



Real-World Experience with Tofacitinib in IBD at a Tertiary Center

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Abstract

Background and Aims Many inflammatory bowel disease (IBD) patients do not respond to medical therapy. Tofacitinib is a first-in-class, partially selective inhibitor of Janus kinase, recently approved for treating patients with ulcerative colitis (UC). We describe our experience with the use of tofacitinib for treatment of patients with moderate-to-severe IBD.

Methods This is a retrospective, observational study of the use of tofacitinib in IBD. Patients with medically resistant IBD were treated orally with 5 mg or 10 mg twice daily. Clinical response and adverse events were assessed at 8, 26, and 52 weeks. Objective response was assessed endoscopically, radiologically, and biochemically.

Results 58 patients (53 UC, 4 Crohn's, 1 pouchitis) completed at least 8 weeks of treatment with tofacitinib. 93% of the patients previously failed treatment with anti-TNF. At 8 weeks of treatment, 21 patients (36%) achieved a clinical response, and 19 (33%) achieved clinical remission. Steroid-free remission at 8 weeks was achieved in 15 patients (26%). Of the 48 patients followed for 26 weeks, 21% had clinical, steroid-free remission. Of the 26 patients followed for 12 months, 27% were in clinical, steroid-free remission. Twelve episodes of systemic infections were noted, mostly while on concomitant steroids. One episode of herpes zoster infection was noted during follow-up.

Conclusions In this cohort of patients with moderate-to-severe, anti-TNF resistant IBD, tofacitinib induced clinical response in 69% of the patients. 27% were in clinical, steroid-free remission by 1 year of treatment. Tofacitinib is an effective therapeutic option for this challenging patient population.

Keywords Ulcerative colitis · Inflammatory bowel disease · Tofacitinib · Jak inhibitors

Introduction

Inflammatory bowel disease (IBD), which includes Crohn's disease (CD) and ulcerative colitis (UC), is a chronic inflammatory condition affecting 3.1 million Americans with an increasing incidence worldwide [1]. The pathogenesis of the disease is thought to involve a complex interaction between the immune system and genetic, environmental, and microbial factors [2]. Until recently, the major treatment options have included 5-ASAs, immunomodulators, and biologic therapies that consist of antibodies that target tumor necrosis factor- α (TNF), integrins, as well as other cytokines [3].

However, despite these diverse treatment options, a large number of patients are not responsive or eventually lose response to therapy [4, 5].

Tofacitinib is an oral, partially selective Janus kinase (JAK) inhibitor. It is a small molecule that works intracellularly to inhibit JAK-dependent cytokine signaling. JAK1 and JAK3, which mediate the intracellular effects from several inflammatory cytokines, are the major targets of the drug *in vivo*, and their inhibition results in modulation of the immune and inflammatory response [6]. Several inflammatory cytokines play a specific role in IBD pathogenesis by utilizing the JAK pathway. These include IFN- α , IFN- β , IL-6, IL-7, IL-10, IL-12, IL-15, IL-21, and IL-23 [7]. Tofacitinib has been FDA-approved for the treatment of adults with moderate-to-severe rheumatoid arthritis (RA) since 2012. Three large clinical trials have demonstrated tofacitinib's effectiveness in inducing (OCTAVE 1 and 2) and maintaining (OCTAVE Sustain) remission in patients with UC [8]. Tofacitinib was recently approved by the FDA

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and EMA for the treatment of adult patients with moderate-to-severe active UC. We report our experience with tofacitinib for medically resistant IBD.

Methods

Patients and Data Collection

We performed a retrospective observational study describing the use of tofacitinib at the IBD Center at the University of Chicago. All adult patients with IBD treated with tofacitinib between December 2014 and July 2018 were included in the study. The diagnosis of CD or UC was established using standard clinical, endoscopic, and histologic criteria. All patients had completed at least 8 weeks of treatment of either 5 or 10 mg of tofacitinib given twice daily. All patients treated until May 30, 2018, received off-label tofacitinib. Patients treated after FDA approval received the drug as part of their standard of care management. In some cases, corticosteroids were given with the drug due to active symptoms. Later, it was tapered, according to the clinical response, at the treating physicians' discretion.

Patients' demographic, clinical, laboratory, radiographic, and endoscopic data were attained by a comprehensive review of their electronic medical records. The following baseline characteristics were recorded: patient features (age, gender, smoking status, and other medical history), disease features (age at diagnosis, duration of disease, disease location and phenotype according to Montreal classification, and prior treatment), tofacitinib treatment (induction and maintenance doses, duration of treatment, and concomitant therapy), biochemical inflammatory markers [C-reactive protein (CRP), fecal calprotectin (FCP)], and endoscopic findings. Clinical response and adverse events were assessed at 8 weeks (induction), at 26 weeks (maintenance), at 52 weeks, and at the last available follow-up. Objective outcomes were evaluated when possible from the patient's medical record including CRP, FCP, imaging, and endoscopy. The study was approved by the institutional ethics review board. None of the patients participated in other tofacitinib clinical trials (including the OCTAVE program).

Outcomes

Response to treatment was determined as defined by the patient's provider and the decision to continue therapy. Response was defined as symptomatic improvement but not resolution, and remission was defined as complete resolution of clinical symptoms. Endoscopic improvement was defined as decrease in the Mayo endoscopic subscore determined by the physician performing the procedure. The absence of significant improvement in symptoms, cessation of treatment

with tofacitinib, or referral for surgery was defined as failure to response. A relapse was defined as a therapeutic failure developing after the initial response was achieved or when the patient or provider decided to stop treatment. Adverse events which have previously been associated with tofacitinib treatment were retrospectively assessed. These include infections, changes in lipid profile, reduced creatinine clearance, elevation in liver enzymes, and changes in hematological counts.

Statistical Analysis

Descriptive statistics are provided using means and standard deviation for continuous variables and proportions with 95% confidence interval for discrete variables. Student's *t* test was used for comparison of continuous variables. Mann–Whitney *U* test was used as nonparametric test for the relevant comparisons. Kaplan–Meier analysis was performed for treatment failure-free survival. *P* value < 0.05 was considered as a threshold of statistical significance. Prism version 7 was used for statistical analysis.

Results

Patient Characteristics

A total of 80 patients were prescribed with tofacitinib in our center between December 2014 and July 2018. Of those, 13 patients have not yet completed 8 weeks of treatment, and 9 were excluded due to other reasons (treatment was denied by insurance, decision was made to proceed to surgery, adherence, and lost to follow-up). Fifty-eight patients completed at least 8 weeks of treatment with tofacitinib during the 3-year study period. Of those, 49 patients were treated before the drug was ultimately approved by the FDA. Fifty-three patients (91%) had a diagnosis of UC, four (7%) had ileocolonic CD, and one patient had resistant pouchitis after ileal pouch–anal anastomosis (IPAA). The median follow-up time was 10.6 months (interquartile range 5.6–21.8 months). All but four patients had previously failed treatment with anti-TNF (93%), and 81% had failed anti-integrin. The patients' clinical and demographic characteristics are described in Table 1.

Clinical Response and Remission

A total of 58 patients completed 8 weeks of treatment. Of those, 21 patients (36%) had a clinical response. Nineteen patients (33%) achieved clinical remission, of which 14 (24%) were also steroid-free.

Forty-eight patients were followed up for at least 26 weeks. Of those, 13 patients (27%) had clinical

Table 1 Patients’ characteristics

Total number of patients	58
<i>Disease</i>	
Ulcerative colitis	53
E2	24
E3	29
Crohn’s disease	4
Pouchitis	1
Gender (M/F)	36/22
Age at induction (years) {median (IQR)}	39.7 (29–53)
Duration of disease (years) {median (IQR)}	10.4 (3.1–14.3)
Hemoglobin at induction (gr/dL) {median (IQR)}	13.55 (12.5–14.8)
LDL cholesterol at induction (mg/dL) {median (IQR)}	100 (76–118.5)
<i>Previous medications {number (%)}</i>	
Anti-TNF	54 (93%)
Vedolizumab	47 (81%)
Immunomodulators	46 (79%)
Calcineurin inhibitors	23 (40%)
Ustekinumab	2 (3%)
<i>Concomitant medications {number (%)}</i>	
Systemic corticosteroids	27 (47%)
Immunomodulators	5 (9%)
Vedolizumab	3 (5%)
Prednisone dose equivalent, mg {median (IQR)}	15 (10–27.5)
Clinical follow-up duration, months {median (IQR)}	10.6 (5.6–21.8)

response, and 12 (25%) were in clinical remission. All but two patients were also steroid-free at this time point (21%). Out of 25 patients, 24 (96%) in this group were already responsive at the end of induction.

A total of 26 patients completed 52 weeks of follow-up. Five patients (19%) were clinically responsive to the drug. Seven patients (27%) were in clinical, steroid-free remission at this time (Fig. 1).

The proportion of patients still being maintained on tofacitinib at 3 months, 6 months, and 12 months was 69%, 55%, and 51%, respectively (Fig. 2), demonstrating sustained efficacy of therapy in a majority of patients. Furthermore, patients receiving tofacitinib were able to reduce their corticosteroid doses from a median of 10 mg to a median of 0 mg.

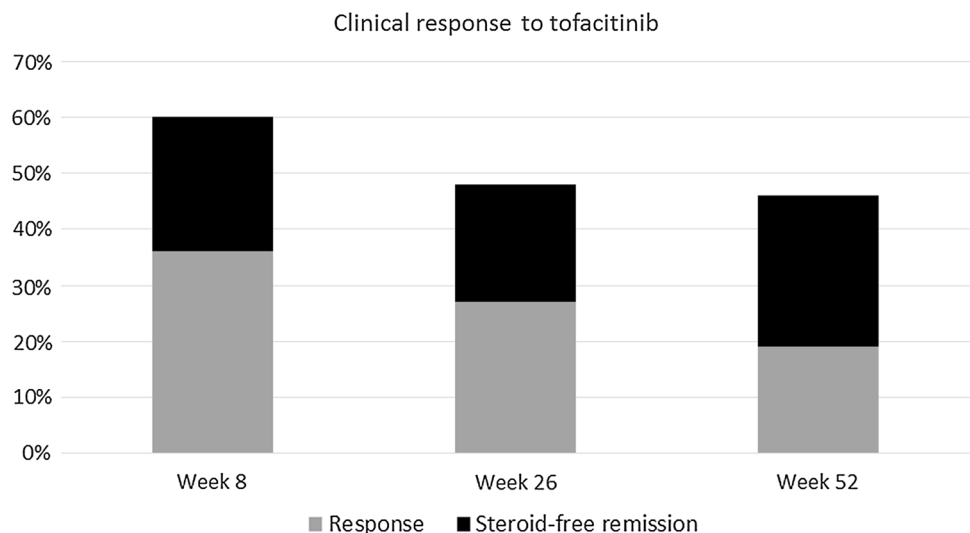
Twenty-six patients discontinued the drug secondary to poor response or adverse events and were subsequently treated surgically or medically. Fourteen patients with UC underwent total proctocolectomy, and one patient with CD required fecal diversion to achieve remission (and was left with diverting ileostomy by the end of follow-up after 2 years). There was a washout period of at least 24 h before surgery. The other patients who failed the drug were treated medically with anti-TNF- α , anti-integrin, anti-IL-12/23 (without prior washout period), or experimental clinical trial drug.

Dose

The induction dose was 5 mg twice daily for 22 patients (38%) and 10 mg twice daily for 35 patients (60%). One patient received a daily dose of 11 mg of the extended release formulation. The initial dose of tofacitinib was not correlated with clinical response at 8 weeks (Table 2). Ten patients on 5 mg twice daily required dose escalation to 10 mg twice daily, and eight had a positive clinical response.

A trial of off-label, short-time (2–4 weeks), high-dose treatment (15 mg twice daily) was done in seven patients with severe resistant disease and showed limited effect.

Fig. 1 Response rates to tofacitinib



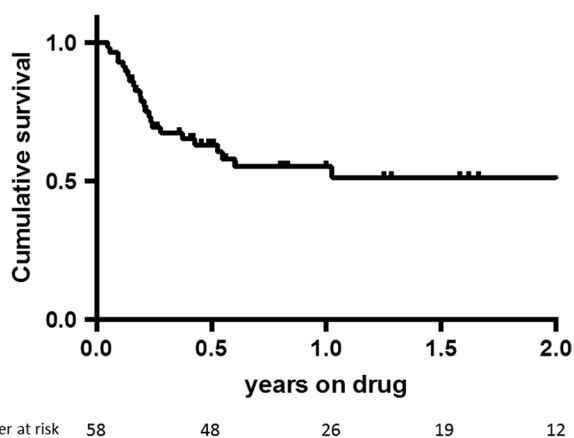


Fig. 2 Kaplan–Meier analysis of failure-free response to tofacitinib

Three patients had subsequent clinical improvement that was sustained with the standard dose of 10 mg twice daily.

Predictors of Response

Patients' demographic characteristics, disease extent, previous medical therapy, and steroid exposure were not predictive of clinical response during induction or maintenance treatment. Drug dose at induction was not correlated with the clinical response at 8 weeks or during maintenance follow-up. There was no significant difference between clinical response in UC and CD patients (data shown for week 8 response in Table 2).

Objective Evaluation

Prior to tofacitinib initiation, all patients had active disease evaluated by endoscopy. During follow-up, endoscopic re-evaluation was performed in 13 out of 58 patients at least 8 weeks after drug initiation. Mucosal healing (defined as Mayo endoscopic subscore of 0) was demonstrated in two patients, and endoscopic improvement was noted in five others. Prior to therapy initiation, 25 patients had elevated levels of inflammatory biomarkers (CRP and FCP); eight of these patients had a demonstrable reduction of at least one-third in these markers after being treated with tofacitinib.

Crohn's Disease

Four patients with CD were treated with tofacitinib with an inconsistent effect. One patient discontinued the treatment secondary to poor response. Three patients demonstrated clinical response to the treatment. One patient, treated with concomitant thiopurine, achieved clinical remission that was sustained through week 140. At that point, however, his treatment was switched to ustekinumab (as monotherapy) due to active disease demonstrated on endoscopy. Clinical response was observed in one patient by week 10 (end of follow-up), and another patient achieved sustained clinical remission through week 26 accompanied by decrease in FCP.

Table 2 Clinical and demographic characteristics of patients with and without response

	Response week 8 (40 patients)	Non-response week 8 (18 patients)	<i>P</i> value
Disease			
UC–E2	18 (45%)	6 (33%)	0.57
UC–E3	18 (45%)	11 (61%)	
Crohn's disease	4 (10%)	1 (6%)	
Gender (M/F)	25/15	11/7	1
Age at induction {median (IQR)}	41.5 (28.8–53)	37.5 (31–46.8)	0.77
Duration of disease {median (IQR)}	10.66 (2.1–17.2)	10.3 ± 8.2	0.44
Previous medications {number (%)}			
Anti-TNF	39 (98%)	15 (83%)	0.08
Vedolizumab	33 (83%)	14 (78%)	0.72
Immunomodulators	29 (73%)	12 (67%)	0.76
Objective active disease at induction	22 (55%)	11 (61%)	0.57
Treatment dose			
5 mg	19 (47%)	4 (22%)	0.08
10 mg	21 (53%)	14 (78%)	
Concomitant steroids {number (%)}	17 (43%)	10 (56%)	0.70
Prednisone dose equivalent, mg {median (IQR)}	15 (10–20)	10 (8.1–40)	0.95

Safety

Systemic infections were noted in 12 patients (20.1%). Seven of them were treated with immunosuppressive therapy in addition to tofacitinib at the time of infection (Table 3). Cellulitis was diagnosed in one patient, and upper respiratory tract infections were diagnosed in two patients. All three patients were treated with concomitant steroids. Tofacitinib was halted temporarily for two of the patients and was re-administered once infection was controlled. Four patients were diagnosed with a *Clostridium difficile* infection while on the drug. Three of them were on concomitant steroid therapy. Tofacitinib was temporarily halted at that time, and the patients were treated with vancomycin. Three of the four patients continued to have clinically severe colitis, and two underwent total proctocolectomy. One patient was diagnosed with aspergillus sinusitis which required surgical debridement. The patient had a history of recurrent allergic fungal sinusitis that began prior to initiation of tofacitinib. One patient was diagnosed clinically with herpes zoster at an outside location. She was treated with valganciclovir for 14 days with complete resolution of her symptoms.

Tofacitinib was later continued with no subsequent infectious events.

Three patients had an incline in their cholesterol level with maximal LDL of 143 mg/dL (increased from 115 mg/dL). None needed pharmacologic treatment, and tofacitinib was not stopped. No cardiovascular events were noted. One case of constitutional symptoms including headaches, dizziness, and cough resulted in drug discontinuation.

Discussion

Despite myriad new treatment options, management of patients with moderate-to-severe IBD remains a challenge. Our cohort included patients with moderate-to-severe IBD, of which the majority had previously failed to improve with at least two classes of biologic therapy. In this challenging patient population, a substantial percentage of patients responded to treatment with tofacitinib; after 8 weeks of treatment, clinical remission was achieved in 33% of patients. These rates are consistent with the rates reported in recent clinical trials. After a year of treatment, 42% of the

Table 3 Adverse events

Patient ID	Infection	Concomitant therapy	Treatment stopped	Treatment restarted
1	CMV colitis and <i>C. diff</i> Colitis	Prednisone 10 mg	Yes	No
2	CMV colitis and <i>C. diff</i> Colitis	Prednisone 10 mg	Yes	No
3	Aspergillus Sinusitis	Prednisone 5 mg	No	–
4	<i>C. diff</i> colitis	None	Yes	No
5	GBS sepsis	Tacrolimus 1 mg	Yes	Yes
6	<i>C. diff</i> colitis	Prednisone 10 mg	Yes	No
7	Shingles	Prednisone 5 mg	Yes	Yes
8	EBV	None	Yes	Yes
9	Cellulitis	None	Yes	Yes
10	Parainfluenza	Vedolizumab	Yes	No
11	URI	Prednisone 10 mg	No	–
12	<i>E. Coli</i> gastroenteritis	Mesalamine 1.2 g	No	–

Patient ID	Abnormality	Max value	Concomitant therapy	Treatment stopped	Treatment restarted
<i>Laboratory abnormalities</i>					
13	Acute kidney injury	Cr 2.1	Methotrexate, mesalamine	No	–
14	Hyperlipidemia	LDL 120	Mesalamine, entyvio	No	–
15	Hyperlipidemia	LDL 143	None	No	–
16	Hyperlipidemia	LDL 113	None	No	–

Patient ID	Abnormality	Concomitant therapy	Treatment stopped	Treatment restarted
17	Cough, dizziness, parasthesias	Mesalamine	Yes	No

List of individual adverse events experienced in the study (*CMV* Cytomegalovirus, *C. diff* *Clostridium difficile*, *EBV* Epstein Barr Virus, *URI* upper respiratory infection, *E. Coli* *Escherichia coli*, *Cr* creatinine, *LDL* low-density lipoprotein)

patients still on follow-up remained in steroid-free clinical remission.

Phase III clinical trials have suggested a dose–response relationship with tofacitinib treatment during induction and maintenance. In our cohort, there was no statistically significant difference in clinical remission rates between patients receiving 5 mg and 10 mg for induction. However, there was an insignificant trend toward higher remission rates among the patients in the lower-dose group. This surprising finding may be explained by a selection bias to treat sicker patients with higher doses.

Almost all the patients in our cohort had previously failed treatment with anti-TNFs, and more than 80% had also failed anti-integrins. Treating these patients can be challenging, considering the limited treatment options in the arsenal for UC and the low efficacy rates of second-line therapy after failure of the first biologic [9, 10]. In our cohort, as has been demonstrated in clinical trials, previous failure of biologic therapy did not affect the efficacy of treatment. The majority of patients failing tofacitinib eventually underwent total proctocolectomy, further demonstrating the extreme refractoriness of this unique group of patients.

The JAK-STAT system plays a major part in the pathogenesis of Crohn's disease [11]. Yet, tofacitinib had not been shown to be effective in the treatment of Crohn's disease. A phase II clinical trial reported that tofacitinib treatment at a dose between 1 and 15 mg twice daily did not demonstrate a beneficial effect in induction or maintenance of clinical response compared to placebo. However, response and remission rates with placebo were higher than expected, and reductions in CRP and fecal calprotectin levels were observed with tofacitinib treatment, suggesting some level of biological activity [12, 13]. However, our experience using tofacitinib in CD is limited to four patients with dissimilar results. Interestingly, another recent phase II clinical trial demonstrated the benefit of a selective JAK1 inhibitor, filgotinib, in CD [14].

The most commonly reported adverse events in the tofacitinib clinical trials were influenza-like symptoms, nasopharyngitis, and increased levels of total cholesterol and high- and low-density lipoprotein (HDL, LDL). Age above 65 years, corticosteroid dose above 7.5 mg, diabetes, and a tofacitinib dose of 10 mg vs. 5 mg were independently linked to the risk of serious infection [15]. Specifically, higher rates of herpes zoster were observed among tofacitinib-treated patients with RA and UC [16, 17]. In these studies, age and prior anti-TNF- α failure were found to be independent risk factors for herpes zoster among UC patients using tofacitinib. Among our cohort, 12 patients (20%) experienced infectious complications during the entire follow-up period; most of them were on concomitant immunosuppressive therapy. One patient discontinued the drug due to an adverse event that was not infectious. We observed one case

of HZ in a patient, who was not vaccinated, and the infection resolved completely with antiviral therapy.

There are several limitations to our study. First, it is retrospective. Accordingly, the follow-up and decision-making processes were biased. In addition, a considerable portion of the patients who reached clinical remission did not have objective evidence of disease quiescence (e.g., endoscopic evaluation or biochemical markers). Nevertheless, steroid-free clinical response and discontinuation of medical therapy are both well-known, clinically relevant endpoints. These limitations are inherent in this type of real-world publication and come alongside its advantages. This is the first report on the effect of tofacitinib for induction and maintenance in moderate-to-severe IBD in a real-world tertiary center setting. Our cohort is a real-life patient population that includes participants with complicated, long-standing, extremely resistant disease, and reflects real-life follow-up and decision-making process. We demonstrate good efficacy and safety of this new oral option for our patients.

Compliance with ethical standards

Conflict of interest RW, MAG, KEJ, and PHS have no relevant disclosures. DTR is a consultant and has received grant support from Abbvie, Abgenomics, Allergan Inc, Ferring Pharmaceuticals, Genentech/Roche, Janssen Pharmaceuticals, Merck & Co Inc., Medtronic, Napo Pharmaceuticals, Takeda, Pfizer, Shire and Target Pharmaceuticals.

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