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Emerging drugs for the treatment of ulcerative colitis

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Abstract

Background—Ulcerative colitis (UC) is a chronic, relapsing inflammatory disorder of the colon for which the etiology is currently unknown. At present, strategies to treat UC are primarily targeted to control inflammation during active phases of disease as well as maintain remission during quiescence. As such, several unmet needs in the treatment of UC still remain. In recent years, basic research has led to the recognition of several key factors in the pathogenesis of UC, translating into the development of several novel therapeutic agents.

Objective—The aim of this study is to review emerging therapies that may advance the treatment and improve the overall care of UC patients.

Methods—An extensive literature search on published manuscripts and meeting proceedings has been performed to provide a comprehensive review of future drug therapies to treat UC.

Results/conclusion—The translational application of new discoveries in the basic understanding of UC pathogenesis is continuing and critical for the development of novel treatment strategies. Design of novel biologic therapies to treat UC has the challenge of addressing potential safety issues, while more traditional drugs should be further developed to facilitate patient compliance to treat this chronic, debilitating disease.

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Declaration of interest

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Keywords

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1. Background

Inflammatory bowel disease (IBD), including ulcerative colitis (UC) and Crohn's disease (CD), represents disorders characterized by an uncontrolled inflammatory response in the gut. In CD, inflammation primarily involves all layers of the intestinal wall (transmural inflammation) and can affect any area of the gastrointestinal tract, from mouth to anus. UC, on the other hand, is usually confined to the colonic mucosa, where it consistently affects the rectum and can variably extend proximally to involve portions of, or the entire, large intestine. However, in the vast majority of patients, the involvement is confined to the more distal parts of the colon, which accounts for 60 – 85% of all UC cases at diagnosis [1]. The histopathologic features of UC include intense neutrophil and lymphoplasmacellular infiltration of the mucosa, epithelial crypt destruction and distortion, cryptitis and cryptic abscesses, as well as extensive mucosal erosions.

The typical onset of disease for UC is during the third and fourth decades of age, and is characterized by a chronic and relapsing behavior, with a very small proportion of patients experiencing symptoms once in a lifetime, without any further recurrence. More commonly, it has been shown that 67% of UC patients have at least one disease relapse during a 10-year period [2]. Depending on correlation with disease extent, UC patients experience rectal bleeding, diarrhea, mostly with bloody stools, urgency, tenesmus and abdominal pain. These symptoms significantly affect the patients' quality of life and cause loss of work and productivity.

An undetermined percentage of patients can experience a severe attack of UC that can potentially be life threatening, requiring hospitalization, intensive medical regimen, and in 25% of the cases, total colectomy [3]. Long standing UC is an important risk factor for colorectal cancer (CCR) [4], with its incidence increasing and dependent on the duration and extent of disease [5], along with other known risk factors.

The estimated prevalence of UC is ~ 0.2% of the total North American population [6] and it seems to grow year after year in Western countries. Therefore, such a high prevalence, together with the young age of disease onset as well as the chronic and relapsing nature of UC, explain the elevated medical costs over the past several years resulting from this disease. In fact, in 1998, it was calculated that the annual cost in the US alone, both in terms of direct medical expenses and work loss, was up to $5228 per person with symptomatic IBD, for a total amount of $3.6 billion nationwide [7].

As the etiopathogenesis of UC is still unclear, no known cure exists. Current therapeutic strategies are aimed to reduce/shut down the inflammatory response activated during relapse of the disease, as well as to prevent further disease flareups. However, several patients do not respond, or experience loss of response, to treatment leading to prolonged

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hospitalization and increased medical expenses that eventually leave surgery as the only therapeutic option.

2. Medical need

In spite of great efforts by basic and clinical researchers, as well as the increasing number of therapeutic agents tested so far, relatively few compounds are currently available for the management of UC. Moreover, for most of the commonly used drugs, the number needed to treat (NNT) (i.e., number of patients who need to be treated to achieve one positive outcome) is roughly equal to 2 or greater [8], signifying that a real therapeutic effect is obtained only in ~ 50% of treated patients. Indeed, considering these data, novel therapeutic options are extensively needed to treat refractory patients. In fact, this particular clinical setting results in a lifetime risk of colectomy that, although variable from country to country and lower than in past years, still represents a significant problem. Indeed, the development of molecules capable of decreasing neoplastic risk in UC patients is of utmost importance because, as mentioned earlier, UC patients are also exposed to an increased risk of developing CCR.

As such, the ideal strategy to design novel therapeutic agents to treat UC would be to develop molecules that have the ability of treating the causative events that lead to alteration(s) in intestinal homeostasis, or at least to potently shut down the inflammatory response in the gut mucosa, while simultaneously lowering the risk of CCR. In addition, efforts should be made to improve drug delivery systems, formulations and bioavailability. In fact, a great part of success in treating UC relies on the amount of drug that can reach the site of inflammation. Therefore, a variety of different formulations have been developed to target differences in disease involvement. This is particularly relevant for left-sided colitis that is preferably treated with topical formulations, facilitating achievement of high drug concentrations at the site of the disease and results in increasing effectiveness and reducing systemic side effects of the given molecule. However, although effective, patients often consider topical treatments (i.e., enemas, rectal foams and suppositories) inconvenient and/or intrusive. Another important issue to consider and frequently included in patient complaints is the high number of pills required to be taken throughout the day to achieve targeted drug efficacy. Although these last aspects of UC therapy could be considered trivial and insignificant for the general management of the disease, they can significantly affect the patients' perception of their own quality of life [6] and can strongly alter medication adherence rates [9,10], which can eventually result in treatment failure.

As such, current medical needs in the treatment of UC point towards: i) the development of novel, more effective drugs; and ii) improvement of currently available formulations to obtain optimal therapeutic outcomes, with maximal safety and minimum annoyance for patients suffering from this devastating disease.

3. Existing treatment

Traditionally, the therapeutic management of UC has been divided into two main categories: i) treatments targeting the active phase of disease; and ii) treatments designed to maintain disease remission. Furthermore, the therapeutic algorithm is dictated by the severity and

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extent of disease. Therefore, different compounds in various formulations are selected to fulfil these aforementioned criteria. While a few compounds play a role in both the treatment of relapse as well as in the maintenance of remission and/or are available in different formulations, others more commonly have a restricted mechanism of action. Typically, the therapeutic approach to a disease flare-up consists of a 'step-up' strategy, starting with a first-line therapy, generally characterized by decreased toxicity, and climbing stepwise up the 'treatment pyramid' towards more potent (and potentially toxic) drugs if response to previous medications fails. The current artillery of drugs commonly used to treat UC are the aminosalicylates, the steroids, the immunomodulators and the biologics (**Table 1**).

3.1 Aminosalicylates

This class of drugs represents the most diffuse first-line therapy for mild to moderate UC. Aminosalicylates are considered to be effective both for the induction as well as the maintenance of remission in mild to moderate disease. However, although obviously superior to placebo, aminosalicylates' capability to induce remission is quite low, at least for oral formulations, with an estimated remission rate of 20% and a NNT = 10 [8]. Better performances are obtained when considering treatment for maintenance of remission (NNT = 6) [8,11]. Remarkably, several retrospective correlative studies show that aminosalicylate maintenance therapy decreases the risk of developing CCR [12-14]. The first compound belonging to this class of drugs and used for the treatment of IBD is sulfasalzine, which was formerly developed for the treatment of rheumatoid arthritis (RA), but was later shown to be active on intestinal inflammation [15]. Sulfasalazine in the colon is metabolized by bacterially-derived azo-reductase into sulfapyridine and 5-aminosalicylic acid (5-ASA), which is the actual biologically active and effective moiety. Sulfasalazine can be considered the first in a long line of various delayed-release formulations that allows 5-ASA, administered *per os*, to reach the colonic mucosa. A common concern with the classic oral 5-ASA preparation is the high burden of pills that patients are required to take daily to obtain the proper drug effect, which can easily lead to a significant loss of patient compliance [9,10]. In addition to oral formulations, 5-ASA can also be administered topically, in the form of suppositories, rectal gel/foam as well as enemas. Rectal formulations allow the treatment of distal disease quite effectively; however, as mentioned earlier, their use is often considered by patients to be intrusive and associated with socially embarrassing situations [16].

3.2 Corticosteroids

Glucocorticosteroids are the first choice for disease relapses not responding to 5-ASA or for moderate to severe flares. Their use is limited to the induction of remission because they have no role in maintenance therapy [17]. According to disease extent and severity, steroids can be administered topically, orally or parenterally. Topical administration is preferred for distal disease and has the advantage of reducing steroid absorption and, therefore, potential deleterious side effects, but at the same time, shares all the disadvantages of rectal-delivered formulations. The parenteral route is chosen for severe disease because of its efficacy and capability to act fast. Although corticosteroids are quite effective in achieving remission, their long-term use is burdened by the occurrence of various side effects, sometimes severe and irreversible [18]. This issue is further magnified by the presence of a considerable

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percentage of patients who can become steroid-dependent, relapsing as soon as steroid therapy is stopped or reduced in dosage [19]. To address this problem, low bio-availability steroids, such as budesonide and beclomethasone diproprionate, have been introduced in the treatment of IBD; this class of compounds includes corticosteroidal molecules that because of their high hepatic first-pass metabolism or low intestinal absorption, have little, if any, systemic side effects. As far as treatment efficacy is concerned, clinical trials show that beclomethasone diproprionate is comparable to 5-ASA for mild-left sided UC with regard to either oral or topical administration routes [20,21]. Importantly, although effective in improving clinical symptoms of disease relapse, corticosteroids seem to have a poor effect on prevention of recurrence of disease and on mucosal healing [22]; thus, they do not seem to be able to change the natural course of disease and the future need of further medical intervention.

3.3 Immunomodulators

Two different kinds of immunomodulators can be used in the treatment of UC, specifically, thiopurines and cyclosporine. Thiopurine analogues, including azathioprine and 6-mercaptopurine, are the most commonly prescribed immunomodulators for the treatment of UC. The mechanism(s) of action of these molecules seem to reside in the incorporation of 6-thioguanine into leukocyte DNA, instead of the normal nucleic acid bases, thus, interfering with subsequent leukocyte-dependent inflammatory responses. The onset of their activity is very slow, obtaining a full therapeutic effect in up to 6 months from the beginning of therapy [23,24]. The clinical indication of thiopurines is in the maintenance of remission, particularly in patients requiring frequent courses of corticosteroids. Some placebo-controlled studies suggest the superiority of azathioprine over placebo in maintaining remission and sparing steroid usage [8,23-25]. Unfortunately, the use of thiopurines is complicated by several deleterious side effects, both dose-independent and dose-related, that may lead to drug discontinuation [23]. In addition, it has been suggested that long-term administration of thiopurine may correlate with an increased risk of developing lymphoma; however, this issue remains quite controversial and existing data are conflicting [26], despite a recent meta-analysis showing a fourfold increase of risk in IBD patients taking thiopurines in comparison to patients not treated with immunomodulators [27].

Cyclosporine (CSA) belongs to the family of calcineurin inhibitors and has the ability to downregulate IL-2 production as well as inhibit T-helper cell proliferation and activation. CSA has been used as a rescue therapy for severe refractory UC, obtaining good results with short-term therapy [28], but not for a long-term treatment [29]. Significant morbidity is associated with CSA administration, including renal and neurologic toxicity and hypertension [30].

3.4 Biologics

Biologic agents are drugs engineered to specifically target an immune or genetic mediator of a given disease. Biologic therapies are the best example of drugs whose design is primarily driven by basic research discoveries in disease pathogenesis. Until now, among this constantly expanding therapeutic class, the current market offers infliximab as the only option for the treatment of UC. Infliximab is a chimeric monoclonal anti-TNF-α antibody

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that, in the last decade, has definitively proven its efficacy in the treatment of CD. Recently, two large studies, namely the Active Ulcerative Colitis trial 1 and 2, clearly demonstrated infliximab effectiveness in UC patients who were refractory or intolerant to standard therapy [31]. Another recent study showed that infliximab is superior to placebo as a rescue therapy for moderate-severe and fulminant UC that is refractory to IV steroids [32]. The major concerns regarding anti-TNF treatment are related to several potential serious adverse events, such as opportunistic infections, including tuberculosis, as well as congestive heart failure in cardiopathic patients [33], therefore, requiring accurate patient screening for appropriate suitability for this treatment. Allergic reactions to infusion are also possible, as well as the loss of therapeutic activity; both these events seem to be related to the formation of antibodies to infliximab [31,34]. A remaining controversial issue is the increased risk of developing non-Hodgkin's lymphoma, as well as other malignancies, because no conclusive data are available at the present time [33].

3.5 Leukocytapheresis

The selective physical apheresis of immune cells involved in the inflammatory process that characterizes IBD is an alternative strategy proposed for the treatment of active UC. Its role in UC therapy, however, remains controversial. Japanese trials showed that leukocytapheresis is equal to steroid therapy in inducing remission, with much fewer side effects [35-37] and a European multi-center, open-label study suggested that this approach could be effective even in chronically active, steroid refractory UC, at least in the short term [38]. However, a recent large, randomized, double-blind, sham-controlled trial, including patients from the US, Europe and Japan, showed no significant differences in clinical outcome between the apheresis- and sham-treatment groups [39].

4. Current research goals

Current research goals in the development of novel drugs for UC are:

- To better understand the pathophysiology of disease to discover new selective therapeutic targets, particularly for inflammatory mediators and adhesion molecules
- To improve the efficacy of existing therapeutics, while simultaneously reducing their associated side effects and
- To develop new formulations capable of delivering high concentrations of active compound in the colon, particularly targeting the distal tract, with the overall objective to: i) achieve increased effectiveness of the drug; ii) limit deleterious side effects related to systemic absorption; and iii) avoid rectal administration and daily pill burden to improve patient compliance.

5. Scientific rationale

The pathophysiology of IBD is quite complex, involving the coexistence of at least three different components: the immune system, epithelial barrier function and the intestinal flora. Physiologically, each of these components interplays with the others, creating a delicate balance between inflammation and immune tolerance, as well as absorption of essential nutrients and defense against harmful exogenous molecules. The desired end result is to

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maintain gut mucosal homeostasis. In the course of IBD, this balance is upset and results in a chronic, relapsing inflammation.

The host immune system represents a main effector of the inflammatory response in IBD; therefore, it has been the main target of classic therapies for the treatment of IBD. Moreover, the existing biologic treatments are commonly aimed to block different inflammatory molecules produced by the immune cells. The development of new biologics includes strategies to both reduce their immunogenicity and, therefore, the incidence of allergic reactions and loss of response, as well as to discover novel targets, and to block alternative immune pathways important in IBD pathogenesis. In addition, an increasing body of evidence shows that intestinal barrier function, exerted through the production of mucus, the maintenance of epithelial barrier integrity and the initiation of epithelial innate immune responses are pivotal in maintaining gut inflammatory homeostasis [40]. In fact, it has been shown that IBD patients often display a primary, intrinsic increase in intestinal permeability and a leaky epithelial layer [41] that may initiate disease. Indeed, drugs that have the ability to improve intestinal epithelial barrier function may represent a potential target for future IBD therapy. Finally, the intestinal flora has been shown to modulate gut mucosal immune function, playing a major role in the development of IBD. In fact, one type of innate countermeasure the host has evolutionarily developed is the production of antimicrobial peptides called defensins, which can regulate the intestinal microbiota composition and has been shown to be dysregulated in the setting of UC [42,43]. The importance of the luminal flora in IBD is even more evident considering mounting evidence suggesting a role of sulfate-reducing bacteria and hydrogen sulfide, their primary metabolic product, in the pathogenesis of UC and idiopathic pouchitis (as reviewed by Coffey *et al*. [44]); a further confirmation to this hypothesis is the ability of 5-ASA to regulate gut sulfide production through a bactericidal effect on sulfate reducing bacteria [45]. As such, the manipulation of the luminal flora represents a novel target of paramount importance for the treatment of IBD. Further knowledge of these two last components of the intestinal environment has the potential to lead to the development of new therapeutic approaches that may represent alternative or complementary treatments for IBD.

6. Competitive environment

6.1 New biologic drugs

6.1.1 Targeting cytokines—A common approach in the development of biologic therapy for the treatment of IBD is to target single inflammatory cytokines to neutralize their biological effects, thus, restoring mucosal immune homeostasis (see **Table 2**).

Adalimumab is a monoclonal antibody against TNF-α, administered subcutaneously, which is fully humanized; thus, it should not be recognized by the patient's immune system as a foreign protein, avoiding the formation of antibodies and reducing the risk of allergic reaction as well as the loss of activity. These features should benefit those patients who experienced a previous allergic reaction or lost of response to infliximab. Adalimumab has already shown efficacy in CD patients, either naive or refractory to anti-TNF therapy [46]. A small French, open-label 4-week study evaluated the clinical responses to adalimumab in 10 UC patients who had lost response or became intolerant to infliximab [47]. At the end of the

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study, 3 out of 10 patients achieved remission, defined as a CAI score < 4, with one patient showing clinical improvement. However, six patients did not improve their clinical course and among these, two underwent colectomy. None of the patients with severe disease activity achieved remission [47]. The same group reported their single center long-term experience with adalimumab in the treatment of this particular subset of patients. Thirteen patients received adalimumab loading injections and then received the drug every 4 weeks, with a total follow-up of 42 weeks. A total of 8 out of 13 patients stopped the study drug: 1 because of intolerance, 7 because of lack of efficacy; among these 7, 6 underwent colectomy [48]. Similar results for infliximab refractory UC were described in a recent Australian open-label study [49]. Taken together, these data suggest a small advantage of adalimumab treatment in patients who failed infliximab treatment; however, large randomized placebo-controlled trials are warranted to evaluate adalimumab in the general setting of UC.

Golimumab is another anti-TNF-α antibody that is currently under clinical evaluation. It is a fully humanized antibody, generated and affinity-matured in an *in vivo* system to obtain high affinity and specificity for human TNF-α. Golimumab can be administered by both subcutaneous injection and intravenous infusion. Results of clinical studies on RA patients who were non-responders to methotrexate therapy are promising [50], and a Phase III trial is currently in progress for the treatment of UC.

IL-2 is a cytokine produced by activated T cells that, by itself, stimulates T-cell activation and proliferation. Basiliximab, which is a chimeric antibody against the IL-2 receptor-α, was used in two different uncontrolled, open-label trials on a small number of UC patients with moderate to severe disease, and who were steroid refractory UC. In these two trials, remission was achieved by most treated patients [51,52]. Large placebo-controlled studies are needed to evaluate the feasibility and efficacy of the anti-IL-2 receptor α strategy.

TGF-β1 is a molecule produced by regulatory T cells and has the ability to exert an inhibitory function on immune cell activation. In IBD, the imbalance between pro-inflammatory and anti-inflammatory cytokines is characterized by defective TGF-β1 signaling, secondary to high levels of SMAD7, which is a natural antagonist of TGF-β1 [53]. The oral administration of an antisense oligonucleotide capable of binding SMAD7 mRNA, thereby inhibiting its translation into protein, has been tested on murine models of colitis. The study showed the effectiveness of this compound in ameliorating experimental colitis [54]; thus, a pilot study on human UC using SMAD7 antisense oligonucleotide strategy is in the initial stages of development.

NF-κB is a transcription factor involved in several inflammatory pathways. An antisense oligonucleotide inhibitor of the NF-κB p65 subunit, which is critical for NF-κB activation, has recently been developed and is currently in clinical evaluation (Phase II trials), under the name of Kappaproct, as a topical treatment for UC. The topical route for a biological agent is new, and indeed interesting, blocking a pivotal molecule in inflammatory responses selectively in the gut. It should be considered, however, that NF-κB is critical in maintaining host innate immunity, especially in the epithelium [55], and animal models have shown that selective blockade of the NF-κB pathway in intestinal epithelial cells causes the

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development of gut inflammation [56]. Therefore, the inhibition of this nuclear factor, specifically in the intestinal mucosa, may result in a paradoxical increase of inflammation.

Theoretically, the modulation of the inflammatory response with biological therapy can be carried out also by the administration of recombinant anti-inflammatory cytokines. Actually, the systemic treatment with the anti-inflammatory cytokines, IL-10 and IL-11, failed to show significant efficacy in IBD; however, a new strategy to deliver high concentrations of 'good' cytokines to the site of inflammation has been developed: *Lactococcus lactis*, genetically engineered to synthesize high levels of IL-10, was orally administered to animal models of intestinal inflammation, resulting in amelioration of disease [57]. The same approach provided promising results in a Phase I trial in CD patients [58] and is now under evaluation for UC.

6.1.2 Targeting adhesion molecules—Adhesion molecules are pivotal in recruiting immune cells from circulating blood to the site of inflammation. Some adhesion molecules, such as $\alpha_4\beta_7$ integrin or mucosal addressin cell adhesion molecule-1, are quite specific for the intestinal homing of leukocytes. As such, they are, at least theoretically, very good targets for site-directed biologic therapies. Natalizumab was the first anti-integrin antibody to be developed and it is directed towards the α_4 subunit [59]. This drug is currently available in the US and European market for the treatment of demyelinating disorders, such as multiple sclerosis. However, it has also been shown to be effective in CD [60], while data regarding its efficacy in UC are still scarce. In fact, only one open-label pilot study conducted on UC patients is available. In this study, 10 patients were treated with a single injection of natalizumab; none of them experienced adverse effects, and at 2 weeks from the injection, 5 presented with a good clinical response, which was lost, however, by 4 of them, at week 4 [61]. However, although natalizumab has been approved in the US for CD patients who are refractory to other therapies, in Europe it is not available for this purpose due to the report of serious, although rare, adverse events. In fact, during clinical trials and in the post marketing surveillance of natalizumab, a few cases of progressive multifocal leukoencephalopathy were reported [62], raising great concerns over the safety of natalizumab use.

Vedolizumab, another anti-integrin antibody, has been developed and tested on UC patients. This antibody selectively blocks the $\alpha_4\beta_7$ integrin, a dimer that is specific for intestinal homing. A multi-center, double-blind, placebo-controlled trial on 181 active UC patients showed clinical response, defined as a 3 point improvement in UC clinical score, in 59% of treated patients and in 33% of patients receiving placebo, and a remission rate equal to 32% in the drug group, and to 14% in the placebo group. Moreover, a large number of patients in the treatment group achieved endoscopic remission in comparison to the placebo group. Adverse events occurred at the same rate in both groups; however, it should be considered that three patients in the vedolizumab group experienced severe infectious diseases and one had an allergic reaction to the drug characterized by hives and angioedema [63]. Therefore, further data are needed to assess the safety of this biologic agent. Theoretically, it could be hypothesized that vedolizumab has less side effects than natalizumab, given the more specific localization of its target; in fact, natalizumab can block both $\alpha_4\beta_7$ and $\alpha_4\beta_1$ integrins, the latter being expressed in most of the tissues, while vedolizumab binds $\alpha_4\beta_7$

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only, which is restricted to expression only in the gut mucosa. However, this hypothesis must be proven in a controlled, clinical setting. Thus, more information and studies are needed to further understand the true therapeutic value of vedolizumab.

Alicaforsen is an antisense oligonucleotide against intracellular adhesion molecule-1 mRNA. Although the parenteral administration of this compound was not beneficial in the treatment of active CD [64], topical administration in UC and pouchitis seemed to be effective in a dose-dependent fashion, in a placebo-controlled study [65].

6.1.3 Targeting immune cell surface molecules—Immune cells present cell surface molecules that are pivotal for their function during the activation of the inflammatory cascade. Targeting these molecules with monoclonal antibodies may represent a novel strategy to downregulate the inflammatory response in IBD. Visilizumab is a monoclonal antibody that selectively binds to the CD3 receptor on activated T cells, without affecting resting T cells. The binding of the CD3 receptor by visilizumab leads to subsequent apoptosis of the targeted T cells. It has been shown that in IBD patients, this drug induces apoptosis in $CD4^+$ lamina propria T cells, but not in peripheral blood T cells, through the activation of caspase 3 and 8, suggesting a specific and targeted effect in the gut [66]. In a Phase I open-label study, visilizumab was administered to patients affected by severe UC, who had not responded to intravenous corticosteroids [67]. At day 30, 84% of the patients had a clinical response (defined as a Modified Truelove and Witts Severity Index score < 10 with a minimum decrease of 3 points), 41% achieved clinical remission, defined as an index score < 4, and 45% obtained endoscopic remission, defined as a Mayo endoscopic subscore of 0 or 1. After 1 year, 45% of the treated patients did not require salvage therapy or colectomy. No significant infectious diseases were reported. During the treatment period, the vast majority of patients experienced mild to moderate symptoms of the cytokine releasing syndrome [67], which is characterized by high fever, hypotension and flu-like symptoms, and is caused by the sudden, massive activation of T cells following CD3 binding, and before the apoptotic process has begun. However, despite the promising results obtained during this trial, in a recent (larger) controlled Phase III study, the efficacy of visilizumab in the management of intravenous steroid refractory UC was found to be no different from placebo (response and remission rates at day 45 were 55 and 8%, respectively, with visilizumab, and 47 and 9% with placebo). In addition, treatment was associated with an increased rate of infections, as well as cardiac and vascular adverse events [68]. Thus, further data are warranted to clarify the conflicting outcomes of Phase I and III trials.

Abatacept is a biologic agent currently in the market for RA. It is a fusion protein composed of the extracellular domain of cytotoxic T-lymphocyte antigen-4 with the hinge, CH2 and CH3 domains of an IgG1 [69]. Cytotoxic T-lymphocyte antigen-4 is a molecule that naturally binds B.7, a surface antigen expressed by antigen presenting cells (APCs) that is a pivotal co-stimulatory molecule in the interaction between APCs and T cells. The blockade of B.7 with abatacept prevents full activation of T cells during antigen presentation by APCs [69]. At the present time, no data are available regarding the therapeutic role of this drug in IBD. However, Phase III, multicenter, randomized, placebo-controlled studies are currently continuing to assess abatacept safety and efficacy in the treatment of severe, active UC and

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CD that are refractory to conventional therapies. Data available thus far regarding the safety profile in RA patients, however, are promising, with no differences in the incidence of either infection or neoplasm between treated and untreated patients [70,71].

6.2 Alternative agonists of PPAR-γ

Recently, it has been shown that 5-ASA exerts at least part of its anti-inflammatory effects through the binding of PPAR-γ, a nuclear receptor highly expressed in the colon, particularly in epithelial cells [72], and to a lesser extent in cells of the monocyte/macrophage lineage [73,74]. This molecule participates in the regulation of insulin metabolism [75], cell proliferation and in the downstream signaling of innate immune pathways [76,77]. Interestingly, thiazolidinediones, drugs widely used for the treatment of insulin-resistance and type 2 diabetes, are ligands to PPAR-γ. As such, rosiglitazone, a PPAR-γ agonist, was administered to rodent models of colitis and was successful in amelioration of disease [78,79]. Rosiglitazone has also been tested in patients with UC in a multi-center, randomized, double-blind, placebo-controlled clinical trial, which included 105 UC patients with a mild to moderate disease activity [80]. At week 12 of the treatment protocol, clinical response (defined as a 2 point reduction in the Mayo Disease Activity Index (DAI)), was obtained in 44% of rosiglitazone-treated patients and in 23% of the placebo group. However, endoscopic remission, measured as a secondary end point, was achieved in a low percentage of patients in both groups [80]. Yet another study compared the efficacy of combination therapy with rosiglitazone and 5-ASA to a monotherapy with 5-ASA alone [81] in mild to moderately active UC. In this study, clinical remission (defined as a DAI score ≤ 2 after a 4 week therapy) was considered the primary end point. Remission was achieved by 71% of patients treated with the combination regimen, and by 57% in the 5-ASA only group [81]. Despite the need for more data assessment, the therapeutic value of rosiglitazone is promising, particularly if considered as an alternative or supplemental drug (i.e., in addition to 5-ASA), before moving forward to the next step of the ‘therapeutic pyramid’, which would probably be use of steroids. It is possible, however, that patients who do not respond to 5-ASA will not respond to thiazolidinedione molecules because both rosiglitazone and 5-ASA act through the binding of the same therapeutic target. In addition, a recent meta-analysis of studies conducted on diabetic patients pointed out an increased risk for cardiovascular events in subjects treated with rosiglitazone [82]. In fact, this increased risk would obviously limit the use of rosiglitazone in clinical practice.

6.3 Enhancer of epithelial barrier function

6.3.1 Phosphatidylcholine—Phosphatidylcholine is a major component of intestinal mucus that covers and protects epithelial cells, and whose production is generally decreased in IBD patients [83]. Based on this rationale, a slow releasing formula of phosphatidylcholine has been recently tested for its efficacy in UC. A Phase IIA, randomized and controlled trial was performed on 60 UC patients, showing that phosphatidylcholine treatment ameliorates inflammatory activity [84]; in fact, 53% of patients treated with this compound achieved clinical remission, which was obtained in 10% of cases in the placebo group. An improvement of ≥ 50% of the DAI score was seen in 90% of treated patients and in 10% of the placebo group [84]. Similarly, another placebo-controlled study was performed on steroid refractory UC. In this study, 80% of the

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phosphatidylcholine-treated group was able to discontinue steroids without disease exacerbation, while only 10% of the placebo group obtained similar results [85]. Further development of this product for use in UC treatment is moving forward as a new formulation containing phosphatidylcholine and 5-ASA is currently under evaluation in a Phase III clinical trial.

6.3.2 EGF—Intestinal barrier function is maintained also by the integrity of the epithelial cell layer itself. Growth factors that are able to enhance epithelial repair and restitution, therefore, may serve as a potential therapeutic agent for the treatment of UC. Indeed, EGF was recently identified as a possible compound to be administered to UC patients in a small controlled trial [86]. A total of 24 patients affected with mild to moderate left-sided UC were randomized to receive enemas containing EGF, or an inert carrier, for 2 weeks, while continuing oral mesalamine at a fixed dose. At the end of the study, 83% of the patients treated with EGF enemas were in remission compared to 8% in the placebo group. Quite interestingly, the treatment greatly improved both the endoscopic and histologic scores, and the positive effects were maintained at follow-up visits at 4 and 12 weeks from the beginning of treatment [86]. Thus, EGF treatment not only potentiated 5-ASA's therapeutic effect, but also improved the endoscopic healing rate. However, despite the promising potential of this molecule in UC therapy, critical questions still remain regarding its safety, particularly given EGF's potent mitogenic effects.

6.4 Changing the intestinal microenvironment

6.4.1 Probiotics—Probiotics, given their capability to modulate mucosal defenses through toll-like receptor and cytokine regulation as well as antimicrobial peptide-specific induction [87-89], have been investigated for their potential therapeutic effect in UC. The efficacy of administering *Escherichia coli* Nissle 1917 (EcN) to UC patients was compared to 5-ASA in three double-blind double-dummy studies [90-92]. In two of the aforementioned studies, EcN was equivalent to 5-ASA in maintaining remission for 3 and 12 months, respectively [90,91]. The third study assessed EcN efficacy in achieving remission in active UC patients and maintaining quiescence for 12 months. Similar response rates, albeit low, were observed in the two groups with remission obtained in 68% of the probiotic group and in 75% of the 5-ASA group; relapse occurred in 67% of the EcN treated patients and in 73% of the mesalazine group [92]. Interestingly, a recent open-label study on pediatric UC obtained a lower relapse rate after 1 year of treatment, both in the EcN (25% relapse rate) and in the 5-ASA (30% relapse rate) groups.

VSL #3 is another probiotic preparation that contains a high number of colony forming units of eight different bacterial species (one streptococcus, three bifidobacteria and four lactobacilli). The results of two open-label studies testing the use of VSL #3 in adult UC patients are available so far [93,94]. The first evaluated the efficacy of VSL #3 in inducing remission in patients with mild to moderate disease who failed previous treatment with 5-ASA. After 6 weeks of treatment, remission was achieved in 53% of patients, with a further 24% who had a therapeutic response, defined as a drop in the UCDAI score equal to or greater than 3 points [93]. In a second study, patients who were allergic or intolerant to 5-ASA received a maintenance treatment of VSL #3. After 1 year on the study protocol, 75%

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of patients were still in remission [94]. In addition, an open-label pilot study on a UC pediatric population showed a remission rate of 56% in children affected by mild to moderate disease when treated with VSL #3 [95]. Finally, in a more recent randomized placebo-controlled trial on pediatric patients, remission was achieved in 93% of patients treated with VSL #3 in combination with conventional IBD therapy (i.e., steroids and 5-ASA), compared to 36% in the placebo plus conventional therapy-treated group. The relapse rates after 1 year were 21 and 73% in the two aforementioned groups, respectively [96].

Other probiotic preparations have been tested in UC, such as *Saccharomyces boulardii* or fermented milk containing *Bifidobacterium breve* and *bifidum*, as well as *Lactobacillus acidophilus*, mostly in small trials, with notable success [97,98]. Taken together, the efficacy of probiotics in the treatment of UC seems to be overall positive in mild to moderate disease, particularly if administered together with standard therapies, although patient pill burden is increased and therefore, patient compliance may be an issue [99]. However, the lack of known adverse effects is a significant advantage to be considered with probiotic use. At present, it is unknown whether probiotics may play a role in the treatment of severe disease or simply used as an alternative to other conventional therapies for the treatment of UC.

6.4.2 Helminths—Not only bacteria can modulate immune activation in the intestinal mucosa: helminths can also interact with host immune cells and participate in the overall immune regulation of the gut mucosa. In fact, helminth exposure inversely correlates with the development of several immune-mediated diseases, such as asthma, multiple sclerosis, autoimmune diabetes, as well as IBD [100]. Indeed, how these parasites exert this protective effect is still largely unknown. Helminth administration was reported to significantly decrease disease severity and overall colonic inflammation in experimental colitis. After initial success in a clinical trial to treat CD patients [101], *Trichiuris suis* ova were administered to active UC patients in a double-blind, randomized placebo-controlled study [102]. The results of this study showed remission rate at week 12 in 43% of patients receiving parasite ova and only 16.7% in the placebo group; importantly, no adverse events were reported [102]. However, although considering the lack of apparent adverse effects and the non-pathogenicity in humans for this pinworm, safety still needs to be considered with *T. suis* ova administration in the treatment of UC.

6.5 Novel formulations with selective delivery features

A significant advance in the technology of colonic drug delivery has been recently developed using multimatrix (MMX) strategies, which consists of lipophilic and hydrophilic excipients enclosed within a gastro-resistant, pH-dependent coating [103,104]. This novel, extended release tablet has been recently patented, wherein the embedded drug is delayed in its release, due to the gastro-resistant coating, until the tablet is exposed to a pH of 7 or higher, which is normally reached in the terminal ileum. The tablet core, consisting of hydrophilic excipients (thought to drive the tablet to swell into a viscous gel mass, slowing the release of the drug) and lipophilic excipients (thought to slow the penetration of aqueous fluids into the tablet core), allows prolonged exposure of the embedded drug to the colonic mucosal surface. This approach has been used to deliver several drugs with a more homogeneous and progressive release within the colonic region compared to the existing

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delivery systems. The *in vivo* release profile of such new formulations was recently assessed by γ-scintigraphy, which allows the evaluation of plasma and urine pharmacokinetics of the ingested formulation by correlating scintigraphic distribution patterns of the drug within the gastrointestinal tract. In this manner, the rate and extent of absorption in a defined region of the gastrointestinal tract can be assessed. Several molecules have been incorporated into the MMX that represent possible therapeutic agents for several colonic diseases, including UC. The molecules whose use is potentially intended for UC are at different stages of development. For example, a MMX-mesalazine formulation has been recently made commercially available in the US and in most European countries. This drug has been tested in several trials on both active and quiescent forms of UC [105-108]. Two major Phase III placebo-controlled trials reported the efficacy of this new approach in mild to moderate active UC. In the first one, two different doses of MMX-mesalazine (2.4 and 4.8 g/day) were shown to be more effective than placebo in inducing clinical and endoscopic remission after 8 weeks of treatment (remission rate of 40.5, 41.2 and 22.1%, respectively). In the same trial, a group of patients was treated with a classic 5-ASA formulation (Asacol; Procter and Gamble Pharmaceuticals Ltd; Egham, Surrey, UK; Cincinnati, OH, USA), and obtained a remission rate not statistically different from placebo (32.6%) [106]. In the second trial, patients were randomized into three different groups, taking MMX-mesalazine 2.4 g twice a day, 4.8 g once a day or placebo, respectively. Again, remission rates at 8 weeks were superior in the treatment groups than in placebo (34, 29 and 13%, respectively) [107]. Therefore, the overall data emerging from these studies suggest that MMX-mesalazine is superior to placebo, and frequently to the parent drug, in inducing clinical and endoscopic remission in mildly to moderately active UC. Indeed, in patients with left-sided UC, oral MMX-mesalazine at a dose of 3.6 g/day was equivalent to 4 g/day of mesalamine enemas in the induction of disease remission, with an obvious improvement in patient compliance [105]. Patient compliance is thought to be a major issue not only when topical treatment is needed, but also when sustained oral maintenance therapy is warranted, which is mandatory in a chronic disease, such as UC. Using this strategy, high doses of mesalazine, incorporated in a single MMX capsule (1.2 g), can be delivered over time, which is considered a significant advancement compared to most of the currently available preparations. In addition, a recent multi-center study [108] showed that MMX-mesalazine (2.4 g/day), administered as a single or divided dose, was safe and effective as maintenance treatment and that high clinical and endoscopic remission rates can be achieved also with once-daily dosing. Thus, most of these studies suggest that, when using MMX-mesalazine, therapeutic efficacy can be reached by means of single, high-dose administrations of the drug.

Another molecule that has been tested with the MMX formulation, with probable application to the treatment of UC, is budesonide. Most of the current preparations of this drug are known to release the drug at the terminal ileum, suggesting a major site of action in the terminal ileum-right colon. A recent report addressing the release and pharmacokinetics of MMX-budesonide has been published [104], and a multi-center trial has been performed comparing budesonide-MMX (dosed at 9 mg daily) to placebo in the short term (4 weeks) treatment of 36 active, left-sided UC cases, followed by a further 4 week treatment period of all patients with the drug. This study, however, has not been published with complete details at present; yet, initial findings show a significant therapeutic effect of MMX-budesonide and

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a good safety profile of the drug [109]. Currently, a large, international, randomized study comparing MMX-budesonide (9 and 6 mg daily) with conventional release budesonide as well as with placebo is continuing with a planned enrolment of > 800 patients in the four arms of the study. A subsequent follow-up study of MMX-budesonide in maintenance treatment lasting for 12 months is also in the initial stages at this time. Budesonide has also been embedded into TARGIT, another type of novel delivery system. TARGIT technology is based on a combination of polymer coatings and starch capsules that has the ability to target the release of drugs in the terminal ileum and colon [110]. At present, a clinical Phase II trial on budesonide TARGIT is currently active.

Because heparins have been suggested as a possible therapeutic agent in UC, probably due to their documented anti-inflammatory activity [111], a preliminary, dose finding, open trial has been recently performed using a low molecular weight heparin embedded in the MMX matrix. On the basis of experimental data obtained in rats, the heparin chosen to be embedded in the MMX formulation was parnaparin [112], which is a low molecular weight heparin commercially available for the subcutaneous treatment of thrombosis. The number of patients enrolled in the human study is small and, therefore, it is difficult to evaluate any therapeutic efficacy of this molecule; however, the preliminary findings seem to support the safety of MMX-parnaparin oral treatment in UC [113]. As a result, a large, international, randomized, placebo-controlled, study has been performed, the results of which have not yet been published.

Another novel drug delivery system is based on the use of red blood cells as carriers and bioreactors. The rationale is based on the possibility of temporarily opening the membrane pores, measuring 200 – 500 Å, of red blood cells through which the products to be encapsulated (conventional drugs, peptides, proteins, nucleic acids, dyes, nanoparticles, etc.) can be subsequently incorporated into the cell [114]. These pores are then sealed and the drug excess is washed away. Once administered back to the donor, these erythrocytes circulate normally, and maintain their property of oxygen transport, with normal morphology as well as biochemical and rheological features [115]. The first clinical application of this technology has been developed by encapsulating the corticosteroid analogue, dexamethasone sodium phosphate, which can be easily loaded into erythrocytes and where, because of the phosphate group hydrophilicity, the drug can be retained until slow dephosphorylation by resident red cell enzymes to its active dexamethasone form. Dexamethasone is diffusible through the red cell membrane and is subsequently released into the circulation. The significantly slow dephosphorylation rate suggests that the cells can perform as a slow-releasing dexamethasone system to achieve the lowest, but most effective, maintenance dose. Three main applications have been explored thus far, such as cystic fibrosis, chronic obstructive pulmonary disease, as well as IBD, with ~ 250 patients treated and 2200 treatments administered. In fact, following encouraging results obtained in a small pilot study on a small group of patients with CD and UC [116], a randomized-controlled study was performed. In this study, 40 patients with mild to moderate UC, refractory to mesalamine, were randomly assigned to two infusions of erythrocyte-encapsulated dexamethasone 14 days apart, oral prednisolone (0.5 mg/kg for 14 days followed by a 6 mg/ weekly tapering) and sham infusions [117]. The results showed that infusions with erythrocyte-encapsulated dexamethasone were equally effective to conventional steroids

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with regard to clinical and endoscopic remission, but had no steroid-related adverse events compared to 8/10 patients treated with the prednisolone. Although the data using this application are still relatively preliminary, the delivery system seems to be promising, particularly for the treatment of steroid-dependent patients. The possibility of its use as a substitute for traditional steroids would be interesting to evaluate in the future.

6.6 Other new approaches to modify intestinal inflammation

Several new molecules with the ability to modify intestinal inflammation through different mechanisms are currently under clinical evaluation. Dersalazine, an interesting and novel 5-ASA formulation, combining one molecule of 5-ASA with UR12715, a potent anti-TNF-α molecule, is one of these compounds. In the colon, dersalazine is cleaved by commensal bacteria into the two active components, which are able to subsequently exert their respective effects on PPAR-γ and TNF-α directly within the colonic mucosa. The administration of this compound in a chemically-induced rodent model of colitis showed promising results [118]; thus, a Phase II trial on UC patients is currently underway.

CCR9 is a chemokine that is pivotal in the homing of T cells to the gut, and, therefore, represents a suitable target for IBD therapy. Traficet-EN is an antagonist of CCR9 and at the present time, Phase II/III clinical trials testing the safety and efficacy of this compound in CD, celiac disease and UC are continuing.

HE-3286 is a synthetic analogue of steroid hormones capable of regulating the NF-κB pathway, whose effectiveness in ameliorating the severity of rodent collagen-induced arthritis has already been documented [119]. Phase II trials are currently active for use of HE-3286 in UC, RA and diabetes mellitus. Similarly, HMPL-004 is a botanical extract that can be orally administered and has the capability to inhibit several cellular targets, resulting in the suppression of NF-κB and of several different cytokines, exerting an overall anti-inflammatory effect. This molecule is now in the process of clinical evaluation in Phase II trials for the treatment of IBD.

7. Potential development issues

UC does not affect patient life expectancy and UC patients very rarely experience life-threatening events secondary to the disease (i.e., fulminant colitis); therefore, the main feature of any novel therapy for the treatment of UC must be safety. For most of the drugs that are currently in development, the data regarding safety profiles are good, but for a few of them, clinical trials have highlighted potential safety issues that may prevent the use of the drug for conventional UC therapy. For example, natalizumab has not been approved in Europe for the treatment of CD, while in the US it is available for refractory CD only, due to the presumed increased risk of progressive multifocal leukoencephalopathy. Concerns were also raised for the long-term safety of all biologic agents because these powerful drugs can potently manipulate normal immune system functions. Further data regarding the relative risk of developing neoplasia in patients treated with biologics are warranted. Moreover, the development of emerging biologic agents will have to face an increasingly competitive market, with expensive molecules having similar medical indications and similar efficacy.

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8. Expert opinion and conclusion

As both basic and clinical research continues to further explain the precise etiology of UC and to develop a potential cure for this devastating disease, efforts in recent years have focused on several unmet needs for the medical management of UC patients. One of the most important of these needs is to develop drugs that have the ability to treat UC patients who are refractory to currently available therapies, thus, avoiding the need for surgery. In recent years, a significant advance in the understanding of key pathogenic mechanisms in UC pathogenesis has been made, and has led to the development of specific inhibitors targeting some of these pathogenic pathways. The development of anti-TNF compounds and its application to UC is a good example of this advance. Further knowledge in the next few years should undoubtedly facilitate the development of new therapeutically-active molecules. Indeed, a variety of novel, bioengineered therapies that target a range of inflammatory molecules are in currently in development. On the other hand, enhancement of protective host defense and epithelial barrier function should be an important aim of future therapeutic strategies. Although the efficacy and safety of new treatments require further evaluation in larger patient populations, they may potentially be added to the current armamentarium of UC therapies. A second important issue to be considered in the long-term management of UC is the ability of current drugs to effectively maintain disease remission and possibly perform a chemoprophylactic effect against the risk of colon cancer. Novel 5-ASA formulations, including high-dose tablets and micropellets, which require less frequent administration and have demonstrated efficacy in active mild to moderate colitis and in the maintenance of remission have recently been developed. The resulting new dosing regimens will probably improve patient compliance, which seems to be one of the major obstacles to the successful performance of long-term therapies. It is also possible that future genetic and immunologic studies will be able to characterize patient subgroups to identify specific phenotypes and stratify treatment protocols based on predicted disease behavior and therapeutic response. Therefore, in the future, clinicians may look towards more personalized therapeutic modalities rather than treating patients based simply on a global UC diagnosis.

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Table 1

Existing treatments.

Treatment	Main probable mechanism(s) of action	Available formulations	Indication	Side effects	Pros	Cons
Aminosalycilates	PPAR-γ agonism Inhibition of arachidonic acid metabolism Inhibition of lymphocytes proliferation	Oral and topical	Induction and maintenance of remission	Hypersensitivity reactions Interstitial nephritis Acute pancreatitis Blood disorders	Low incidence of side effects Availability of many different formulation for different disease localization	Not suitable for severe disease
Steroids	Inhibition of NF-κB activation	Oral, topical and parenteral	Induction of remission	Hyperglicemia Hypertension Osteoporosis Cataracts Glaucoma Psycosis Skin fragility Malar fat pad increase Visceral and truncal fat deposition Adrenal insufficiency Increased infection	Good efficacy Availability of many different formulation for different disease localization and severity	High rate of side effects Not suitable for maintenance treatment
Low bioavailability steroids	Inhibition of NF-κB activation	Oral and topical	Induction of remission	Theoretically the same as steroids	Low incidence of side effects Availability of different formulation for different disease localization	Not suitable for severe disease
Azathioprine 6-Mercaptpurine	Inhibition of leukocyte proliferation Induction of lymphocyte apoptosis	Oral	Maintenance of remission	Leukopenia Hepatitis Pancreatitis Hypersensitivity Increased risk of lymphoma (?)	Usually well tolerated	Delayed therapeutic effect Not suitable in a subset of patients because of intolerance/side effects
Cyclosporine	Inhibition of calcineurin	Oral and parenteral	Induction and maintenance of remission	Hypertension Nephropaty Potassium retention Gengival hyperplasia Increased infections	Fast therapeutic effect Suitable for induction, much less for maintenance of remission	High incidence of side effects
Infliximab	Circulating and membrane-bound TNF-α blockade Apoptosis of TNF-α producing cells	Parenteral	Induction of remission Maintenance of remission (?)	Allergic reactions Increased risk of serious infection Heart failure in cardiopathic patients	Good efficacy Fast therapeutic effect	Expensive Unknown long-term effects
Leukocytoapheresys	Physical removal of activated leukocytes Induction of immune tolerance	Not applicable	Induction of remission	Few and minor	Safe	Data not clear regarding efficacy

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Table 2

Competitive environment.

Compound	Company	Structure	Indication	Stage of development	Mechanism of action
Adalimumab	Manufactured: AstraZeneca; Licensed: Abbott and Eisai	Human IgG1 anti-TNF-α	Ulcerative colitis	Phase III clinical trial	TNF-α blockade
Golimumab	Manufactured: Johnson & Johnson; Licensed: Schering-Plough and Mitsubishi Tanabe Pharma	Human IgG 1 anti-TNF-α	Ulcerative colitis	Phase III clinical trial	TNF-α blockade
Basiliximab	Manufactured: Novartis; Licensed: Cerimon	Chimeric IgG1 anti IL-2R	Ulcerative colitis	Phase II clinical trial	Blockade of IL-2 signaling
Kappaproct	Manufactured: InDex Pharmaceuticals	Antisense nucleotide for p65	Ulcerative colitis	Phase II clinical trial	Inhibition of NF-κB activation
IL-10, ActoGeniX	Manufactured: ActoGeniX	Genetically engineered *Lactococcus lactis* producing recombinant IL-10	Ulcerative colitis	Phase II clinical trial	Inhibition of IFN-γ, IL-2 and TNF-α production
Natalizumab	Manufactured: Elan Licensed: Biogen Idec	Humanized IgG4 anti-α_4 integrin	None for ulcerative colitis; refractory CD in US	Little clinical data for Ulcerative colitis; on the market in US for refractory CD	Blockade of leukocyte trafficking
Vedolizumab	Manufactured: Takeda	Humanized IgG4 anti-$\alpha_4\beta_7$ integrin	Ulcerative colitis	Phase III clinical trial	Blockade of leukocyte trafficking
Alicaforsen	Manufactured: Isis Pharmaceuticals; Licensed: Atlantic Healthcare and Orphan Australia	Antisense nucleotide for ICAM-1	Ulcerative colitis	Phase II clinical trial	Blockade of leukocyte trafficking
Visilizumab	Manufactured: PDL BioPharma	Humanized IgG2 anti-CD3	Ulcerative colitis	Phase III clinical trial	T-lymphocyte apoptosys
Abatacept	Manufactured: Bristol-Myers Squibb; Licensed: GTC Biotherapeutics	Fully human CTLA-4-immunoglobulin fusion protein	Ulcerative colitis	Phase III clinical trial	T-lymphocyte apoptosys
Rosiglitazone maleate	Manufactured: GlaxoSmithKline	5-[4-(2-[methyl(pyridin-2-yl) amino]ethoxy)benzyl]thiazolidine-2, 4-dione	Ulcerative colitis	Phase III clinical trial	PPAR-γ agonism
EGF	Manufactured: Heber Biotec	Recombinant human EGF	None	One clinical study	Epithelial barrier restoring
Phosphatidylcholine + 5-ASA	Manufactured: PLx Pharma	5-aminosalycilic acid [5-amino-2-hydroxybenzoic acid] associated with phosphatidylcholine	Ulcerative colitis	Preclinical studies	PPAR-γ agonism and intestinal barrier restoring
Mesalazine MMX	Manufactured: Giuliani; Licensed: Cosmo Pharmaceuticals, Shire, Takeda and Mochida	5-aminosalycilic acid [5-amino-2-hydroxybenzoic acid] embedded into the MMX	Ulcerative colitis	Available on market in US, Canada, UK, Ireland and Germany	PPAR-γ agonism
Budenoside MMX	Manufactured:Cosmo Pharmaceuticals; Licensed: Ferring and Santarus	Budesonide [16,17-(butylidenebis(oxy))-11, 21-dihydroxy-, (11-β,16-α)-pregna-1,	Ulcerative colitis	Phase III clinical trial	Inhibition of NF-κB activation

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Compound	Company	Structure	Indication	Stage of development	Mechanism of action
		4-diene-3,20-dione] embedded into the MMX			
Budesonide TARGIT	Manufactured: Archimedes; Licensed: InvaMed Pharma and Pharmalink	Budesonide [16,17-(butylidenebis(oxy))-11, 21-dihydroxy-, (11-β,16-α)-pregna-1, 4-diene-3,20-dione] embedded into the TARGIT system	Ulcerative colitis	Phase II clinical trial	Inhibition of NF-κB activation
Parnaparin MMX	Manufactured: Cosmo Pharmaceuticals	Low molecular weight heparin embedded into the MMX	Ulcerative colitis	Phase II clinical trial	Inhibition of INF-γ production
Dersalazine	Manufactured: Palau Pharma	5-aminosalycilic acid [5-amino-2-hydroxybenzoic acid] azo-bound to UR12715 [1- ((1- (3- (4- aminophenyl)-3- phenylpropenoyl)- 4- piperidyl)methyl)-1H- 2- methylimidazo(4,5- c)pyridine]	Ulcerative colitis	Phase II clinical trial	PPAR-γ agonism and inhibition of TNF-α production
Taficet-EN	Manufactured: ChemoCentryx	Synthetic small molecule	Ulcerative colitis	Phase II clinical trial	Antagonism of CCR9 chemokine
HE-3286	Manufactured: Hollis-Eden Pharmaceuticals	Synthetic 17-ethynyl derivative of dehydroepiandrosterone	Ulcerative colitis	Phase II clinical trial	Inhibition of NF-κB activation
HMPL-004	Manufactured: Hutchison China MediTech	Botanic extract	Ulcerative colitis	Phase II clinical trial	Inhibition of NF-κB activation and suppression of several pro-inflammatory cytokines

5-ASA: 5-Aminosalicylic acid; CD: Crohn's disease; CTLA-4: Cytotoxic T-lymphocyte antigen-4; ICAM-1: Intracellular adhesion molecule-1; MMX: Multimatrix system.