

ANSWERING REVIEWERS

Reviewer 1569271

A useful review on a topic which has not received enough attention especially in view of the fact that the disease involves the adult age group.

Response

There are no critiques from this referee.

We appreciate the review of our manuscript.

Reviewer 1574245

The review manuscript is well written and addresses a clinically important topic that has received only modest attention in the past. Critiques in sequence of manuscript:

Comment-1

1. *In abstract please correct the "little attention". There are 43 articles in PubMed on the topic and Crohn's disease and 54 in respect to ulcerative colitis. While many of these articles overlap, one can not state that this is little attention. "Modest" seems more appropriate.*

Response-1

We have changed the word 'little' to 'modest' in abstract.

Comment-2

2. *I recommend updating the cited data on IBD presentation (ref 1) to provide more recent data on that.*

Response-2

We have altered and updated ref 1. We have also changed the sentence "About 50% of patients are <35 years of age at diagnosis^[1]" to "The incidence of IBD has been found to be the highest between the second and fourth decade of life^[1]."

Comment-3

3. *Table 1. Please include some detail in respect to the causes. For example, what do the*

authors indicate by lifestyle? Additionally, add references to support listing the cause. "Psychological", i.e. fear of passing on the disease is not listed, please explain.

Response-3

Thank you for this suggestion. According to the reviewer's suggestion, we have corrected Table 1. To describe specifically, we have deleted the heading of 'Lifestyle,' and added the headings of 'Alcohol use,' 'Tobacco use' and 'Psychological factor.' We also added the column of reference number.

Comment-4

4. Table 3 is too crowded, difficult to follow. Please edit it.

Response-4

We have modified Table 3.

Comment-5

5. Please indicate that mesalazine is denoted as mesalamine in the USA pharmacology literature

Response-5

We have transcribed 'mesalazine' into 'mesalamine (also called mesalamine)' at its first appearance.

Comment-6

6. Please correct mercaptopurine to 6-mercaptopurine

Response-6

We have corrected mercaptopurine to 6-mercaptopurine, and also changed its abbreviation (MP→6-MP).

Comment-7

7. Include cyclosporine in brackets after ciclosporin since both spellings are used. Additionally, please correct the subheading to Cyclosporine/Tacrolimus and clarify in the introduction of that chapter that their molecular targets are different, but both inhibit calcineurin.

Response-7

We have corrected the subheading and the manuscript according to the

reviewer's advice.

Comment-8

8. *Under the Treatment... section, I would recommend rephrasing "Discontinuation of MTX is recommended 3-4 months before attempting to conceive". Based on this review, there is insufficient evidence to support this statement. Rather it seems to be anecdotal practice and should be challenged! It is important for reviews to highlight such gaps in knowledge. Please make a strong statement here and modify Table 3 accordingly. The risks of MTX discontinuation may significantly outweigh the unsubstantiated hypothetical benefits from it. Please modify the conclusion section accordingly as well.*

Response-8

We agree to this important comment.

We have changed the sentence "Discontinuation of MTX is recommended 3-4 months before attempting to conceive." to "Although discontinuation of MTX is recommended 3-4 months before attempting to conceive in most of the past reviews, there is insufficient evidence for males to support this recommendation." We added the following sentences in the Treatment... section: "The risks of MTX discontinuation might outweigh the unsubstantiated hypothetical benefits. Discontinuation should be considered only in the case of erectile dysfunction."

In the conclusion section, We have changed the sentence "Although further evidence is needed, discontinuation of MTX is recommended at least 3 months before a planned conception not only in women but also in men. MTX appears to be associated with erectile dysfunction." to "In the case of erectile dysfunction, discontinuation of MTX should be considered because MTX appears to be associated with erectile dysfunction."

We have also modified Table 3.

Reviewer 02927318

To the Editor and the Authors: In this paper, the authors reviewed articles describing male fertility in IBD, and provide information on fertility-related issue in men with

IBD. Because there are limited data on the effect of drugs for IBD on male fertility and pregnancy outcome, this review article is interesting and very helpful for doctors to treat the patients with IBD. However, in my opinion, a revision of this manuscript is needed before it can be acceptable for publication. I have several concerns as follows;

Comment-1

1. Manuscript page 4 line 6 to 15 (Infertility is defined as a disease of the reproductive system characterized by failure to achieve a clinical pregnancy after ≥ 12 months of regular unprotected sexual intercourse[2]. Although difficult to ascertain precisely, the prevalence of infertility in women with IBD varies between 7% and 12%, which is not significantly different from that in the general population[3,4]. Tavernier et al reviewed fertility in non-surgically treated inflammatory bowel disease and observed a 17-44% reduction in fertility in women with CD[5]. They suggested that this reduction was linked to voluntary childlessness rather than physiological causes, and they also found no reduction in fertility in women with UC.) are confusing. Do the author emphasize that the fertility in women with non-surgically treated CD is significantly reduced but the overall fertility in women with IBD is not affected by IBD?

Response-1

As the reviewer pointed out, our sentences were confusing. We have deleted the sentences about the prevalence of infertility in women with IBD because this review focuses on only men.

Comment-2

2. Perianal abscesses and fistulas are frequent manifestations in the patients with CD and surgical treatments are often needed. The authors should add some descriptions about this point to "the surgery causing male infertility" section.

Response-2

We added the following sentences according to the reviewer's recommendation. "Especially in patients with CD, complications such as perianal abscesses, fistulas, and stenosis can occur during the course of the disease, and surgery is often indicated in these cases^[12,13]. Surgical treatment of perianal fistulas ranges from minimal surgery like seton and fistulotomy to definitive surgery with closure of the fistula tract or proctectomy and fecal diversion^[13]."

Comment-3

3. *The authors stated that life style (alcohol, tobacco, and stress) may cause infertility in men with IBD in abstract. However, the authors do not show enough data to support this in the "treatment of infertility in men with IBD" section. The authors should add some explanations.*

Response-3

We have added the subheadings of alcohol use, tobacco use and psychological factor to the 'other factors causing male infertility' section before 'treatment of infertility in men with IBD' section. In these new subheadings, we have explained the associations between alcohol, tobacco or psychological factor and male infertility. We have also modified the abstract.

Comment-4

4. *As you know, generally, active tobacco smoking has a protective effect in the patients with UC. Therefore, the effect of tobacco smoking on infertility should be discussed separately in the patients with UC and CD.*

Response-4

According to the reviewer's suggestion, we have added the subheading of "tobacco use" to the 'other factors causing male infertility' section. In this subheading, we have precisely described the effect of tobacco use on infertility in IBD patients. We have also denoted the conflicting effects of smoking on CD and UC.