vary, which can be illustrated by Figure 1.

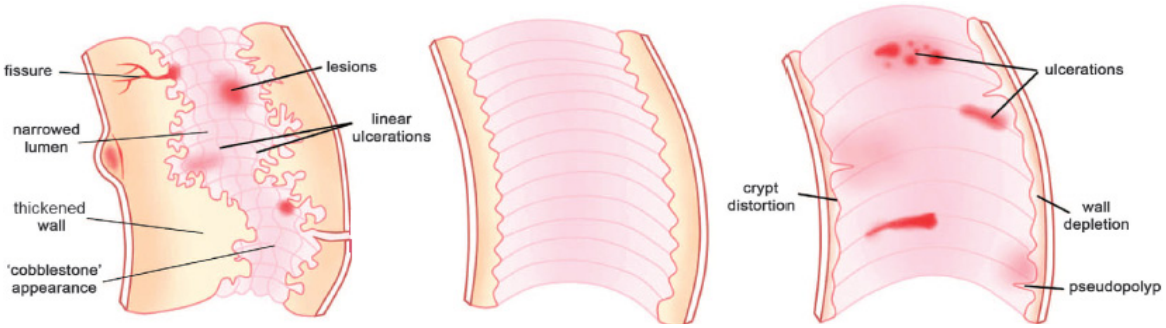

Figure 1: CD and UC in colon tissue [17].
Legend: Left panel - CD; Middle panel - Healthy colon; Right panel - UC.

Diagnosis of IBD has in consideration several parameters, such as history and physical examination, laboratory values and the findings of endoscopic, histological, and radiological studies [18]. In some cases, it is difficult to diagnose the correct phenotype, where it is referred that about 7-10% of IBDs are not fully clear [3].

Epidemiology

IBD is known as a health-care problem worldwide with a prevalence exceeding 0.5% of the population, in westernized countries, with an increased incidence in newly industrialized nations, such as China and India [1,19]. This increased incidence accompanies the growing adoption of a westernized lifestyle around the world [6]. Additionally, IBD is typically observed in developed countries with different frequencies depending on certain factors, such as age, ethnicity, and geographic localization [20,21]. The incidence varies according to the specific phenotype, where CD is more frequent in women than men, and it is more prevalent in developed countries in comparison to UC. On the other hand, UC does not seem to affect a specific gender, and emerged before CD in developed countries but has a higher prevalence in still-developing countries [6].

Currently, it is estimated that nearly 3.9 million females and 3 million males are living with IBD, and there is an upward trend of new cases (Figure 2) [22].

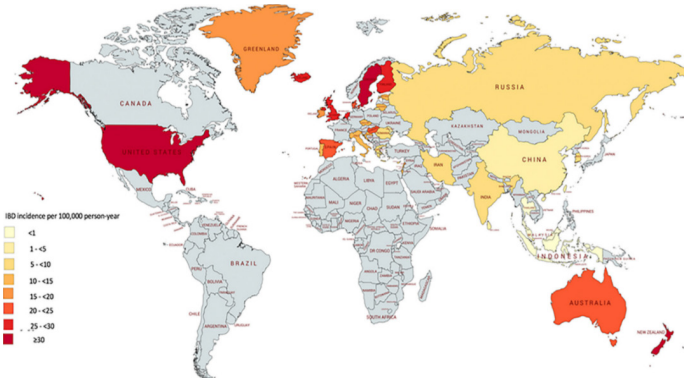

Figure 2: Worldwide IBD incidence between 2010 and 2019 [22].

Etiology

IBD is a chronic immune-mediated pathology, which its etiology is not fully understood but seems to have a multifactorial origin. This disease can be triggered by an interaction between several factors, such as genetic, environment, host immune system, lifestyle, and intestinal microflora [1,23-25].

Environmental factors have been associated as a powerful trigger to IBD development and severity, such as smoking, recurrent utilization of non-steroidal anti-inflammatory drugs, antibiotic treatment during childhood, oral contraceptives, and diet [26,27].

Another key factor related to the development of IBD is genetics, where a family history with this disease confers a higher probability of developing it in the future [28-30]. Specifically, genome-wide associated studies have identified, at least, 163 loci related to an increased risk for the development of IBD [30]. These genetic regions are associated to several cellular functions, such as autophagy, microbial recognition and lymphocyte signaling [20]. More specifically, there are several genes correlated with the appearance of IBD along with its severity, such as NOD2 (Nucleotide-binding Oligomerization Domain-containing protein 2), ATG16L1 and Interleukin (IL)-23R (Figure 3) [32,33].

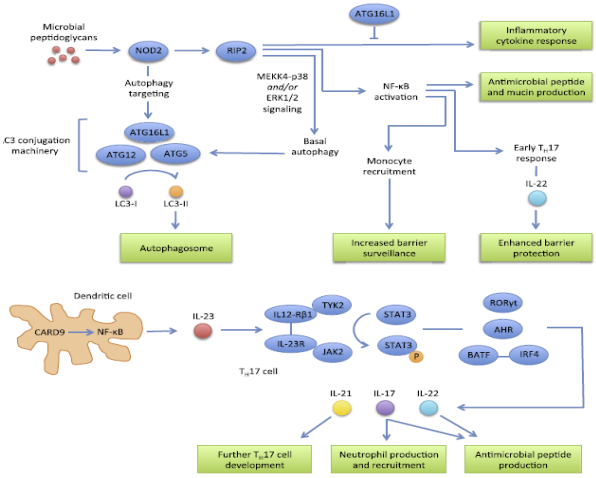

Figure 3: Biological pathways involved in IBD setting [6].
Legend: A - NOD2 gene signaling pathway (related to innate immune response); B - IL-23 signaling pathway (related to adaptive immune response).

Additionally, there are other genes related to the development of IBD, which are represented in Table 1 [34].

Table 1: Genes associated to IBD development [34].

	Gene	Chromosome	Function
CD	SLC22A4 & SLC22A5	5	Organic cation, carnitine transporters, transportation of xenobiotic substances
	DLG5	10	Epithelial scaffolding protein
	PPARG	3	Intracellular inhibitor of NF-κB and cellular activation
UC	MDR1	7	Efflux transporter for drugs and, possibly, xenobiotic compounds

Legend: CD: Chron's Disease; DLG5: discs large homolog 5 (*Drosophila*); MDR1: multidrug resistance 1; PPARG: Peroxisome Proliferative-Activated Receptor Gamma; SLC22A4 & SLC22A5; solute carrier family 22 (organic cation transporter); members 4 and 5 (formerly OCTN1 and OCTN2); UC: Ulcerative Colitis.

Pathogenesis

The underlying mechanism behind the development of IBD is not fully understood but there are two broad hypotheses. The first one suggests a dysfunctional interaction between the bacterial microflora present in the gut and the mucosal immune system. According to this theory, there is an excessive immunological response to an intestinal microflora that is both quantitatively and qualitatively normal. The second one refers the presence of an abnormality in the intestinal microflora and/or a deranged epithelial barrier function that elicit a pathological response from a normal mucosal immune system. At the overall, it is well accepted that IBD is characterized by an abnormal mucosal immune response, but microbial factors and epithelial cell abnormalities may facilitate it [1,35].

The innate immune response normally starts with the action of neutrophiles, that are known to play a central role in the inflammatory response and are responsible for the production of chemokines and pro-inflammatory cytokines, such as Tumor Necrosis Factor-α (TNF-α), IL-1β, IL-6, and IL-8. This process allows the recruitment of other white blood cells like macrophages [12,36]. The activation of these cells into the inflamed gut leads to a dislocation of leukocytes, macrophages and granulocytes from systemic circulation into the mucosa, which perpetuates the inflammatory response [36,37]. This results in an oxidative burst, release of reactive oxygen species, granule exocytosis and tissues degradation, which contributes to a chronic intestinal inflammation [37].

Although the similarity between the innate responses of CD and UC, T-cell profiles are clearly distinct [34]. Indeed, CD is characterized by an excessive T helper (Th)1 and Th17 cells response, where an increased Th4 cells response is linked to UC [12,32,38]. An overproduction of IL-12 and IL-27 induces Th1 cells response and promotes the production of interferon-γ, TNF-α, IL-2 and IL-6 [12,38]. Additionally, Th17 cells are known to produce IL-17A, IL-17F, IL-21 and IL-22, and are induced by IL-6 and Transforming Growth Factor-β (TGF-β) [32] In the other hand, Th2 cells differentiate under the influence of IL-4, and are responsible by the production of TGF-β, IL-4, IL-5 and IL-13 [12,36,37].

Current pharmacological treatment of inflammatory bowel disease

Currently, there is not a cure for IBD, and pharmacological approaches aims to induce and maintain the patients in remission and ameliorate the disease's secondary effects, and not by reversing the underlying pathogenic mechanism [1,7,9,39]. Additionally, therapeutic approaches for IBD have specific objectives, such as: resolution of the acute inflammatory response; resolution of complications, such as fistulas and abscesses; alleviation of systemic manifestations, like for example arthritis, and surgical palliation [40].

Current therapeutic approaches for IBD passes by: regulation of the intestinal microflora balance; immunosuppression by inhibiting leukocytes activation and proliferation; inhibition of leukocyte activity and/or the function of pro-inflammatory cytokines, and surgery [41]. In term of non-pharmacological approaches, dietary changes may help in reducing symptomology [42]. Additionally, probiotic formulas have been effective for inducing and maintaining remission in patients along with a favorable safety profile [40].

Regarding the therapeutic options currently available, it is important to identify the most suitable treatment protocol for each individual patient, where the major goal is to predict the response to the therapy, minimizing unnecessary exposure to inefficient approaches and adverse effects [38,43]. Indeed, there are two types of therapy to be aware of, where the first one called "induction therapy", is introduced in patients exhibiting signs and symptoms of active disease. On the other hand, the second one is considered after remission has been achieved, where patients switch to a "maintenance therapy" to ensure that remission and quality of life are maintained as long as possible [44].

Pharmacological treatment used in IBD context can be divided in: anti-inflammatory drugs, such as 5-Aminosalicylates (5-ASA); immunomodulators; corticosteroids; biological agents; antibiotics, and agents that inhibit leukocyte adhesion and migration [1,9,36,40,43]. These therapies have shown to have a relatively high efficacy but are inappropriate for long-term use due to their side effects and complications, like for example, an increased rate of infectious diseases and/or malignancies [43,45]. Surgical intervention is equated in case of unresponsiveness to pharmacological treatment and/or in a more severe prognosis [46].

Pharmacotherapeutic classes

Aminosalicylates

Aminosalicylates, or 5-ASA, are considered a mainstay approach for IBD management, which can be used in combination with steroids to induce and maintain remission in patients [45,47]. However, 5-ASA has shown to be more effective in UC, compared with CD [43,48]. This pharmacological group includes mesalamine, which can be administrated orally or rectally, and oral pro-drugs such as, sulfasalazine, olsalazine and balsalazide [40,45,49,50].

Sulfasalazine consists of a linking between a 5-ASA, called mesalamine, and sulfapyridine, through an azo bond, which prevents the absorption of these individual components in the stomach and small intestine [45]. This pro-drug is split by intestinal microbiota into its constituents, mesalamine and sulfapyridine, which the first one is the active metabolite [45,51]. Sulfa-

pyridine is absorbed into systemic circulation, from the colon, and is the major responsible for most of the hypersensitivity and side-effects related to the administration of sulfasalazine, such as cyanosis, hemolysis, transient retinocytosis and vomiting[45,51,52]. In order to avoid the side-effects of this drug, it has been proposed a topical administration of 5-ASA for UC management [52]. Additionally, a combination of oral and topical aminosalicylates could be used when only oral treatment is not clearly effective [53].

Sulfasalazine and mesalamine demonstrates several potential sites of action, such as the inhibition of IL-1β and TNF-α, the inhibition of lipoxygenase pathway and inhibition of Nuclear Factor-kB (NF-kB). Its therapeutic effect does not appear to be associated to the inhibition of cyclooxygenase pathway, where the use of traditional non-steroidal anti-inflammatory drugsanti may exacerbate the development of IBD [45].

In order to minimize the side-effects related to the presence of sulfapyridine, it has been developed other pro-drugs, with is the result of replacing this molecule with another 5-ASA, such as olsalazine, or an inert compound, balsalazide. There are some side-effects related to the administration of these drugs, such as: headache, nausea, and fatigue, with a dose-related pattern; allergic reactions; rash; fever; Stevens-Johnson syndrome, hepatitis, pneumonitis, hemolytic anemia, and bone marrow suppression [45,54]. In case of dose-related side effects, it can be minimized by decreasing the dose or by administrating the medication in combination with meals [45].

Corticosteroids

Corticosteroids are known to be the treatment of choice in cases of moderate to severe flare-ups of CD and UC [45]. These drugs can also be used in combination with 5-ASA to induce remission of mild to moderate IBD [44,45,55]. There is no evidence, in terms of efficacy, on the use of corticosteroids in maintaining remission, given their significant side-effects related to its long-term use [43-45,56]. More specifically, the side-effects that are associated to the use of these drugs are, for example: fluid retention; infections; hypertension; mood changes, and adrenal suppression [54,57].

Corticosteroids inhibits the inflammatory cascade by suppressing the arachidonic acid metabolism, through the inhibition of phospholipase A2. This will have consequences in terms of vascular permeability, vasodilatation and in the infiltration by neutrophils [38,41,58]. Additionally, these drugs will inhibit the leukocyte function, by downregulate the production of inflammatory cytokines, and also interfere with NF-kB production [32,59].

The corticosteroid preferably used in IBD management is prednisolone, which can be administered orally, rectally, or parenterally in emergency events [45]. The initial dose for prednisolone is 40 mg daily to adult patients. Higher doses are not more effective in most of the cases and exacerbates the toxicity by augmenting the incidence and severity of side-effects [40,45,54,56]. Taking in account that some patients might become steroid dependent, and the characteristic adrenal suppression appearance upon the use of these drugs, the dose should be reduced by 5 or 10 mg per week, once the patient reveals an improvement in terms of symptomology [43,45]. Additionally, the use of steroids must be minimized to the minimum necessary, where the goal is to remove the patients from corticosteroids within a short period of time while maintaining disease remission [56]. In case of patients treated with these drugs and an absence of signs in terms of clinical improvement, the therapy should change to cyclosporine or biological agents [43].

Other corticosteroid that has proved to be an effective and relatively safer option is budesonide. This drug is active in the distal ileum and colon, demonstrating its efficacy in the management of mild to moderate exacerbations of CD, in a dose of 9 mg per day, for 10 to 12 weeks [44,45,47,56]. Taking in account the fact that budesonide has an extensive first-pass hepatic metabolism, its systematic bioavailability is lower ad, consecutively, presents a lower rate of systemic adverse effects in comparison to another corticosteroids, such as prednisolone. However, another consequence of its characteristic metabolism is the fact that is not as effective in inducing remission [44].

Topical corticosteroids had demonstrated to be also effective, but not as much as topical 5-ASA. It may be preferred in some patients since it is easier to administer and more comfortable to retain. Additionally, in cases that the disease is limited to the rectum, this approach is more useful. In these cases, systemic absorption occurs but in a reduced form, where the adrenal suppression and other adverse effects rarely occur with a long-term use [45,53].

Antibiotics

The use of antibiotics in the management of IBD assumes that bacteria present in the gut microflora are involved in the pathogenesis of this disease [43]. Normally, the administration of antibiotics occurs in specific cases, such as: association with other drugs for the management of IBD; treatment of a specific complication associated to CD, and as prophylaxis for disease recurrence in CD [45].

Antibiotics are mostly used in cases of CD, since there are relatively few trials using these in UC patients allied with the fact that the results are inconclusive. Therefore, it is required further studies to better clarify their role in both active and inactive UC [43]. The most used antibiotics are ciprofloxacin, metronidazole, and clarithromycin. These drugs have also shown to be effective in the treatment of complications, such as intraabdominal abscesses and inflammatory masses, perianal disease like fistulas, bacteria overgrowth, and secondary infections [45]. Additionally, antibiotics can also be used to induce remission in mild to moderate CD, and its long-term use is required since its stopping induces relapse. However, this prolonged use is related to a higher risk for promoting adverse effects, such as nausea, anorexia, dyspepsia, dysgeusia, and peripheral neuropathy [43,45].

Ciprofloxacin has demonstrated to be effective in a proportion of patients with active CD, mainly localized in the colon tissue. In the other hand, clarithromycin is recognized to have a good penetration into macrophages, and it has shown a benefit during the first month, which suggests that an initial effect may be attenuated by subsequent bacterial resistance [43]. Finally, metronidazole is most used in CD patients, at a dosage of 10 to 20 mg/kg per day. This drug promotes less pain and tenderness, eventually decreased erythema and swelling, and wound healing. Additionally, it is also used in cases of perianal disease. Other antibiotics related to the management of IBD, and more specifically, in a CD context, include trimethoprim plus sulfamethoxazole and tetracycline [45].

Immunomodulators

The use of immunomodulators in the management of IBD has been since the early 1970s, with the utilization of azathioprine and 6-mercaptopurine. These drugs have demonstrated to be superior in comparison to a placebo but since it is required several weeks to achieve their therapeutic effect, they have a limited role in an acute setting and are preferably used for a long-term spectrum of time [45]. Therefore, immunomodulators are effective for maintaining the remission but not for inducing it [44,60].

Azathioprine is a pro-drug, which is converted to 6-mercaptopurine, and both are used in long-term IBD [43-45-56]. Both drugs act through their active metabolite, 6-thioguanine nucleotide, which causes inhibition of DNA and RNA synthesis as well as promoting T-cell apoptosis [61]. These drugs are effective at maintaining remission in both UC and CD. Additionally, they are used to treat patients with a severe prognosis of IBD or those who are steroid-dependent or steroid-resistant [45,56]. The initial dose is 50 mg per day, where azathioprine is administrated at a dosage of 2 to 2.5 mg/kg and mercaptopurine at a dosage of 1.5 mg/kg. Indeed, a therapeutic benefit usually occurs at doses of 75-150 mg per day of azathioprine and 50-100 mg per day for mercaptopurine [43,45]. These drugs are known to have several side effects, such as: myelosuppression; hepatotoxicity, and several allergic reactions [45]. Since these medicines also induces mild leukopenia, it is highly recommended to obtain a complete blood count analysis, every two weeks, during the initial treatment phase in patients with active disease and every three months when patients are on a maintenance therapy [45,56]. A contraindication for the continued use of these agents is pancreatitis, since they may induce it. Comparing with long-term corticosteroids therapy, thiopurines are safer, however side effects and treatment alternatives should be discussed with the patients before initializing the therapy [45]. According to recent data, the concomitant use of 5-ASA and azathioprine appears to be beneficial to some patients[43,45].

Other immunomodulator used in the management of IBD, more specifically, inducing and maintaining remission in CD, is methotrexate, which have a potent anti-inflammatory effect when used in low doses. It is administrated through an intramuscular injection at 25 mg/week for induction and 15-25 mg/week for maintenance [43-45]. Methotrexate is an anti-metabolite, which inhibits DNA synthesis and concurrent folic acid supplementation is advisable [56]. The characteristic side effects of this drug are leukopenia, hepatic fibrosis, and hypersensitive interstitial pneumonitis [43,45]. Additionally, patients with an history of alcohol abuse or morbid obesity are more susceptible to develop hepatic fibrosis, and therefore, methotrexate should not be used in these cases. Renal and hepatic function should be monitored every two weeks until the patient is receiving oral therapy and every three months after [43-45].

The calcineurin inhibitor, cyclosporine, is a potent immunosuppressant drug commonly used in organ transplantation. This drug has been used in patients with severe flare-ups of UC, which are not responding to corticosteroid treatment [43-45]. Cyclosporine is highly effective in inducing remission, which allow patients to avoid surgery, however after one year, the same patients still require surgery [45]. Normally, this drug is administrated in severely ill patients through an Intravenous (IV) administration, which promotes a significant improvement in their prognosis within seven days, at a dosage of 2 to 4 mg/kg, daily. Since cyclosporine has a narrow therapeutic margin, it is necessary to monitor the serum levels and maintain a therapeutic level in whole blood between 300-400 ng/ml [45]. Oral cyclosporine is less effective at maintaining remission in IBD due to its limited intestinal absorption and presents a limited benefit with a relatively high relapse rate. However, new formulations, such as microemulsion, might increase its oral bioavailability and effectiveness [45]. Its mechanism of action is not fully understood, however it showed in experimental colitis, the upregulation of the expression of TGF-β in colonic tissue, enhance the expression of p-Smad2 and cFLIP in epithelial cells, and the inhibition of caspase-8 activity [43]. This drug presents a significant side effect profile, including seizures, renal insufficiency and hypertension [45].

Monoclonal antibodies

Humanized monoclonal antibodies is a relatively recent approach for the treatment of IBD, which provide an alternative tool to traditional treatments, once these molecules modify, specifically, the affected biochemical inflammatory pathway [45].

Generally, the monoclonal antibodies used in IBD context are related to the inhibition of TNF-α, being expected to be a powerful treatment strategy in patients with CD or UC [43,45,62]. Also, TNF-α is recognized as one of the principal cytokines which mediates the Th1 immune response, characteristic of CD [45]. The first anti-TNF-α drugs approved by regulatory authorities, such as Food and Drug Administration (FDA), for the management of IBD were infliximab, adalimumab, certolizumab and golimumab [61]. Adalimumab and infliximab can be used in both CD and UC management, certolizumab is only used in CD context, and golimumab demonstrates to be more effective in UC [42,50]. All of these drugs have a comparable efficacy in inducing and maintaining remission for UC and CD [56,57]. The use of anti-TNF-α monoclonal antibodies is recommended in patients with moderate to severe CD, refractory to previous agents or in patients who have a poor tolerance to those same agents [43].

Adalimumab and certolizumab are human monoclonal antibodies administered subcutaneously [42,61]. Adalimumab seems to be well-tolerated in most patients, in particular those with reactions to infliximab [43,45,60]. Its anti-inflammatory effect is due to the blockage of TNF-α and the correct dose is 160 mg in the first week, followed by 80 mg at week two. Additionally, the number of draining fistulas decreased significantly in patients treated with this drug [43,63].

Infliximab is a mouse-human immunoglobin G1 chimeric monoclonal antibody [45,60]. It is used for the treatment of refractory UC and CD, through the inhibition of functional activity of TNF-α by binding to the circulating and membrane-bound of this cytokine, inducing a cell-mediated cytotoxic reaction and then enhancing the programmed cell death of activated T-cells. Additionally, this drug is a stronger inducer of mucosal healing, and it is administrated IV at a dosage of 5 mg/kg at intervals between several weeks to months [43,45,56,60].

In terms of safety profile, the drugs inserted on this pharmacological group present several adverse effects, such as: delayed-type hypersensitivity reactions; dyspnea; nausea; flushing; headache; drug-induced lupus; injections site reactions, and hearth failure [43,56].

Treatment protocols for inflammatory bowel disease

Ulcerative Colitis

The first-line therapy for active, mild to moderate, and extensive UC is sulfasalazine and mesalamine [26,40]. The combined use of oral and rectal formulations of 5-ASA demonstrates a faster and higher remission rate in patients [26]. In case of a more extensive and/or severe disease, or unresponsiveness to oral 5-ASA, such as sulfasalazine or mesalamine, it is required oral or parenteral corticosteroids in order to induce remission [26,40]. Oral agents, including sulfasalazine, mesalamine and balsalazide are effective options once remission is achieved. On the other hand, corticosteroids are not administrated to maintain remission and taking in account its safety profile, they should be gradually withdrawn after remission is induced [40]. The pharmacological treatment strategy for UC is represented in Table 2 [40,64].

Table 2: Treatment Protocol for ulcerative colitis [40,64].
Legend: IV, Intravenous.

	Induction of Remission		Maintenance of Remission	
	Drug(s)	**Administration**	**Drug(s)**	**Administration**
Mild to Moderate	**Distal** Sulfasalazine or Mesalamine **Or** Mesalamine 2-4 g per day **Or** Mesalamine 1g per day **Or** Corticosteroids	 Oral Enema Suppository Enema	**Distal** Reduce sulfasalazine or mesalamine dose **Or** Mesalamine 4g every 1-2 days **Or** Mesalamine 1g every 1-2 days	 Oral Enema Suppository
	Colitis Sulfasalazine 4-6 g per day **Or** Mesalamine 2,4g to 4,8g per day	 Oral Oral	**Colitis** Reduce sulfasalazine dose **Or** Reduce mesalamine dose to 2,4 g per day	 Oral Oral
Moderate to Severe	Sulfasalazine 4 to 6 g per day **Or** Mesalamine 2,4g to 4,8g per day **Plus** Prednisolone 40mg to 60mg per day	Oral Oral Oral	Reduce prednisolone dose **Plus** Reduce sulfasalazine or mesalamine dose after 1 to 2 months **In case of unresponsiveness** Add azathioprine or mercaptopurine, and consider infliximab in case of refractivity	Oral Oral Oral or IV
Severe to Fulminant	Hydrocortisone 100 mg every 6 to 8 hours **In case of unresponsiveness in 5 to 7 days** Cyclosporine 4 mg/kg per day	 IV IV	Change hydrocortisone to prednisolone **After 1 to 2 months** Withdraw steroids and add sulfasalazine or mesalamine **Then** Maintenance dose of sulfasalazine	Oral Oral Oral

	Location	Drug(s)	Administration
Mild to Moderate	**Ileocolonic or Colonic**	Sulfasalazine 3g to 6 g per day **Or** Mesalamine 3g to 4 g per day	Oral or enema Oral
	Perianal	Sulfasalazine or mesalamine **And/or** Metronidazole 10mg to 20 mg/kg per day	Oral IV
	Small Bowel	Mesalamine 3g to 4g per day **Or** Metronidazole **Or** Budesonide 9 mg/day in case of terminal ileal or ascending colonic disease	Oral Oral IV
Moderate to Severe	**As demonstrated above** **Plus** Prednisolone 40mg to 60 mg per day **In case of unresponsiveness and fistulizing disease** Add infliximab		 Oral IV
	In case of response Reduce prednisolone dose after 2-3 weeks **Plus** Azathioprine, mercaptopurine or methotrexate **In case of unresponsiveness** Switch to adalimumab		 Oral IV IV
Severe to Fulminant	Hydrocortisone 100 mg every 6 to 8 hours **In case of unresponsiveness in the next 7 days** Cyclosporine 4mg/kg per day		IV IV

Chron's Disease

Management of CD depends primarily on the site, extent, severity, and the presence of complications. The therapeutic goal is the same as UC management, which is the induction and maintenance of remission, heal the mucosa and optimize quality of life for the patient [20,56]. The initial use of 5-ASA, such as sulfasalazine and mesalamine, is due to its favorable safety profile, although the fact that does not demonstrate a significant efficacy in CD context. For this condition, oral corticosteroids are known to be the first-line therapy [40]. Additionally, immunomodulators, monoclonal antibodies and antibiotics are also used in CD [20]. The pharmacological treatment strategy for this disease is represented in Table 3 [40].

Table 3: Treatment protocol for Chron's disease [40].
Legend: IV, Intravenous.

Drug	Phase of Clinical Trial	Route of Administration	Mechanism of Action	Phenotype	Clinical Trial
UTTR1147A	II	SC	Induction of IL-22 pathway	CD and UC	NCT03558152 NCT03650413

Recent pharmacological approaches for inflammatory bowel disease

Nowadays, there are several molecules which are being studied on the context of IBD, and indeed, some of them already has the approval by the regulatory entities, such as FDA and European Medicines Agency (EMA), for the introduction on the pharmaceutical market of United States of America and Europe, respectively. However, the more recently approved drugs, such as tofacitinib, vedolizumab and ustekinumab, are applied in more specific cases, depending on the respective patient and its individual needs [65-67].

Tofacitinib

The Janus Kinase (JAK) cellular signaling pathway is intimately related to the development of IBD, where JAK1 and JAK3 play a key role [65]. To inhibit this signaling pathway, a small molecule denominated tofacitinib, which is used in moderate-to-severe rheumatoid arthritis, has demonstrated an interesting role on the future management of IBD [68]. Indeed, this drug is currently approved for the management of moderate-to-severe UC patients, by the FDA and EMA. Additionally, the utilization of molecules with a relatively low size presents several advantages, such as the possibility to be administrated orally and by not causing an immune response, preventing the concomitant administration of immunosuppressors [65]. The combination of these properties promotes a more favorable safety profile at a long-term use, which is a well-known gap on the current pharmacological strategies.

In Octave Induction 1, Octave Induction 2 and Octave Sustain trials, it was showed that tofacitinib had a beneficial effect on moderate to severe UC patients [69]. Indeed, the administration of 5 and 10 mg of this drug, twice daily, for 8 and 52 weeks, demonstrated a relatively high rate of maintenance of remission on patients, in comparison to placebo groups [69]. In terms of safety profile, tofacitinib exhibited the induction of headache, arthralgias and nasopharyngitis as the most common adverse effects. Additionally, it was also observed cardiovascular events, but with a lower rate. Currently, this drug is inserted on a black box warning, by the FDA, taking in account the increase rate of pulmonary embolism in older rheumatoid arthritis patients, which have at least one cardiovascular risk factor. However, this effect appears to be more prevalent in higher doses of tofacitinib [69].

Taking in account the efficacy and safety profiles of tofacitinib, it should be administrated only in patients which failed to the biological therapy. Additionally, it is highly recommended the reduction of the dose to 5 mg, twice daily, after a successful induction with 10 mg. Between both phenotypes of IBD, tofacitinib appears to be mostly effective in CD comparing with UC [70,71].

Vedolizumab

Monoclonal antibodies are recognized as a powerful tool for the treatment of several pathologies due to their specificity. Actually, there are several monoclonal antibodies which are used on the management of IBD, and more recently, it has been approved another one, vedolizumab, both in Europe and United States of America [66,72]. This drug is an anti-α4β7 integrin monoclonal antibody capable of modulating the inflammatory response throughout the gastrointestinal tract, due to the inhibition of adhesion between peripheral blood lymphocytes to MAdCAM-1 [73]. Indeed, the efficacy and safety of vedolizumab has been evaluated both on moderate-to-severe UC and CD patients.

Firstly, vedolizumab was administrated on moderate-to-severe UC patients, present on the Gemini 1 trial, where the objective was evaluating the capability of this molecule in inducing and maintaining the remission phase. Briefly, the patients were initially enrolled to either vedolizumab or placebo to evaluate the induction efficacy. The treatment on this phase constituted by two intravenous administration of 300 mg of vedolizumab, on days 1 and 15. Then, the patients that had a clinical response at week 6, were subjected to vedolizumab every 4 weeks, vedolizumab every 8 weeks, or placebo until completing 52 weeks. The results showed that vedolizumab demonstrated a significant effect on inducing the remission phase, at week 6 of treatment, in comparison with the placebo (47.1% vs 25.5%). Additionally, this drug also demonstrated a significant effect on maintaining the remission on the patients, taking in account its administration every 4 weeks (44.8%) and every 8 weeks (41.8%), in comparison to the placebo (15.9%) [74].

Vedolizumab was also evaluated on moderate-to-severe CD patients, through Gemini 2 and 3 trials, which had a similar experimental design in comparison to Gemini 1 trial. About the Gemini 2 trial, it was observed that patients treated with vedolizumab had a higher rate of clinical response, at week 6, in comparison to placebo (14.5% vs 6.8%). Additionally, it was also observed that the treatment with this drug had a significant effect on maintaining the remission phase, at week 52, taking in account the administration every 4 weeks (36.4%) and 8 weeks (39%), comparing to placebo (21.6%) [75]. On the other hand, at Gemini 3 trial the efficacy and safety of vedolizumab was evaluated mostly in patients which did not respond to prior therapy, more specifically with anti-TNF-α drugs. Firstly, the clinical response of patients treated with vedolizumab, at week 6, was

not significantly increased in comparison to placebo (15.2% vs 12.1%). However, at week 10 it was observed a significant difference, in terms of clinical response, between both groups, where the vedolizumab arm demonstrated around 26.6% of patients on remission, against 12.1% in placebo (p=0.001) [76].

Vedolizumab presented nasopharyngitis as the most common adverse effect and a relatively increased risk for infections, especially on the gastrointestinal tract [74,75]. One interesting point about the use of vedolizumab is the significant reduction of risk of developing progressive multifocal leukoencephalopathy, in comparison to natalizumab, which is an anti-α-4-integrin monoclonal antibody, that cause immunosuppression. The underlying reason is derived from the high specificity of vedolizumab to the gastrointestinal tract [73].

Ustekinumab

Ustekinumab is a monoclonal antibody that binds to the p40 subunit of IL-12 and IL-23, and it is approved for the treatment of psoriasis and psoriatic arthritis. Additionally, more recently it has been also approved for the management of moderate-to-severe CD and UC patients, by the FDA and EMA [67]. Firstly, it was demonstrated a beneficial effect of ustekinumab on patients with IBD, through phase IIa and IIb trials, which originated further phase III trials consisting of 8-week induction trials (UNITI-1 and UNITI-2) and 44-week maintenance trials (IM-UNITI), or both phases (UNIFI) [77-79].

Regarding UNITI-1 trial, it was composed by moderate-to-severe CD patients with no response anti-TNF agents or the appearance of serious adverse effects. Additionally, UNITI-2 trial had in consideration also patients with moderate-to-severe CD patients, which did not respond to the treatment with immunosuppressants and/or glucocorticoids or experienced serious adverse effects. In both clinical trials, patients received a single dose of 130 mg of ustekinumab intravenously at the beginning. Then, at week 6, patients who received ustekinumab revealed a significant higher clinical response in comparison to the placebo (UNITI-1 trial: 34.3% vs 21.5%; UNITI-2 trial: 51.7% vs 28.7%), which reveals the capability of this drug to induce the remission phase [77-79]. The IM-UNITI trial consisted of a maintenance phase, composed by individuals present on UNITI-1 and UNITI-2 trials clinical response at week 6, which then received the treatment with ustekinumab or placebo for 44 weeks. Briefly, patients received 90 mg of ustekinumab every 8 weeks or every 12 weeks, through a subcutaneous injection. The results showed that the number of patients in clinical remission at week 44 were significantly higher in ustekinumab arm comparing to placebo (35.9%), taking in account its administration every 8 weeks (53.1%) and every 12 weeks (48.8%). In terms of safety profile, the administration of ustekinumab did not present a significant increase of adverse effects comparing to placebo [79].

Posteriorly, it was developed a follow-up study, up to 5 years from induction, with the patients enrolled on the UNITI/IM-UNITI trials and with the same treatment design. The results showed that, at week 152, 38% of patients receiving ustekinumab every 8 weeks were still in remission, and 43% of those subjected to the treatment every 12 weeks. There was not a significant difference in terms of incidence of adverse effects between the patients treated with ustekinumab or placebo [80].

Regarding UC, UNIFI trial was developed with the presence of an 8-week induction and a 44-week maintenance phases, composed by patients with a moderate-to-severe prognosis, with a similar treatment design that UNITI-1 and UNITI-2 trials [67,77-79]. The patients were included taking in account an inadequate response to anti-TNF drugs, vedolizumab or nonbiological therapy, or by the appearance of serious adverse effects from them. Firstly, the number of patients with clinical response at week 8 was significantly increased in ustekinumab arm, in comparison to the placebo (15.6% vs 5.3%). Then, the patients with clinical response were subjected to a maintenance phase trial, for 44 weeks. Finally, at week 52, ustekinumab also showed to be significantly more effective that the placebo (24%), on the maintenance of the remission phase, taking in account its administration every 8 weeks (43.8%) and 12 (38.4%) weeks. Comparing the incidence of adverse effects between the patients treated with ustekinumab or placebo, there was a slightly increase on the last one. In this sense, ustekinumab can be described as a relatively safe pharmacological approach for the future [67].

Drug under research for inflammatory bowel disease

Repurposing drugs

Currently, it is possible to observe an exponential advance in technology and the increasing knowledge of human pathologies, however it has not been translated into therapeutic advance, at the same rate of time [81]. Indeed, pharmaceutical industries worldwide face several challenges, which are multifold and include attrition rates. Additionally, the spectrum of time for presenting new drugs for the community is increasing gradually, which is allied to the changing regulatory requirements, concluding in an increased cost throughout the process of research and development of new drugs [81,82].

Drug repurposing is recognized as an alternative strategy to identify new possible utilizations for already approved or investigational drugs, which are outside the scope of the first original medical indication(s). This strategy reveals several advantages, such as: reduced risk of failure since there is already clinical and non-clinical information about the safety profile of the specific drugs; reduced spectrum of time for drug development taking in account that most non-clinical and clinical testing has been performed and there is probably sufficient information already, and less investment need, however it may vary since it will depend on the stage of development of the specific repurposed candidate drug [81,82]. Additionally, drugs that are subjected to the process of repurposing may show new biological targets and pathways [81].

Nowadays, it has been evaluated the efficacy and safety of several drugs, approved originally for other pathologies, and natural products on the context of IBD, specially through non-clinical studies, such as in animal models of colitis.

Erythropoietin

Erythropoietin (EPO) is a multifunctional glycoprotein, which is used in clinical practice in anemic patients with renal insufficiency due to its capability of regulation of erythrocyte production, by the differentiation and inhibition of apoptosis of erythroid progenitor cells [9,82-84]. The hematopoietic function of this glycoprotein can be explained by its binding to a homodimeric receptor, denominated EPOR [85-89]. Recently, it has been also discovered non-hematopoietic properties from EPO, like for example in brain, kidney, skeletal muscle, and endothelial cells. As examples of non-erythroid effects, it can be emphasized the anti-inflammatory, wound healing and antiapoptotic properties. These can be explained by the binding of EPO to a heterodimeric receptor, composed by the junction of EPOR and

beta common receptors, such as CD-131 (EPOR-βcR) [86,90,91]. Theoretically, this binding promotes the blockage of NF-kB p65 activation and inactivation of GSK-3β, via activation of PI3K-Akt. Additionally, it also inactivates cyclooxygenase 2, caspases 3 to 8 and stimulates the production of IL-10 [9,83].

Taking in account the information above, it would be interesting to evaluate its efficacy and safety on IBD context, and indeed, it was performed in a TNBS-induced animal model of IBD. At the final of the experiment, it was possible to conclude a beneficial effect of EPO taking in account the reduction of the expression of TNF-α, IL-1β and myeloperoxidase, and the increased production of IL-10. Additionally, it was also observed a reduction in fecal hemoglobin and alkaline phosphatase, as well as a more favorable histopathological score afterwards. In terms of safety profile, it was not seen any significant different on hematocrit concentration and in renal and hepatic biomarkers [9].

Hemin

Hemin is an iron-containing metalloporphyrin approved for the management of acute attacks of inducible porphyria and recurrent attacks of acute intermittent porphyria related to menstrual cycle [7,92]. Also, hemin has demonstrated the capability of inducing heme-oxygenase (HO) [93,94]. Indeed, there are three well-known mammalian HO, namely HO-1, HO-2, and HO-3, which the first one has shown promising results in non-clinical studies, such as in hippocampal injury, cardiac ischemia, renal fibrosis, lung injury, and sepsis [93-95]. The upregulation of HO-1 have shown cytoprotective, antiapoptotic, and anti-inflammatory properties, which increases the curiosity of its effect in a IBD context [95].

Indeed, it was demonstrated a beneficial effect of the increased expression of HO-1, due to the administration of hemin, in TNBS-induced animal models of colitis [7,96]. It was showed that the administration of this drug promoted the reduction of reactive oxygen species, nitric oxide, inducible nitric oxide synthase, fecal hemoglobin, alkaline phosphatase, TNF-α, IL-1β, and a more favorable histopathological score at the end [7,96]. In this sense, hemin have shown to be a promising candidate as a pharmacological approach in IBD in the future.

Topiramate

Topiramate is an anticonvulsant drug allied with an anti-depressant activity, which its mechanism of action is not fully described but it seems to be related to its capacity of increasing gamma-aminobutyric acid-activated chloride channels. Additionally, it also shows activity on kainite and AMPA receptors, and inhibits the activity of several carbonic anhydrase enzymes [97]. Theoretically, there was not an interesting role of topiramate in a IBD context, however a study that utilized an *in silico* approach to ascertain and discover new possible pharmacological approaches for the treatment of this pathology, recognized this drug as a promising approach. Indeed, through the development of a TNBS-induced animal model of colitis, it was possible to observe a beneficial effect of topiramate through the significant reduction of gross pathological signs and microscopic damage in primary affected colon tissue [97]. In this sense, the preliminary results available shows an arise of a new possible pharmacological tool for IBD, but it is still needed further studies to ascertain its efficacy and safety.

New pharmacological approaches

Currently, there is a considerable number of drugs and standard treatment strategies, taking in account each patient and its needs, however there is a need to discover new pharmacological approaches with a more favorable safety profile. Indeed, many efforts have been done to evaluate novel treatment strategies for several pathologies, such as IBD, and it can be considered already known drugs or even new molecules, recently developed. Throughout the process of research and development of medicines, it is performed several experiments, including both non-clinical and clinical approaches, in order to evaluate the respective efficacy and safety profiles, and make a final decision about its effect on a certain pathology. Generally, it is a process that needs a great investment in terms of time and capital, which makes imperative the existence of conditions that requires new and better pharmacological approaches in order to justify the final effort [98,99].

In the specific case of IBD, there are several known drugs and new molecules that were already tested in non-clinical studies, such as in vitro and in vivo, and are now being evaluated in humans, throughout clinical trials, presenting promising results as new possible pharmacological tools to be taken in account (Table 4) [100-102].

Table 4: New Drugs for Management of Inflammatory Bowel Disease [100-102].

Drug	Phase of Clinical Trial	Route of Administration	Mechanism of Action	Phenotype	Clinical Trial
Abrilumab	II	SC	Inhibition of α4β7 integrin	UC	NCT01694485
AJM300	III	Oral	Inhibition of α4 integrin	UC	NCT03531892
Amiselimod	II	Oral	Modulation of S1PR	CD and UC	NCT02378688 NCT04857112
Apremilast	II	Oral	Inhibition of PDE4	UC	NCT02289417
AVX-470	I	Oral	Anti-TNF-α	UC	NCT01759056
BMS-986165	II	Oral	Inhibition of TYK2	CD and UC	NCT04877990
Brazikumab	II/III	IV/SC	Inhibition of p19 IL-23	CD and UC	NCT03759288 NCT04277546
Brepocitinib	II	Oral	Inhibition of TYK2	CD and UC	NCT03395184 NCT02958865
Cobitolimod	II	Topical	Activation of TLR-9	UC	NCT03178669

Etrasimod	II/III	Oral	Modulation of S1PR1, S1PR4 and S1PR5	CD and UC	NCT04607837 NCT04176588 NCT04173273
Etrolizumab	III	SC	Inhibition of α4β7 and αEβ7 integrins	CD and UC	NCT02136069 NCT02165215 NCT02100696 NCT02171429 NCT02163759 NCT02394028
Filgotinib	II/III	Oral	Inhibition of JAK-1 and JAK-3	CD and UC	NCT03046056 NCT02914522
Guselkumab	II/III	IV/SC	Inhibition of IL-23	CD and UC	NCT03466411 NCT04397263 NCT04033445
Mirkizumab	III	IV/SC	Inhibition of p19 IL-23	CD and UC	NCT02589665 NCT03926130
OPRX-106	II	Oral	Anti-TNF-α	UC	NCT02768974
Ozanimod	III	Oral	Modulation of S1PR	CD and UC	NCT02435992 NCT03464097 NCT03440372 NCT03440385
PF-00547659	II	SC	Inhibition of MAdCAM	CD and UC	NCT01620255 NCT01771809 NCT01276509
PF-04236921	II	SC	Inhibition of IL-6	CD	NCT01287897
PF-06651600	II	Oral	Inhibition of TYK2	CD and UC	NCT02958865 NCT03395184
Risankizumab	II/III	IV/SC	Inhibition of p19 IL-23	CD and UC	NCT03105128
TD-1473	II/III	Oral	Inhibition of Pan-JAK	CD and UC	NCT03920254 NCT03635112 NCT03758443
Upadacitinib	III	Oral	Inhibition of JAK-1	CD and UC	NCT03653026 NCT03345849

Legend: CD: Chron's Disease; IL: Interleukin; IV: Intravenous; JAK: Janus Kinase; MAdCAM: Mucosal Addressin Cell Adhesion Molecule 1; PDE4: Phosphodiesterase 4; S1PR: Sphingosine-1-Phosphate Receptor; SC: Subcutaneous; TLR-9: Toll Like Receptor-9; TNF-α: Tumor Necrosis Factor-α; TYK2: Tyrosine Kinase 2; UC: Ulcerative Colitis.

Conclusion and future perspectives

Currently, the established treatment of IBD is organized according to the stages of severity observed on the patients and can be described as relatively effective therapeutic approaches for the induction of remission. However, the safety profile is not that favorable in a longer spectrum of time, which makes essential the process of research and development of new possible pharmacological tools. Indeed, there are several strategies that can be discussed, such as the introduction of new drugs, the repurposing of medicines with another original approved indication, or even the use of natural products. Additionally, there are several molecules under clinical trials with promising results and well-known candidates for the future treatment of IBD. Indeed, this disease is recognized as a chronic and relapsing pathology, so it is important to consider that is needed therapeutic tools which can induce the remission phase thus having a more favorable safety profile in a long-term utilization. Finally, the use of natural products is increasing throughout the time, which can be considered as an interesting tool for the future prevention and treatment, taking in account their safety profile and the efficacy demonstrated in non-clinical and clinical studies.

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