Comprehensive overview of novel chemical drugs for ulcerative colitis: focusing on phase 3 and beyond

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Comprehensive overview of novel chemical drugs for ulcerative colitis: focusing on phase 3 and beyond

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Abstract

Introduction. Despite the growing number of highly efficacious biologics and chemical drugs for Ulcerative Colitis (UC), steroid-free disease control is still difficult to achieve in subgroups of patients due to refractoriness, adverse events, primary or secondary failure. New treatments are therefore still required in order to optimize clinical management of patients with UC.

Areas covered. The efficacy and safety of both currently available and newly developed small molecules have been summarized. The PubMed database and clinicaltrials.gov were considered in order to search for phase 2b and 3 trials on new chemical drugs for UC. The study drugs reviewed included Janus Kinases (JAK) and sphingosine-1-phospate receptor (S1Pr) inhibitors, α4 integrin antagonist and micro-RNA-124 upregulators.

Expert Opinion. Rapidity of onset, low immunogenicity and safety are the main characteristics of small molecules currently available or under evaluation for treatment patients with UC. Among the currently available chemical drugs, the selective JAK and the S1Pr inhibitors are characterized by a good safety profile combined with the ability to induce clinical remission in UC. A relatively low frequency of endoscopic improvement and healing currently appears associated with their use, being higher in UC patients treated with S1Pr inhibitor Etrasimod. Overall, additional new safe and effective drugs are still required in order to optimize disease control in a larger majority of UC patients.

Keywords: JAK, S1Pr, α4 integrin, mi-RNA-124, Ulcerative Colitis, clinical trials, chemical drugs, small molecules.

Article highlights

- The key role of the mucosal immune response in the pathogenesis of UC has led in the last decades to the development of highly effective immunomodulatory drugs.
- Mucosal healing is associated with a better clinical outcome and it can be induced by immunomodulatory treatments, thus representing the current therapeutic target in UC.
- In the last years, orally administered small molecule drugs have been developed and introduced in the market.
- The first oral chemical drug approved for UC treatment was the pan JAK inhibitor Tofacitinib.
- Since the introduction of Tofacitinib, multiple mechanisms of action have been identified leading to the development of new drugs, apart from JAK-inhibition, such as sphingosine-1-phospate receptor (S1Pr) inhibition, α4 integrin antagonism and micro-RNA-124 upregulation.
- The safety combined with the ability to induce clinical remission are the most relevant characteristic of the newly proposed chemical drugs for UC.

1. Introduction

1.1. Background

Ulcerative Colitis (UC) is characterized by a chronic relapsing course associated with inflammatory lesions involving the rectum, possibly extending to proximal colonic segments in a continuous fashion [1,2]. The etiology of UC is currently undefined, while the pathogenesis appears related to an inappropriate immune response towards luminal antigens in genetically susceptible individuals [1,3-5].

Treatment strategies for UC are focused on the induction and maintenance of clinical and endoscopic remission [6]. Therapeutic targets in UC have been recently updated. Clinical response represents the first goal of treatment, followed by clinical remission and endoscopic response and remission [6]. The latter, defined as mucosal healing (MH), currently represents the main therapeutic target when managing patients with UC [1, 6-8]. The achievement of MH has indeed been recently associated with all the major outcomes for UC, including lower need of disease-related hospitalization, surgery and corticosteroids use [6,8].

More interestingly, histological remission has subsequently been suggested as a new promising therapeutic target, and this achievement may become one of the most relevant targets when managing patients with UC [9-10]. Histological healing has indeed been indicated as a non-formal target in the STRIDE II recommendations [6]. Persistent microscopic inflammation of UC colon has been associated with increased rates of clinical relapse, disease-related hospitalization, need of surgery and occurrence of colorectal cancer (CRC) [9, 11-13]. Since the study from Bryant et al. [9], growing evidence suggest that UC patients reaching histological healing carry a lower risk of corticosteroids use and hospitalization than those with MH only [10,14,15]. Nevertheless, whether the achievement of histological healing is associated with better outcomes than MH alone needs further investigations.

On the basis of these observations, some of the latest clinical trials using new treatments for UC include histological healing among secondary aims [16]. More recently, molecular remission is currently being investigated [17].

1.2 Current medical management

First-line therapy in mild to moderate UC is represented by the salicylates including 5-aminosalicylic acid (5-ASA) and sulfasalazine, administered either as suppositories, enemas, or by mouth [1,18,19]. Sulfasalazine is a molecule metabolized to 5-ASA in the colon. The efficacy of sulfasalazine is comparable to that of 5-ASA, although burdened by a higher frequency of mild adverse events (AEs) [1,18,19]. However, 5-ASA release in the colon determines a higher efficacy of sulfasalazine than 5-ASA compounds released in the small bowel or proximal colon [20].

Oral corticosteroids are needed in UC patients with mild to moderately active disease despite salicylates [1,18,19,21]. Oral corticosteroids with minimal systemic activity (due to high first-pass liver metabolism) such as budesonide-multimatrix and prolonged release beclomethasone dipropionate, may be effective in UC patients with mild active disease, failing salicylates.

Systemic corticosteroids are known to be effective for inducing remission in patients with moderate to severe UC [1,18,19]. The optimal dose of systemic corticosteroids is 0.8-1 mg/kg of methylprednisolone up to 60 mg overall, or the equivalent dose of oral corticosteroids [18,21]. In moderate-to-severe UC not requiring hospitalization, oral prednisolone doses of >40-60 mg/day were not reported to be useful, being doses >40 mg/day associated with a higher frequency of AEs [18,22]. Clinical response should be observed within 2 weeks, followed by steroids tapering in responsive patients [18,21]. In acute severe UC, optimal treatment initially includes high-dose intravenous (i.v.) corticosteroids (methylprednisolone 60 mg daily or hydrocortisone 100 mg every 6 hours), for maximum 3-7 days, followed by either anti-Tumor necrosis factor-α (TNFα) antibody Infliximab (5 mg/Kg i.v., see below), cyclosporine (2 mg/Kg iv with a target concentration of 150–250 ng/mL, followed in responders by oral cyclosporine 5 mg/day) or surgery [18,21,22].

Despite the proved efficacy of systemic and low-absorbable steroids for inducing clinical remission, these treatments are ineffective in maintaining remission. Therefore, at this purpose, treatment indication for this subgroup of UC patients includes thiopurines, biologics or both. Thiopurines include Azathioprine (2-2.5 mg/Kg) or 6-mercaptopurine (1-1.5 mg/Kg), showing efficacy in maintaining remission in patients with steroid-dependent moderate to severe UC [18,19].

Since 1995, biologic treatments aimed to modulate the gut mucosal immune response have been developed. The first biologic treatments approved for UC include TNF-antagonists, including Infliximab and Adalimumab [23-25]. These drugs showed a marked and worldwide proven efficacy in both moderate-to-severe UC, and in inducing and maintaining clinical and endoscopic remission in UC [23-25].

A gut-selective anti-α4β7 integrin antibody Vedolizumab was subsequently developed [26] followed by Ustekinumab, an antibody against the p40 subunit of interleukin (IL)-12/23 [27]. More recently, novel oral small molecules have been approved for treating UC, including Tofacitinib [28], Upadacitinib [29], Filgotinib [30] and Ozanimod [31]. All the above reported treatments showed efficacy in inducing and maintaining clinical and endoscopic remission in patients with moderate-to-severe UC. However, only Infliximab is approved for treating patients with acute severe UC not responsive to systemic corticosteroids and this treatment currently represents the most widely used biologic in UC [18,19].

1.3 Do we need novel drugs for Ulcerative Colitis?

Despite their proven efficacy, subgroups of patients show refractoriness to conventional first line treatments for UC. Therefore, immunomodulators, biologics and small molecules have been developed for proper management of these patients. However, primary or secondary failure, and intolerance or AEs may occur, although in a limited proportion of patients [18,19,32]. AEs, including severe AEs (SAEs) are more frequently observed when using TNF-antagonists or Tofacitinib [33-35]. New orally administered small molecules for treating UC are characterized by a high tolerance

and efficacy. Moreover, these treatments determine a reduced burden for hospitals, due to their oral route of administration. A low immunogenicity, observed in subgroups of patients treated with TNF antagonists also characterizes these treatments [35]. However, secondary failure, loss of response may also occur using these novel drugs and solid long-term real-world data on efficacy and safety of the small molecules for treating UC are still required. Overall, there still is up to one third of UC patients not achieving treatment optimization. Moreover, therapeutic ceiling when using current treatments for UC currently represents one of the major reasons for searching newer therapies. All these observations support the idea that new effective therapies targeting different inflammatory pathways in UC are currently required. This is also in relation to current treatment strategies aimed at preventing irreversible intestinal damage. At this purpose, second level treatments, including biologics or small molecules, are currently indicated for patients characterized by a severe clinical course of UC, in order to deeply control the disease [6]. The achievement of remission - defined as the combination of clinical and mucosal remission - and ultra-deep remission - which also includes histological remission - currently represents the most relevant therapeutic target in UC [6-8, 18,19]. This treatment goal is mostly observed when using biologics or small molecules, associated with better overall outcomes. Taking into account the reported evidence, further drug development represents a major issue in the management of patients with UC.

1.4 Methods

The PubMed database and clinicaltrials.gov were consulted using the following search terms: 'JAK,' 'JAK inhibitor,' 'Janus Kinases,' 'Tofacitinib,' 'Filgotinib,' 'Upadacitinib,' 'Ivarmacitinib,' 'SHR0302', 'Ritlecitinib', 'Brepocitinib', 'S1PR1, S1PR4 and S1PR5 modulators', 'AJM300', 'α_4 integrin' individually or in combination with 'IBD,' 'UC,' 'Ulcerative colitis,' 'inhibitors,' 'safety,' 'efficacy,' 'study,' 'trial'. The search was focused on full-text papers published in English and no publication date restrictions were imposed. Only findings from phase 2b (dose-finding) and

phase 3 (safety and efficacy) trials, including new orally administered drugs for UC were summarized in the present review.

In order to provide a comprehensive review regarding chemical drugs in UC, the efficacy and safety of currently available small molecules based on the same mechanism of action (Janus Kinases, JAK, inhibitors, Sphingosine-1-phospate receptor, S1Pr, inhibitors) are also initially summarized.

2. Chemical drugs for Ulcerative Colitis

2.1 Currently available chemical drugs for Ulcerative Colitis

In recent years, small molecules have been introduced for treating patients with UC. Advantage of these drugs include the oral administration, able to increase the compliance of patients. Moreover, these drugs are characterized by low immunogenicity, thus reducing both the risk of allergic reactions and the loss of response due to neutralizing antibodies.

Several mechanisms of action are recognized for these small molecules, characterized by their ability to modulate the mucosal immune response, thus interfering with mechanisms involved in the pathogenesis of Inflammatory Bowel Disease (IBD) [36,37]. Several cytokines playing a central role in the pathogenesis of immune-mediated and autoimmune diseases target different immunocompetent cells involved in inflammatory processes [36,37]. In IBD, the pathogenesis currently appears to be related to an inappropriate immune response towards luminal antigens sustained by the innate and adaptive immune system, thus determining higher levels of inflammatory mediators most of them mediated by JAKs [38]. The characteristics of the currently approved small molecules for UC treatment are reported in Table 1.

JAK-STAT signaling. JAKs are involved in cell growth, survival and differentiation of immunocompetent cells [38]. JAKs and signal transducers and activators of transcription (STAT) DNA-binding proteins mediate the signaling and downstream biological effects in response to cytokine receptor binding, including several effects involved in IBD pathology. [36,37]. The JAK-STAT pathway is used not only by cytokines, but also by other molecules, including growth factors

and hormones [36,37]. The subsequent gene regulation exerts several biological effects, including hematopoiesis, immunoregulation, tissue repair, apoptosis and adipogenesis. This pleiotropic function is warranted by four JAKs: JAK1, JAK2, JAK3, and tyrosine-protein kinase 2 (TYK2) and 7 STATs: STAT 1, STAT 2, STAT 3, STAT 4, STAT 5a, STAT 5b, and STAT 6, showing different expressions in different cells and tissues [36,37].

In sporadic autoimmune and autoinflammatory conditions, several disease-causing cytokines rely on JAK-STAT signaling to exert their pathogenic effect [37]. These observations have led to the development of JAK inhibitors for treating human diseases, including UC, showing the involvement of dysregulation of the host immune in their pathogenesis [38].

2.2 Current available JAK inhibitors for Ulcerative Colitis

Tofacitinib is the first small molecule approved for treating patients with UC, both in U.S. and in Europe. Tofacitinib is a pan-JAK inhibitor mostly targeting JAK1 and JAK3, associated with moderate activity against JAK2 and tyrosine-protein kinase 2 (TYK2) [28].

The efficacy of Tofacitinib in inducing clinical remission in moderate to severe refractory active UC patients was first assessed in 2 randomized, double-blind, placebo-controlled trials (OCTAVE 1-2) [28]. In these induction trials, clinical remission at week 8 was observed in a significantly higher proportion of UC patients treated with Tofacitinib versus placebo (OCTAVE 1 and 2: 18.5% vs 8,2%, p=0.007 and 16.6% vs 3.6%, p<0,001, respectively) [28]. A very rapid onset of efficacy of Tofacitinib was observed in treated patients, showing by day 3 a significant reduction of UC-related symptoms and particularly of rectal bleeding [28].

In the In the OCTAVE Sustain trial, a dose-dependent efficacy of Tofacitinib was observed [28]. At 52 weeks, clinical remission was observed in 34.3% of UC patients treated with 5 mg Tofacitinib vs 40.6% of those treated with 10 mg and 11.1% of patients on placebo (p<0.001 for both comparisons) [28].

Tofacitinib was also associated with the achievement of endoscopic remission (defined as Mayo endoscopic subscore 0-1) [28] in a high proportion of UC patients. At 52 weeks, MH was indeed observed in a significantly higher proportion of UC patients treated with 5 mg (37.4%) or 10 mg tofacitinib (45.7%) when compared to placebo (13.1%; p<0.001 for both) [28].

In the OCTAVE induction trials [28], the reported safety profile was satisfactory at both doses and several current meta-analyses supported a comparable safety of Tofacitinib and biologics [35]. However, initial findings mainly regarding rheumatoid arthritis (RA) patients receiving Tofacitinib raised concerns about the potential risk of venous thromboembolism (VTE) [33]. Available data currently suggest that patients treated with tofacitinib 10 mg b.i.d, over a long period show a higher risk of VTE patients *per se* [33,35]. Therefore, maintenance doses of 10 mg b.i.d. are currently not recommended in UC patients with known risk factors for VTE, unless no alternative treatment is available [18,19,35]. It seems worthwhile to note that patients with active UC are at higher risk of thrombotic events, not related to common risk factors for VTE or to treatments [39,40]. Tofacitinib use has also been associated with a higher risk of Herpes Zoster virus (HZV) infection even though mostly mild [28,35]. While for anti-TNFs tuberculosis (TB) risk is a relevant issue, in the OCTAVE trials no cases of TB have been reported [28]. Even though few cases of TB have been reported in RA, in UC this risk seems to be low and thus of concern only in endemic areas [34].” In a recent single center, double blind, placebo controlled randomized trial, patients with acute severe UC (ASUC) were randomized to either tofacitinib (10 mg thrice daily) or placebo for 7 days while on i.v. corticosteroids (hydrocortisone 100 mg q6h). The authors concluded that in 104 patients with ASUC, combined tofacitinib and corticosteroids improved treatment responsiveness (Tofacitinib vs placebo at day 7: 44/53 (83.01%) versus 30/51 (58.82%) (OR 3.42 [1.37-8.48], p=0.007). The need for rescue therapy by day 7 was also reduced using Tofacitinib (OR 0.27, 95% CI 0.09-0.78, p=0.01) [41]. In terms of safety, dural venous sinus thrombosis was observed in 1 patient and other treatment-related AEs were mild [41]. Despite encouraging results, this trial shows some methodological limitations.

Overall, further trials and real-world evidences are required in order to define the place of Tofacitinib in ASUC.

Selective JAK inhibitors. Filgotinib and Upadacitinib, two oral compounds preferentially inhibiting JAK1, have been recently approved for treating patients with of moderate to severe UC [29,30]. As for Tofacitinib, both drugs are administered by mouth, thus increasing the compliance of patients. Recently, clinical trials supported their efficacy in inducing and maintaining clinical remission in patients with UC [29,30]. As for Tofacitinib, a dose dependent effect has been reported for both Filgotinib and Upadacitinib [29,30]. Both treatments are characterized by satisfactory rates of endoscopic remission (defined as Mayo subscore 0-1)(13.4% and 15.6% for Filgotinib 100 mg and 200 mg, respectively, and 24% and 26% for Upadacitinib 15 mg and 30 mg, respectively) [29,30]. In terms of safety profile, the use of these 2 selective JAK inhibitors currently appears not associated with serious AEs [29,30,35]. Clinical trials including Filgotinib and Upadacitinib do not report a higher risk of VTE or HZV infection. The observed AEs were mild, particularly for Filgotinib whose safety profile appears to be particularly favorable, and included worsening of UC, nasopharyngitis and other mild infections [29,30].

2.3 Cancer, pregnancy, lipid and liver function tests abnormalities

Cancer risk. Among potential AEs related to the use of the currently approved small molecules for treating patients with UC, particular concern regards cancer risk. The short-term follow-up of patients included in clinical trials significantly reduce the relevance of current findings regarding the cancer risk associated with the use of small molecules in patients with UC. Nevertheless, in clinical trials using Tofacitinib in UC, 22 treated patients overall developed malignancy, including non-melanoma skin cancers (NMSC) in 11 patients. Among patients enrolled in clinical trials using Tofacitinib, history of NMSC (HO 9.09; p = 0.0001), anti-TNF failure (HR 3.32; p = 0.0363) and age (HR 2.03; p = 0.0004) were reported as independent risk factors for NMSC [42]. The risk of malignancies was comparable to that observed in patients receiving Tofacitinib with RA and

psoriasis, although being comparable to the risk observed in UC patients treated with other biologics [43]. However, in a trial comparing the safety of Tofacitinib and TNF inhibitors in patients with RA, the incidence of any cancer was reported to be higher in patients treated with Tofacitinib (at any dose) than with TNF inhibitors (122 [4.2%] vs 42 [2.9%], HR 1.48 [1.04–2.09]) [44]. In order to provide a more comprehensive view of the cancer risk using Tofacitinib, additional findings not limited to clinical trials and with longer follow-up data are required. The only systematic review and meta-analysis using JAK inhibitors for RA, psoriasis, ankylosing spondylitis and IBD, a comparable risk of developing either NMSC or any cancer excluding NMSC was reported [45], as stated by current ECCO guidelines [46].

When considering trials using Upadacitinib, any malignancy occurred in only 1 patient in the induction trial and in 2 patients in the maintenance phase (1 cancer type and 2 cancer type respectively) [29]. No malignancies were reported in the Filgotinib induction and maintenance trials [30]. Moreover, in long-term studies in RA patients, similar malignancy rates versus the overall population have been observed using Upadacitinib and Filgotinib [47]. Nevertheless, long-term real-world and safety registry data are required for proper assessment of cancer risk using selective JAK-1 inhibitors in patients with UC, including comparisons with UC patients treated with Tofacitinib or anti-TNF agents.

Pregnancy. The active metabolite of JAK inhibitors, as also other small molecules, can cross the placenta during the first trimester [48], thus raising concern about the safety of this treatment during pregnancy. Preclinical studies using Tofacitinib showed that exposure to doses much higher than the therapeutic dose can cause fetal malformations [49]. At therapeutic dose, no fetal deaths were reported. Embryotoxicity and teratogenicity at higher doses than those administered in humans were observed in animal models [50]. Current data regarding women exposed to JAK inhibitors during pregnancy are limited. Indeed, only for Tofacitinib these data are available. In a 2018 study involving 45 woman patients exposed to Tofacitinib the incidence of spontaneous abortions and malformations were 10.7% and 3.6%, respectively, suggesting a fetal malformations and spontaneous abortion risks

comparable to the risk observed in the general population [50,51]. However, current indications include the discontinuation of Tofacitinib and Upadacitinib at least 4 weeks before conception, while a 1-week wash-out is recommended for Filgotinib [52-54].

Effects on lipids metabolism.

As reported in UC trials using Tofacitinib [28], both LDL and HDL levels increased at 8 weeks, even though normalizing after treatment discontinuation, associated with stable total-to-HDL cholesterol ratio. Taking into account the VTE risk in Tofacitinib-treated patients, the dose-dependent serum lipid increase appears as a relevant issue. Current indications therefore include serum lipids monitoring ≤2 months since treatment. However, long term Tofacitinib use has been reported to determine no significant changes in terms of lipid profile and overall, when reported, it currently appears not associated with an increased risk for major cardiovascular AE [28,39]."

In a recent meta-analysis, all the JAK inhibitors approved for RA were reported to determine a mean increase of 8.11 mg/dL of HDL and of 11.37 mg/dL LDL serum levels when compared to baseline [55]. For the newer selective JAK inhibitors, this risk currently appears to not raise significant concern.

2.4 New therapeutic targets in UC

Three more JAK inhibitors are being tested in Phase 2b/3 clinical trials, including Ritlecitinib, Brepocitinib and Izencitinib. Main characteristics of these drugs are summarized in Table 2.

2.5 Ritlecitinib and Brepocitinib: mechanism of action

Oral kinase inhibitors in clinical development include Ritlecitinib (PF-06651600), and Brepocitinib (PF-06700841). Ritlecitinib (PF-06651600) is a JAK3 and tyrosine kinase expressed in hepatocellular carcinoma (TEC) family inhibitor, while Brepocitinib (PF-06700841) is a TYK2/JAK1 inhibitor [56,57].

Ritlecitinib, a highly selective inhibitor of JAK3, also inhibits the TEC kinase family (Bruton's tyrosine kinase, bone marrow tyrosine kinase on chromosome X, IL-2–inducible T-cell kinase, TEC, tyrosine kinase expressed in T cells) [58,59]. JAK3 inhibition modulates cytokine pathways including IL-7, IL-9, IL-15, and IL-21, involved in UC pathogenesis. Differently from other JAK1 inhibitors, Ritlecitininb does not inhibit IL-10, IL-27, and IL-21, cytokines playing a role in maintaining the mucosal immune homeostasis and also inhibiting the cytotoxic functions of CD8 T and natural killer cells, involved in the pathogenesis of IBD [56-62].

Inhibitors of Bruton's tyrosine kinase and IL-2–inducible T-cell kinase contribute to signal transduction from antigen receptors on B and T cells [63-65]. These kinases are therefore being explored for treating UC [63-65].

Brepocitinib is also a dual inhibitor exerting prevalent anti-inflammatory effects by inhibiting both JAK1 and TYK2-mediated IL-12 and IL-23 signaling [57]. JAK1 inhibition impacts the signaling of proinflammatory cytokines [37]. Differently, TYK2 inhibition blocks the production of interferon (IFN)-ϒ and IL-17, by inhibiting the IL-12/Th1 and IL-23/Th17 pathways, involved in the pathogenesis of IBD. Blocking these pathways has shown efficacy in patients with active IBD [66-68].

2.6 Ritlecitinib and Brepocitinib: clinical trials

The efficacy and safety of Ritlecitinib and Brepocitinib given by mouth in patients with active, moderate-to-severe UC were assessed in VIBRATO, a phase 2b, parallel-arm, double-blind umbrella study [69]. The primary endpoint was clinical response, assessed by using the total Mayo Score (TMS) at week 8 (stool frequency, rectal bleeding, endoscopic activity, physician global assessment, PGA). Patients received an 8-week induction therapy with Ritlecitinib (20, 70, 200 mg), Brepocitinib (10, 30, 60 mg), or placebo once daily [70]. Overall, 317 patients were enrolled: 150 (47.3%) received Ritlecitinib, 142 (44.8%) Brepocitinib and 25 (7.9%) placebo [69].

Patients treated with Ritlecitinib and Brepocitinib showed a significant decrease in TMS compared to the placebo group, and this occurred using all doses, showing greater effect using higher dosages. At week 8, the rates of clinical remission were significantly higher in Ritlecitinib 200 mg and 70 mg groups (32.7% [20.2%-45.3%], and 36.0% [23.6%-48.6%]; p<0.001 for both) and Brepocitinib 60 mg and 30 mg (25.5% [11.0%-38.1%]), and 25.5% [11.0%3-8.1%]; p<0.001 for both) compared to the placebo group [69].

Similar results were obtained in terms of reduction of TMS without the PGA, reaching a stool frequency subscore ≤1 and a rectal bleeding subscore =0. Same results were observed for endoscopic improvement, defined as an endoscopic subscore ≤1 in both Ritlecitinib (42% and 34.2 %) and Brepocitinib (29.8% and 31.9%) groups compared to placebo. The frequency of AEs, mostly mild or moderate in terms of severity, was comparable between placebo, Ritlecitinib and Brepocitinib groups (52%, 43.3% and 47.9%). Most common AEs included opportunistic infections and gastrointestinal disorders. The proportion of patients who experienced herpes zoster was also similar to that observed using JAK-inhibitors. No dose-related effects were observed within either treatment group, and there were no clinically significant findings for any laboratory parameter evaluated for either Ritlecitinib or Brepocitinib [69].

Interestingly, among preliminary findings, some serum and microbiome proteins have been studied as potential non-invasive predictors of responsiveness. An analysis on proteomics, transcriptomics, and fecal metagenomics on tissue, stools and peripheral blood was carried out before and after 8-week oral Ritlecitinib induction therapy [69]. This in order to establish both the predictivity and the relevance of these markers in evaluating the efficacy of the drug. Peripheral blood serum proteomics identified 4 baseline potential serum predictors (LTA, CCL21, HLA-E, MEGF10) of modified clinical remission (MR), endoscopic improvement (EI), histologic remission (HR), and integrative score of tissue molecular improvement. A changing of 37 proteins was reported in patients considered responders. Among these, 4 proteins (IL4R, TNFRSF4, SPINK4, and LAIR-1) were

identified as possible markers of EI and HR response. Fecal metagenomics analysis revealed baseline and treatment response signatures correlated with EI, MR, and tissue molecular improvement. [70].

2.7 Izencitinib (TD-1473): mechanism of action

Izencitinib (TD-1473) is an orally administered, gut-selective, pan-JAK inhibitor aimed to minimize the systemic effects of the drug. The gut-selectiveness is related to the drug structure aimed to combine cellular penetration and inhibition of the JAK targets in the gastrointestinal (GI) tissue. "In vitro", TD-1473 showed a strong affinity for TYK2 (about 40 times). A pan-JAK inhibitor with higher potency for TYK2, was reputed to possibly provide additional clinical benefits, due to its IL-23 and IL-12 signal via JAK2 and TYK2 but not via JAK1 or JAK3 [70]. In murine models of colitis, findings suggest local efficacy associated with minimal systemic plasma drug levels [72].

In a preliminary phase 1b study, moderate-to-severe UC patients were randomized to TD-1473 20 mg, 80 mg, or 270 mg versus placebo for 28 days [73]. The authors reported low drug plasma levels associated with biologically active colonic tissue drug levels. This study was not powered for efficacy analyses [73]. However, a higher proportion of UC patients achieved clinical and endoscopic response in all TD-1473 groups when compared to placebo [73].

2.8 Izecitinib: clinical trial

Several studies assessed the efficacy and safety of Izencitinib for inducing and maintaining remission in moderately-to-severely active UC. These included: phase 2b/3 multicenter, randomized, double-blind, multi-dose, placebo-controlled, parallel-group set of studies [74]. These included an 8-week phase 2b dose-finding induction study, an 8-week dose-confirming phase 3 induction study, and a 44-week phase 3 maintenance study [74]. Primary endpoints included change from baseline in TMS at week 8 and, a phase 3 maintenance at week 44. Clinical remission was assessed by using the Adapted Mayo Score Components [74]. Current available data report that the study drug failed to

meet the primary efficacy endpoint of change in the TMS at week 8 in patients with moderate-to-severe UC [75].

2.9 S1PR modulators: mechanism of action

S1P is a bioactive lipid involved in multiple pathophysiological processes, including cellular chemotaxis, migration, growth and proliferation. Among other activities, S1P supports the intestinal epithelial barrier by increasing vascular endothelial (VE)-cadherin, thus being involved in inflammation and cancer [76]. S1P is secreted by erythrocytes, vascular and lymphatic endothelial cells [76] acts directly on several intracellular targets and on 5 different G protein-coupled receptors (S1PR), expressed in several tissues, thus exerting multiple functions [77]. S1PR1, S1PR4 and S1PR5 play a relevant role in immune-mediated pathophysiology. S1PR1 is crucial for lymphocyte chemotaxis from the thymus, bone marrow and secondary lymphoid organs to peripheral blood and tissues [78]. The lack of degradative S1P enzymes in the peripheral blood, determines a gradient of its concentration between lymphoid tissues and blood. The higher S1P blood level induces S1PR1 internalization and desensitization on naïve T cells, thus inhibiting their migration through the endothelium [79]. In lymphoid tissues, S1PR1 re-expression in T cells, allows their exit from tissue or the lymph node. In inflamed tissues, CXCL9 and CXCL11 chemokines induce the T cell expression of S1PR1 and S1PR4 and the stop and extravasion of T cells in inflamed tissues. In the inflamed tissue, T cells are retained by downregulation of S1PR1. S1PR4 mainly determines immunosuppression, by exerting several activities [80]. Among these, the inhibition of the secretion of pro-inflammatory cytokines, by enhancing IL-10 [80-83] and the stimulation of neutrophil trafficking from inflamed tissues to lymph nodes [82].

2.10 Ozanimod: clinical trials

Ozanimod is a sphingosine-1-phosphate receptor (S1P1) inhibitor approved for treating patients with moderate to severe active UC by both FDA and EMA [31]. In the phase 3 multicentre,

randomized, double blind, placebo-controlled trial, the proportion of UC patients achieving clinical remission was significantly higher in patients treated with Ozanimod than with placebo [31]. This finding was observed for both induction at 10 weeks [14.8% vs 6%, p<0.001] and for maintenance at 52 weeks (37% vs 28.5%, p<0.001) [30]. In this trial, mucosal and histological healing rates were higher in UC patients treated with Ozanimod than with placebo [31]. At week 52, higher rates of MH were observed in UC patients treated with Ozanimod versus placebo (29.6% vs 14.1%, p < 0.001). The achievement of MH when using Ozanimod, when confirmed by larger studies, is highly relevant in relation to the treat to target strategy currently applied for managing patients with UC. The most common reported AEs included alanine aminotransferase (ALT) increase (≥2 times the upper limit) and lymphopenia (13.9% and 2.2%, respectively) [31,35]. However, all these AEs spontaneously disappeared after treatment discontinuation. A decrease in the absolute lymphocyte count was rather common in Ozanimod-treated patients (2.2%). However, no increased risk of serious infections was observed (1.8% for placebo, 0.9% for Ozanimod), even in patients with an absolute lymphocyte count of <200 cells/μL [31,35]. In conclusion, current available data suggest the safety and efficacy of this new oral compound in UC.

The S1P1 receptor is involved in embryogenesis, particularly in vascular and neural development [52]. In animal models, S1P modulators showed embryo-fetal toxicity, including embryo-fetal deaths and malformations. On the basis of these observations, Ozanimod is currently contraindicated during pregnancy and in women in childbearing age not using effective contraception. It is therefore currently mandatory to clearly inform patients about this risk and contraceptive methods need to be used Ozanimod treatment (as stated by EMA [87]), and up to 3 months after delivery. Risks using Ozanimod in patients with UC appear comparable to those observed in the general population. Although Ozanimod use currently appears not associated with changes in the lipid profile [31], abnormal liver function tests have been reported in clinical trials including patients with UC [31]. In the True North and Touchstone trials, a ≥ 3-fold increase upper the normal serum levels of ALT were reported (Ozanimod vs placebo: 2.6% vs 0.5% in the induction and 2.3% vs 0% in the

maintenance period, respectively) [31,54]. In most of these UC patients developing this AE (96%), serum levels of ALT reduced to < 3-fold the upper normal limit within 2-4 weeks of continued Ozanimod therapy, thus apparently suggesting no need to discontinue the drug [31,85]. This issue, however, needs to be further evaluated.

2.11 Etrasimod: clinical trials

Etrasimod modulates S1PR1, S1PR4 and S1PR5, with no detectable activity on S1PR 3 and S1PR2. Etrasimod has been recently approved for moderately-to-severely active UC by the FDA and has received a positive opinion from the EMA's Committee for Medicinal Products for Human Use. The first trial in UC is the OASIS Study, a phase 2, proof-of-concept, double-blind, parallel-group study [86]. Overall, 156 UC patients showing inadequate response, loss of response or intolerance to ≥1 conventional treatment or biologic, were randomly treated with placebo or Etrasimod (1 mg or 2 mg) daily. The primary endpoint was an increase in the mean improvement in modified Mayo Clinic scores (MCSs) (stool frequency, rectal bleeding, endoscopy findings) at week 12. Secondary endpoints included the proportion of UC patients with endoscopic improvement (subscores ≤1) at week 12 [86]. Findings indicate that Etrasimod 2 mg (but not Etrasimod 1 mg) significantly increased the mean improvement in modified MCS from baseline versus placebo (p=0.009 and p=0.1, respectively). Endoscopic improvement was also observed in a higher proportion of patients with Etrasimod 2 mg vs versus placebo (41.8% 17.8% p=0.003). Most AEs were mild to moderate (UC flaring, anemia, respiratory infections). Overall, 3 patients with atrioventricular block before entering the trial showed a transient, asymptomatic, low-grade atrioventricular block spontaneously resolving [86].

Due to these findings, an open-label extension trial [OLE] assessed the safety and efficacy of Etrasimod for up to 52 weeks [86]. After completing OASIS, 118 of 156 patients were therefore enrolled to be treated with Etrasimod 2 mg for an additional 34-40 weeks [87]. Overall, 112/118 patients received Etrasimod at any time and 92 [82%] patients completed the study. AEs occurred in

60% of patients and UC worsening and anemia were the more common. Overall, 94% of AEs were mild to moderate. At end of the study, clinical response, clinical remission and endoscopic improvement was achieved by 64%, 33% and 43% of patents, respectively. At week 12, clinical response, clinical remission, or endoscopic improvement was maintained up to the end of treatment in 85%, 60%, or 69% of patients, respectively. Steroid-free clinical remission was reported in 22% of UC patients [87].

The efficacy of Etrasimod in active moderate-to-severe UC was assessed in 2 independent randomized, multicentre, double-blind, placebo-controlled, phase 3 trials (ELEVATE UC 52 and ELEVATE UC 12) [87]. In these trials, patients showing an inadequate/loss of response or intolerance to ≥1 approved UC therapy were enrolled. Patients were randomly assigned (2:1) to once-daily oral Etrasimod 2 mg or placebo. Randomized patients were stratified according to previous exposure to major treatments, corticosteroid use and UC activity [88]. ELEVATE UC 52 included an induction period at 12-week, followed by maintenance period at 40-week. ELEVATE UC 12 evaluated the induction at week 12. The primary efficacy endpoint was clinical remission at weeks 12 and 52. Safety was also assessed in both trials. UC patients were randomly enrolled in ELEVATE UC 52 (n=433) and ELEVATE UC 12 (n=354) [88]. In ELEVATE UC 52, treatment included were assigned to Etrasimod for 289 patients and placebo for 144 patients. In ELEVATE UC 12, 238 patients were assigned to Etrasimod and 116 to placebo, respectively. In ELEVATE UC 52, clinical remission was achieved in a significantly greater proportion of UC patients in the Etrasimod group versus patients randomized to placebo group, when considering either the end point at 12-week induction period (27% vs 7%; $p<0.0001$) and at week 52 (32% vs 7%; $p<0.0001$). In ELEVATE UC 12, clinical remission occurred in 25% of patients randomized to Etrasimod and in 15% of patients randomized to placebo ($p=0.026$). The rate of SAEs was reported to be low and comparable between the 2 treatment groups [88].

AEs (observed in ≥1% of patients) most frequently included headache, anemia, and UC worsening or relapse [88]. No deaths or cancer occurred. In ELEVATE UC 52, in the maintenance

trial, UC worsening was the most common AE requiring discontinuation of both Etrasimod and placebo. Study drug discontinuation due to treatment-related AE was 4% in ELEVATE UC 52 and 5% ELEVATE UC 12, with no significant difference between groups [88]. In relation to the mechanism of action of Etrasimod, an about 50% decrease of lymphocyte count was observed at week 2, followed by stable values during the study and by normalization at treatment discontinuation. AEs occurred in 71% of patients treated with Etrasimod and in 56% of patients treated with placebo, during the maintenance period. Similar rate of AEs (mostly mild or moderate) was observed in ELEVATE UC 12 (47%) [87]. Infections (overall, serious or opportunistic) were considered mild or moderate, occurred in a comparable proportion of UC patients randomized to Etrasimod or placebo and did not require treatment discontinuation [88]. A higher proportion of patients treated with Etrasimod showed elevated liver enzymes, requiring drug discontinuation in 2. In both trials, bradycardia or sinus bradycardia occurred in 9 patients treated with Etrasimod and in no patients randomized to placebo. These AEs were reported in the first 2 days of treatment, being symptomatic in 2 cases, thus leading to drug discontinuation followed by spontaneous resolution [88].

2.12 Alpha 4 integrin: mechanism of action

Integrins are cell adhesion receptors mediating cell-cell and cell-extracellular matrix interactions. Integrins are classified according to combination of α and β subunit [89]: the α_4 subunit can couple with β_7 or β_1 subunits. $\alpha_4\beta_1$ integrin (very late antigen-4, VLA-4) is expressed on leukocytes (lymphocytes, monocytes, eosinophils, natural killer cells, macrophages, mast cells, basophils) and modulates differentiation, survival homing, activation and trafficking of $\alpha_4\beta_1$ expressing cells [89]. Physiological ligands for $\alpha_4\beta_1$ integrin include vascular cell adhesion molecule-1 (VCAM-1), fibronectin, mucosal vascular addressin cell adhesion molecule-1 (MAdCAM-1), and junctional adhesion molecule-B (JAM-B) [90]. The $\alpha_4\beta_1$ integrin plays a crucial role in inflammation. As the $\alpha_4\beta_1$ integrin is mainly involved in leukocytes tethering and rolling on activated endothelial cells [91], targeting this integrin may show efficacy in inflammatory disorders.

$\alpha_4\beta_7$-MAdCAM-1 interaction is crucial for T lymphocytes homing to the gut. Vedolizumab, a humanized mAb anti-$\alpha_4\beta_7$, has therefore been developed and approved for treating patients with UC and Crohn's Disease (CD) [92]. Although Natalizumab targeting α_4 integrin subunit, has been approved for treating multiple sclerosis and CD, its use is very limited for CD due to potentially fatal AEs [92]. Recently, homing of T cells into the gut has been reported to be not reduced by Vedolizumab, but rather by blocking $\alpha_4\beta_1$ [93,94].

AJM300: clinical trials.

The efficacy of anti-α4 integrin antibody in order to inhibit lymphocyte trafficking has been clinically validated in IBD. In a mouse colitis model (induced by transfer of IL-10 deficient T cells), the orally active small molecule α4 integrin antagonist, AJM300 and his active metabolite HCA2969 were used [95]. Findings showed that HCA2969 selectively inhibited the "in vitro" binding of α4 integrin (α4β7/α4β1) to the cell adhesion molecules, preventing the development of experimental colitis in mice [95]. A double-blind, placebo-controlled, phase 2a trial investigated the activity and safety of AJM 300 [96]. In this trial, 102 patients with moderately active UC with a history of inadequate response/intolerance to mesalamine or corticosteroids were randomized to either AJM300 (960 mg) or placebo 3 times daily for 8 weeks. The primary end point was clinical response at week 8, defined as: decrease of the Mayo Clinic score ≥3 points and ≥30% from baseline, decrease in the rectal bleeding subscore ≥1 point or an absolute rectal bleeding subscore of 0 or 1. Clinical response, clinical remission and endoscopic remission were reported in 62.7%, 23.5% and 58.8 % patients from the AJM300 group and in 25.5%, 3.9% and 29.4%of patients in the placebo groups, respectively (p=0.0002, p=0.0099, p=0.0014, respectively) [96]. No serious AEs was observed [96].

More recently, the efficacy of AJM300 was investigated in a multicentre, randomized, double-blind, placebo-controlled, phase 3 study, including 82 Japanese hospitals and clinics [97]. AJM300 was given by mouth (960 mg/daily), for 8 weeks, then continued for up to 24 weeks in patients not reaching endoscopic remission or stop of rectal bleeding. The primary endpoint was clinical response at week 8. Overall, 203 patients were randomly assigned to AJM300 (n=102) or placebo (n=101). At

week 8, clinical response was achieved by 46 (45%) patients in the AJM300 group and by 21 (21%) patients in the placebo group (p=0.00028). During the 8-week and 16-week periods, a comparable proportion of patients treated with AJM300 or placebo developed AEs (39/102 [38%] vs 39/101 [39%], respectively). Most AEs were mild-to-moderate, being nasopharyngitis the most common, although headache, upper respiratory tract inflammation, nausea, abdominal bloating or pain were also reported. No deaths were reported. UC-related AEs were higher in placebo group than in treated patients. Drug discontinuation was required due to UC relapse (1 patient using AJM300, 8 patients placebo), while elevation of liver enzymes occurred in in 1 patient [97].

2.13 micro-RNA (miR)-124.

Obefazimod (ABX464): mechanism of action

Obefazimod, a quinoline inducing the anti-inflammatory micro-RNA (miR)-124 has been proposed for treating UC. Selective upregulation of miR-124 by ABX464 can downregulate various inflammatory pathways [98]. MiR-124 is a modulator of monocyte and macrophage activation [98], playing a key role in both the innate and adaptive immune responses also by reducing IL-6, TNF-α, and CCL2 (monocyte chemoattractant protein-1) production [99]. miR-124 expression has been reported to be upregulated by ABX 464 in colonic and blood samples from UC patients [99]. A concomitant decrease in Th17 cells and IL17 levels was reported in serum samples. In a mouse model of dextran sulfate sodium-induced colitis, ABX464 reversed the higher levels of multiple proinflammatory cytokines in the colon and the upregulation of IL17a secretion in the mesenteric lymph nodes [99].

2.14 Obefazimod (ABX464): clinical trials

The safety and efficacy of Obefazimod was assessed in a randomized, phase 2a, placebo-controlled, double-blind trial including an induction phase of 8 weeks followed by an open-label, long-term extension phase [100]. In the induction phase, all moderate-to-severe UC patients were randomized to oral ABX464 (50 mg/day) or placebo for 8 weeks, while in the long-term extension

phase all patients received the drug [101]. Overall, 29 patients completed the induction phase and 22 patients entered in the long-term extension phase [100].

At week 8, clinical remission, clinical response and endoscopic improvement was observed in 35%, 70% and 50% of patients receiving ABX464 and in 11.1%, 33.3% and 10% of patients receiving placebo, respectively (p=0.1588, p=0.06, p=0.928, respectively). Clinical remission was maintained by the 55% of UC patients completing the long-term extension trial. [100]. AEs occurred in 78.3% and 55.6% of patients receiving ABX464 or placebo, respectively. Abdominal pain and headache occurred in 17.4% of patients (for both treatments), presenting the most common AEs in the ABX464 group.

The efficacy of oral ABX464 was further assessed in a phase 2b, double-blind, randomized, placebo-controlled induction trial. In this trial, patients with moderate-to-severe, active UC showing a modified Mayo Score (MMS) ≥ 5 points, and refractoriness or intolerance to previous treatment were considered [100]. Enrolled patients were randomly assigned (1:1:1:1) to receive once daily oral ABX464 (100 mg, 50 mg or 25 mg) or placebo [101]. Randomization was stratified according to study site (US vs non-US) and according to previous history of second-line biologics or JAK inhibitors treatment. The primary endpoint was the change of MMS at week 8. Overall, 254 UC patients were randomized to 4 groups [100]. A significant difference in MMS from baseline was reported in all 3 ABX464 groups versus placebo (ABX464 100 mg: p=0.0039; ABX464 50 mg: p=0.0003; ABX464 25 mg: p=0.0010). The more frequently reported AE included headache (ABX464 100 mg group: 42%; 50 mg group: 30%; 25 mg group: 21%; placebo 8%). A phase 3 clinical program is ongoing [101].

3. Conclusions

Many new chemical drugs for moderate-to-severe UC are in advanced phase of development. Most importantly, since the approvement of the first small molecule for UC (the pan-JAK inhibitor Tofacitinib) [28], the search for new drugs expanded towards two directions: the development of

JAK-selective inhibitors and new mechanisms of action. The first small molecule approved for UC treatment with a different mechanism of action from JAK inhibitions was Ozanimod [31], a sphingosine-1-phospate receptor inhibitor. From the first to the most recently approved small molecule drug (Etrasimod, approved only by FDA) [86-88], efforts have been made for reducing the frequency and severity of AEs. Indeed, the safety profile from pan-JAK inhibitor Tofacitinib to selective JAK inhibitors (Filgotinib and Upadacitinib) and to S1Pr inhibitors (Ozanimod and Etrasimod), fewer SAEs have been described [47]. In particular, the most feared AEs related to JAK inhibitors use, the occurrence of VTE, has been reported to be significantly less relevant in the more recent selective JAK inhibitors [34,35].

All the newly proposed chemical drugs for treating moderate-to-severe UC are characterized by a favorable safety profile. Despite different mechanisms of action, current evidence suggests that the occurrence of SAEs using treatments under development is extremely limited for all [59,69,86,87,95-97,98]. In the AJM300 trial, AEs occurred more frequently in the placebo group than in the treatment group, leading to drug discontinuation in 1 treated patient vs 8 placebo group patients [97]. Even in the Ritlecitinib/Brepocitinib trial the AEs frequency was higher in the placebo group, even though not significantly (52%, 43.3% and 47.9% for placebo, Ritlecitinib and Brepocitinib, respectively) [69]. Moreover, the majority of AEs were mild [69]. In the Etrasimod trials study drug discontinuation due to treatment-related AE was low, being 4% in ELEVATE UC 52 and 5% ELEVATE UC 12, with no significant difference with placebo [88].

All these new oral compounds for treating patients with UC are also characterized by the fast onset and the high clinical remission and response rates, as confirmed by the maintenance phase of the trials. Indeed, the clinical remission rates observed range between the 17% of ABX464 and the 60% of Etrasimod [86-88]. Among all the reported treatments, only Izencitinib, a pan-JAK inhibitor, has failed to meet the primary endpoint of clinical remission [74].

The issue with these novel oral chemical drugs for UC appears to be the relatively low frequency of endoscopic improvement and healing. Indeed, in some cases, the endoscopic remission

rates were comparable between the drug and placebo, as for ABX464 (10% VS 11.1%, p=0.928) [101]. Most studies assessed endoscopic improvement rather than endoscopic healing, reporting significantly higher rates for the drug compared to placebo.

In conclusion, there are many new oral chemical drugs for UC in advanced phases of development, all reporting favorable safety data. Indeed, treatment-related AEs occurrence represents a relevant concern in clinical management of UC patients, particularly in special situations such in the elderly and frail. However, the endoscopic healing data raise questions whether these drugs will be highly efficacious as reported in the clinical trials in the real world, taking into account the relevance of this clinical target in the management of patients with UC.

4. Expert opinion

Growing evidence supporting the key role of the mucosal immune response in the pathogenesis of UC are giving rise to the development of highly effective immunomodulatory drugs [1-3]. Biologics and the currently available small molecule allow the achievement, in responsive UC patients, of both clinical and endoscopic remission [6]. Mucosal healing is associated with a better clinical outcome, thus representing the current therapeutic target in UC [6]. Despite the marked efficacy of biologic therapies and small molecules, subgroups of UC patients may develop secondary failure or may still require corticosteroids or surgery. Moreover, safe treatments for special UC populations such as the elderly and frail are still needed. In this context, the development of new oral chemical drugs is very relevant for optimizing patients with UC.

The first small molecules entering the market were JAK and S1Pr inhibitors [38,74]. These treatments summarized the characteristics of the majority of the small molecules: rapidity of onset, low immunogenicity and safety, improving from the first approved to the last. Among the currently available chemical drugs, the selective JAK and the S1Pr inhibitors are characterized by the better safety profile combined with a comparable efficacy when compared to the same-class drugs. The safety profile, combined with the ability to induce clinical remission, currently appear as the most

relevant characteristic of the newly proposed chemical drugs for UC. Endoscopic improvement and healing seem to be less frequent, being higher in in patients treated with S1Pr inhibitor Etrasimod [86-88].

When using Ritlecitinib and Brepocitinib in preliminary findings, serum and microbiome proteins have been proposed d as non-invasive predictors of responsiveness [70]. As most efforts are currently finalized to tailor treatments on the basis of characteristics of each patient, the identification of non-invasive predictors of responsiveness is highly relevant.

Most of the new oral compounds for treating moderate-to-severe UC summarized in the present review currently appear characterized by safety and fast onset of action, but also by a relatively low rate of induction of endoscopic healing. These characteristics coupled with the novelty of their mechanism of action, may well fit in the therapeutic armamentarium for treating patients with UC, particularly in subgroups of patients, including refractory or frail patients.

The early use of the cheaper available generic Tofacitinib has recently been proposed in low middle income countries (LMIC) for treating active UC [102]. This aspect appears relevant in an era characterized by the role of pharmacoeconomic in choosing therapeutic strategies, particularly in LMIC.

Overall, new safe and effective and safe drugs for UC is therefore still required in order to allow disease control in a largest majority of UC patients. Whether promising new chemical dugs may add new modalities of treatments in patients with UC, need to be confirmed by further studies and by post-marketing data.

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Table 1. Clinical trials of currently approved oral chemical drugs for Ulcerative Colitis.

Drug	Dose	Trial Type	N. of patients	End-Points	Success Rate	Mucosal Healing
Tofacitinib	10 mg t.i.d. vs placebo for 8 weeks.	OCTAVE Induction 1: phase 3, randomized, double-blind, placebo-controlled trials [27]	598	Primary endpoint: Clinical remission at 8 weeks. Secondary endpoint: MH (endoscopic Mayo ≤1) at 8 weeks.	Clinical remission: 18.5% of treated patients vs. 8.2% (p=0.007)	MH at 8 weeks 31.3% of treated patients vs 15.6% (p<0.001)
Tofacitinib	10 mg t.i.d. vs placebo for 8 weeks.	OCTAVE Induction 2: phase 3, randomized, double-blind, placebo-controlled trials [27]	541	Primary endpoint: Clinical remission at 8 weeks. Secondary endpoint: mucosal healing (endoscopic Mayo ≤1) at 8 weeks.	Clinical remission: 16.6% of treated patients vs. 3.6% (p<0.001)	MH at 8 weeks 28.4% of treated patients vs 11.6% (p<0,001)
Tofacitinib	Maintenance therapy with tofacitinib (either 5 mg or 10 mg twice daily) or placebo for 52 weeks.	OCTAVE Sustain trial: phase 3, randomized, double-blind, placebo-controlled trials [27]	593	Primary end point: clinical remission at 52 weeks. Secondary endpoint: Mucosal healing at 52 weeks, sustained remission (occurring at both 24 and 52 weeks), steroid-free remission.	Clinical remission occurred in 34.3% of patients in the 5 mg group and in 40.6% in the 10 mg group vs 11.1% in the placebo group (p<0.001 for all comparisons with placebo)	Mucosal healing at 52 weeks occurred in 37.4% of patients in the 5 mg group and 45.7% in the 10 mg group versus 13.1% in the placebo group (p<0.001 for both comparisons)

Tofacitinib	Tofacitinib (10 mg t.i.d.) or a matching placebo for 7 days while continuing i.v. corticosteroids (hydrocortisone 100 mg every 6 hours)	TACOS: randomized, double-blind, placebo-controlled trial [40]	104	Primary end point: response to treatment (decline in the Lichtiger index by >3 points and an absolute score <10 for 2 consecutive days without need for rescue therapy) by day 7. Secondary outcome: cumulative probability of requiring initiation of infliximab or undergoing colectomy within 90 days following randomization.	Response: 83.01% of patients receiving tofacitinib vs 58.82% of patients receiving placebo (OR 3.42 [1.37-8.48], p=0.007).	n/a
Ozanimod	Cohort 1: oral ozanimod hydrochloride at 1 mg or placebo once daily. Cohort 2: open-label ozanimod at the same daily dose. At 10 weeks, patients with clinical response to ozanimod in either cohort underwent randomization to receive double-blind	Phase 3, multicenter, randomized, double-blind, placebo-controlled trial [30]	Cohort 1: 645 Cohort 2: 367 Maintenance period: 457	Primary end point: clinical remission at week 10 (for the induction period) and at week 52 (for the maintenance period) Secondary end point: clinical response, endoscopic improvement, mucosal healing (endoscopic improvement plus histologic remission, defined as a mucosal endoscopy score ≤1)	Clinical remission: 18.4% of patients on Ozanimod vs 6% on placebo during induction (p<0.001) and in 37.0% vs. 18.5% among patients with a response at week 10 (p<0.001)	MH during induction: 12.6% of treated patients vs 3.7% in the placebo group (p<0.001). MH during maintenance: 29.6% of treated patients vs 14% in the placebo group (p<0.001).

	ozanimod or placebo for maintenance period			and a Geboes score <2.0)		
Upadacitinib	Upadacitinib 45 mg o.d. vs placebo for 8 weeks	UC1: phase 3, multicentre, double-blind, randomised trial [28]	474	Primary endpoint: clinical remission per Adapted Mayo score at 8 weeks	Clinical remission: 26% of the patients on Upadacitinib vs 5% on placebo (p<0·0001)	Endoscopic remission: 14% of treated patients vs 1% (p<0.0001) MH: 11% of treated patients vs 1% (p<0.0001)
Upadacitinib	Upadacitinib 45 mg o.d. vs placebo for 8 weeks	UC2: phase 3, multicentre, double-blind, randomised trial [28]	522	Primary endpoint: clinical remission per Adapted Mayo score at 8 weeks	Clinical remission :34% of the patients on Upadacitinib vs 4% on placebo (p<0·0001)	Endoscopic remission: 18% of treated patients vs 2% (p<0.0001) MH 13% of treated patients vs 2% (p<0.0001)
Upadacitinib	Upadacitinib 15 mg o.d. vs Upadacitinib 30 mg o.d. vs placebo for 52 weeks	UC3: phase 3, multicentre, double-blind, randomised trial [28]	451	Primary endpoint: clinical remission per Adapted Mayo score at 52 weeks	Clinical remission: 42% of the patients on Upadacitinib 15 mg vs 52% of the patients on Upadacitinib 30 mg vs 12% on placebo (p<0·0001; p<0.0001).	Endoscopic remission: 24% of patients on Upadacitinib 15 mg vs 26% of the patients on Upadacitinib 30 mg vs 6% on placebo (p<0.0001) MH: 18% of patients on Upadacitinib 15 mg vs 19% of the patients on Upadacitinib 30 mg vs 5% on placebo (p=0.0003; p=0.0001)
Filgotinib	filgotinib 200 mg, filgotinib 100 mg, or placebo once per day	SELECTION: phase 2b/3 double-blind, randomised, placebo-	659 in induction study A	Primary endpoint: clinical remission by Mayo endoscopic, rectal bleeding, and stool frequency	Clinical remission at week 10 (induction study A: 6.1% vs 15.3%, p=0·0157; induction study B 11.5% vs 4.2%, p=0·0103).	Induction study A: 5.8% 100 mg p=0.3495 12.2% 200 mg p=0.0.0047 3.6% placebo

		controlled trial [29]	689 in induction study B 664 maintenance study (391 from induction study A, 273 from induction study B)	subscores at weeks 10 and 58	Clinical remission in maintenance study at week 58 (37·2% vs. 11·2%, p<0·0001).	Induction study B:100 mg 2.1% p=0.9987 200 mg 3.4% p=0.4269 Placebo 2.1% Maintenance study 52w; 100 mg 3.4% p=0.1808 200 mg 15.6% p=0.0157

Abbreviations: MH= Mucosal healing; vs=versus.

Table 2. Clinical trials of phase IIb/III oral chemical drugs for Ulcerative Colitis.

Drug	Dose	Trial Type	N. of patients	End-Points	Success Rate	Mucosal Healing
Ritlecitinib/ Brepocitinib	Ritlecitinib (20, 70, 200 mg) 8-week induction therapy Brepocitinib (10, 30, 60 mg) or placebo once daily	VIBRATO: Randomized, Phase 2b Study [68]	319	Primary end point: remission defined as per Total Mayo Score at week 8. Secondary end point: Clinical remission, endoscopic improvement, clinical response, and mucosal healing.	TMS decrease at week 8; significantly different for all doses of both ritlecitinib (200, 70, and 20 mg) and brepocitinib (60, 30, and 10 mg) vs placebo, with ritlecitinib 200 mg showing the largest decline.	Endoscopic improvement: 42% of patients receiving Ritlecitinib vs 34.2% receiving placebo. Endoscopic improvement: n 29.8% of patients receiving Ritlecitinib vs 31.9% receiving placebo

Etrasimod	Etrasimod 1 mg, Etrasimod 2 mg or placebo, once daily for 12 weeks	OASIS: phase 2, randomized, double-blind, placebo-controlled study [85]	156	Primary endpoint: increase in the mean improvement in modified Mayo Clinic Scores from baseline to week 12. Secondary endpoints: endoscopic improvement (subscores of 1 or less) from baseline to week 12.	Clinical response at 12 week 50.6% of Etrasimod 2 mg treated patients vs 32.5% (p<0,0001). Clinical remission at 12 week occurred in 33% of Etrasimod 2 mg treated patients vs 8.1% (p<0,0001).	Endoscopic improvement at 12 week; 41.8% of Etrasimod 2 mg treated patients vs 17.8% (p<0,003)
Etrasimod	Etrasimod 2 mg for an additional 34-40 weeks.	OLE: Open-label Extension of the OASIS Study [86]	118	Primary endpoint: the long-term safety and tolerability of Etrasimod.	Week 12 clinical response and clinical remission: maintained to end of treatment in 85% and 60% of patients, respectively.	Week 12 endoscopic improvement: maintained to end of treatment in 69% of patients.

Etrasimod	Etrasimod 2 mg or placebo for 12 weeks of induction followed by 40 weeks of maintenance therapy.	ELEVATE UC 52: randomised, double-blind, placebo-controlled, phase 3 studies [87]	433	Primary end point: patients with clinical remission at weeks 12 and 52. Secondary end point: endoscopic improvement, symptomatic remission, endoscopic improvement–histological remission with histological remission at week 12 and at week 52	Remission at 12 weeks: 27% of treated patients vs 7% (p<0,0001); at week 52, in 32% vs 7% at (p<0.0001).	Endoscopic improvement at 12 weeks: 35% of treated patients vs 14% (p<0,0001) Endoscopic improvement - histological remission at week 12, 21% of treated patients vs 4% (p<0,0001)
Etrasimod	Etrasimod 2 mg or placebo for 12 weeks.	ELEVATE UC 12: randmized, double-blind, placebo-controlled, phase 3 studies [87]	354	Primary end point: clinical remission at week 12. Secondary endpoint: endoscopic improvement, symptomatic remission, and endoscopic improvement-histological remission at week 12.	Remission at 12 weeks: 25% of treated patients vs 15% (p=0.026)	Endoscopic improvement at 12 weeks: 31% of treated patients vs 19% (p=0.0092) Endoscopic improvement - histological remission at week 12: 16% of treated patients vs 9% (p=0.036)

AJM300	AJM300 (960 mg) or placebo 3 times daily for 8 weeks.	Randomized, double-blind, placebo-controlled, phase 3 trial [96]	203	Primary end point: clinical response at week 8 Secondary endpoint: clinical remission and mucosal healing (endoscopic Mayo ≤1)	Clinical response at week 8: 45% of treated patients and 21% in the placebo group (p=0.0028) Clinical remission at week 8: 23% of treated patients and 14% in the placebo group	Endoscopic improvement at week 8: 55% of treated patients vs 27% Endoscopic remission at week 8: 14% of treated patients vs 3%
ABX464	ABX464 50 mg or placebo once daily for 8 weeks.	Phase IIa Trial [99]	32 in the induction phase; of the 29 patients who completed the induction phase 22 continued into the long-term extension.	Primary endpoint: safety. Secondary end point: clinical remission, endoscopic remission and improvement.	Clinical response rates: 70% in the ABX464 group and 33.3% in the placebo group at week 8 (p =0.06). Clinical remission rates: 35% in the ABX464 group and 11.1% in the placebo group at week 8 (p =0.1588).	Endoscopic improvement at 8 week: 50% of treated patients vs 11.1% (p=0.0341) Endoscopic remission at week 8: 10% of treated patients vs 11.1% (p=0.928)

ABX464	ABX464 100 mg, ABX464 50 mg, ABX464 25 mg, or placebo.	Phase IIb, double-blind, randomized, placebo-controlled induction trial [100]	254	Primary endpoint: change from baseline in modified Mayo Score at week 8.	The difference in Modified Mayo Score from baseline: significantly greater in all three ABX464 groups compared with placebo (p=0.0039 for ABX464 100 mg, p=0.0003 for ABX464 50 mg, and p=0.0010 for ABX464 25 mg). Clinical remission at 8 weeks: 25% of treated patients with ABX464 100 mg, 17.5% of treated patients with ABX464 50 mg, 26.2% of treated patients with ABX464 25 mg vs 12.5%.	Endoscopic improvement at week 8: 44.4% of treated patients with ABX464 100 mg, 39.6% of treated patients with ABX464 50 mg, 34.5% of treated patients with ABX464 25 mg vs 13.6%

Abbreviations: MH= Mucosal healing; vs=versus; TMS: total Mayo score.

Table 3. Mechanisms of action of oral chemical drugs for Ulcerative Colitis (either approved or tested in phase IIb/III trials).

Drug	Mechanisms of action
Tofacitinib	Pan-JAK inhibitor
Upadacitinib	JAK 1 preferential inhibitor
Filgotinib	JAK 1 preferential inhibitor
Ritlecitinib/ Brepocitinib	Ritlecitinib JAK3 / TEC family kinase inhibitor Brepocitinib TYK2 / JAK1 inhibitor
Ozanimod	S1Pr inhibitor
Etrasimod	S1Pr modulator
AJM300	α4 integrin subunit antagonist
Obefazimod (ABX464)	miR-124 selective upregulator in immune cells

Abbreviations: JAK=Janus Kinase; S1Pr=Sphingosine-1-phosphate receptor; TEC= tyrosine kinase expressed in hepatocellular carcinoma; TYK2=Tyrosine Kinase2; miR= micro RNA.