REVISTA ESPAÑOLA DE
ENFERMEDADES DIGESTIVAS
The Spanish Journal of Gastroenterology

Title:
Clinical settings with tofacitinib in ulcerative colitis

Authors:
Carlos Taxonera, Daniel Carpio López, Ana Cabez Manas, Joaquin Ernesto Hinojosa del Val

DOI: 10.17235/reed.2022.8660/2022
Link: PubMed (Epub ahead of print)

Please cite this article as:
Taxonera Carlos, Carpio López Daniel, Cabez Manas Ana, Hinojosa del Val Joaquin Ernesto. Clinical settings with tofacitinib in ulcerative colitis. Rev Esp Enferm Dig 2022. doi: 10.17235/reed.2022.8660/2022.

REVISTA ESPAÑOLA DE
ENFERMEDADES DIGESTIVAS
The Spanish Journal of Gastroenterology

Clinical settings with tofacitinib in ulcerative colitis

Authors:

Carlos Taxonera [1], Daniel Carpio López[2], Ana Cabez Manas[3], Joaquín Hinojosa del Val[4].

Institutional affiliations:

[1]Inflammatory Bowel Disease Unit. Department of Gastroenterology. Hospital Clínico Universitario San Carlos, and Research Institute of Hospital Clínico San Carlos [IdISSC], Madrid, Spain.

[2]Inflammatory Bowel Disease Unit. Department of Gastroenterology. Complexo Hospitalario Universitario de Pontevedra. Galicia Sur Health Research Institute (IISGS), Pontevedra, Spain.

[3]Medical Department of Pfizer S.L.U, Alcobendas, Madrid, Spain

[4]Inflammatory Bowel Disease Unit. Hospital Vithas Virgen del Consuelo, Valencia, Spain.

Corresponding author:

Joaquín Hinojosa del Val. Inflammatory Bowel Disease Unit. Hospital Vithas Virgen del Consuelo, Valencia.

Email: jhinojosad@gmail.com

Conflicts of interest:

CT has worked as a speaker or consultant for MSD, AbbVie, Pfizer, Takeda, Janssen, Ferring, Faes Farma, Shire Pharmaceuticals, Dr. Falk Pharma, Galápagos and Tillots. **DC** has been engaged as a speaker or advisory member by/received funding for research from Abbvie, Amgen, Dr Falk, Faes Farma, Ferring, Fresenius Kabi, Galapagos, Gilead, Janssen, Kern, MSD, Pfizer and Takeda. **AC** is an employee of Pfizer Spain. **JH** has been engaged as a rapporteur, consultant or advisory member by/ received funding for research from MSD, Abbvie, Janssen, Takeda, Pfizer, Ferring, Faes Farma, Shire Pharmaceuticals, Chiesi, Otsuka Pharmaceutical, Kern Pharma, UCB Pharma, Vifor Pharma, Sandoz, Biogen, and Dr. Falk Pharma. **CT**, **DC** and **JH** have received consulting fees from Pfizer S.L.U for writing this paper.

REVISTA ESPAÑOLA DE
ENFERMEDADES DIGESTIVAS
The Spanish Journal of Gastroenterology

Funding: The medical writing and editorial assistance involved in preparing this article were funded by Pfizer Spain. This assistance was provided by Dr Eliana Mesa through Springer Healthcare Communications.

Abstract

There are aspects of *Janus kinase* (JAK) inhibitors, specifically tofacitinib, that distinguish them from other drugs used in the treatment of ulcerative colitis (UC), such as their oral administration, their short half-life and their lack of immunogenicity. With the available evidence, we can highlight tofacitinib's quick action and flexibility of use, and its efficacy in patients, irrespective of whether or not they have previously been exposed to TNF inhibitors (anti-TNF drugs) and other biologic agents. Moreover, their safety profile is known and manageable, with certain considerations and precautions being factored in before and during treatment. In this review, we have defined various scenarios pertaining to this drug, e.g. its use in the event of failure or intolerance to previous treatment with biologics, when a quick response is required or in patients with other concurrent 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, sustaining long-term steroid-free clinical remission, minimising any loss of response in the patient to prevent further flare-ups and improving quality of life(1-3). TNF inhibitors are the most widely-used drugs for patients who do not respond to conventional medical treatment (aminosalicylates, steroids) or thiopurine salvage therapy. However, there is still a large group of patients for whom control is not achieved, so alternative treatments are required(4).

Janus kinases (JAKs) are a family of four proteins, JAK1, JAK2, JAK3 and tyrosine kinase 2 (Tyk2), which are responsible for the intracellular signalling of different cytokines.

Their inhibition has an immunomodulatory effect. There are significant differences between JAK inhibitors, such as tofacitinib, and biologics, 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 neutralising 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 aim of this article is to examine the distinguishing characteristics of JAK inhibitors, specifically tofacitinib, with respect to other drugs used to treat UC. For this purpose, we have defined various scenarios pertaining to this drug, always following the recommendations of the European Medicines Agency (EMA) when writing this paper.

SCENARIO 1

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

Tofacitinib is indicated for patients with active UC, moderate to severe, with a suboptimal response, loss of response or intolerance to the previous treatment. The recommended induction dose is 10 mg administered orally, twice daily (BID), for eight weeks. This dose can be extended for a further eight weeks for patients who do not achieve a therapeutic benefit by week eight. The maintenance treatment is 5 mg BID, by the oral route(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 to 10 mg BID may be considered; this dose should be maintained for as short a time as possible(7). This dose is not recommended for the maintenance treatment of patients with risk factors for venous thromboembolism, unless no suitable alternative treatment is available(7).

Advantages of the oral route

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, chiefly 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 clinical practice (8, 12).

Administration flexibility

Several aspects have been studied with tofacitinib (13).

- **Extended induction -** In the OCTAVE studies (**Figure 1A**) they examined the efficacy of induction therapy with tofacitinib 10 mg BID and maintenance therapy with 5 mg or 10 mg BID, versus placebo(14). Over half of the patients with no response during the 8 weeks of induction therapy at 10 mg BID, achieved a clinical response after 8 additional weeks at the same dose(15). Most of the patients who responded to extended induction maintained the response at 36 months.
- **Dose reduction -** Of the patients in remission following maintenance therapy with tofacitinib 10 mg BID (*OCTAVE Sustain*), who were included in the open study (*OCTAVE Open*), most of the patients remained in clinical remission and sustained their endoscopic improvement at 12 months (65.8% and 75%, respectively) and at 36 months (48% and 53%, respectively) after the dose was reduced to 5 mg BID, irrespective of whether or not they had previously been exposed to anti-TNF therapy(16). In turn, the *RIVETING* study (**Figure 1B**) included patients from *OCTAVE Open* who had received tofacitinib 10 mg BID for at least two years and were in stable remission at that dose for at least 6 months. Most of the patients who reduced the dose to 5 mg BID remained in remission 6 months after the reduction(2). Efficacy in this group was consistently higher among patients with an initial Mayo endoscopic score of 0 than it was among those with an initial score of 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 to 10 mg BID. A clinical response was observed in 57.9%, 64.9% and 54.7% of the patients after 2, 12 and 24 months, respectively(13).
- **Retreatment -** Due to its characteristics, tofacitinib poses no risk of immunogenicity(5). If the 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 a dose

of 10 mg BID restored the clinical response at month 2 in 74.3% of patients. At months 12, 24 and 36, the percentage of patients in remission was 43.6, 40.6 and 37.4% respectively(17).

Prevention in the clinical management of tofacitinib

Tofacitinib's safety profile is well established, based on long-term data from clinical trials of up to 9.5 years for RA(18), up to 7.8 years for UC(19) and 3 years for psoriatic arthritis(20). In patients with UC, its safety is acceptable and it is well tolerated(21, 22), taking into account certain precautions due to possible risks associated with its use. Therefore, taking certain special considerations into account is recommended before starting the treatment (Tables 1A and 1B) and for its duration (Figure 2 and Table 2)(7).

- Due to serious infections being reported during treatment with tofacitinib, the risks and benefits should be considered before starting to use it to patients from populations that are more susceptible to a higher incidence of infections(7). In patients over 65 years old, tofacitinib should only be considered if there is no other suitable alternative treatment available(7). As with all other biologic treatments, before starting the treatment, screening should be performed for latent tuberculosis and viral infections(7). Specifically, there may be an increased incidence of herpes zoster (HZ) in certain population groups, depending on the dose(7) but not the duration of the treatment(23). Patients being 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, so for these patients, it recommends vaccinating with the glycoprotein E vaccine (HZ/su)(24) (Shingrix®). The administration of two doses with a two-month gap is recommended for them, if possible, before starting the treatment(25).
- Dose-related severe venous thromboembolic events (VTE) have also been observed, so tofacitinib should be used with caution in patients with VTE risk factors, e.g. patients with a history of VTEs, who are going to undergo major

surgery or immobilisation, with a myocardial infarction in the past 3 months, heart failure, who are using combined hormonal contraceptive or hormone replacement therapy, or with hereditary bleeding disorder or malignant neoplasm. Furthermore, additional risk factors should be considered such as age, obesity, diabetes, high blood pressure and smoking(7). Tofacitinib 10 mg BID is not recommended for the maintenance treatment of patients with UC who have known risk factors for VTE, unless no suitable alternative treatment is available(7).

- In the *ORAL Surveillance* study, a post-authorisation study in patients with rheumatoid arthritis who were 50 years of age or older and with at least one additional cardiovascular risk factor, the co-primary endpoint of major adverse cardiac events (MACEs) did not meet the pre-specified criterion of non-inferiority of tofacitinib (both doses) to anti-TNF drugs, with a hazard ratio (HR) of 1.33 (95% CI 0.91-1.94). The observed difference was attributable to an imbalance in non-fatal myocardial infarction, with the 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 being 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=1157; exposure up to 6.8 years) 7 cases of MACE were observed with an IR of 0.26 (0.11-0.54) cases per 100 patient-years(27, 28).
- Additionally, the results of the aforementioned study show an increase in the incidence of malignant neoplasms (excluding non-melanoma skin cancer - NMSC), in particular lung cancer and lymphoma, in patients treated with tofacitinib compared with those treated with anti-TNF drugs. The incidence 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 incidence of NMSC is rare, it is more likely in patients with known risk factors (older and previous NMSC) and in patients with anti-TNF treatment failure(29) so regular skin tests are recommended for these risk groups(7).
- In light of the above, it has been determined that in patients over 65 years old, smokers or ex-smokers and those with other cardiovascular risk factors, with current malignant tumours or a history of malignant tumours other than NMSCs

who have been treated successfully, tofacitinib should only be used if there are no suitable alternative treatments available(26).

- Test abnormalities have been observed during treatment with tofacitinib(7):
    - A higher incidence of neutropenia and lymphopenia and a fall in haemoglobin 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 below 750 cells/mm^3, if the absolute neutrophil count (ANC) is below 1000 cells/mm^3 and if the haemoglobin levels are below 9 g/dl. Additionally, close monitoring of these parameters is recommended from the start of the treatment **(Figure 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 8th week of treatment and managed in accordance with the clinical guidelines for their treatment, e.g. with statins(7).

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

SCENARIO 2

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

- In the OCTAVE studies (21), tofacitinib was more effective than placebo at inducing and maintaining response, remission and endoscopic improvement and no differences were observed between 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 the treatment was similar between patients who failed treatment to 1 and ≥2 anti-TNF. During maintenance, the effect of treatment with tofacitinib on patients with previous failed anti-TNF treatment was more pronounced with the 10 mg BID dose than with 5 mg BID. However, there were also significant differences between the 5 mg BID dose and the placebo.

- In the ENEIDA real-world registry, all patients had been treated with an anti-TNF drug, 89% with vedolizumab and 4% with ustekinumab. Tofacitinib was shown to have a quick effect and it induced remission in 16% and 31% of 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 treatment, 74% responded to tofacitinib at week 8 and 44% achieved remission at week 26. Prior exposure to biologics had no impact on the response or remission rates(33).
- In the prospective study of patients in the Danish registry (*ICC Registry*), 95.1% of patients had received one or more anti-TNF drugs, 62.3% vedolizumab, 59.3% both anti-TNF and vedolizumab, and 3.3% had received ustekinumab. Treatment with tofacitinib achieved combined biochemical remission (faecal 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 randomised clinical trials, showed that in patients with UC who had previously been exposed to anti-TNF therapy, tofacitinib and ustekinumab had a higher rate of induction of clinical remission and endoscopic improvement than vedolizumab or adalimumab(35).
- Another meta-analysis on the efficacy of tofacitinib in clinical practice included 13 studies in which 84.4% of the patients (n=793) had previously received biologics (62.9% both anti-TNF and vedolizumab)(36). The response at 8 weeks among patients with previous exposure to biologics was 58.1%. A single study compared steroid-free remission rates and observed no significant differences between patients exposed to biologics (48%) and unexposed patients (55%). A more recent study, in which 98.3% of patients had been exposed to biologics, confirms the efficacy of tofacitinib in a highly refractory population(37).
- The 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 who failed conventional or anti-TNF treatment"(38). The ECCO guidelines recommend tofacitinib due to its efficacy -

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 frequency of bowel movements and blood in stools three days after treatment was started, indicating that this drug is quick-acting 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 with acute severe UC and required intravenous steroids. Forty patients received tofacitinib in a 1:3 ratio to controls (n = 113). The risk of colectomy at 90 days was significantly lower with tofacitinib than with the 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), wider studies are required to determine their safety, optimal dose and frequency, in addition to the duration of the treatment(41).

Moreover, the rapid clearance of tofacitinib is advantageous in the event of the drug having to be discontinued due to an adverse event or before an operation with a high risk of infection(44) or an urgent colectomy(41). However, it must be borne in mind that the duration of the pharmacodynamic activity is greater than the half-life and the effect continues for 2-6 weeks following discontinuation of the treatment(7).

SCENARIO 4

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

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

Tofacitinib is indicated for ulcerative colitis, rheumatoid arthritis, and psoriatic arthritis(7) and, recently, it was approved by the EMA for juvenile idiopathic arthritis in patients aged 2 and above with an inadequate response to previous disease-modifying anti-rheumatic drug therapies(7) and for active ankylosing spondylitis in patients who have responded inadequately to conventional therapy(46). Table 3 shows tofacitinib studies for 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 to biologics. It is a small-molecule JAK inhibitor that is characterised by its synthetic composition, oral administration, short half-life and lack of immunogenicity.
- It is notable for its rapid action and flexibility of use, allowing the dose to be reduced following induction, the dose to be increased in the absence of a response and the treatment to be interrupted and subsequently resumed without any risk of immunogenicity.
- It is effective in patients irrespective of whether or not they have previously been 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.

References

1. Informe de Posicionamiento Terapéutico de tofacitinib (Xeljanz®) en Colitis Ulcerosa. IPT, 40/2019. V1. 9 octubre 2019.

2. Vermeire S, Su C, Lawendy N, et al. Outcomes of Tofacitinib Dose Reduction in Patients with Ulcerative Colitis in Stable Remission from the Randomised RIVETING Trial. J Crohns Colitis. 2021 Jul 5;15(7):1130-41.

3. Turner D, Ricciuto A, Lewis A, et al. STRIDE-II: An Update on the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) Initiative of the International Organization for the Study of IBD (IOIBD): Determining Therapeutic Goals for Treat-to-Target strategies in IBD. Gastroenterology. 2021 Apr;160(5):1570-83.

4. Muñoz F. Nuevas dianas terapéuticas en la enfermedad inflamatoria intestinal. Enfermedad Inflamatoria Intestinal al Día. 2017;16:138-50.

5. Danese S, Grisham M, Hodge J, et al. JAK inhibition using tofacitinib for inflammatory bowel disease treatment: a hub for multiple inflammatory cytokines. Am J Physiol Gastrointest Liver Physiol. 2016 Feb 1;310(3):G155-62.

6. Lopez-Sanroman A, Esplugues JV, Domenech E. Pharmacology and safety of tofacitinib in ulcerative colitis. Gastroenterol Hepatol. 2021 Jan;44(1):39-48.

7. Ficha técnica Xeljanz. CIMA. AEMPS. Available from: https://cima.aemps.es/cima/dochtml/ft/1171178003/FT_1171178003.html.

8. Casellas F, Guinard Vicens D, Garcia-Lopez S, et al. Consensus document on the management preferences of patients with ulcerative colitis: points to consider and recommendations. Eur J Gastroenterol Hepatol. 2020 Dec;32(12):1514-22.

9. Edel Y, Sagy I, Pokroy-Shapira E, et al. A Cross-sectional Survey on the Preference of Patients with Rheumatoid Arthritis for Route of Administration of Disease-Modifying Anti-Rheumatic Drugs: Oral Target-Specific Versus Parenteral Biologic. The Israel Medical Association journal : IMAJ. 2020 Mar;22(3):154-9.

10. Hagelund LM, Elkjaer Stallknecht S, Jensen HH. Quality of life and patient preferences among Danish patients with ulcerative colitis - results from a survey study. Curr Med Res Opin. 2020 May;36(5):771-9.

11. Louder AM, Singh A, Saverno K, et al. Patient Preferences Regarding Rheumatoid Arthritis Therapies: A Conjoint Analysis. American health & drug benefits. 2016 Apr;9(2):84-93.

12. Dassopoulos T, Cohen RD, Scherl EJ, et al. Ulcerative Colitis Care Pathway. Gastroenterology. 2015 Jul;149(1):238-45.

13. Sands BE, Armuzzi A, Marshall JK, et al. Efficacy and safety of tofacitinib dose de-escalation and dose escalation for patients with ulcerative colitis: results from OCTAVE Open. Aliment Pharmacol Ther. 2020 Jan;51(2):271-80.

14. Sandborn WJ, Su C, Sands BE, et al. Tofacitinib as Induction and Maintenance Therapy for Ulcerative Colitis. N Engl J Med. 2017 May 4;376(18):1723-36.

15. Sandborn WJ, Peyrin-Biroulet L, Quirk D, et al. Efficacy and Safety of Extended Induction With Tofacitinib for the Treatment of Ulcerative Colitis. Clin Gastroenterol Hepatol. 2020 Oct 27:S1542-3565(20)31496-8.

16. Colombel JF, Osterman MT, Thorpe AJ, et al. Maintenance of Remission With Tofacitinib Therapy in Patients With Ulcerative Colitis. Clin Gastroenterol Hepatol. 2020 Oct 9:S1542-3565(20)31389-6.

17. Panes J, Vermeire S, Dubinsky MC, et al. Efficacy and Safety of Tofacitinib Retreatment for Ulcerative Colitis After Treatment Interruption: Results From the OCTAVE Clinical Trials. J Crohns Colitis. 2021 Apr 22.

18. Wollenhaupt J, Lee EB, Curtis JR, et al. Safety and efficacy of tofacitinib for up to 9.5 years in the treatment of rheumatoid arthritis: final results of a global, open-label, long-term extension study. Arthritis Res Ther. 2019 Apr 5;21(1):89.

19. Sandborn W, Dhaens G, Sands B, et al. S777 Tofacitinib for the Treatment of Ulcerative Colitis: Up to 7.8 Years of Safety Data from Global Clinical Trials. American Journal of Gastroenterology. 2021 10/01;116:S360-S.

20. Nash P, Coates LC, Kivitz AJ, et al. Safety and Efficacy of Tofacitinib in Patients with Active Psoriatic Arthritis: Interim Analysis of OPAL Balance, an Open-Label, Long-Term Extension Study. Rheumatology and therapy. 2020 Sep;7(3):553-80.

21. Sandborn WJ, Peyrin-Biroulet L, Sharara AI, et al. Efficacy and Safety of Tofacitinib in Ulcerative Colitis Based on Prior Tumor Necrosis Factor Inhibitor Failure Status. Clin Gastroenterol Hepatol. 2021 Mar 6:S1542-3565(21)00222-6.

22. Sandborn WJ, Lawendy N, Danese S, et al. Safety and efficacy of tofacitinib for treatment of ulcerative colitis: final analysis of OCTAVE Open, an open-label, long-term extension study with up to 7.0 years of treatment. Aliment Pharmacol Ther. 2021. Available from: http://www.ncbi.nlm.nih.gov/pubmed/34854095. [Online ahead of print]

23. Winthrop KL, Melmed GY, Vermeire S, et al. Herpes Zoster Infection in Patients With Ulcerative Colitis Receiving Tofacitinib. Inflamm Bowel Dis. 2018 Sep 15;24(10):2258-65.

24. Ministerio de Sanidad, Consumo y Bienestar Social. Vacunas y Programa de Vacunación. Herpes zóster. Recomendaciones de vacunación actuales acordadas en el Consejo Interterritorial del Sistema Nacional de Salud. Available from: https://www.mscbs.gob.es/profesionales/saludPublica/prevPromocion/vacunaciones/vacunas/ciudadanos/zoster.htm.

25. Grupo de trabajo de vacunación frente a herpes zóster de la Ponencia de Programa y Registro de Vacunaciones. Comisión de Salud Pública del Consejo Interterritorial del Sistema Nacional de Salud. Ministerio de Sanidad, marzo 2021. Available from: https://www.mscbs.gob.es/profesionales/saludPublica/prevPromocion/vacunaciones/programasDeVacunacion/docs/HerpesZoster_RecomendacionesVacunacion.pdf.

26. Agencia española de medicamentos y productos sanitarios. Notas de seguridad. Xeljanz (tofacitinib): nuevas precauciones de uso. Available from: https://www.aemps.gob.es/informa/notasinformativas/medicamentosusohumano-3/seguridad-1/2021-seguridad-1/xeljanz-tofacitinib-nuevas-precauciones-de-uso/.

27. Sandborn WJ, Panés J, D'Haens GR, et al. Tofacitinib for the Treatment of Ulcerative Colitis: Up to 6.8 Years of Safety Data From Global Clinical Trials. Official journal of the American College of Gastroenterology | ACG. 2020;115:S353-S4.

28. Sands BE, Colombel JF, Ha C, et al. Lipid Profiles in Patients With Ulcerative Colitis Receiving Tofacitinib-Implications for Cardiovascular Risk and Patient Management. Inflamm Bowel Dis. 2021 May 17;27(6):797-808.

29. Sands BE, Long MD, Reinisch W, et al. Tofacitinib for the Treatment of Ulcerative Colitis: Analysis of Nonmelanoma Skin Cancer Rates From the Ulcerative Colitis Clinical Program. Inflamm Bowel Dis. 2021 Mar 20 Mar 20.

30. Panes J, Gisbert JP. Efficacy of tofacitinib treatment in ulcerative colitis. Gastroenterol Hepatol. 2019 Jun - Jul;42(6):403-12.

31. Dubinsky MC, Peyrin-Biroulet L, Melmed GY, et al. Efficacy of Tofacitinib in Patients With Ulcerative Colitis by Prior Tumor Necrosis Factor Inhibitor Treatment Status: Results From OCTAVE Induction and Maintenance Studies. Available from: https://eventscribe.com/2017/wcogacg2017/ajaxcalls/PosterInfo.asp?efp=S1lVTUxLQVozODMy&PosterID=114733&rnd=5.004501E-02.

32. Chaparro M, Garre A, Mesonero F, et al. Tofacitinib in Ulcerative Colitis: Real-world Evidence From the ENEIDA Registry. J Crohns Colitis. 2021 Jan 13;15(1):35-42.

33. Honap S, Chee D, Chapman TP, et al. Real-world Effectiveness of Tofacitinib for Moderate to Severe Ulcerative Colitis: A Multicentre UK Experience. J Crohns Colitis. 2020 Oct 5;14(10):1385-93.

34. Biemans VBC, Sleutjes JAM, de Vries AC, et al. Tofacitinib for ulcerative colitis: results of the prospective Dutch Initiative on Crohn and Colitis (ICC) registry. Aliment Pharmacol Ther. 2020 May;51(9):880-8.

35. Singh S, Murad MH, Fumery M, et al. First- and Second-Line Pharmacotherapies for Patients With Moderate to Severely Active Ulcerative Colitis: An Updated Network Meta-Analysis. Clin Gastroenterol Hepatol. 2020 Sep;18(10):2179-91 e6.

36. Taxonera C, Olivares D, Alba C. Real-World Effectiveness and Safety of Tofacitinib in Patients With Ulcerative Colitis: Systematic Review With Meta-Analysis. Inflamm Bowel Dis. 2021 Feb 15:Feb 15:izab011. doi: 10.1093/ibd/izab011. Online ahead of print.

37. Hernández Martínez A, Navajas Hernández P, Martín Rodríguez MDM, et al. Efficacy and safety of tofacitinib in the treatment of ulcerative colitis: real-life experience in Andalusia. Rev Esp Enferm Dig. 2022. Available from: https://www.reed.es/ArticuloFicha.aspx?id=6513&hst=0&idR=0&AspxAutoDetectCookieSupport=1. [Online ahead of print]

38. Sicilia B, Garcia-Lopez S, Gonzalez-Lama Y, et al. GETECCU 2020 guidelines for the treatment of ulcerative colitis. Developed using the GRADE approach. Gastroenterol Hepatol. 2020 Aug;43 Suppl 1:1-57.

39. Raine T, Bonovas S, Burisch J, et al. ECCO Guidelines on Therapeutics in Ulcerative Colitis: Medical Treatment. J Crohns Colitis. 2021 Oct. [Epub ahead of print]

40. Hanauer S, Panaccione R, Danese S, et al. Tofacitinib Induction Therapy Reduces Symptoms Within 3 Days for Patients With Ulcerative Colitis. Clin Gastroenterol Hepatol. 2019 Jan;17(1):139-47.

41. Berinstein JA, Sheehan JL, Dias M, et al. Tofacitinib for Biologic-Experienced Hospitalized Patients With Acute Severe Ulcerative Colitis: A Retrospective Case-Control Study. Clin Gastroenterol Hepatol. 2021 Oct;19(10):2112-20 e1.

42. Kotwani P, Terdiman J, Lewin S. Tofacitinib for Rescue Therapy in Acute Severe Ulcerative Colitis: A Real-world Experience. J Crohns Colitis. 2020 Jul 30;14(7):1026-8.

43. Uzzan M, Bresteau C, Laharie D, et al. Tofacitinib as salvage therapy for 55 patients hospitalised with refractory severe ulcerative colitis: A GETAID cohort. Aliment Pharmacol Ther. 2021 Aug;54(3):312-9.

44. D'Amico F, Parigi TL, Fiorino G, et al. Tofacitinib in the treatment of ulcerative colitis: efficacy and safety from clinical trials to real-world experience. Therap Adv Gastroenterol. 2019;12:1756284819848631.

45. Argollo M, Gilardi D, Peyrin-Biroulet C, et al. Comorbidities in inflammatory bowel disease: a call for action. The lancet Gastroenterology & hepatology. 2019 Aug;4(8):643-54.

46. Pfizer's XELJANZ® (tofacitinib) Receives Marketing Authorization in the European Union for the Treatment of Active Ankylosing Spondylitis. Available from: https://www.ema.europa.eu/en/medicines/human/summaries-opinion/xeljanz-2.

47. Kerschbaumer A, Smolen JS, Nash P, et al. Points to consider for the treatment of immune-mediated inflammatory diseases with Janus kinase inhibitors: a systematic literature research. RMD open. 2020;6(3):e001374.

48. Jamilloux Y, El Jammal T, Vuitton L, et al. JAK inhibitors for the treatment of autoimmune and inflammatory diseases. Autoimmun Rev. 2019 Nov;18(11):102390.

49. Damsky W, Peterson D, Ramseier J, et al. The emerging role of Janus kinase inhibitors in the treatment of autoimmune and inflammatory diseases. J Allergy Clin Immunol. 2021 Mar;147(3):814-26.

50. Silfen A, Cohen N, Traboulsi C, et al. Tofacitinib Therapy is Effective for Arthralgias Associated with Active Inflammatory Bowel Disease. Poster presentations: Clinical: Therapy and Observation 2021. Available from: https://www.ecco-ibd.eu/publications/congress-abstracts/item/p455-tofacitinib-therapy-is-effective-for-arthralgias-associated-with-active-inflammatory-bowel-disease.html.

51. Mease P, Hall S, FitzGerald O, et al. Tofacitinib or Adalimumab versus Placebo for Psoriatic Arthritis. N Engl J Med. 2017 Oct 19;377(16):1537-50.

52. Gladman D, Rigby W, Azevedo VF, et al. Tofacitinib for Psoriatic Arthritis in Patients with an Inadequate Response to TNF Inhibitors. N Engl J Med. 2017 Oct

19;377(16):1525-36.

53. Nash P, Coates LC, Fleischmann R, et al. Efficacy of Tofacitinib for the Treatment of Psoriatic Arthritis: Pooled Analysis of Two Phase 3 Studies. Rheumatology and therapy. 2018 Dec;5(2):567-82.

54. van der Heijde D, Deodhar A, Wei JC, et al. Tofacitinib in patients with ankylosing spondylitis: a phase II, 16-week, randomised, placebo-controlled, dose-ranging study. Ann Rheum Dis. 2017 Aug;76(8):1340-7.

55. Papp KA, Menter MA, Abe M, et al. Tofacitinib, an oral Janus kinase inhibitor, for the treatment of chronic plaque psoriasis: results from two randomized, placebo-controlled, phase III trials. Br J Dermatol. 2015 Oct;173(4):949-61.

56. Papp KA, Krueger JG, Feldman SR, et al. Tofacitinib, an oral Janus kinase inhibitor, for the treatment of chronic plaque psoriasis: Long-term efficacy and safety results from 2 randomized phase-III studies and 1 open-label long-term extension study. J Am Acad Dermatol. 2016 May;74(5):841-50.

57. Ruperto N, Brunner HI, Zuber Z, et al. Pharmacokinetic and safety profile of tofacitinib in children with polyarticular course juvenile idiopathic arthritis: results of a phase 1, open-label, multicenter study. Pediatr Rheumatol Online J. 2017 Dec 28;15(1):86.

58. Kennedy Crispin M, Ko JM, Craiglow BG, et al. Safety and efficacy of the JAK inhibitor tofacitinib citrate in patients with alopecia areata. JCI insight. 2016 Sep 22;1(15):e89776.

59. Kong X, Sun Y, Dai X, et al. Treatment efficacy and safety of tofacitinib versus methotrexate in Takayasu arteritis: a prospective observational study. Ann Rheum Dis. 2021 Aug 6.

60. Khanna D, Bush E, Nagaraja V, et al. Tofacitinib in Early Diffuse Cutaneous Systemic Sclerosis-Results of Phase I/II Investigator-Initiated, Double-Blind Randomized Placebo-Controlled Trial. Arthritis & rheumatology. 2019;71(10).

61. Liu LY, Strassner JP, Refat MA, et al. Repigmentation in vitiligo using the Janus kinase inhibitor tofacitinib may require concomitant light exposure. J Am Acad Dermatol. 2017 Oct;77(4):675-82 e1.

62. Orfaly VE, Kovalenko I, Tolkachjov SN, et al. Tofacitinib for the treatment of refractory pyoderma gangrenosum. Clin Exp Dermatol. 2021 Aug;46(6):1082-5.

63. Salmon Olavarria P, Rubio Iturria S, Nantes Castillejo O. Tofacitinib, a useful option for the treatment of pyoderma gangrenosum in an ulcerative colitis patient. Rev Esp Enferm Dig. 2021 Oct;113(10):733-4.

64. Levy LL, Urban J, King BA. Treatment of recalcitrant atopic dermatitis with the oral Janus kinase inhibitor tofacitinib citrate. J Am Acad Dermatol. 2015 Sep;73(3):395-9.

65. Chen Z, Wang X, Ye S. Tofacitinib in Amyopathic Dermatomyositis-Associated Interstitial Lung Disease. N Engl J Med. 2019 Jul 18;381(3):291-3.

66. Kurtzman DJ, Wright NA, Lin J, et al. Tofacitinib Citrate for Refractory Cutaneous Dermatomyositis: An Alternative Treatment. JAMA dermatology. 2016 Aug 1;152(8):944-5.

67. Damsky W, Thakral D, Emeagwali N, et al. Tofacitinib Treatment and Molecular Analysis of Cutaneous Sarcoidosis. N Engl J Med. 2018 Dec 27;379(26):2540-6.

68. Zhu KJ, Yang PD, Xu Q. Tofacitinib Treatment of Refractory Cutaneous Leukocytoclastic Vasculitis: A Case Report. Front Immunol. 2021;12:695768.

Figures and Tables

Figure 1A.- Overview of the OCTAVE studies: *Induction*, *Sustain* and *Open*

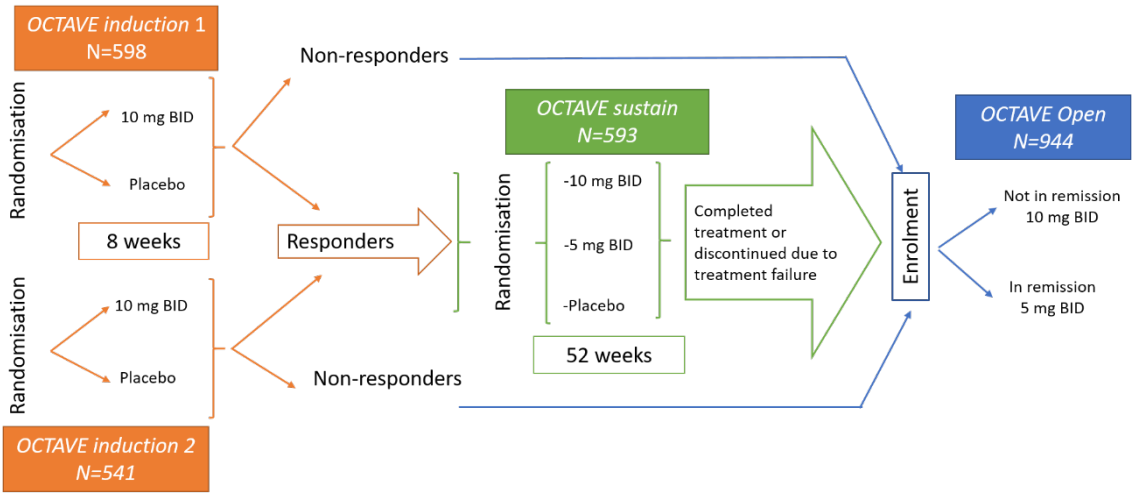


Figure 1B.- Overview of the RIVETING study design

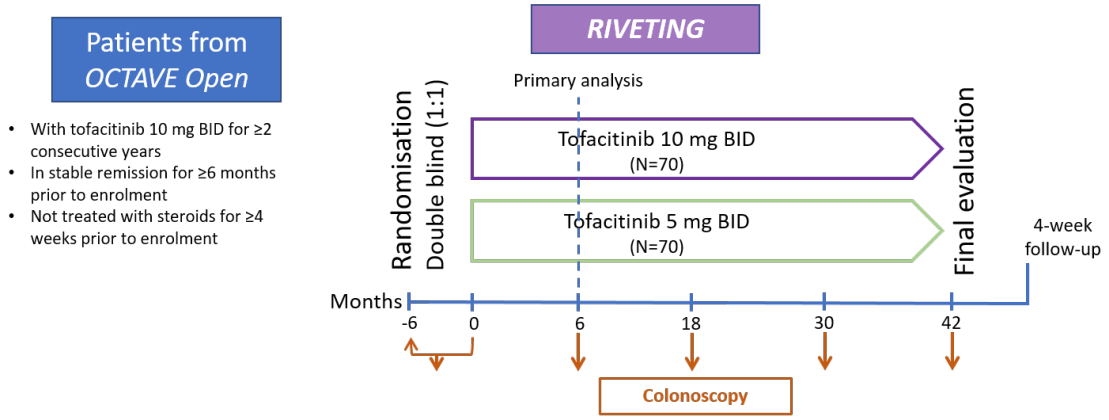
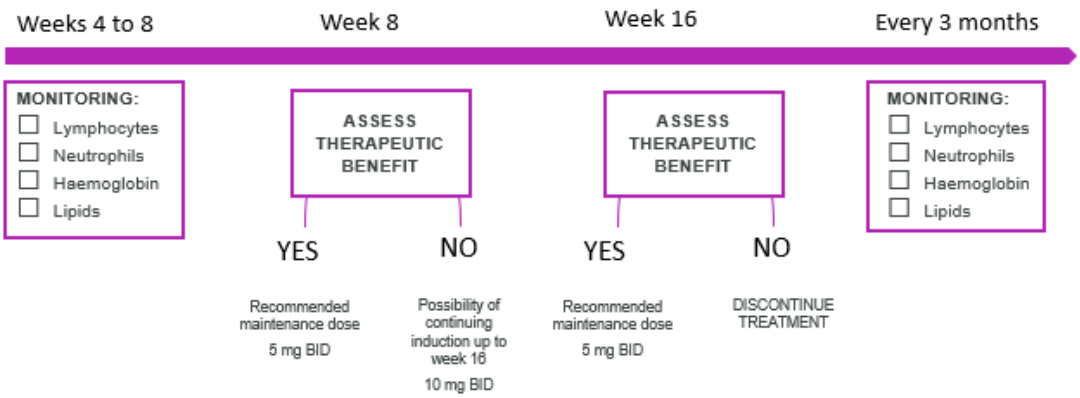


Figure 2- Follow-up of patient treated with tofacitinib*.



*Also regularly re-evaluate patients during treatment with tofacitinib to assess any changes to the risk of venous thromboembolism, major adverse cardiac events, neoplasms, infections and herpes zoster. Consider regular skin examinations.

Tables 1A and 1B - Considerations prior to **STARTING TREATMENT** with tofacitinib.

A- CONTRAINDICATIONS:

☐ Hypersensitivity to the active substance or to any of the excipients

☐ Active tuberculosis, severe and active infections such as sepsis or opportunistic infections

☐ Acute liver failure

☐ Pregnancy and breastfeeding

B- REVIEW AND ASSESS:

☐ Vaccination status

- Vaccination with live attenuated vaccines should be administered at least 2 weeks before starting the treatment, although 4 weeks are preferable

☐ Latent/active tuberculosis.

☐ The co-administration of potent CYP3A4 inducers (e.g. rifampicin) is not recommended

☐ Screen for viral hepatitis

☐ Check test parameters. Start if:

- Lymphocytes >750/mm^3
- Neutrophils >1,000/mm^3
- Haemoglobin >9 g/dl
- Normal liver enzymes (ALT/AST)

☐ It is not recommended for use in combination with:

- Biologics
- Potent immunosuppressants (azathioprine, cyclosporine, 6-mercaptopurine, tacrolimus)

☐ Tofacitinib should only be used for the following patients if there are no suitable alternative treatments available:

- Patients over 65 years old
- Past or present smokers
- Patients with cardiovascular risk factors
- Patients with malignancy risk factors (e.g. current malignant tumours or a history of malignant tumours, excluding non-melanoma skin cancer, that have been treated successfully)

Table 2 - Recommendations for adjusting the dose or discontinuing the treatment

Situation	**Recommendation**
Severe infection	Discontinue until it is resolved
Signs and symptoms of VTE	Discontinue the treatment
ALC between 500 and 750 cells/mm^3 and/or ANC between 500 and 1000 cells/mm^3	Reduce to 5 mg BID if it is currently 10 mg BID Discontinue if it is currently 5 mg BID Resume when ALC is >750 cells/mm^3 and/or ANC > 1000 cells/mm^3
ALC < 500 cells/mm^3 ANC < 500 cells/mm^3	Discontinue the treatment
Haemoglobin <8.0 g/dl or reduction >2 g/dl	Discontinue the treatment until it returns to normal level
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 <30 mL/min)	Adjust the dose from 5 mg BID to 5 mg QD or from 10 mg BID to 5 mg BID

*The co-administration of tofacitinib and potent CYP3A4 inducers (e.g. rifampicin) is not recommended as it may lead to a loss of/reduction in clinical response. QD, every day; BID, twice a day.

Table 3. - Clinical studies and case reports with 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)

*EMA-approved indication

STUDIES
CASES