IBD REVIEWS

Scientific and technological research article

TOFACITINIB FOR THE MANAGEMENT OF ULCERATIVE COLITIS

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Abstract

Tofacitinib is a small molecule that inhibits the Janus-associated kinase, is a non-biological medication that lacks immunogenicity, and can be administered orally. The OCTAVE trials have proven effective in inducing clinical response, clinical remission, and mucosal healing in moderate-to-severe ulcerative colitis (UC). When using tofacitinib in clinical practice, physicians need to know its benefits and risks to stratify patients and use the medication in the safest possible way. The main objectives of this article are to provide a practical guideline for the use of tofacitinib in UC and to identify potential risk factors and complications to avoid them.

Keywords: inflammatory bowel disease, tofacitinib, ulcerative colitis, Janus kinase inhibitor.

Resumen

Tofacitinib es una pequeña molécula que inhibe la cinasa asociada a Janus, es un medicamento no biológico que carece de inmunogenicidad y se puede administrar por vía oral. Los ensayos OCTAVE han demostrado su eficacia para inducir la respuesta clínica, la remisión clínica y la cicatrización de la mucosa en la colitis ulcerosa (CU) de moderada a grave. Al usar tofacitinib en la práctica clínica, los médicos deben conocer sus beneficios y riesgos para estratificar a los pacientes y usar el medicamento de la manera más segura posible. Los objetivos principales de este artículo son proporcionar una guía práctica para el uso de tofacitinib en la CU e identificar los posibles factores de riesgo y complicaciones para evitarlos.

Palabras clave: enfermedad inflamatoria intestinal, tofacitinib, colitis ulcerosa, inhibidor de la Janus cinasa.

INTRODUCTION

Ulcerative colitis (UC) is a chronic autoimmune disease that affects the colonic mucosa, starting in the rectum and extending proximately through part or the entire colon. The clinical course may present with alternating episodes of exacerbation and remission; bloody diarrhea and abdominal pain are the pivotal symptoms of this pathology [1,2].

Many patients do not have a proper or sustained response to classic therapies, including mesalamine, thiopurines, antagonists to tumor necrosis factor (TNF), and vedolizumab.. Evidence has shown that one-third of patients will not respond to anti-TNF induction, and about half will lose response through time [3,4].

With the description of intracellular mechanisms associated with the pathogenesis of inflammatory bowel disease (IBD), new medications have been developed, including tofacitinib as the first small-molecule oral therapy for the treatment of moderate-to-severe UC. [5]

CHARACTERISTICS OF TOFACITINIB

The Janus kinase (JAK) family includes four tyrosine kinases (JAK1, JAK2, JAK3) and nonreceptor tyrosine-protein kinase 2; they are related to different processes, including innate and adaptive immunity, inflammation, and hematopoiesis [6]. Their molecular role is the activation of the signal transducers and activators of transcription (STATs) using auto-phosphorylation [2].

Tofacitinib, a non-biologic, small molecule, inhibits all JAKs; however, it is more selective to inhibit JAK1 and JAK3. As a result, STATs are not activated, and nuclear transcription and cytokine production is impeded [7] (Figure 1).

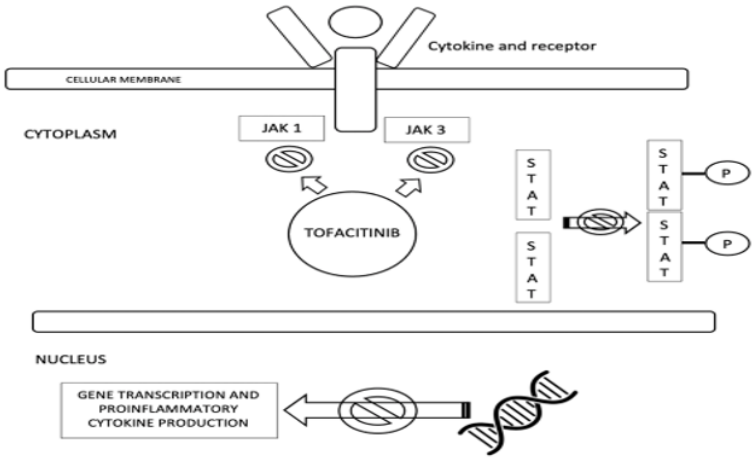

FIGURE 1. Mechanism of action of tofacitinib Tofacitinib inhibits the phosphorylation and activation of the Janus kinase JAK 1 and 3 therefore signal transducer and activator of transcription proteins STAT cannot be phosphorylated This mechanism interferes with gene transcription and proinflammatory cytokine production

The pharmacokinetic properties that tofacitinib possesses include the fact that it can be administered orally, a low molecular weight (<700 Da), rapid absorption with or without food, bioavailability up to 74%, and peak plasma concentrations between 30-60 minutes. The half-life of this medication is around 3 hours, with hepatic metabolism and renal elimination [8].

EFFICACY EVIDENCE FROM CLINICAL TRIALS

Approval of tofacitinib by different regulatory agencies was obtained from the data of the OCTAVE program, which included three phase 3, randomized, double-blind, placebo-controlled trials that evaluated the efficacy of the medication in moderate-to-severe UC [2,7].

The OCTAVE 1 and 2 induction trials included patients with failure to conventional therapy and anti-TNF that were assigned to receive tofacitinib (10 mg two times a day, b.i.d) or placebo for eight weeks. Tofacitinib was superior to placebo achieving clinical remission (18.5% versus 8.2%, p=0.007 in OCTAVE 1 and 16.6% versus 3.6%, p<0.001 in OCTAVE 2). As the main secondary outcome, mucosal healing was superior in both trials in the tofacitinib groups (31.3% versus 15.6%, in OCTAVE 1 and 28.4% versus 11.6%, in OCTAVE 2; p<0.001 for both) [2].

Responders of the induction trials were rerandomized to receive placebo, tofacitinib 5 mg b.i.d. or 10 mg b.i.d. for 52 weeks in the OCTAVE Sustain trial. Clinical remission was achieved with statistical significance in both active treatment groups (40.6% in 10 mg group vs. 34.3% in 5 mg group vs. 11.1% in placebo, p<0.001 for both comparisons with placebo). Mucosal healing was achieved at week 52 in more patients in the 5 mg tofacitinib group (37.4%) and the 10 mg tofacitinib group (45.7%) than in the placebo group (13.1%, p <0.001 for all comparisons) [2].

SPECIAL CONSIDERATIONS FOR DAILY CLINICAL PRACTICE

1. Induction and Maintenance

Tofacitinib is approved in most countries to treat moderate-to-severe UC patients with inadequate response or intolerance to anti-TNF [9]. The initial induction dose is 10 mg b.i.d. for eight weeks aiming for clinical response, defined as a decrease from baseline in the total Mayo score of at least 3 points and at least 30%, with an accompanying

reduction in the rectal bleeding subscore of at least 1 point or an absolute rectal bleeding subscore of 0 or 1 [2,9].

Patients that do not achieve an adequate clinical response at week 8 may be candidates to complete an extended 16-week induction [9]. The evidence to support this came from the non-responders in the OCTAVE induction trials included in an open-label parallel trial completing a 16-week induction conferring a gain of additional 17% clinical response rate [10,11]. Maintenance treatment in these patients was with 10 mg b.i.d., with data up to 36 months of clinical response of 56.1%, endoscopic improvement of 52%, and clinical remission of 44.6% [10].

An essential factor to consider is stopping therapy if there is no adequate response by week 16. In general, the maintenance dose recommended is 5 mg b.i.d. [9]. However, some patients may need a dose adjustment to recapture and sustain response; subgroup analysis of the OCTAVE study has shown that dose adjustment from 5 mg b.i.d. to 10 mg b.i.d. is effective in recapturing and maintaining the clinical response [10]. Dose de-escalation can be considered in patients in remission; however, this should be decided carefully because data from the OCTAVE Open-Label Extension (OLE) reported a loss of remission up to 25.4% at month twelve [12]. According to the label, the dose of 10 mg b.i.d. should be considered the shortest period possible, contemplating risk and benefits for every specific case [9].

2. Immunosuppression and other precautions

Due to its intracellular mechanism of action, tofacitinib is a potent immunosuppressant therapy; thus, it is not recommended to be used concomitantly with other immunosuppressants, including biological treatments, thiopurines, tacrolimus, and cyclosporine [9]. Before starting therapy, all patients need to be screened for infectious diseases, including tuberculosis and hepatitis B, before starting therapy [13].

Also, patients must be evaluated with a baseline complete blood count, including total neutrophils, lymphocytes, and hemoglobin. According to these results, dose adjustments may be needed or are a contraindication for starting therapy. Tofacitinib dose needs adjustment with creatinine clearance under 50 mL/min and in patients with hepatic impairment (contraindicated in patients with advanced liver disease Child-Pugh C) [9]. Dose adjustment may also be needed when strong CYP3A4 inhibitors (e.g., ketoconazole) are used or with moderate CYP3A4 inhibitors and strong CYP2C19 inhibitors (e.g., fluconazole) (see Table I). A complete laboratory panel workup is recommended after 4-8 weeks of starting therapy and every 3 months [9].

TABLE I. Tofacitinib treatment monitoring

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Parameter	Scenario	Action recommended
Total lymphocytes	<500/mm³ before induction	Do not start
	<500/mm³ maintenance	Stop until improvement
Total Neutrophils	<1000/mm³ before induction	Do not start
	500-1000/mm³ taking 10 mg b.i.d.	Adjust to 5 mg b.i.d. until improvement
	500-1000/mm³ taking 5 mg b.i.d.	Stop until improvement
	<500/mm³ with any dose	Stop until improvement
Hemoglobin	<9g/dL before induction	Do not start
	<8 g/dL o Hb drop over ≥ 2g/dL	Stop until improvement
Creatinine clearance < 50 mL/min	10 mg b.i.d.	Adjust to 5 mg b.i.d. until improvement
	5 mg b.i.d.	Adjust to 5 mg every day until improvement
Hepatic impairment	Child-Pug A or B taking 10 mg b.i.d.	Adjust to 5 mg b.i.d. until improvement
	Child-Pug A or B taking 5 mg b.i.d.	Adjust to 5 mg every day until improvement
Strong CYP3A4 inhibitors or Moderate CYP3A4 inhibitors + strong CYP2C19 inhibitors	10 mg b.i.d.	Adjust to 5 mg b.i.d.
	5 mg b.i.d.	Adjust to 5 mg every day

b.i.d.: two times a day,

3. Dyslipidemia

IBD represents an elevated risk of cardiovascular morbidity compared to the general population [14]. Tofacitinib has been associated in clinical trials with an increase in the lipid profile with a peak at week 6 [13,15]. Data analyzed from the OCTAVE OLE did not find major changes from baseline lipids, and the rate of cardiovascular events was 0.26/100 patient-years [16].

It is strongly recommended to stratify every patient and identify cardiovascular risk factors before starting tofacitinib, considering age, obesity, diabetes mellitus, arterial hypertension, smoking, and family history of coronary disease [13]. Lipids should be monitored at baseline and after induction; if a significant increase in lipids is documented, lifestyle modifications and therapy with statins can be initiated as needed and according to low-density lipoprotein cholesterol levels [16].

If there are persistent lipid abnormalities, adherence to medications needs to be evaluated; therapy intensification or combination with lipid-lowering treatments is acceptable. It is also recommended to consider a referral to a specialist in case of persistence of dyslipidemia [16].

4. Thrombotic and thromboembolic events

Patients with IBD have an increased risk of deep vein thrombosis (DVT) and pulmonary embolism (PE) [17]. A post-hoc analysis including 1157 patients with UC from phase 2 and 3 trials treated with tofacitinib documented an incidence rate (IR) of 0.04 (0.00 – 0.23) for DVT and IR 0.16 (0.04-0.41) for PE. A higher risk for PE/DVT was documented with patients with 10 mg b.i.d. dosing [18].

It is recommended to use tofacitinib with precaution in patients that have known additional risk factors for PE/DVT, including previous venous thromboembolism, recent major surgery, immobilization, myocardial infarction (within last three months), heart failure, use of hormonal replacement therapy, or hormonal contraceptives, inherited coagulation disorders, malignancy, diabetes, obesity, hypertension, and smoking [7].

Recently, an international consensus on preventing venous and arterial thrombotic events in patients with IBD was published, addressing that tofacitinib can be associated with a dose-dependent risk of PE/DVT in patients with rheumatoid arthritis (RA) with risk factors. However, it also states that with currently available evidence, there is no observed increase in the risk of PE/DVT in patients with UC treated with this medication. It is recommended that the dose of 10 mg b.i.d. be used for up to 16 weeks. Then 5 mg b.i.d. should be the preferred maintenance dose, considering 10 mg b.i.d. preferably in patients without known PE/DVT risk factors and without other therapeutic options [19].

5. Other considerations

A post-marketing open-label, multicenter safety trial with patients with RA and methotrexate randomized to either tofacitinib 10 mg b.i.d., tofacitinib 5 mg b.i.d. and anti-TNF with a median follow-up time of 4 years evidenced an increased risk of death, major adverse cardiovascular events (MACE), malignancies, and thrombosis associated with both doses of tofacitinib in comparison to anti-TNF. This study included patients over 50 years old with at least one cardiovascular risk factor [20].

There was evidence of a tofacitinib dose-dependent effect related to MACE, all-cause mortality, and thrombosis and non-dose dependent increased risk for neoplasia (lymphoma and lung cancer at a higher rate), excluding non-melanoma skin cancer. For these results, the Food and Drug Administration (FDA) from the United States issued a *black box warning* to all JAK inhibitors available in the US market [20].

Herpes zoster (HZ) incidence in IBD is twice in comparison to healthy population [21], the review of all the evidence from phase 2 and 3 trials of tofacitinib in UC showed that 65 patients (5.6%) developed HZ while on therapy, the majority of cases non-serious. The risk is higher with higher doses of treatment, and there was an increased risk in patients over 65 years, Asians, and with previous exposure to anti-TNF therapy [22]. A recombinant HZ vaccine has demonstrated efficacy in reducing the risk of HZ infection in patients with IBD, including patients with systemic immunosuppressive therapy [23,24].

Regarding pregnancy and breastfeeding, tofacitinib is contraindicated during this scenarios [9], however, there is evidence from the OCTAVE trials with 34 pregnancies documented and 15 cases of maternal exposure to the medication, all during the first trimester. Results include 9 healthy newborns, 2 medical terminations, 2 spontaneous abortions, and 2 cases lost to follow-up. No claims of fetal death or congenital malformations were reported [25].

CONCLUSION

Tofacitinib has proven to be an effective medication for treating moderate-to-severe UC, with a novel mechanism of action that adds value to the therapeutical options available today. It has convenient characteristics (e.g., oral administration, short half-life, and lack of immunogenicity); however, some safety features require proper follow-up and correct patient selection (according to risk stratification) to guarantee the best results in the most suitable patients. Head-to-head trials are still needed to define its position against the biological therapies available in the market.

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