To the *Editor of World Journal of Gastroenterology*

Dear Dr. Lian-Sheng Ma

Thanks for your mail of the 18th of May and for the opportunity to submit a revised version of the paper entitled "**Azathioprine Monotherapy Withdrawal in Inflammatory Bowel Diseases: A Retrospective Monocentric Study".**

All the authors have read and approved the revised version of the paper.

All the points raised by the reviewers were carefully addressed and answered point by point below. The authors are extremely grateful to the reviewers for the nice comments. The authors believe that the paper's revised version is substantially improved compared to the original version: We hope that the paper is now acceptable for publication in WJG.

Sincerely,

Dr. Fabiana Zingone

| **Reviewer 1**<br><br>The authors are extremely grateful to the reviewer for the nice comments and the helpful criticisms. | |
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| Comment | Response |
| 1- It is a nice study which tries to address an unanswered question but with a small number of patients. I would suggest using the word cessation rather than suspension throughout the paper. (suspension implies something temporary) | We replaced the word cessation instead of suspension in the manuscript. |
| **AIM**<br><br>2- We described the events that led to and following the cessation of AZA in IBD Under Materials and Methods to define your cohort: We selected IBD patients aged >18 years who were already on AZA or started then discontinued AZA monotherapy. (this takes into account some of your data that you presented for the <18-year-old) | In our study we selected IBD patients older than 18 years, who were already on AZA. We have reported the age distribution of AZA introduction and there were patients, that had started taking this drug before 18 years old (see Figure 2). We have observed a difference about AZA introduction between CD and UC patients in keeping with the different therapeutic management of paediatric UC and CD based on ECCO/ESPGHAN guidelines. |
| **METHODS**<br><br>3- Sentence to restructure:<br><br>All patients were assessed every six months in our outpatients' clinic or earlier when needed using clinical and laboratory parameters. | The sentence: "All patients were clinically and laboratory evaluated every six months in our outpatient clinic or earlier when needed." has been reworded as follows:" All patients were assessed every six months in our outpatients' clinic or earlier when needed using clinical and laboratory parameters. (3rd Paragraph under Materials and Methods) |
| **RESULTS**<br>Under results the 69 patients that were in remission that AZA was stopped is a | This group was in sustained remission for |

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| crucial group. How long was this group in sustained remission. | an average time of 5 years and 4 months (SD 3.2), without differences between sex or type of diseases. This information has been added in the text (under Paragraph" Side effects and reasons for discontinuation"). |
| Figure 1 - Is it showing patients that were started or remained on Azathioprine? the body and discussion implies started the legend says remained. It is somewhat surprising before 2011 the use of Azathioprine was low | Figure 1 was modified according to the reviewer's comments. Regarding the low use if Azathioprine before 2011, it could be explained by a lower tendency to its use in our center. |
| **DISCUSSION**<br>4- IBD is an inflammatory disease of the gastrointestinal tract with a chronic intermittent course. | The sentence: "IBD are chronic inflammatory diseases of the gastrointestinal tract with a chronic intermittent course" was reworded as follows "IBD is an inflammatory disease of the gastrointestinal tract with a chronic intermittent course". |
| 2nd paragraph 2nd line consistent with published data regarding the efficacy... However, we found a higher percentage of CD patients started AZA before 18 years when compared to UC patients. | The 2nd line of the 2nd paragraph of the revised version was modified according to the reviewer's comments. |
| At the end of paragraph 2 I would include anti TNF together with vedolizumab and ustekinumab | In the revised version we included Anti TNF at the end of the second paragraph as requested. |
| Paragraph 4 and table 2 don't seem to correlate. Your criteria in Table 2 says ALT X2?? Myelosuppression in your table says 8.4% in the discussion you say 9.9% | Table 2 of the revised version was modified according to the reviewer's comments and also the fourth Paragraph of the Discussion was modified:<br><br>The most common adverse events that led to AZA suspension were pancreatic |

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| | disorders, including acute pancreatitis (AP) and elevated liver enzymes, which were detected in 17.5% of patients. We reported leukopenia as the second most frequent adverse effect (8.4%), which is consistent with the literature. |
| At the end of the discussion you have quoted a very low relapse rate in your cohort which is a crucial outcome in your study. You will need to hypothesise why - maybe data of how long these 69 patients were in remission before stopping may shed some light. | The penultimate paragraph of discussion of the revised version was modified to address the reviewer's point.<br>Our study revealed a lower rate of disease relapse than these previous studies and reported a risk of 10% at one-year follow-up among the 69 patients who had interrupted AZA for remission. It was sustained for an average time of 5 years and 4 months (SD 3.2), without differences between sex or type of diseases. In line with what is suggested by Holtmann et al., we suggest to discontinue AZA after a five years of complete remission. |
| Your study is much smaller compared to the other 2 studies (N when it comes to sustained remission n=69 vs =237 and 215) and that limitation must be highlighted. | The last paragraph of discussion of the revised version was modified to address the reviewer's point.<br>The main strengths of our study were the inclusion of a homogeneous population followed at the same tertiary centre and the very low relapse rate in our cohort. The first limitation was the small size of patients included. Moreover, our data were retrospectively collected, which has risks of missing data and recall bias |

| **Reviewer 2**<br><br>The authors thank the review for his/her comments. | |
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| Comments | Response |
| The manuscript entitled Azathioprine Monotherapy Withdrawal in Inflammatory Bowel Diseases: A Retrospective Monocentric Study was reviewed and considered there is no new remarkable fact in this research. For advanced evidence, prospective research could be needed as outcomes after withdrawal of AZA after long term remission of IBD. Thanks. | We added a sentence regarding the need of future research at the end of the discussion. |

| **Reviewer 3**<br><br>The authors are extremely grateful to the reviewer for the nice comments and the helpful criticisms. | |
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| Comment | Response |
| This paper performed a retrospective monocentric study aiming to evaluate azathioprine monotherapy withdrawal in inflammatory bowel diseases. I enjoyed reading this paper. However, there are some problems to be resolved.<br><br>**RESULTS**<br>1- I would strongly suggest that the author evaluate the recurrence rate of CD and UC after AZA suspension separately, instead of evaluating the recurrence rate of IBD. | As the reviewer's indication we have separately evaluated the recurrence rate of CD and UC after AZA suspension and we didn't find any significant difference between CD and UC (See table 4 below). We added the table as Supplementary Table 1 (under Paragraph" The incidence rate of disease relapse"). |
| **DISCUSSION**<br>2- Please add a section where potential clinical implications of these findings in real world clinical practice are presented. Moreover, please also discuss the limitations of this study. | Our study revealed a lower rate of disease relapse than these previous studies and reported a risk of 10% at one-year follow-up among the 69 patients who had interrupted AZA for remission. It was sustained for an average time of 5 years and 4 months (SD 3.2), without differences between sex or type of diseases. In line with what is recommended by Holtmann et al. we suggest indeed to discontinue AZA after a five years of complete remission. (5 th Paragraph under Discussion). |
| 3- English should be improved. | The manuscript was edited for proper English language by one of the highly qualified native English speaking editor at AJE. |

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| | Events | Rate per 10 py (95% CI) | HR (95% CI) |
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| Crohn's Disease | 77 | 1.5 (1.2-1.8) | |
| Active patients | 38 | 13.6 (9.9-18-7) | 1 |
| Patients in remission | 10 | 0.6 (0.3-1.1) | 0.12 (0.06-0.3) |
| Other groups | 29 | 0.9 (0.6-1.3) | 0.17 (0.2-0.4) |
| Ulcerative Colitis | 64 | 1.4 (1.1-1.7) | |
| Active patients | 28 | 4.2 (2.9-6.1) | 1 |
| Patients in remission | 11 | 0.8 (0.4-1.4) | 0.22 (0.1-0.4) |
| Other groups | 25 | 0.9 (0.6-1.4) | 0.4 (0.2-0.6) |

**Supplementary Table 1:** the recurrence rate of CD and UC after AZA suspension separately