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Novel oral-targeted therapies for mucosal healing in ulcerative colitis

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Abstract

Ulcerative colitis (UC), a chronic, relapsing, remitting disease of the colon and rectum, is characterized by inflammatory ulceration of the mucosa. Current UC therapy relies on controlling acute episodes and preventing relapse. To predict modifications in the natural course of UC, mucosal healing (MH) has emerged as a major treatment goal. Endoscopic evaluation is considered the gold standard for assessing MH, which can be achieved by conventional drugs and biologics in many, but not all, patients. Consequently, interest is focusing on the development of new substances for UC therapy, and new oral agents are in the pipeline. This review will focus on the ability of newly developed oral drugs to induce and maintain MH in UC patients.

Key words: Mucosal healing; New oral treatments; Ozanimod; Peficitinib; Tofacitinib; Ulcerative colitis

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Core tip: The disease activity of ulcerative colitis (UC) is not sufficiently controlled in a subgroup of patients under the current therapeutic regimens. New oral substances are in the pipeline for treating UC. Mucosal healing (MH) has emerged as an important predictor of modifications in the natural disease course of UC. This review describes the efficacy of new oral drugs in inducing and maintaining MH in UC.

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INTRODUCTION

Ulcerative colitis (UC) is a chronic, relapsing, remitting inflammatory disease of the colon and rectum, causing ulceration of the mucosa. Although UC usually has a mild to moderate course, approximately 20%-25% of patients suffer at least one severe acute attack, requiring hospitalisation^[1].

Current UC treatment relies on controlling acute attacks and preventing relapse^[2] by means of first-line agents like aminosalicylates, steroids, and immunosuppressants. When conventional therapy fails because of lack of efficacy or drug intolerance, biological agents may be administered to gain disease control. However, the available agents (infliximab, adalimumab, and golimumab) are often associated with primary and, more importantly, secondary loss of response^[3]. In addition to tumor necrosis factor (TNF)- α inhibitors, the $\alpha 4\beta 7$ integrin inhibitor vedolizumab has recently been playing a major role in the therapeutic arsenal^[4].

Advances in understanding the pathophysiology of UC led to strategies that were designed to alter cytokine levels^[5]. When attempting cytokine targeting, it is important to remember the role of the cells that produce and respond to those cytokines, and that efficacy may be linked to the role of cytokines in non-immune cells, all of which may limit therapeutic success or cause unpredictable adverse events^[6].

Fortunately, additional new therapeutic options have been, and are still being, actively explored and some have already entered daily clinical practice. Mucosal healing (MH) has emerged as a major treatment goal for patients with UC^[7-9]. Although endoscopy is the gold standard for assessing MH^[10], there are several endoscopic definitions of MH, most of which are not validated. In a recent consensus agreement called the Ulcerative Colitis Endoscopic Index of Severity (UCEIS), 0 was defined as endoscopic response as were a ≥ 1 grade decrease in the Mayo endoscopic score or ≥ 2 point drop in the UCEIS^[11].

Ideally, clinical recovery should be followed by mucosal repair^[12], which is assessed by evaluating the macroscopic appearance of the mucosa at endoscopy. MH is defined as resolution of visible mucosal inflammation and ulceration at endoscopy^[13], and diverse endoscopic scoring systems were developed to assess its presence or absence^[14]. Even though the Mayo Endoscopic Score^[15] is one of the most frequently used, only the UCEIS^[16] has been validated to date^[17].

MH is crucial because it predicts long-term remission,

reduces the risk of dysplasia or cancer, lowers hospitalisation and surgery rates, and improves quality of life, thus modifying the natural course of UC by slowing down, or even preventing, disease progression^[18]. Since inflammation is limited to the mucosa in UC patients, MH has become a central therapeutic goal, which may be achieved by means of several classes of drugs, including mesalamine^[19], corticosteroids^[20], immunomodulators^[21], and biologics^[22].

In this review, we discuss the efficacy of new oral drugs, which have been recently developed and successfully tested for UC therapy, in inducing and maintaining MH.

JANUS KINASE INHIBITORS

Janus kinases (JAKs), a family of intracellular proteins, consist of JAK 1, 2, and 3 and the related kinase tyrosine kinase 2 (TYK2)^[23]. Several JAK inhibitors were developed as therapy for immune-mediated diseases like rheumatoid arthritis, IBD, and psoriasis^[24]. Some compounds with JAK inhibitor activity have been tested for efficacy as potential UC treatments. They are small molecules characterized by oral administration, short serum half-life, intracellular target, and non-antigenicity^[25]. The results of JAK treatment for UC are summarized in Table 1.

Tofacitinib

Tofacitinib^[26], a non-selective JAK inhibitor, has recently been approved in Europe for adult patients with moderate to severe active UC who responded poorly, lost response, or were intolerant to either conventional therapy or a biologic agent^[27]. A few years ago, a phase II clinical trial demonstrated for the first time that tofacitinib was effective in UC^[28]. This trial was conducted on 194 patients with moderate to severe UC who had not responded to conventional therapy, anti-TNF agents or a combined approach. Tofacitinib at doses of 0.5, 3, 10 or 15 mg was administered twice daily vs placebo for 8 wk. Patients displayed an excellent clinical response, with the highest dose group having an almost 78% response rate. The endoscopic response was defined as a decrease of at least 1 from baseline in the endoscopy subscore, and endoscopic remission was defined as an endoscopic subscore of 0. At 8 wk, endoscopic remission occurred in 1/48 patients (2%) receiving placebo, compared with 3/31 (10%) receiving 0.5 mg of tofacitinib ($P = 0.14$), 6/33 (18%) receiving 3 mg of tofacitinib ($P = 0.01$), 10/33 (30%) receiving 10 mg of tofacitinib ($P < 0.001$), and 13/49 (27%) receiving 15 mg of tofacitinib ($P < 0.001$). The post hoc analysis^[29] showed that median fecal calprotectin (FCP) concentrations at week 8 were significantly lower ($P < 0.001$) in responders than in non-responders ($P < 0.001$) with respect to endoscopic remission (44 mg/kg vs 489 mg/kg) and MH (127 mg/kg vs 753 mg/kg). Moreover, an FCP cut-off value of 150 mg/kg displayed

Table 1 Summary of treatment results with Janus kinase inhibitors in ulcerative colitis patients

Study	Drug	Study population	Treatment arm	Endoscopy endpoint	Time of observation, wk	Rate of mucosal healing
Sandborn <i>et al</i> ^[28]	Tofacitinib	Moderate to severe UC patients (<i>n</i> = 194)	Doses of 0.5, 3, 10, or 15 mg/twice daily <i>vs</i> placebo for 8 wk	Secondary end points; Endoscopic remission: an endoscopic subscore of 0	At 8 wk	Placebo 2% Tofacitinib 0.5 mg = 10%, (<i>P</i> = 0.14) Tofacitinib 3 mg = 18%, (<i>P</i> = 0.01) Tofacitinib 10 mg = 30%, (<i>P</i> < 0.001), Tofacitinib 15 mg = 27%, (<i>P</i> < 0.001) Placebo 15.6% Tofacitinib 10 mg = 31.3%, (<i>P</i> < 0.001)
Sandborn <i>et al</i> ^[30]	Tofacitinib	Moderate to severe UC patients (<i>n</i> = 614)	Dose of 10 mg/ twice daily <i>vs</i> placebo for 8 wk 16 patients received tofacitinib 15 mg twice daily	Key secondary endpoint was MH (Mayo endoscopic subscore of 0 or 1)	At 8 wk	Placebo 11.6% Tofacitinib 10 mg = 28.4%, (<i>P</i> < 0.001)
Sandborn <i>et al</i> ^[30]	Tofacitinib	Moderate to severe UC patients (<i>n</i> = 547)	Dose of 10 mg twice daily <i>vs</i> placebo for 8 wk; 6 received tofacitinib; 15 mg twice daily	Key secondary endpoint was MH; Mayo endoscopic subscore of 0 or 1	At 8 wk	Placebo 13.1% Tofacitinib 5 mg = 37.4%, (<i>P</i> < 0.001) Tofacitinib 10 mg = 45.7%, (<i>P</i> < 0.001)
Sandborn <i>et al</i> ^[30]	Tofacitinib	Moderate to severe UC patients (<i>n</i> = 593)	Dose of 5 mg twice daily, 10 mg twice daily, or placebo for 52 wk	Key secondary end points were mucosal healing; Mayo endoscopic subscore of 0 or 1	At 52 wk	Placebo 7.7% Tofacitinib 5 mg = 24.2% (OCTAVE Induction 1 and 2) Placebo 20% Tofacitinib 5 mg = 45.5% Tofacitinib 10 mg = 57.1% (OCTAVE Sustain)
Motoya <i>et al</i> ^[31]	Tofacitinib	Moderate to severe UC patients (<i>n</i> = 121 OCTAVE Induction 1 and 2) (<i>n</i> = 63, OCTAVE Sustain)	Dose of 5 mg twice daily (OCTAVE sustain only), 10 mg twice daily, or placebo	Key secondary endpoint was MH (Mayo endoscopic subscore of 0 or 1)	At 8 wk (OCTAVE Induction 1 and 2); At 52 wk (OCTAVE sustain)	Placebo 18.6% Peficitinib 25 mg qd = 20.5% Peficitinib 75 mg qd = 29.5% Peficitinib 150 mg qd = 45.5% (<i>P</i> < 0.05) Peficitinib 75 mg bidmg = 36.4%
Sands <i>et al</i> ^[35]	Peficitinib	Moderate-to-severe UC (<i>n</i> = 219)	Dose of 25 mg once daily (qd), 75 mg qd, 150 mg qd, 75 mg twice daily (bid) or placebo	Secondary endpoint was MH; Mayo endoscopic subscore of 0 or 1	At 8 wk	

UC: Ulcerative colitis; OCTAVE: Oral Clinical Trials for tofacitinib in ulcerative colitis.

the highest sensitivity and specificity for clinical (0.68 and 0.79, kappa = 0.44) and endoscopic (0.79 and 0.75, kappa = 0.38) remission. The authors concluded that daily fluctuations in FCP concentrations might account for the low agreement between FCP and endoscopic remission. In addition, residual inflammation might still persist histologically despite MH and endoscopic remission. Since safety concerns (hyperlipidemia and viral infections) emerged for patients receiving the highest dose, the US Food and Drug Administration subsequently authorized only the 10 mg dose for clinical development. Consequently, the most recent OCTAVE (Oral Clinical Trials for tofacitinib in ulcerative colitis) trials on tofacitinib induction were conducted using a 10 mg dose twice daily^[30].

OCTAVE trials: Three multi-centre, randomized, double-blind, placebo-controlled trials (OCTAVE Induction 1; OCTAVE Induction 2; and OCTAVE Sustain) were conducted on moderate to severe UC^[30]. In the OCTAVE Induction 1 and 2 trials, 1139 eligible patients were randomly assigned to induction therapy with oral tofacitinib at a dose of 10 mg twice daily or placebo for 8 wk. The primary endpoint was remission at the end of the study, and the key secondary endpoint was MH (Mayo endoscopic subscore of 0 or 1) at 8 wk. Of note, endoscopic results were centrally assessed by a blinded observer, a methodological advance that has been adopted in recent UC studies. In the OCTAVE Induction 1 trial, 18.5% of patients receiving tofacitinib achieved the primary end point, *i.e.*, remission at 8 wk compared with

8.2% of the placebo group ($P = 0.007$). In the OCTAVE Induction 2 trial, remission rates were 16.6% vs 3.6% ($P < 0.001$). Both trials displayed similar results for the key secondary endpoint. MH was achieved in 31.3% (OCTAVE 1) and 28.4% (OCTAVE 2) patients receiving tofacitinib vs 15.6% and 11.6% in the placebo groups, respectively ($P < 0.001$ for both comparisons). Although these success rates may appear unimpressive, it should be emphasized that both study populations were highly treatment-refractory. All patients had, in fact, failed to respond to conventional therapies for UC, including TNF-blockers, and approximately half were receiving corticosteroids at baseline. Nevertheless, in subgroup analyses, a consistent treatment effect of tofacitinib was observed in anti-TNF naïve and anti-TNF exposed patients.

In the OCTAVE Sustain trial, 593 patients who had completed the OCTAVE Induction 1 or 2 trial and had responded clinically to induction therapy were assigned to tofacitinib maintenance therapy (5 or 10 mg twice daily) or placebo for 52 wk. MH, a key secondary endpoint, occurred in significantly more patients than placebo in both groups. Specifically, MH was observed in 74/198 patients (37.4%) in the 5 mg group and in 90/197 (45.7%) in the 10 mg group, vs 26/198 (13.1%) in the placebo cohort ($P < 0.001$ for both comparisons). At week 24, MH was observed in 43.9% of the 5 mg group and in 46.2% of the 10 mg group vs 17.2% of the placebo group. Also at week 24, MH was maintained in 52.4% of participants with MH at baseline who received the 5 mg tofacitinib dose and in 66.3% who received 10 mg tofacitinib, compared with 21.8% in the placebo group ($P < 0.001$). Endoscopic remission, defined as an endoscopic subscore of 0, was another end-point. After 24 and 52 wk, it was observed in 16.2% and 14.6% of the 5 mg tofacitinib group and in 12.2% and 16.8% of the 10 mg tofacitinib group, respectively, vs 4% of placebo patients. Sustained endoscopic remission, defined as responses at both week 24 and 52, was 6.1% and 5.1% in the 5 mg and the 10 mg tofacitinib groups, respectively.

In post-hoc analyses of East Asian patients with active UC who were enrolled in global phase 3 induction and maintenance studies^[31], twice daily doses of 10 mg oral tofacitinib induced MH with greater efficacy than placebo. At week 8, 10 mg tofacitinib was associated with a 24.2% response rate vs 7.7% with placebo. Similarly, MH was achieved at week 52 in 45.5% of patients receiving 5 mg tofacitinib, and in 57.1% of those given 10 mg twice daily of tofacitinib vs 20.0% receiving placebo.

An ongoing, open-label, long-term extension study (OCTAVE Open)^[32] included non-responders from OCTAVE Induction 1 and 2, and patients who had completed or experienced treatment failure in OCTAVE Sustain. This trial was conducted in a subpopulation of 58 patients who achieved clinical response following 8 wk induction therapy with 10 mg twice daily tofacitinib.

The patients entered OCTAVE Sustain receiving 5 mg twice daily tofacitinib, but experienced treatment failure between week 8 and 52. In the OCTAVE Open, these patients were escalated to 10 mg tofacitinib twice daily, which induced MH in 41.4% and 60.4% patients at months 2 and 12, respectively, compared with baseline (5.2%)^[33].

Peficitinib

Peficitinib, a JAK1, JAK2, and JAK3 oral inhibitor, has an *in vitro* potency that is approximately 6- to 7-fold greater for JAK3 than for JAK1 and JAK2^[34]. In a phase 2b randomized, double-blind, placebo-controlled, dose-ranging trial, its efficacy and safety were evaluated in 219 patients with moderate-to-severe UC^[35]. Patients were equally randomized to receive oral placebo or 25, 75 or 150 mg peficitinib once daily, or 75 mg peficitinib twice daily. At week 8, patients were assessed for clinical response, and MH was one of the secondary endpoints. The Mayo endoscopic subscores were assigned by the local reader (blinded to treatment assignment) and the central reader (blinded to treatment assignment and clinical examination). Few patients achieved normal or inactive mucosal disease (endoscopy subscore of 0). At week 8, MH was observed in 20.5% (25 mg daily), 29.5% (75 mg daily), 45.5% (150 mg daily), 36.4% (75 mg twice daily) vs 18.6% of patients (placebo). While no dose-response of peficitinib was demonstrated in patients with moderate-to-severe UC, evidence of efficacy in achieving MH was suggested at doses ≥ 75 mg daily vs placebo.

Upadacitinib

Upadacitinib, a JAK 1 inhibitor, is being developed to treat rheumatoid arthritis and other inflammatory diseases. At present, it is being investigated as an oral treatment of UC^[36,37], but no results are yet available.

MODULATION OF SPHINGOSINE-1-PHOSPHATE RECEPTOR

The sphingosine-1-phosphate (S1P) receptor family consists of widely expressed receptors (S1P1 through S1P5) that are implicated in regulating multiple immunological and cardiovascular functions such as cell proliferation and migration, immune cell tracking, angiogenesis and the epithelial barrier^[38]. Targeting S1P receptors for inflammatory conditions was successful in clinical trials and is presently being investigated as a potential therapy for UC patients^[39]. The results of S1P receptor modulation to treat UC patients are summarized in Table 2.

Ozanimod

Ozanimod (RPC1063, Celgene) is a new oral selective S1P1 and S1P5 receptor modulator that is under investigation for the treatment of UC^[40]. The

Table 2 Summary of treatment results with sphingosine-1-phosphate receptor modulators, AJM300, and phospholipids in ulcerative colitis patients

Study	Drug	Study population	Treatment arm	Endoscopy endpoint	Time of observation, wk	Rate of mucosal healing
Sandborn <i>et al</i> ^[41]	Ozanimod	Moderate to severe UC patients (<i>n</i> = 197)	Dose of 0.5 mg or 1 mg or placebo, once daily	Mucosal healing (endoscopy subscore ≤ 1)	At 8 wk; at 32 wk	Placebo 12% Ozanimod 0.5 mg = 28%, (<i>P</i> = 0.03) Ozanimod 1 mg = 34%, (<i>P</i> = 0.002) At week 8 Placebo 12% Ozanimod 0.5 mg = 32%, (<i>P</i> = 0.006) Ozanimod 1 mg = 33%, (<i>P</i> = 0.005) At week 32 Placebo 29.4% AJM300 960 mg = 58.8% (<i>P</i> = 0.0014)
Yoshimura <i>et al</i> ^[46]	AJM300	Moderate to severe UC patients (<i>n</i> = 102)	Dose of 960 mg or placebo, 3 times daily	Mucosal healing, (endoscopic subscore of 0 or 1)	At 8 wk	None of 29 placebo patients DEAI (> 50%) in 11 of 29 evaluated of PC patients <i>P</i> = 0.00016
Stremmel <i>et al</i> ^[50]	Phosphatidylcholine-rich phospholipids	Chronic active, ulcerative colitis, with a clinical activity index (CAI) of > 4 (<i>n</i> = 60)	Dose of PC rich phospholipids (1.5 g / dose) or placebo, four times daily	Mucosal healing, was not formally assessed 48 patients were examined using the standard endoscopic activity index (EAI); Secondary end point analysis DEAI (> 50%)	At three mo	
Karner <i>et al</i> ^[51]	LT-02	Ulcerative colitis patients with an inadequate response to mesalazine, a disease activity score (Simple Clinical Colitis Activity Index (SCCAI)) of ≥ 5, and bloody diarrhea (<i>n</i> = 156)	Dose of LT-2 (0.8, 1.6 or 3.2 g) or placebo	Mucosal healing (endoscopic Mayo Score ≤ 1)	At 12 wk	Placebo 40.0% LT-2 0.8 g = 57.5%, (<i>P</i> = 0.097) LT-2 1.6 g = 56.1%, (<i>P</i> = 0.097) LT-2 3.2 g = 51.4%, (<i>P</i> = 0.097) Pooled LT-02 groups 55.2 (<i>P</i> = 0.098)

UC: Ulcerative colitis; OCTAVE: Oral Clinical Trials for tofacitinib in ulcerative colitis.

TOUCHSTONE study^[41], a randomised, double-blind, placebo-controlled phase II trial that recruited 197 patients with moderate to severe active UC, tested the efficacy and safety of ozanimod through induction and maintenance. Patients were randomised in a 1:1:1 ratio to receive once daily oral ozanimod at 1 mg (*n* = 67) and 0.5 mg (*n* = 65) concentrations or placebo (*n* = 65) for 8 wk (induction phase). Flexible sigmoidoscopy, with blinded central reading, was performed at screening and at week 8 and 32. The primary endpoint was clinical remission (defined as Mayo score ≤ 2 and no subscore > 1) at week 8. One of the exploratory secondary endpoints was MH (defined as an endoscopy subscore ≤ 1). Although ozanimod provided some benefits, most endpoints did not reach statistical significance. At 8 wk, 16% and 57% of patients receiving 1 mg daily ozanimod achieved clinical remission and clinical response, respectively, vs 6% and 37% of the placebo group, respectively. At 8 wk, significant endoscopic improvements were observed in patients receiving all doses of ozanimod compared with placebo. MH occurred

in 18/65 patients (28%) in the 0.5 mg group (*P* = 0.03), and in 23/67 patients (34%) in the 1 mg group (*P* = 0.002) vs 8/65 patients (12%) in the placebo group. However, no significant differences emerged in histological remission. The 32 wk double-blind maintenance phase included 103/197 (52.3%) patients who had been recruited in the induction phase and wanted to continue with their original treatment, with 91 (88.3%) patients completing maintenance. Explorative outcome measures at week 32 included clinical response, histological remission, clinical remission and MH. At weeks 8 and 32, MH was observed in 32% (0.5 mg) and 33% (1 mg) of patients, respectively, compared with 12% in each placebo group, however these differences did not reach statistical significance. One limitation of the study was the time point for primary outcome analysis, since 8 wk might not have been long enough for ozanimod to target lymphocyte trafficking. Moreover, the long-term safety profile could not be assessed because the cohort of patients was relatively small and the follow-up was short. Larger studies with longer follow-ups

are therefore needed. Since ozanimod displayed some potential benefits and the results appeared promising, two phase III studies for induction and maintenance therapy are currently underway to further evaluate the potential role of ozanimod in moderate to severe UC^[42,43].

Other S1P modulators

Etrasimod (APD334), a S1P-R₁ modulator, is currently being investigated in a phase 2 study as a potential therapeutic agent for UC patients^[44].

SMALL-MOLECULE $\alpha 4$ INTEGRIN ANTAGONISTS

AJM300

AJM300, a new, orally active small molecule, is classified as a phenylalanine derivative and is currently being developed for UC^[45]. Both the efficacy and safety of AJM300 were tested in a Japanese randomized, double-blind, placebo-controlled phase IIa study^[46] conducted on 102 patients with moderately active UC who were intolerant or showed an inappropriate response to mesalazine or steroids. For 8 wk, patients were orally administered 960 mg of AJM300 or placebo 3 times daily. The primary endpoint was clinical response. Secondary endpoints were clinical remission (defined as a Mayo Clinic score of 2 or lower and no sub-score higher than 1) and MH (defined as an endoscopic sub-score of 0 or 1, and a partial Mayo Clinic score). Endoscopic assessment with biopsy was performed at baseline and at week 8, and the endoscopic sub-scores were analysed by a central evaluation committee. In this study, 62.7% of patients receiving AJM300 and 25.5% of the placebo group had a clinical response at week 8. MH was achieved by 58.8% of patients (30/51) in the active treatment arm and by 29.4% (15/51) in the placebo group. Although the difference was not significant, more patients in the active treatment arm achieved endoscopic subscores of 0 at week 8 than in the placebo group.

The most concerning adverse event of an $\alpha 4$ integrin blockade is the development of progressive multifocal leukoencephalopathy, a demyelinating central nervous system disorder caused by JC viral infection and reactivation. However, neither infection nor neurological symptoms were observed in this study. These data demonstrated the feasibility of AJM300 treatment, particularly when it is delivered in a gut-specific manner. A phase III Study of AJM300 in UC patients is currently ongoing^[47]. The results of AJM300 treatment for UC patients are summarized in Table 2.

SUBSTITUTION OF PHOSPHATIDYLCHOLINE

LT02

Phosphatidylcholine, which prevents bacterial invasion,

is reduced by up to 70% in the colonic mucus of UC patients^[48]. Therefore, phosphatidylcholine substitution in the colonic mucus might be an interesting future therapeutic approach^[49]. In a double-blind, randomized, placebo-controlled phase IIa study, 60 patients with UC were treated with 6 g of phosphatidylcholine-rich phospholipids for 3 mo^[50]. The phospholipids were released in the distal ileum in a pH-dependent manner. Significant improvements in clinical remission and clinical response, the primary endpoints, were observed compared with placebo, together with significant positive effects in endoscopic and histological assessments. However, MH was not formally assessed.

LT-02, a novel modified-release phosphatidylcholine agent, was investigated for mucosal barrier enhancement in UC. In a double-blinded, randomized, placebo-controlled, multi-centre phase II study^[51], LT-02 was administered to a total of 156 patients with an inadequate response to mesalazine, characterized by a disease activity score ≥ 5 [Simple Clinical Colitis Activity Index (SCCAI)] and bloody diarrhea. The patients were randomized into three treatment groups orally receiving 0.8, 1.6 or 3.2 g of LT-02 or placebo. The primary endpoint was clinical response after 3 mo therapy, as indicated by changes in SCCAI from baseline to the end of treatment. Data analysis showed a 33.3% SCCAI drop in the placebo group compared with 44.3% in the 0.8 g LT-02 group ($P > 0.05$) and 40.7% in the 1.6 g group ($P > 0.05$). The 3.2 g group improved by 51.7%, falling from 8.5 to 4.1 ($P = 0.030$ vs placebo). The remission rate was 15% (6/40) in the placebo group vs 31.4% (11/35) in the highest LT-02 dose group ($P = 0.089$). MH was achieved in 32.5% of the placebo group vs 47.4% in the pooled LT-02 groups ($P = 0.098$). The histological healing rate (histological index = 1) was 20.0% in the placebo cohort vs 35.3% in the LT-02 groups ($P = 0.016$). In a second analysis, considering dropouts as failures, endoscopic remission but not clinical remission reached statistical significance. Histological remission was reached significantly more often in the treatment groups. No serious adverse events were observed and there were no deviations in adverse events in the treatment groups. The authors concluded that, compared with placebo, LT-02 is useful for reducing disease activity in UC and is associated with a good safety profile. The results of such treatments for UC patients are summarized in Table 2.

CONCLUSION

The new oral-targeted therapies seem to be effective for UC patients. They share some common characteristics, such as shorter half-lives, potential off-target effects, relatively narrow dosing windows and lack of immunogenicity. The mechanisms of action of the four classes of these oral synthetic drugs include: (1) Jak-inhibitors, which reduce the production of several cytokines, (2) AJM300, which blocks lymphocyte

trafficking from blood vessels into the lamina propria, (3) ozanimod, which prevents egression of lymphocytes from lymph nodes by following the S1P gradient *via* receptor internalization, and (4) LT-02, a substitute of phosphatidylcholine. Further studies are ongoing and will establish the value of these agents for the treatment of UC patients in clinical practice. They could potentially offer three major advantages: (1) As an alternative for patients who mount immunogenic responses to biologics, (2) in association to other drugs, as innovative combination strategies, and (3) to investigate stop and start therapeutic strategies. Moreover, with convenient storage, they might be potentially transported into the site of action and act as topical therapy. On the other hand, multiple daily dosing, uncertainties about bioavailability at the right target site and adverse events may constitute the potential disadvantages of this therapeutic approach.

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