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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 41380

Title: Loss of efficacy and safety of the switch from Infliximab Original to Infliximab Biosimilar (CT- Y3) in patients with inflammatory bowel disease.

Reviewer's code: 03260089

Reviewer's country: Italy

Science editor: Xue-Jiao Wang

Date sent for review: 2018-08-29

Date reviewed: 2018-08-30

Review time: 1 Day

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection	[ ] Accept (High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: [Y] Advanced [ ] General [ ] No expertise Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

"This trial proved that switching from infliximab RP to CT-P13 was not inferior to continued treatment with infliximab RP. However, this study has received much criticism because of its methodological limitations and is not powered to perform a

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subgroup analysis, especially IBD patients." Cite "Ribaldone DG, Saracco GM, Astegiano M, Pellicano R. Efficacy of infliximab biosimilars in patients with Crohn's disease. Lancet. 2017;390:2435-2436. "infliximab original" to change in "infliximab originator" "In patients with CD and UC remission was considered when: … 3. No use of steroids. …" What is the percentage of use of thiopurine in the retrospective group? "Median time of the disease before starting the follow-up was 44 (Interquartile range [IQR] = 18; 100 months). Median duration of ongoing infliximab original treatment at the start of the study was 55 (IQR = 28.7; 72 months). Etc…" To express with 95% I.C. and not with Interquartile range [IQR] = …; … months "Of the 56 patients who were in initial remission this was maintained in 69.8% (37/53) (95%CI: 56.5; 83.1) of patients at the 12-month follow-up (p = 0.634)." This p is not useful "The basal remission rate of the infliximab original group was 77.6% versus 82.7% of infliximab biosimilar (P = 0.474). At 12 months the remission rate was 71% in infliximab original versus 68.2% of biosimilar infliximab (P = 0.806) without achieving statistical significance. The loss of overall efficacy at 12 months in the infliximab original group was 6.6% and 14.5% in the infliximab biosimilar group, without achieving statistical significance (P = 0.806)." It is very strange that two different comparison (percentage of remission at twelve months 71% in infliximab original versus 68.2% of biosimilar infliximab and the loss of overall efficacy in the twelve months in the infliximab original group was 6.6% and 14.5% in the infliximab biosimilar group) give the same identical p (0.806) are you sure that you have correctly analyzed the difference in the loss of efficacy? To perform another statistical test To include in the analysis the use of thiopurine or the switch or the swap to other biologics in the year of follow-up "When we analyzed patients, who were in basal remission, the loss of efficacy was 16.3% in the infliximab original vs. 27.1% in the infliximab biosimilar at the 12-month follow-up." "We conclude that the overall efficacy and loss of treatment response with Infliximab biosimilar (CT-P13 Remsima®) is similar

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to that observed with Infliximab original (Remicade®) in patients who were switching at the 12-month follow-up." You have to change your conclusion including that "although it is to be stressed that the higher loss of efficacy in the patients in clinical remission treated with biosimilar is 10.8%, close to the non-inferiority margin of 15%".

INITIAL REVIEW OF THE MANUSCRIPT

Google Search:

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 41380

Title: Loss of efficacy and safety of the switch from Infliximab Original to Infliximab Biosimilar (CT- Y3) in patients with inflammatory bowel disease.

Reviewer's code: 03538272

Reviewer's country: Australia

Science editor: Xue-Jiao Wang

Date sent for review: 2018-09-03

Date reviewed: 2018-09-11

Review time: 8 Days

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] 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) [Y] Minor revision [ ] Major revision [ ] Rejection	Peer-Review: [Y] Anonymous [ ] Onymous Peer-reviewer's expertise on the topic of the manuscript: [ ] Advanced [Y] General [ ] No expertise Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

The authors have performed a prospective single center cohort study of patients with inflammatory bowel disease switching from maintenance originator infliximab to CTP-13 biosimilar and then compared outcomes in this group to a historical cohort who

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had remained on originator infliximab for an entire 12 month period. Efficacy, loss of response and adverse events were comparable between the groups, although there was a numerically higher rate of loss of response in the CTP-13 group. The use of a historical cohort allows comparison of the outcomes following switch to be compared to remaining on originator therapy which is an important comparison. Similar results have been published elsewhere. The authors acknowledge the major limitations of their study but these require further explanation. The major issue with the study relates to further defining the retrospective cohort. How many patients from the retrospective cohort were also a part of the prospective cohort? If there was significant overlap in the groups this may explain the (non-significant) higher loss of response noted in the biosimilar group and should be discussed. Were the HBI/ Mayo scores measured at the time of assessment or calculated retrospectively? The other component is the lack of objective markers used to assess disease activity. The use of clinical remission to include CRP and drug dosage changes is a reasonable attempt to provide some objective. The authors mention that drug levels, calprotectin and endoscopy were not available, does this mean that they were not collected/ performed in a systematic manner, or that no patient had these tests performed? A study by Kumaran et al (Scand J Gastroenterol. 2018 Jun;53(6):700-707.) recently reported treatment response, loss of response and adverse events for patients on originator and biosimilar infliximab over a 12 month period. Differences and similarities to this study should be added to the discussion. Minor comments: More details on prior medication exposures and duration on anti-TNF therapy should be given in Table 1. P values for the two groups should also be used. It would be better to avoid use of brand names after their initial use and continue using infliximab originator and infliximab biosimilar in the manuscript. Line 10 in the first paragraph – the only biologics that are close to expiration are adalimumab and infliximab, consider revising this sentence.

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Manuscript NO: 41380

Title: Loss of efficacy and safety of the switch from Infliximab Original to Infliximab Biosimilar (CT- Y3) in patients with inflammatory bowel disease.

Reviewer's code: 03017551

Reviewer's country: Poland

Science editor: Xue-Jiao Wang

Date sent for review: 2018-09-03

Date reviewed: 2018-09-11

Review time: 8 Days

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SPECIFIC COMMENTS TO AUTHORS

Firstly- the effect of infliximab original and infliximab biosimilar (CT-P13) was compared, Secondly - the authors critical of the results of the research, Thirdly - these studies have a high cognitive value,

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[Y] No