PEER-REVIEW REPORT

We want to thank the reviewers for the recommendations and suggestions made to our article. We have made the changes that you have requested.

Reviewer's code: 03260089

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 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.

Thank you for your recommendation. We have added it to the references. (N. 28)

"infliximab original" to change "infliximab originator"

Thank you for your recommendation. We have changed the word in the text (Page 18)

"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?

Thank you for your question. 40.8% used concomitant thiopurines before starting the follow-up in the retrospective group. We added this information to the article (page 8 and table 1)

"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

Thank you for your recommendation. In our analysis, most of the variables had an asymmetric distribution, for this reason we expressed it with the median and the interquartile range. We present in the following tables all the data about the analysis.

Prospective cohort

Variable	N	X (DE)	IC 95%	Me (P_{25}; P_{75})
Duration of infliximab original treatment (months)	98	47,0 (33,8)	34,6; 59,4	**60,7 (10,5;73,5)**
Time of the disease (months)	98	120,0 (72,0)	93,6;146,5	**100 (77;151)**

Retrospective cohort

Variable	n	X (DE)	95% IC	Me (P_{25}; P_{75})
Duration of infliximab original treatment (months)	98	54,6 (35,7)	47,4; 61,7	**55,0 (28,7;72,0)**
Time of the disease (months)	97	68,0 (65,9)	5,7; 81,3	**44,0(18,0;100,5)**

"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

Thank for your comment. We know that the p is not useful, but we wanted to show that there were no statistical differences when we compared the remission in both periods of time. We have removed p from the article.

"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?

Thank you for your comment. We have reviewed the data and realized that the different values for p that were included was a result of a typographical error in our article. Therefore, we have amended this in our article.

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 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%".

Thank you for your recommendation. We have amended the final conclusion to reflect

your comments.

Reviewer's code: 03538272

SPECIFIC COMMENTS TO AUTHORS

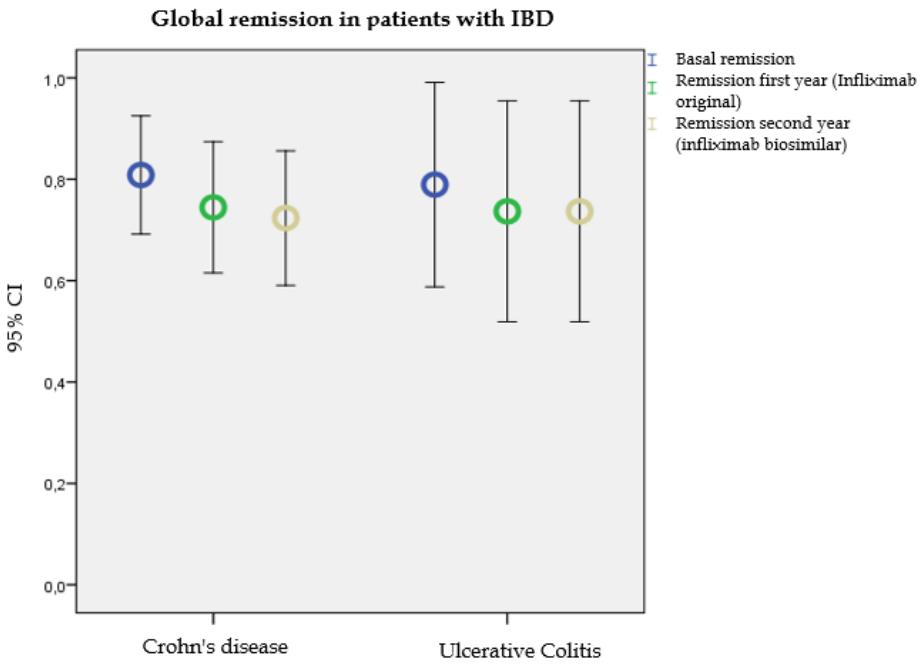
The authors have performed a prospective single center cohort study of patients with inflammatory bowel disease switching from maintenance originator infliximab to CTP-13 biosimilar and then compared outcomes in this group to a historical cohort who had remained on originator infliximab for an entire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

Thank you for your recommendations. We have now added additional details to explain the limitations of our study in the manuscript. Our principal limitation is that we are comparing with a retrospective cohort, which has a methodological deficit, and so there is an error with the interpretation of the data. Second, we can not measure calprotectine, or drug levels, because at the time of the study we did not have the facilities to do these available in our hospital. However, we believe that our results are in accordance with previously published articles. Additionally, the fact that our article uses real data from clinical practice means that it could help hospitals that do not have drug levels, or biochemical parameters like calprotectine, available to them.

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.

Thank you for your question. We also made a separate sub analysis about this topic. 66

patients from the retrospective group were in the prospective group. When we analyzed the overall remission in this period, it was basal 80.3% (53/66) (95%CI: 69.9; 90.7), 74,2% (49/66) (CI 95%: 62.9; 85.6) at first year with infliximab original, and 72.7% (48/66) (95%CI: 61.2; 84.2) at second year with infliximab biosimilar. The intervals of confidence were so high that it was impossible to obtain a statistical difference. Also, we analyzed a subtype of IBD, and again did not find any statistical differences because the intervals of confidence overlapped. You can see these more clearly with the next representation.



Were the HBI/ Mayo scores measured at the time of assessment or calculated retrospectively?

In the retrospective group the scores were calculated using the historical data of each patient that was held by the clinic.

In the prospective group the scores were measured at the time of assessment. These patients were closely monitored at follow-up appointments every three months.

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?

Thank you for your question. When considering clinical remission we included clinical and biochemical parameters (HB ≤4 in patients with CD, partial Mayo score ≤2 in UC, CRP≤ 5mg/dl, no use of steroids, no increased dosage of biological therapy, no surgery related to the disease activity). However, we know other parameters, such as calprotectine, or drug levels, will help to better define the remission. We could not measure them because at the time of the study we did not have these available in our hospital. From the middle of 2016, we are able to measure calprotectine and drug levels in a systematic manner. We have explained these limitations in more detail in the manuscript.

In respect of mucosal healing by endoscopy, we have not collected this data on all the patients.

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 12month period. Differences and similarities to this study should be added to the discussion.

Thank you for your recommendation. This article is now cited in our manuscript. (Reference 26).

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.

Thank you for your recommendations.

We added more detail about prior and concomitant treatments in table 1.

We changed the brands names in the text.

We corrected line 10.

.

PEER-REVIEW REPORT

Reviewer's code: 03017551

We appreciate the positive comments to our article. We hope to provide real-life data about the use of biosimilars in IBD.