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EDITORIAL

Tofacitinib for the treatment of ulcerative colitis: A review of the literature

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Abstract

Ulcerative colitis (UC) is a chronic immune-mediated inflammatory condition affecting the colon. Recently, tofacitinib, an oral small molecule that is an inhibitor of the Janus kinase signal transduction pathway, was proven efficacious for inducing and maintaining remission in adult patients with moderate to severe UC in three global Phase III studies. The purpose of this review is to summarize existing data on the efficacy, safety, and quality of life issues related to use tofacitinib as well as highlight recent real-world experience with this drug among patients with UC.

Key words: Ulcerative colitis; Tofacitinib; Review; Inflammatory bowel disease; Treatment

Core tip: Tofacitinib is a small molecule that is an inhibitor of the Janus kinase signal transduction pathway, and it is the first oral medication approved for chronic use among adults with moderately to severely active ulcerative colitis (UC). Three large phase III trials have shown overall efficacy and safety; however, long-term results and real-world data are lacking in the literature. Our objective is it consolidate the current literature to better understand what is currently known about efficacy, safety, quality of life, and real-world experience with this medication among patients with UC.

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INTRODUCTION

Ulcerative colitis (UC) is a chronic inflammatory condition that primarily affects the colon, due to an abnormal dysregulation of the immune system. The pattern of disease activity is most often described as relapsing and remitting, with some patients experiencing persistent disease activity despite diagnosis and medical therapy. Therapeutic decisions are subcategorized into induction and maintenance modalities, with a primary treatment endpoint of obtaining and maintaining both endoscopic healing and symptomatic remission. The current therapeutic armamentarium for UC treatment includes corticosteroids, immunosuppressants, aminosalicylates, immunomodulators, anti-tumor necrosis factor (TNF) agents, as well as anti-integrins. Recently, tofacitinib, an oral small molecule that is an inhibitor of the Janus kinase (JAK) signal transduction pathway, was found to be effective in both inducing and maintaining remission in adult patients with moderate to severe UC in three global Phase III studies[1,2]. Tofacitinib has been used for the treatment of adults with moderate-to-severe rheumatoid arthritis (RA) since its initial Food and Drug Administration (FDA) approval in 2012, and in 2018 the FDA expanded this approval to include treatment of adults with moderate to severe UC. It should be noted that this medication has not been FDA approved for the use in pediatric populations. It is unique in that it is the first of its kind oral medication with FDA approval for treatment of moderate to severe UC.

Given its status as a relative newcomer in the treatment of UC, there is limited evidence of the long-term safety and efficacy of tofacitinib in this patient population. The purpose of this review is to summarize existing data on the safety, efficacy, and quality of life issues related to the use of tofacitinib as well as highlight recent real-world experience with this drug among patients with UC.

REVIEW OF THE LITERATURE

Data on efficacy

In a phase 2 double-blind, randomized, placebo-controlled trial by Sandborn *et al*[1] involving patients with moderate-to-severe UC, a significantly higher rate of response at 8 wk was found among those who received tofacitinib at a dose of 15 mg twice daily than among those who received placebo and also a significantly higher rate of remission with tofacitinib at doses of 3 mg, 10 mg, and 15 mg twice daily than with placebo.

Subsequently, Sandborn *et al*[2] reported the results of phase 3 trials of tofacitinib as induction therapy (OCTAVE Induction 1 and 2) and maintenance therapy (OCTAVE Sustain) in patients with moderate-to-severe UC. Enrolled patients had moderate-to-severe UC and had experienced previous treatment failure with or unacceptable side effects from glucocorticoid, thiopurine, or anti-TNF therapy. For all three trials, the primary end point was remission, which was based on Mayo scores. The rate of remission at 8 wk was significantly higher in the 10-mg tofacitinib group than in the placebo group in the OCTAVE Induction 1 trial (18.5% *vs* 8.2%, $P = 0.007$) and in the OCTAVE Induction 2 trial (16.6% *vs* 3.6%, ($P < 0.001$)). The rate of remission at 52 wk was significantly higher in the 5-mg and 10-mg tofacitinib groups (34.3% and 40.6%, respectively) than in the placebo group (11.1%) in the OCTAVE Sustain trial.

Although there have been no head-to-head clinical trials comparing tofacitinib to biologics, meta-analyses have been conducted to address this important question. A recent systematic review and network meta-analysis by Bonovas *et al*[3] aimed to comparatively assess efficacy of tofacitinib and biologics (infliximab, adalimumab, golimumab and vedolizumab) in adult patients not previously exposed to anti-TNF agents. In terms of clinical response, clinical remission, and mucosal healing, each drug demonstrated superiority over placebo. However, no indirect comparisons between tofacitinib and biologics reached statistical significance.

A recent network meta-analysis found that tofacitinib has the highest rank for induction of clinical remission among patients with prior anti-TNF exposure. In an effort to analyze the comparative safety and efficacy of differing therapies as first line (biologic-naïve) and second line (previous exposure to anti-TNF agents) therapies for moderate-severe UC, Singh *et al*[4] conducted a systematic review and network meta-

analysis. They found that while infliximab and vedolizumab were ranked highest for induction of clinical remission amongst biologic-naïve patients, among patients with prior anti-TNF exposure, tofacitinib was ranked highest for induction of clinical remission [OR: 11.88 (2.32-60.89)] and mucosal healing.

Safety and adverse events

Tofacitinib has been associated with an increased risk of infections among patients with RA[5] and psoriasis[6]. In the OCTAVE trials[2], there were higher rates of infections with tofacitinib as compared to placebo, and the rate of serious infection was found to be increased with tofacitinib in the induction trials, but similar across treatment groups in the maintenance trial. Overall, 2.9% of subjects suffered at least one serious infection compared with 1.0% of the placebo controls, including anal abscess, pneumonia, herpes zoster (HZ) infection, Clostridium difficile infection, and cytomegalovirus colitis.

In OCTAVE Sustain, HZ infections occurred in 14 patients total, 3 (1.5%) in the 5 mg group, 10 (5.1%) in the 10 mg group and 1 (0.5%) in the placebo group. An analysis of the safety of tofacitinib for the treatment of moderate to severe UC based on more than four years of data from global clinical trials by Sandborn *et al*[7] again suggest what appears to be a dose-dependent relationship with HZ infection, with those taking 10 mg BID at highest risk. For the overall cohort, the incident rate of HZ infection was 4.1 (95%CI: 3.1-5.2). Winthrop *et al*[8] conducted an analysis specifically examining the risk of HZ in patients with UC using tofacitinib. They found that among HZ incidence was 4.07 per 100 person-years among all patients with UC treated with tofacitinib, and again found a dose-dependent risk. It should be noted that the majority of HZ events were uncomplicated and mild to moderate in severity. Independent risk factors for HZ in these patients with UC included advanced age and prior anti-TNF failure[9]. In addition, patients with Asian race (IR: 6.49; 95%CI: 3.55-10.89), oral corticosteroid use at baseline (IR: 5.14; 95%CI: 3.56-7.18), history of diabetes mellitus (IR: 8.06; 95%CI: 2.96-17.55), and those who received the 10 mg twice daily dosing (IR: 4.25; 95%CI: 3.18–5.65) were at higher risk for HZ infection.

The new recombinant HZ subunit vaccine (RZV) could decrease the risk of HZ from tofacitinib; it is currently only recommended for immunocompetent adults aged ≥ 50 years. However, given the known risk of this infection, it remains to be seen whether it may be warranted to administer the RZV vaccine to all inflammatory bowel disease (IBD) patients of all ages treated with tofacitinib, including those younger than 50. A recent study by Caldera *et al*[10] attempts to further clarify this question by calculating the number needed to harm (NNH) in order to quantify the risk of HZ in patients treated with tofacitinib as compared to those with alternative treatments for UC, including infliximab and vedolizumab. They found that the higher 10 mg twice a day dosing of tofacitinib had the highest risk for HZ infection when compared to placebo with an NNH of 22 patients; the combined NNH for both treatment groups (5 mg and 10 mg) combined was 36 patients. The information gathered from these studies can collectively inform our clinical approach towards addressing the potential risk of HZ. Currently suggested approaches for lowering the risk of HZ include potentially vaccinating younger patients including those less than 50 years old on tofacitinib, who demonstrate risk factors for HZ including steroid use, Asian race, or diabetes mellitus. Moreover, educating patients to recognize early symptoms of HZ, and closely monitoring patients with UC during induction therapy in order to maintain the lowest effective dose – or, to withdraw the drug entirely in non-responders are other approaches. Of note, it is recommended to avoid the use of live vaccines concurrently with this medication[11]. Further research is needed both on understanding risk factors for HZ as well as regarding the safety and efficacy of the RZV series in patients receiving tofacitinib for treatment of UC.

Among RA patients, gastrointestinal perforations have been observed with the use of tofacitinib[5]. Across the OCTAVE trials, one intestinal perforation occurred with tofacitinib; in the OCTAVE Induction 1 trial, 1 patient in the 10-mg tofacitinib group had a serious adverse event of intestinal perforation. In the OCTAVE Induction 2 trial, a single patient in the placebo group had a serious adverse event of intestinal perforation. No patients in the OCTAVE Sustain trial experienced intestinal perforation[2].

There is some data to suggest an increase in malignancy risk among RA patients treated with tofacitinib. In a worldwide, 3-year, post-marketing surveillance study on tofacitinib in patients with RA[12], the relative risk per 100 patient-years for neoplasms was 0.45, with the most common neoplasms being nonmelanoma skin cancers (NMSCs). Fifteen cases of lymphoma were documented over approximately 34000 patient-years of exposure, and the risk of lymphoma was not found to increase over time. The data on malignancy risk among UC patients using tofacitinib is much more limited. In an integrated analysis of tofacitinib UC clinical trials, eleven patients had

malignancies (excluding NMSC), all during OCTAVE Open[7]. There 1 case reported for each of the following cancers: Cervical cancer, hepatic angiosarcoma, cholangiocarcinoma, cutaneous leiomyosarcoma, Epstein-Barr-virus-associated lymphoma, renal cell carcinoma, essential thrombocythemia, acute myeloid leukemia, adenocarcinoma of colon, lung cancer, and breast cancer. In the overall cohort, IR of malignancy (excluding NMSC) including all 11 patients with events was 0.7 (95%CI: 0.3-1.2).

Additional studies have analyzed other important safety-related questions regarding tofacitinib. Cases of maternal and paternal exposure to tofacitinib (defined as parental exposure to tofacitinib before or at the time of conception and/or during the course of pregnancy) were identified in the Pfizer safety databases in a study by Mahadevan *et al*[13] Of 1157 patients enrolled in the UC interventional studies, 11 cases of maternal exposure and 14 cases of paternal exposure to tofacitinib (doses of 5 mg or 10 mg twice daily) before or at the time of conception or during pregnancy were identified. Outcomes included 15 healthy newborns, no fetal deaths, no neonatal deaths, no congenital malformations, 2 spontaneous abortions, and 2 medical terminations. Overall, they found that outcomes across other tofacitinib studies and post-marketing cases were consistent, with a healthy newborn being the most common outcome and no fetal deaths. However, it is important to note that tofacitinib has been found to be teratogenic in animal models and is contraindicated in patients who are attempting to become pregnant[11].

There has been interest in understanding the association between tofacitinib and lipid profiles since an early pooled analysis demonstrated dose-dependent increases in total cholesterol, LDL-C, and HDL-C among patients with RA[14]. In the OCTAVE trials, as compared with placebo, tofacitinib was associated with increased lipid levels as well[2]. More recently, Sands *et al*[15] analyzed lipid concentrations and incidence rates of major adverse cardiovascular (CV) events (MACEs) in patients with UC who received and found that after 8 weeks of therapy, there were greater increases from baseline in total cholesterol, HDL-C, and LDL-C in patients on tofacitinib compared with placebo. Four MACEs were reported; the incidence rate was 0.24 (95%CI: 0.07-0.62), and 3 of these patients had 4 or more CV risk factors. Overall, they did not find clinically meaningful changes in lipid ratios or CV risk scores, and MACEs were found to be infrequent and not dose-related.

Importantly, an association between thromboembolic events and higher doses of tofacitinib was recently noted. Early results from the RA Study, an ongoing open-label clinical trial of patients over the age of 50 with at least one cardiac risk factor, show an increased risk of pulmonary embolism and overall mortality among study participants receiving tofacitinib at 10 mg twice daily as compared to 5 mg[16]. Currently, the European Medicines Agency's safety committee is recommending against the use of 10 mg twice daily dose of tofacitinib in patients who are at high risk of thromoembolic disease including pulmonary embolism, as well as those with heart failure, cancer, history of blood clots, or taking combined hormonal contraceptives[17]. Given that the recommended induction dosage for UC is 10mg twice daily, more data is needed to evaluate this potentially serious association.

Quality of life

Paschos *et al*[18] conducted a systematic review with network meta-analysis aiming to compare the impact of interventions for moderate-to-severe UC on health-related quality of life (HRQL); they found that induction therapy with tofacitinib improves quality of life of patients with moderate-to-severe UC, the beneficial effect of which is maintained during maintenance therapy. This was supported by Panés *et al*[19] who found that tofacitinib 10 mg twice daily induction therapy significantly improved HRQL versus placebo at week 8. These improvements were persistent through 52 wk' maintenance therapy with tofacitinib 5 mg and 10 mg twice a day.

Real-world experience

Recently, Weisshof *et al*[20] published their real-world experience with tofacitinib used for treatment of patients with moderate-to-severe IBD. In this retrospective, observational study, 58 patients (including 53 with UC) completed at least 8 wk of treatment with tofacitinib. Clinical response and adverse events were assessed at 8 wk (induction), at 26 wk (maintenance), at 52 wk, and at the last available follow-up. They found that at 8 wk of treatment, 21 patients (36%) achieved symptomatic improvement, and 19 (33%) achieved clinical remission. Steroid-free remission at 8 wk was achieved in 15 patients (26%). Of the 48 patients followed for 26 wk, 21% had clinical, steroid-free remission. Of the 26 patients followed for 12 mo, 27% were in clinical remission and remained steroid-free.

Rapid clinical response has been suggested in several studies. Hanauer *et al*[21] assessed the timing of symptom improvement in post-hoc analyses of data from 2

phase 3 trials of induction therapy with tofacitinib in patients with UC (OCTAVE Induction 1 and 2); they found significant improvements in symptoms among patients given tofacitinib compared with placebo within 3 d, indicating a rapid onset of effect of this drug in patients with UC. In a case study by Griller *et al*[22], tofacitinib and infliximab were used as combination rescue therapy to avoid colectomy in a hospitalized patient with severe UC. The patient received intravenous steroids and 2 loading doses of infliximab with minimal improvement and then started on 10 mg tofacitinib twice daily as rescue therapy; the patient improved dramatically within 48 hours and subsequently achieved clinical remission.

In an off-label use of tofacitinib, Berinstein *et al*[23] presented the first reported use of tofacitinib in 4 in patients with acute severe UC (ASUC) predicted to fail medical management, based on severe Truelove and Witt's criteria, C-reactive protein (CRP) > 100 mg/L at presentation, endoscopic features during admission, and prior failure of IV corticosteroids or infliximab therapy. After receiving tofacitinib, all 4 patients had a rapid improvement in clinical symptoms and decline in CRP. Two patients achieved clinical remission with a combination of tofacitinib and IV corticosteroids, whereas one patient achieved clinical remission with tofacitinib and budesonide only. One patient was unable to achieve clinical remission, although they did experience an initial rapid improvement in symptoms and CRP until tofacitinib was reduced. No major adverse effects directly attributable to the use of tofacitinib were reported during the induction phase of drug administration or up to 18 mo of reported follow-up.

DISCUSSION

IBD is a chronic condition affecting millions of people of all ages worldwide, with prevalence highest in Europe and North America, and rising incidence in newly industrialized countries in Africa, Asia and South America[24]. With ever-increasing targeted research on novel therapeutics, the treatment of IBD continues to evolve. Tofacitinib is currently the only JAK kinase inhibitor with FDA approval for the treatment of patients with moderate-to-severe UC.

Overall, clinical data shows that tofacitinib is effective in inducing and maintaining clinical remission, clinical response, and mucosal healing. Additionally, analysis of the OCTAVE 1 and 2 trials suggests a rapid onset of action with response as early as day 3[21]. Studies also indicate that tofacitinib has a favorable effect on quality of life[18,19].

In the OCTAVE trial, HZ reactivation was more frequent among patients under tofacitinib 10mg twice a day (5.1%) compared with other treatment groups (1.5% and 0.5% across tofacitinib 5mg twice a day and placebo, respectively). Vaccination can help lower the risk of infection, and an inactivated recombinant varicella zoster vaccine is now available, which in clinical trials has demonstrated 97% efficacy among adults ≥ 50 years of age[25]. Further research is needed both on understanding risk factors for HZ as well as regarding the safety and efficacy of the RZV series in patients on tofacitinib.

Recent safety data suggests that pulmonary embolism may potentially be a class-wide issue for JAK inhibitors; however, these data need to be confirmed by future adverse events reporting trends and clinical trials. Currently, the European Medicines Agency's safety committee is recommending against the use of 10 mg twice daily dose of tofacitinib in patients who demonstrate risk factors for thromboembolic disease.

Real-world experiences with the use of tofacitinib are lacking in the literature. Weisshof *et al*[20] published their real-world experience with the use of tofacitinib for treatment of patients with moderate-to-severe IBD; they found that at 8 wk of treatment, 21 patients (36%) achieved symptomatic improvement, 19 (33%) achieved clinical remission, and 15 (26%) achieved steroid-free remission. Overall, tofacitinib induced clinical response in 69% of the patients and 27% were in clinical, steroid-free remission by 1 year of treatment, suggesting that tofacitinib can be an effective treatment alternative for patients with anti-TNF resistant IBD. Tofacitinib has also been used as a combination rescue therapy with infliximab to avoid colectomy in a hospitalized patient with severe UC[22], as well as in inpatients with ASUC predicted to fail medical management[23] with good success.

Currently, there is an ongoing Phase III long-term extension study known as OCTAVE Open that aims to assess the safety, tolerability, and efficacy of long-term tofacitinib therapy; it includes non-responders in OCTAVE Induction 1 or 2, treatment failures in OCTAVE Sustain, and those who completed OCTAVE Sustain. OCTAVE Open will assess safety through an analysis of adverse events, clinical laboratory parameters, and physical examination, as well as efficacy as determined by clinical response and endoscopy at predetermined intervals.

Other future research directions to be pursued include head-to-head trials to determine the most optimal therapies in UC. In addition, there is currently limited data on the efficacy of combining tofacitinib therapy with biologics among patients with UC. Within the RA population, there is some data to support safety with combination therapy; a case series of 6 patients with RA treated with tofacitinib–biologic combination therapy did not find any adverse events after a mean of 14 months of treatment[26]. Le Berre *et al*[27] report a case of successful combination of vedolizumab and tofacitinib in a patient with UC and spondyloarthropathy for whom anti-TNF therapy was contraindicated; after 3 mo of treatment with this combination therapy, the patient achieved clinical remission for both gastrointestinal and rheumatologic symptoms. No adverse events were observed, including no infections. Additionally, rapid remission was achieved recently in an inpatient as described by Griller *et al*[22], when tofacitinib and infliximab were used as combination rescue therapy to avoid colectomy in a hospitalized patient with severe UC. Interestingly, as a stand-alone medication, it should also be highlighted that the economic burden to the patient for the cost of tofacitinib is likely less than compared to alternative therapies such as anti-TNFs and vedolizumab[28]. Overall, the available evidence remains limited regarding UC patients, and larger studies are needed to confirm the efficacy and safety profile of combination therapy in this patient population.

At this time, further novel subtype-selective JAK kinase inhibitors are currently being developed. Additional studies are required to better understand long-term efficacy, safety profiles, and the optimal positioning of agents like tofacitinib in management algorithms for UC.

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