PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Comparative effectiveness of first-line biologic monotherapy use in rheumatoid arthritis: a retrospective analysis of the RECord-linkage On Rheumatic Disease study on health care administrative databases.
AUTHORS	Silvagni, Ettore; Bortoluzzi, Alessandra; Carrara, Greta; Zanetti, Anna; Govoni, Marcello; Scirè, Carlo

VERSION 1 – REVIEW

REVIEWER	Kath Watson The University of Manchester, UK
REVIEW RETURNED	14-Feb-2018

GENERAL COMMENTS	This is a nicely written and well thought out paper that addresses the objectives to assess the comparative effectiveness of different bDMARDs when administered as monotherapy compared to combination therapy in patients with RA. I just have a few questions/comments: 1. Was the level of first line bDMARD prescriptions what you would expect for your study population? 2. You mention the new JAKis in your introduction but this analysis does include these drugs so perhaps remove this reference? 3. The results show data on persistence based on prescriptions but you do not mention that prescription does not equal adherence and what effect this might of had on your results? 3. Although you did stratify your analysis by those who were prescribed bDMARDs before and after 31/12/2009, did you stratify year on year as those who were prescribed the bDMARDs in the very early days, were likely to be those with the most severe disease so may have biased your results? 5. Although you mention unmeasured confounders in the discussion, perhaps you could provide examples in the discussion relating to possible unmeasured confounders in this analysis?

REVIEWER	Professor Ernest Choy Cardiff University
REVIEW RETURNED	26-Apr-2018

GENERAL COMMENTS	This study is based on analysis of a biologic registry to examine persistence of biologic agents when used first line monotherapy is well conducted. The main weakness is that the number of patients receiving non-TNF inhibitors are relatively small so do not have sufficient power to discriminate potential differences. This needs to be highlight in the discussion and abstract. Indeed, given the main comparison is between TNF inhibitors, the title should be changed to

	reflect that the main observation is between TNF inhibitors.

VERSION 1 – AUTHOR RESPONSE

Reviewer(s) Reports:

Reviewer: 1

This is a nicely written and well thought out paper that addresses the objectives to assess the comparative effectiveness of different bDMARDs when administered as monotherapy compared to combination therapy in patients with RA.

We thank the reviewer for this comment.

Was the level of first line bDMARD prescriptions what you would expect for your study population?

Analysing first-line bDMARD in our population, we found a percentage of 17.8% of patients receiving it as monotherapy and 82.2% as combination with csDMARDs. This result is the frequency of concurrent treatment at the beginning of biological treatment. We think that the real frequency of prescription of bDMARD as monotherapy by rheumatologists could have been slightly lower, because of csDMARD withdrawal over time, because of side effects or loss of adherence. Our study is based on administrative databases and results depict the real situation of biologics acquired by patients without concomitant csDMARDs: a small proportion of patients may have suspended csDMARDs when starting bDMARD, despite an indication of the doctor of assuming it as combination. As it is known, studies on healthcare administrative databases reflect drug delivery instead that the real "prescription rate" by specialists, however our results regarding monotherapy are in line with data from other registries, thus suggesting that differences, if present, were not so relevant. A new sentence has been included in the "Discussion" chapter (page 21) and a new citation has been added to better focus on this topic.

You mention the new JAKis in your introduction but this analysis does include these drugs so perhaps remove this reference?

The sentence has been reviewed according to this suggestion (page 5).

The results show data on persistence based on prescriptions but you do not mention that prescription does not equal adherence and what effect this might have had on your results?

Studies on healthcare administrative databases reflect drug dispensing instead that prescription rates or adherence of patients, but pharmacy claims databases are used to examine and estimate drug utilization. As for the first comment, a new sentence has been included in the "Discussion" chapter (page 21) and a citation has been added to better focus on this topic.

Although you did stratify your analysis by those who were prescribed bDMARDs before and after 31/12/2009, did you stratify year on year as those who were prescribed the bDMARDs in the very early days, were likely to be those with the most severe disease so may have biased your results?

We would like to acknowledge the reviewer for this consideration. In the analysis process we have took into account the possibility of stratifying by year. However, we decided to make analysis before and after 31st December 2009 because of the different treatment behaviour and the change in our local drug deliverability. In particular, only INF, ADA and ETA were allowed to be prescribed before this date (only one patient received ABA). We thought that this stratification was sufficient to take into account this confounding factor without reducing the statistical power. Including year in the model did not affect significance of the results; anyway, following reviewer's suggestion, we performed another sub-analysis with patients receiving their first bDMARD before and after 31st December 2006 (data

not shown in the main text). Results confirmed a similar risk of failure for ADA, despite not significantly different from ETA (HR 1.32, 95%CI 0.98-1.81). This result is comparable with results obtained in the general analysis without stratification in time subclasses; equally, INF remained statistically different from ETA with a higher risk of failure (HR 1.80, 95%CI 1.21-2.69). Regarding clinical characteristics of patients starting ADA before 31st December 2006, these patients had no differences in terms of comorbidities or previous infections compared with those starting ADA subsequently, thus resulting in comparability of the clinical characteristics of the two groups. However, these patients were generally older and with a higher glucocorticoid dispensing-rate than those ones starting ADA later on. Whether or not this could reflect a more severe disease course in this subgroup is a possibility, however another explanation could be different treatment behaviours and habits of glucocorticoid utilization which may have changed over time (lacking clinical outcomes is claimed as an important limitation of all AHD-based studies). Moreover, we presented main results of the study as crude and adjusted for pre-specified confounders, with the aim to avoid biases due to different disease-specific features. However, as reported in "Discussion" chapter (page 20-21), some unmeasured confounding factors could have limited our results and the reduction of numbers when stratifying for time subclasses remains an important limitation of our study.

Although you mention unmeasured confounders in the discussion, perhaps you could provide examples in the discussion relating to possible unmeasured confounders in this analysis?

We have expanded the sentence in "Discussion" chapter according to this suggestion (page 20).

Reviewer: 2

This study is based on analysis of a biologic registry to examine persistence of biologic agents when used first line monotherapy is well conducted. The main weakness is that the number of patients receiving non-TNF inhibitors are relatively small so do not have sufficient power to discriminate potential differences. This needs to be highlight in the discussion and abstract. Indeed, given the main comparison is between TNF inhibitors, the title should be changed to reflect that the main observation is between TNF inhibitors.

We would like to thank the reviewer for this comment. Indeed, the relatively small number of patients receiving biological agents different from TNF-inhibitors is one of the most important limitations of this study. According to this suggestion, we have included in the abstract a comment (page 3) and expanded that part in the "Discussion" chapter (page 20-21). About the suggestion to modify the title, after an in deep discussion with all the co-Authors, we reached an agreement that the title of this work should remain similar to the previous one; in support to this decision we considered that, indeed, patients experienced treatment with all biologics (other than rituximab - 380 patients treated with non TNFi) and, despite the limitation of the lower number of these treatment courses, delimiting in the title the reference to only TNF-inhibitors might not correspond to the real content of our work.