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Clinical settings with tofacitinib in ulcerative colitis

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ABSTRACT

There are aspects of Janus kinase (JAK) inhibitors, specially tofacitinib, that distinguish them from other drugs used in the treatment of ulcerative colitis (UC), such as their oral administration, short half-life, and lack of immunogenicity. With the scientific evidence currently available, we should mention tofacitinib quick action, flexibility of use, and efficacy profile in patients regardless of whether these have previously been exposed to TNF inhibitors (anti-TNF drugs) or other biologic agents. Moreover, their safety profile is known and manageable although certain considerations and precautions should be made before and during treatment. In this review, we have defined various scenarios pertaining to this drug like its use in the event of failure or intolerance to previous treatment with biologic agents when a quick response is required or in patients with other concomitant immune-mediated diseases.

Keywords: Tofacitinib. Ulcerative colitis. Inflammatory bowel disease. Janus kinases. Efficacy. Safety. Immune-mediated diseases. Biologic agents.

INTRODUCTION

The main goals in the treatment of ulcerative colitis (UC) are symptom control, mucosal healing, sustenance of long-term steroid-free clinical remission, minimization of loss of response in patients to prevent further flare-ups, and improvement of the patients' quality of life (1-3). TNF inhibitors are the most widely used drugs for patients who remain unresponsive to conventional medical treatment (aminosalicylates, steroids) or thiopurine salvage therapy. However, there is still a large group of patients in whom control is not achieved, so alternative treatments are required (4).

Janus kinases (JAKs) are a family of four different proteins, JAK1, JAK2, JAK3, and tyrosine kinase 2 (Tyk2), which are responsible for the intracellular signaling of different cytokines. Their inhibition has immunomodulatory effects. There are

significant differences between JAK inhibitors like tofacitinib and biologic agents, including the way they are produced, their synthetic composition, the fact that they are administered orally, their shorter half-life, and the fact that they do not elicit neutralizing antibodies due to immunogenicity (5,6). Furthermore, the inhibition that they exert on their specific targets, the JAK proteins, is partial and reversible (4).

The objective of this article is to examine the distinguishing characteristics of JAK inhibitors, specially tofacitinib, compared to other drugs used to treat UC. For this purpose, we defined various scenarios pertaining to this drug always in observance of the recommendations established by the European Medicines Agency (EMA) while drafting this paper.

SCENARIO #1

Tofacitinib as induction and maintenance treatment in patients with UC after failure or intolerance to conventional treatment or biologic agents

Tofacitinib is indicated for patients with active UC, moderate to severe, with suboptimal responses, no response or intolerance to previous treatment. The recommended induction dose is 10 mg administered orally twice daily (BID) for eight weeks. This dose can be extended for another eight weeks for patients who do not achieve any therapeutic benefits by week 8. Maintenance treatment is 5 mg BID through oral administration (7). If a reduction in the response is observed at this dose and they fail to respond to alternative treatment options for UC, increasing the dose up to 10 mg BID may be considered; this dose should be maintained for the shortest time possible (7). This dose is ill-advised for the maintenance treatment of patients with risk factors for venous thromboembolism unless no other suitable alternative treatment becomes available (7).

Advantages of the oral route of administration

Tofacitinib is administered orally. Various studies on rheumatoid arthritis (RA) and inflammatory bowel disease (IBD) have shown that patients prefer the oral route to parenteral administration mainly due to the ease of administration, which improves treatment adherence and has an impact on quality of life (8-11). Therefore, patients'

opinions and preferences should be taken into account in our routine clinical practice (8,12).

Administration flexibility

Several aspects have been studied with tofacitinib (13):

- *Extended induction:* in the OCTAVE trials (Fig. 1A) they examined the efficacy profile of induction therapy with tofacitinib 10 mg BID and maintenance therapy with 5 mg or 10 mg BID *vs* placebo (14). Over half of the patients who remained unresponsive during the eight weeks of induction therapy at 10 mg BID achieved a clinical response after eight additional weeks on the same dose (15). Most patients who responded to extended induction maintained the response at 36 months.
- *Dose reduction:* most patients in remission following maintenance therapy with tofacitinib 10 mg BID (OCTAVE Sustain) who were included in the open study (OCTAVE Open) remained in clinical remission and sustained their endoscopic improvement at 12 (65.8 % and 75 %, respectively) and 36 months (48 % and 53 %, respectively) after the dose was reduced down to 5 mg BID regardless of whether they had previously been exposed to anti-TNF therapy (16). In turn, the RIVETING study (Fig. 1B) included patients from the OCTAVE Open trial who had received tofacitinib 10 mg BID for, at least, two years and were in stable remission on that dose for, at least, six months. Most of the patients who reduced the dose down to 5 mg BID remained in remission six months after such reduction (2). Efficacy in this group was consistently higher among patients with early Mayo endoscopic scores = 0 compared to those with early scores = 1.
- *Dose increase:* the OCTAVE Open study included patients with loss of response at a dose of 5 mg BID during maintenance therapy whose dose was increased up to 10 mg BID. Clinical response was observed in 57.9 %, 64.9 %, and 54.7 % of the patients at 2, 12, and 24 months, respectively (13).
- *Retreatment:* due to its characteristics, tofacitinib poses no risk of immunogenicity (5). If treatment is interrupted, it could be resumed at a later

date (7). In the OCTAVE study, in patients with a response following induction whose treatment had been discontinued, the reintroduction of tofacitinib at doses of 10 mg BID restored the clinical response after two months in 74.3 % of patients. At 12, 24, and 36-month follow-ups, the rate of patients in remission was 43.6, 40.6, and 37.4 %, respectively (17).

Prevention in the clinical management of tofacitinib

Tofacitinib safety profile is well established based on long-term data from clinical trials up to 9.5, 7.8, and three years for the clinical management of RA (18), UC (19), and psoriatic arthritis, respectively (20). In patients with UC, its safety profile is acceptable and well tolerated (21,22) considering certain precautions due to possible risks associated with its use. Therefore, taking certain special considerations into account, it is recommended before starting treatment (Table 1) and for its duration (7) (Fig. 2 and Table 2).

- Due to serious infections being reported during treatment with tofacitinib, the risks and benefits should be considered before it is used in patients from populations more susceptible to higher rates of infections (7). In patients over 65 years-old, tofacitinib should only be considered if no other suitable alternative treatment becomes available (7). As it is the case with all other biologic treatments, before starting therapy, screening should be conducted to rule out the presence of latent tuberculosis and viral infections (7). Specifically, there may be an increased rate of herpes zoster (HZ) in certain population groups depending on the dose (7) but not on the duration of treatment (23). Patients treated with anti-JAK drugs are a priority group for vaccination against HZ. According to the Interterritorial Council of the Spanish National Health Service, attenuated vaccines are contraindicated in immunosuppressed people. Therefore, it is recommended to vaccinate these patients with the glycoprotein E vaccine (HZ/su) (Shingrix®) (24). The administration of two doses with a two-month gap between them is advised in these patients, if possible, before starting treatment (25).

- Dose-related severe venous thromboembolic events (VTE) have also been reported, so tofacitinib should be used with caution in patients with VTE risk factors such as patients with a past medical history of VTE who are going to undergo major surgery or immobilization and have had a previous myocardial infarction three months earlier, heart failure, who are using combined hormonal contraceptive or hormone replacement therapy or with hereditary bleeding disorders or malignant neoplasms. Furthermore, additional risk factors should be considered, such as age, obesity, diabetes, high blood pressure, and smoking (7). Tofacitinib 10 mg BID is ill-advised for the maintenance treatment of patients with UC who have known risk factors for VTE unless no other suitable alternative treatment becomes available (7).
- In the ORAL Surveillance trial, a post-authorization study of patients with rheumatoid arthritis who were ≥ 50 years-old with, at least, one additional cardiovascular risk factor, the co-primary endpoint of major adverse cardiovascular events (MACE) did not meet the pre-specified criterion of non-inferiority of tofacitinib (both doses) compared to anti-TNF drugs with a hazard ratio (HR) of 1.33 (95 % CI: 0.91-1.94). The observed difference was attributed to an imbalance in non-fatal myocardial infarction with incidence rates (IR) (95 % CI) per 100 patient-years for doses of tofacitinib 5 mg BID, tofacitinib 10 mg BID, both doses of tofacitinib, and anti-TNF of 0.37 (0.22-0.57), 0.33 (0.19-0.53), 0.35 (0.24- 0.48), and 0.16 (0.07-0.31), respectively (26). In the integrated safety analysis of tofacitinib for UC (n = 1,157; up to 6.8-year exposure), seven cases of MACE were observed with an IR of 0.26 cases (0.11-0.54) per 100 patient-years (27,28).
- Additionally, the results of the aforementioned study show an increase in the rate of malignant neoplasms (excluding non-melanoma skin cancer [NMSC]), in particular lung cancer, and lymphoma, in patients treated with tofacitinib compared to those treated with anti-TNF drugs. The rates (95 % CI) of lung cancer and lymphoma with tofacitinib (both doses) for every 100 patient-years were 0.28 (0.19; 0.39) and 0.09 (0.04; 0.17), respectively (26). In turn, although the rate of NMSC is rare, it is more likely in patients with known risk factors

(older and previous NMSC) and patients with anti-TNF treatment failure (29) so regular skin tests are advised for these risk groups (7).

- In light of the above, it has been determined that in patients > 65 years, smokers or former smokers, and those with other cardiovascular risk factors, current malignant tumors or a past medical history of malignant tumors other than NMSCs who have been treated successfully, tofacitinib should only be used if no other suitable alternative treatment becomes available (26).
- Test abnormalities have been observed during treatment with tofacitinib (7):
    - Higher rates of neutropenia and lymphopenia and a drop of hemoglobin levels have been observed. Lymphopenia was associated with a higher risk of severe infection. Therefore, it is not recommended to start treatment if the absolute lymphocyte count (ALC) is < 750 cells/mm^3, the absolute neutrophil count (ANC) is < 1,000 cells/mm^3 or if hemoglobin levels are < 9 g/dl. Additionally, close monitoring of these parameters is recommended from the start of the treatment (Fig. 2).
    - Treatment with tofacitinib has been associated with abnormal lipid profiles, an increase in total cholesterol affecting both LDL and HDL cholesterol. These parameters should be evaluated from the 8^{th} week of treatment and managed based on the clinical guidelines for their treatment like with statins (7).

At treatment follow-up, adjusting the dose or discontinuing treatment should be considered according to these test parameters, as shown on table 2 (based on the SmPC of Xeljanz® [7]).

SCENARIO #2

Efficacy following treatment failure with biologic agents (anti-TNF and others)

- In the OCTAVE trials (21), tofacitinib was more effective than placebo at inducing and maintaining response, remission, and endoscopic improvement. In addition, no differences were seen in the effects on patients with and without prior treatment failure with anti-TNF therapy (21,30,31). During the induction phase (week 8) the effect of treatment was similar between patients

with failed treatment to 1 and ≥ 2 anti-TNF agents. During maintenance, the effect of treatment with tofacitinib on patients with previously failed anti-TNF treatment was more pronounced with the 10 mg BID dose compared to the 5 mg BID. However, there were also significant differences between the 5 mg BID dose and placebo.

- In the real-world ENEIDA registry, all patients were treated with an anti-TNF drug, 89 % with vedolizumab and 4 % with ustekinumab. Tofacitinib was shown to have a quick effect and induce remission in 16 % and 31 % of the patients at weeks 4 and 8, respectively, in a highly refractory population (32).
- In a retrospective observational cohort study in which 83 % patients had previously received, at least, one biologic drug, 74 % responded to tofacitinib at week 8 and 44 % achieved remission at week 26. Prior exposure to biologics had no impact whatsoever on response or remission rates (33).
- In the prospective study of patients from the Danish registry (ICC Registry), 95.1 % of patients had received ≥ 1 anti-TNF drug, 62.3 % vedolizumab, 59.3 % both anti-TNF and vedolizumab, and 3.3 % ustekinumab. Treatment with tofacitinib achieved combined biochemical remission (fecal calprotectin ≤ 250 µg/g) and clinical remission (steroid-free clinical remission) in 28.4 % and 19.3 % of patients at 12 and 24 weeks, respectively (34).
- A network meta-analysis, in the context of a systematic review of randomized clinical trials, showed that in patients with UC previously exposed to anti-TNF therapy, both tofacitinib and ustekinumab had a higher rate of induction of clinical remission and endoscopic improvement compared to vedolizumab or adalimumab (35).
- Another meta-analysis on the efficacy profile of tofacitinib in clinical practice included 13 studies in which 84.4 % of the patients (n = 793) had previously received biologic agents (62.9 % both anti-TNF, and vedolizumab) (36). The eight-week response of patients with previous exposure to biologic agents was 58.1 %. A single study compared steroid-free remission rates and saw no significant differences between patients exposed to biologic agents (48 %) compared to unexposed patients (55 %). A more recent study, in which 98.3 %

of patients had been exposed to biologic agents, confirms the efficacy of tofacitinib in a highly refractory population (37).

- The Spanish Working Group on Crohn's Disease and Ulcerative Colitis (GETECCU) 2020 guidelines, developed with the GRADE methodology, states that there is *high-quality* evidence that tofacitinib "induces a clinical and endoscopic response and remission in patients with failed conventional or anti-TNF treatment" (38). The ECCO guidelines recommend tofacitinib due to its efficacy profile, among other benefits, even in patients with previous exposure to anti-TNF treatment (39).

SCENARIO #3

Benefit of tofacitinib when a rapid response is required

Rapid onset of action

A post-hoc analysis of the results of two phase 3 studies in patients with UC (OCTAVE induction 1 and 2 trials) (40) assessed the onset of symptom improvement following treatment with tofacitinib. Compared to placebo, significant improvements were found in the rates of bowel movements and blood in stools three days after treatment started, which is indicative that this drug acts fast in these patients.

A retrospective case-control study assessed the efficacy of tofacitinib induction in patients with previous exposure to biologics who had been admitted due to acute severe UC and required intravenous steroids. A total of 40 patients received tofacitinib in a 1:3 ratio compared to controls (n = 113). The risk of colectomy at 90 days was significantly lower with tofacitinib compared to controls (HR 0.28; 95 %CI: 0.10-0.81; p = 0.018) (41). Although there are published cases of tofacitinib being used as an alternative salvage treatment for patients with acute severe UC (36,42,43), larger studies are required to determine their safety profile, optimal dose, and frequency, in addition to the duration of treatment (41).

In addition, the rapid clearance of tofacitinib is advantageous if the drug has to be discontinued due to an adverse event or before an operation with a high risk of infection (44) or an emergency colectomy (41). However, we should remember that the duration of the pharmacodynamic activity is greater compared to half-life and the

effect continues for 2-6 weeks after treatment has been withdrawn (7).

SCENARIO #4

Patients with extra-intestinal manifestations and other immune-mediated diseases

Various immune-mediated diseases are associated with IBD. Recognizing and treating these diseases may lead to better management (45).

Tofacitinib is indicated for ulcerative colitis, rheumatoid arthritis, and psoriatic arthritis (7) and, recently, it has been approved by the EMA for juvenile idiopathic arthritis in patients ≥ 2 years-old with inadequate responses to previous disease-modifying anti-rheumatic drug therapies (7), and for active ankylosing spondylitis in patients with inadequate responses to conventional therapies (46). Table 3 shows tofacitinib studies regarding immune-mediated diseases (47-49).

Finally, with tofacitinib, treatment-refractory patients with peripheral arthralgia associated with IBD showed significant improvement in joint symptoms with bowel symptoms often improving at the same time (50).

CONCLUSIONS

- Tofacitinib belongs to a different group of treatments compared to biologic agents. It is a small-molecule JAK inhibitor characterized by its synthetic composition, oral administration, short half-life, and lack of immunogenicity.
- It is notable for its rapid action and flexibility of use, which allows the dose to be reduced following induction, increased in the absence of a response, and treatment interrupted and subsequently resumed without any risk of immunogenicity.
- It is effective in patients regardless of whether they were previously exposed to anti-TNF drugs and other biologic agents.
- Its safety profile is known and manageable with certain considerations and precautions being factored in before and during treatment.
- It is a possible candidate for the treatment of ulcerative colitis associated with other inflammatory and autoimmune diseases.

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Table 1. Considerations prior to starting treatment with tofacitinib

Contraindications
☐ Hypersensitivity to the active substance or any of its excipients ☐ Active tuberculosis, severe and active infections such as sepsis or opportunistic infections ☐ Acute liver failure ☐ Pregnancy and breastfeeding
Review and assess
☐ Vaccination status – Vaccination with live attenuated vaccines should be administered, at least, two weeks before starting treatment, although four weeks are preferred ☐ Latent/active tuberculosis ☐ The co-administration of potent CYP3A4 inducers (e.g., rifampicin) is ill-advised ☐ Screen for viral hepatitis ☐ Check lab test results. Start if: – Lymphocytes > 750/mm^3 – Neutrophils > 1,000/mm^3 – Hemoglobin > 9 g/dl – Normal liver enzymes (ALT/AST) ☐ It is ill-advised in combination with: – Biologic agents – Potent immunosuppressants (azathioprine, cyclosporine, 6-mercaptopurine, tacrolimus) ☐ Tofacitinib should only be used for the following patients if no other suitable alternative treatment becomes available: – Patients over 65 years old – Former or current smokers

– Patients with cardiovascular risk factors – Patients with malignancy risk factors (e.g., current malignant tumors or a past medical history of malignant tumors excluding non-melanoma skin cancer successfully treated)

ALT: alanine aminotransferase; AST: aspartate aminotransferase; BMSC: non-melanoma skin cancer.

Table 2. Recommendations for adjusting the dose or discontinuing treatment

Situation	*Recommendation*
Severe infection	Discontinue until resolved
Signs and symptoms of VTE	Discontinue treatment
ALC between 500 cells/mm^3 and 750 cells/mm^3 and/or ANC between 500 cells/mm^3 and 1,000 cells/mm^3	Reduce to 5 mg BID if it currently is 10 mg BID Discontinue if it currently is 5 mg BID Resume when ALC is > 750 cells/mm^3 and/or ANC > 1,000 cells/mm^3
ALC < 500 cells/mm^3 ANC < 500 cells/mm^3	Discontinue treatment
Hemoglobin levels < 8.0 g/dl or reduction > 2 g/dl	Discontinue treatment until coming back to normal levels
Co-administration of potent cytochrome P450* (CYP 3A4) inhibitors (e.g., ketoconazole) or moderate CYP3A4 inhibitors and potent CYP2C19 inhibitors (e.g., fluconazole)	Adjust the dose from 5 mg BID to 5 mg QD or from 10 mg BID to 5 mg BID.
Moderate hepatic impairment (Child-Pugh B)	Adjust the dose from 5 mg BID to 5 mg QD or from 10 mg BID to 5 mg BID
Acute kidney failure (creatinine clearance levels < 30 ml/min)	Adjust the dose from 5 mg BID to 5 mg QD or from 10 mg BID to 5 mg BID

VTE: venous thromboembolic events; ALC: absolute lymphocyte count; ANC: absolute neutrophil count; BID: twice daily; QD: every day. *The co-administration of tofacitinib and potent CYP3A4 inducers (e.g., rifampicin) is ill-advised as it may lead to a loss of/reduced clinical response.

Table 3. Clinical trials and case reports on tofacitinib in immune-mediated diseases

Auto-immune and inflammatory diseases	Tofacitinib (JAK 1-3)
Rheumatoid arthritis*	Wollenhaupt 2019 (18)†
Psoriatic arthritis*	Mease 2017, Gladman 2017, Nash 2017 (51-53)†
Ankylosing spondylitis*	Van der Haijde 2017 (54)†
Plaque psoriasis	Papp 2015, Papp 2016 (55,56)†
Juvenile idiopathic arthritis*	Ruperto 2017 (57)†
Alopecia areata	Kennedy 2016 (58)†
Takayasu's arteritis	Kong 2021 (59)†
Multiple sclerosis	Khanna 2019 (60)†
Vitiligo	Liu 2017 (61)‡
Pyoderma gangrenosum	Orfaly 2021, Salmón 2021 (62,63)‡
Atopic dermatitis	Levy 2015 (64)‡
Dermatomyositis	Chen 2019, Kurtzman 2016 (65,66)‡
Sarcoidosis	Damsky 2018 (67)‡
Leukocytoclastic vasculitis	Zhu 2021 (68)‡

*Indication approved by the European Medicines Agency (EMA). †Clinical trials. ‡Case reports.

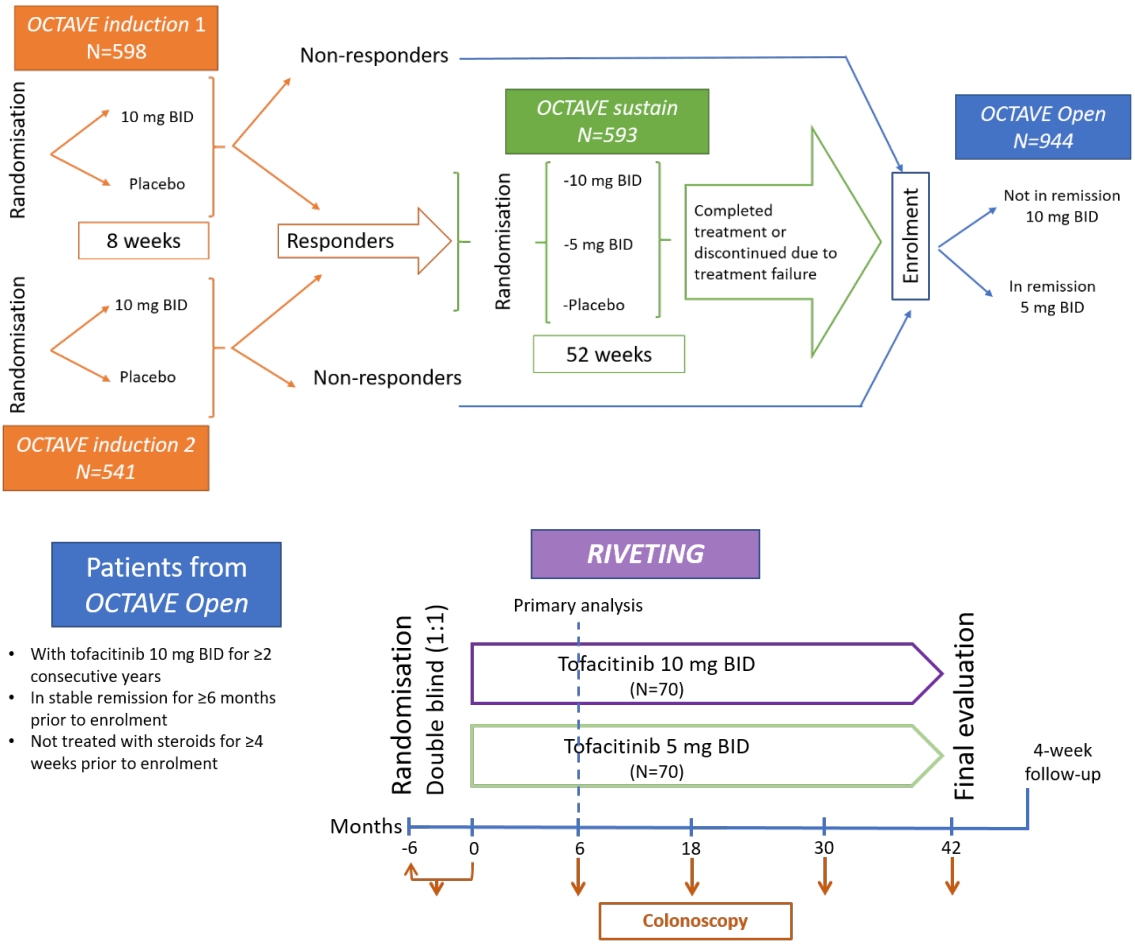

Fig. 1. Overview of the OCTAVE trials: Induction, Sustain, and Open. B. Overview of the RIVETING trial design.

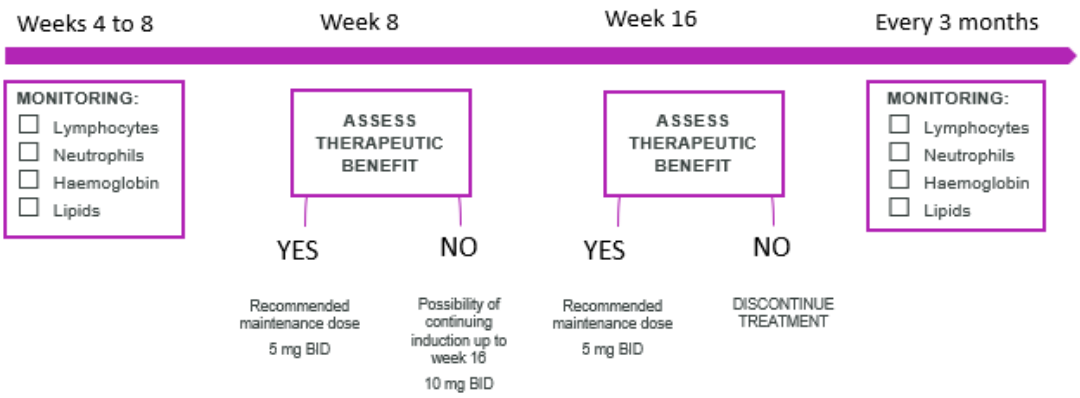

Fig. 2. Follow-up of patient treated with tofacitinib. Also regularly re-evaluate patients during treatment with tofacitinib to assess any changes to the risk of venous thromboembolism, major adverse cardiovascular events, neoplasms, infections, and herpes zoster. Consider regular skin exams.