PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 49567

Title: Real-World Experience with Tofacitinib for the Treatment of Ulcerative Colitis: A Review of the Literature

Reviewer's code: 03645427

Reviewer's country: South Korea

Science editor: Ze-Mao Gong

Reviewer accepted review: 2019-06-21 13:17

Reviewer performed review: 2019-06-22 06:26

Review time: 17 Hours

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish	[Y] Grade A: Priority publishing [ ] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection	[ ] Accept (High priority) [Y] Accept (General priority) [ ] Minor revision [ ] Major revision [ ] Rejection	Peer-Review: [Y] Anonymous [ ] Onymous Peer-reviewer's expertise on the topic of the manuscript: [Y] Advanced [ ] General [ ] No expertise Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

This article is very timely and pertinent. Although you did not suggested the data analyses or aurthor's opinion concerning efficacy and safety of tofacitinib in comparison with other existing biologic agents, I think this reviewing is informative and summarized well.

- Thank you for the comments. Nothing to add.

INITIAL REVIEW OF THE MANUSCRIPT

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 49567

Title: Real-World Experience with Tofacitinib for the Treatment of Ulcerative Colitis: A Review of the Literature

Reviewer's code: 02446483

Reviewer's country: Canada

Science editor: Ze-Mao Gong

Reviewer accepted review: 2019-06-23 14:18

Reviewer performed review: 2019-06-23 14:30

Review time: 1 Hour

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish	[Y] Grade A: Priority publishing [ ] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection	[ ] Accept (High priority) [ ] Accept (General priority) [Y] Minor revision [ ] Major revision [ ] Rejection	Peer-Review: [Y] Anonymous [ ] Onymous Peer-reviewer's expertise on the topic of the manuscript: [Y] Advanced [ ] General [ ] No expertise Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

It remains challenging the management of patients with ulcerative colitis who are dependent on corticosteroid for control of symptoms, or refractory to corticosteroids or standard immunosuppressive therapy. The development of newer medical therapies has increased the options for managing patients with ulcerative colitis in this situation. Access and funding may remain limited for some countries and the potential access for children is not clear. The editorial is well written. I would add and emphasize the potentiality and causalities for failure using Tofacitinib and when a pediatric access may be considered.

- Thank you for the comments - It should be noted that this medication has not been FDA approved for the use in pediatric populations

INITIAL REVIEW OF THE MANUSCRIPT

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 49567

Title: Real-World Experience with Tofacitinib for the Treatment of Ulcerative Colitis: A Review of the Literature

Reviewer's code: 04091933

Reviewer's country: Russia

Science editor: Ze-Mao Gong

Reviewer accepted review: 2019-06-21 10:35

Reviewer performed review: 2019-06-25 10:20

Review time: 3 Days and 23 Hours

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish	[Y] Grade A: Priority publishing [ ] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection	[ ] Accept (High priority) [ ] Accept (General priority) [Y] Minor revision [ ] Major revision [ ] Rejection	Peer-Review: [Y] Anonymous [ ] Onymous Peer-reviewer's expertise on the topic of the manuscript: [Y] Advanced [ ] General [ ] No expertise Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

The review is of undoubted interest, since such phenomena as steroid dependence, steroid resistance and lack of response to biological preparations are widespread. Small molecules like tofacitinib are a real therapeutic alternative for patients with IBD. The review is well written (with the latest literary references) and can be published, however a minor revision is required. 1. The authors made the right safety emphasis on HZ infection and probable thromboembolic events. However, given the lack of safety information, it is desirable to describe the main infectious (not only HZ, but C. difficile colitis, abscesses, etc.), oncological (NMSCs) and other side effects (gastrointestinal perforations, MACE, etc.) of tofacitinib.

- In the OCTAVE trials, (2) infections occurred at higher rates with tofacitinib than with placebo, and the rate of serious infection was higher with tofacitinib in the induction trials but similar across treatment groups in the maintenance trial. Overall, 2.9% of

subjects suffered at least one serious infection compared with 1.0% of the placebo controls, including anal abscess, pneumonia, herpes zoster (HZ) infection, Clostridium difficile infection, and cytomegalovirus colitis.

- Among RA patients, gastrointestinal perforations have been observed with the use of tofacitinib. (5) Across the OCTAVE trials, one intestinal perforation occurred with tofacitinib; in the OCTAVE Induction 1 trial, 1 patient in the 10-mg tofacitinib group had a serious adverse event of intestinal perforation. In the OCTAVE Induction 2 trial, 1 patient in the placebo group had a serious adverse event of intestinal perforation. No patients in the OCTAVE Sustain trial experienced intestinal perforation.
- There is some data to suggest an increase in malignancy risk among rheumatoid arthritis patients treated with tofacitinib. In a worldwide, 3-year, post-marketing surveillance study on tofacitinib in patients with rheumatoid arthritis, (12) the relative risk per 100 patient-years for neoplasms was 0.45, with the most common neoplasms being nonmelanoma skin cancers (NMSCs). Fifteen lymphoma cases were reported over approximately 34,000 patient-years of exposure, and the risk of lymphoma was not found to increase over time. The data on malignancy risk among ulcerative colitis patients using tofacitinib is much more limited. In an integrated analysis of tofacitinib UC clinical trials, eleven patients had malignancies (excluding NMSC), all during OCTAVE Open. (7) There 1 case reported for each of the following cancers: cervical cancer, hepatic angiosarcoma, cholangiocarcinoma, cutaneous leiomyosarcoma, Epstein-Barr-virus-associated lymphoma, renal cell carcinoma, essential thrombocythemia, acute myeloid leukemia, adenocarcinoma of colon, lung cancer, and breast cancer. In the overall cohort, IR of malignancy (excluding NMSC) including all 11 patients with events was 0.7 (95% CI, 0.3–1.2).

2. Since the review reflects the real experience, it is desirable to give an example of a successful combining a biologic with tofacitinib as rescue therapy [Griller & Cohen, 2019].

- In addition, there is currently limited data on the efficacy of combining tofacitinib therapy with biologics among patients with ulcerative colitis. Within the RA

population, there is some data to support safety with combination therapy; a case series of 6 patients with rheumatoid arthritis treated with tofacitinib–biologic combination therapy did not find any adverse events after a mean of 14 months of treatment. (26) Le Berre et al (27) report a case of successful combination of vedolizumab and tofacitinib in a patient with UC and spondyloarthropathy for whom anti-TNF therapy was contraindicated; after 3 months of treatment with this combination therapy, the patient achieved clinical remission for both gastrointestinal and rheumatologic symptoms. No adverse events were observed, including no infections. Additionally, rapid remission was achieved recently in an inpatient as described by_Griller et al, (22) when tofacitinib and infliximab were used as combination rescue therapy to avoid colectomy in a hospitalized patient with severe ulcerative colitis. Overall, the available evidence remains limited regarding UC patients, and larger studies are needed to confirm the efficacy and safety profile of combination therapy in this patient population.

3. It may be worth mentioning the potential efficacy of tofacitinib in pyoderma gangrenosum that affects IBD patients (CD cases on tofacitinib for severe inflammatory arthritis have been described to date [Kochar et al., 2019]).

- Thank you fo rthe comment. We feel that this is out of scope of the article, as Tofacitinib is not approved for treatment in PG.

4. It is advisable to discuss the cost of treatment with tofacitinib, since it is likely that tofacitinib could also be economically viable in comparison with other biologics due to its lower production cost [Milev et al., 2019].

- Interestingly, as a stand alone medication, it should also be hilighted that the economic burden to the patient for the cost of tofacitinib is likely less than compared to alternative therapies such as anti-TNFs and Vedolizumab (28).

5. Another brand name for tofacitinib (Jaquinus) is also worth mentioning.

- Thank you for the comment. As we do not mention Xeljanz by it's

brand name in the body of the article, we do not feel that it is necessary to include Jaquinus.

INITIAL REVIEW OF THE MANUSCRIPT

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 49567

Title: Real-World Experience with Tofacitinib for the Treatment of Ulcerative Colitis: A Review of the Literature

Reviewer's code: 00036517

Reviewer's country: Japan

Science editor: Ze-Mao Gong

Reviewer accepted review: 2019-06-24 07:35

Reviewer performed review: 2019-07-01 06:50

Review time: 6 Days and 23 Hours

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS

[ ] Grade A: Excellent [ ] Grade B: Very good [ ] Grade C: Good [Y] Grade D: Fair [ ] Grade E: Do not publish	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection	[ ] Accept (High priority) [ ] Accept (General priority) [ ] Minor revision [Y] Major revision [ ] Rejection	Peer-Review: [Y] Anonymous [ ] Onymous Peer-reviewer's expertise on the topic of the manuscript: [ ] Advanced [ ] General [Y] No expertise Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

I think authors need to compare the efficacy of tofacitinib for UC patients clearly, and also the difference of efficacy of tofacitinib than TNF alpha antibodies.

In discussion, there are many data from papers of references, but I suggest that suthors need to add their speculations for use tofacitinib to UC patients.

- Thank you - added in more extensive discusison.
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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 49567

Title: Real-World Experience with Tofacitinib for the Treatment of Ulcerative Colitis: A Review of the Literature

Reviewer's code: 03442128

Reviewer's country: United States

Science editor: Ze-Mao Gong

Reviewer accepted review: 2019-06-21 11:17

Reviewer performed review: 2019-07-04 15:26

Review time: 13 Days and 4 Hours

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
[ ] Grade A: Excellent [ ] Grade B: Very good [ ] Grade C: Good [Y] Grade D: Fair [ ] Grade E: Do not publish	[Y] Grade A: Priority publishing [ ] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection	[ ] Accept (High priority) [ ] Accept (General priority) [ ] Minor revision [Y] Major revision [ ] Rejection	Peer-Review: [Y] Anonymous [ ] Onymous Peer-reviewer's expertise on the topic of the manuscript: [Y] Advanced [ ] General [ ] No expertise Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

The authors present a timely and concise overview of the newest therapy for Ulcerative Colitis, the JAK inhibitor tofacitinib. The authors do a good job of summarizing the limited available data, but a number of structural elements the manuscript need to be addressed, along with some additions to content.

Suggested revisions:

Title:

Would remove the reference to "Real-World Experience" from the manuscript title. In fact, very few of the studies reviewed in the manuscript reflect real-world experience.

- Noted, removed.

Abstract:

The abstract is too generalized, and needs to more specifically touch on the major points/subjects to be discussed in the manuscript that follows. E.g. review of efficacy, safety,

- Noted, revised

Minor point: Would also avoid use of superlatives such as "incredible" and "exciting". This should also be the case in the manuscript itself.

- removed

Core tip:

Again, would not address "real world efficacy". The vast majority of the review reflects clinical trial experience.

- removed

Manuscript:

Introduction:

Minor point: use the trademark symbol following us of the word Xeljanz, ®

- Removed "Xeljanz"

Paragraph 2: Would place the discussion of long term safety AFTER review of shorter term efficacy

Major point: WOULD NOT discuss the authors own center's experience until it is either published in a peer review journal or presented at GI conference.

- Removed this section from article

Review of the Literature:

Would start with a review of the Octave clinical trial results before addressing the real world literature

- Noted, revised.

When discussing the Berinstein JA paper about rescue tofacitinib, should address that these were INPATIENTS and prior biologic failures: this is what makes the paper's results important

- Noted, revised.

Minor: overall a good discussion of varicella issues. Would just address the

packaging recommendation regarding live vaccinations in those on tofacitinib, and the differences between the older and newer type of VZV vaccines and.

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

Pregnancy is addressed, but would include what (if anything) the prescribing information for tofacitinib has to say about pregnancy. Would add a line or two about lactation issues, recommendations as well.

- Noted, revised
- Additional studies have analyzed other important safety-related questions regarding

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

Would add a brief paragraph regarding malignancy risk, if any. While little to no data available for UC, may find some more information/reporting in the RA literature

- Added, thank you.
- There is some data to suggest an increase in malignancy risk among rheumatoid arthritis patients treated with tofacitinib. In a worldwide, 3-year, post-marketing surveillance study on tofacitinib in patients with rheumatoid arthritis, (12) the relative risk per 100 patient-years for neoplasms was 0.45, with the most common neoplasms being nonmelanoma skin cancers (NMSCs). Fifteen lymphoma cases were reported over approximately 34,000 patient-years of exposure, and the risk of lymphoma was not found to increase over time. The data on malignancy risk among ulcerative colitis patients using tofacitinib is much more limited. In an integrated analysis of tofacitinib UC clinical trials, eleven patients had malignancies (excluding NMSC), all during OCTAVE Open. (7) There 1 case reported for each of the following cancers: cervical cancer, hepatic angiosarcoma, cholangiocarcinoma, cutaneous leiomyosarcoma, Epstein-Barr-virus-associated lymphoma, renal cell carcinoma, essential thrombocythemia, acute myeloid leukemia, adenocarcinoma of colon, lung

cancer, and breast cancer. In the overall cohort, IR of malignancy (excluding NMSC) including all 11 patients with events was 0.7 (95% CI, 0.3–1.2).

Perspective:

Would again downplay the "Real world post marketing data…" given the limited real world data presented

- Noted, revised, thank you.

INITIAL REVIEW OF THE MANUSCRIPT

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