Comments from Reviewers:

We wish to thank the Reviewers for their helpful comments and suggestions regarding our manuscript. Our point-by-point response follows:

Reviewer 1:
1. I enjoyed reading this review and would like to compliment the authors on a comprehensive and interesting review of the literature However, in my opinion, there was one very important omission in the section on combination therapy; namely the combination of low dose azathioprine with allopurinol (LDAA). Given that not all countries can use or are able to afford monoclonal therapy, and I would expect clinicians from all over the world would read this article, I think it is imperative that this issue is discussed. Albeit not a popular therapeutic option the arguments for and against should be addressed, given this is "Current evidence…" and LDAA is being prescribed up front in some centres. I am sure the authors will be aware of the literature about LDAA, however there are two very recent articles (one which has only just become available on PubMed) that I would strongly advise careful consideration for inclusion into this review: Scand J Gastroenterol. 2016 Dec;51(12):1470-1475. Epub 2016 Aug 10. Randomized clinical trial: a pilot study comparing efficacy of low-dose azathioprine and allopurinol to azathioprine on clinical outcomes in inflammatory bowel disease. Kiszka-Kanowitz M1, Theede K, Mertz-Nielsen A., and Inflamm Bowel Dis. 2016 Jul;22(7):1639-46. doi: 10.1097/MIB.0000000000000827. Long-term Safety and Efficacy of Low-dose Azathioprine and Allopurinol Cotherapy in Inflammatory Bowel Disease: A Large Observational Study. Pavlidis P, Stamoulos P, Abdulrehman A, Kerr P, Bull C, Duley J, Ansari A. With this in mind the conclusion should also acknowledge that combination of low dose azathioprine with allopurinol may become a more widespread treatment option particularly in countries where expensive monoclonal and other new therapies are not an option.

We agree with the reviewer that these data are important. Our discussion of allopurinol in the thiopurine drug metabolism section was updated to include:
"More recently, several studies have examined the impact of low-dose weight-based azathioprine in combination with allopurinol in patients with normal TPMT activity. In a small prospective cohort, 69.6% patients with IBD randomized to low-dose azathioprine in combination with allopurinol 100mg were in clinical remission without the need for steroid or biologic treatment, and with less adverse events, at 24 weeks compared to 34.7% of the patients treated with azathioprine monotherapy[112]. In an uncontrolled, retrospective, observational cohort of patients treated with low-dose weight-based azathioprine in combination with allopurinol, 69% with CD and 61% with UC had a clinical response at a median of 19 months with 52% and 54% in clinical remission, respectively, with the highest response rates for thiopurine-naïve patients[113].

These studies suggest that low-dose weight-based azathioprine in combination with allopurinol may be effective therapeutic strategy."

2. One minor point, on page 15 second paragraph the units after 235 have been omitted.

Corrected to read: 235 pmol/8 x 10(8) RBCs

Reviewer 2:
1. Dear Author, Axelrad and coworkers have reviewed Thiopurines and inflammatory bowel disease— Current evidence and a historical perspective. Overall it's a good study, detailed comments that need author's attention are given below: In "Introduction section", the chemical structure of compounds should be given for each compound used for inflammatory bowel disease.

A figure with the chemical compounds are now provided in Figure 1.

2. Thiopurines and their metabolits should be explained as reaction scheme in "Thiopurine drug metabolism and blood level monitoring" section.

A figure delineating the steps in thiopurine metabolism and salient metabolites are now provided in Figure 2.

3. In "Abstract section" to replace "anti-TNF" with "anti-tumor necrosis factor (anti-TNF). "Thiopurine Indication" and "Evidence and dose" given in Table 1 should be noted that the names of thiopurines.

Corrected abstracted and indicated dosing is for azathioprine in Table 1.