

Dear Editor and Reviewers,

Thank you for your kind comments on our work. Our responses to your suggestions are detailed below.

### **Editor**

We have amended the references and citations as requested.

### **Reviewer 1**

Thank you for your comments.

**Page 2, 2nd paragraph, sentence 2: please reference.**

We have added this.

**Page 2, 2nd paragraph, last sentence: Please avoid undocumented opinion, ie, how is symptom-related drug withdrawal "not a major clinical difficulty"?**

We have deleted this.

**Page 2-3: When discussing dose-related toxicity, some objective data should be provided. The terms "daily..., or much higher dosing" and "very high doses" do not provide any guidance for the clinician.**

This information was included in the referenced articles. We have now added dose examples to the text. The intention was not to provide guidance to clinicians on modern dosing (which is all "low dose" in inflammatory disease), it was to illustrate that clinicians should not extrapolate adverse event data from doses far in excess of those which would currently be considered appropriate.

**Page 3, paragraph 1: Sentence beginning with "Examination..." is speculative and should be deleted.**

We have edited this sentence.

**Page 3, paragraph 2, sentence 1 (beginning with "Methotrexate..."): Please reference or delete.**

We have referenced this.

**Page 3 paragraph 2, sentences 3 and 4: Please reference, or modify biased statements.**

We have referenced these sentences.

**Page 3, paragraph 4: Run-on sentences, not referenced, appear to reflect personal bias.**

We have referenced these sentences.

**"Epidemiology" section, last paragraph: Please reference the stated clinical trials.**

We have done this.

**Last sentence - please state mean duration of these trials.**

We have added this

**"Meta-Analysis" section, penultimate sentence - Please define surrogate measures (this reviewer assumes the authors are referring to transaminase elevations).**

We have done this.

**Tables: The manuscript would benefit from a table offering guidance as to the approach to managing suspected hepatotoxicity (eg MTX dose reduction or withdrawal), which should also include recommendations regarding monitoring and indications for liver biopsy.**

We have added this.

**Additional recommendation: Since MTX is now extensively used as a substitute immunomodulator for 6-MP in patients with IBD, particularly when prescribed in conjunction with a biologic agent, some comparative data regarding liver toxicity between these 2 drugs would be of great interest.**

We have added data on hepatotoxicity with thiopurines.

## **Reviewer 2**

Thank you, we trust the revision provides a wider view.

## **Reviewer 3**

Thank you for your kind comments. We have added the suggested reference and revised for clarity as suggested.

**Reviewer 4**

Thank you for your kind comments.