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Title: Access to biologicals in Crohn's disease in ten European countries

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Dear Editors,

Thank you for giving us the opportunity to revise and resubmit the manuscript mentioned above. We found the reviewers' comments relevant and helpful. We attach to this letter our revision notes giving a point-by-point response to the reviewers' comments explaining how we addressed the feedback.

Sincerely,

The authors

24-06-2017

Revision notes

Reviewer #1

The authors present that the difference of accessibility to biologicals, namely availability, affordability, and acceptability, for Crohn's disease in ten selected European countries and the associations between these dimensions with the uptake of biologicals and economic development. Because limited data exist describing the accessibility to biologics according to economic development, I regard this to be an important study. However, several comments need to be addressed.

Major Comments

1. The lack of consideration of the difference in the prevalence of Crohn's disease is a major issue; the prevalence of Crohn's disease varies across European countries as mentioned in the manuscript. Therefore, the number of patients on biologicals per 100000 patients with Crohn's disease could be a better way to demonstrate the uptake of biologicals than the number of patients on biologicals per 100000 population.

We agree with the reviewer that there are considerable differences in the prevalence of Crohn's disease across the European countries. These differences can show real diversities across countries, but can be also the result of different methodological approach or time of the epidemiological studies as well as of the different prevalence of undiagnosed CD patients. In our study, data on the total number of patients also comes from different resources (administrative databases, epidemiology studies, estimation of experts – we added some clarification to Table 4), which makes comparison of estimates less reliable.

The reason why we chose to present and analyze the number of patients on biologicals per 100000 population is that this approach disregards the differences in prevalence across the 10 countries [1], and thus results in a more comparable estimate.

Nevertheless, we calculated the number of patients on biologicals per 1000 CD patients and added this as an extra column to Table 4. These estimates indeed show a different picture, due to the differences in prevalence across the countries. Thus, we kept using the number of patients on biologicals per 100000 population in the correlation analysis. We also added this explanation to the Limitation section of the Discussion on why we used this measure for the calculations.

2. Please clarify the health insurance system in ten selected European countries. To assess the potential influence of insurance system, compare the differences in the public and private medical insurance systems.

We thank the reviewer for the suggestion. We added a short description on the financial aspect of the health care system of the countries included in the analysis. See the last paragraph of the Introduction section.

"These countries differ not only regarding their economic development but the organization and financing of their health care system, which might also influence access to biological treatments [1-3]. While Spain and Sweden have a tax-based health care system, France and Germany follow the Bismarkian model with social health insurance. In the CEE countries, the share of public financing is usually lower than in the Western-European countries (except for the Czech Republic). The source of public resources is mainly tax revenue in Sweden and Spain, while it is social health insurance contribution in the rest of the countries. Thus, in our study, we also aim to explore whether differences in availability and affordability of biologicals are associated with the uptake of biologicals (in terms of number of patients on biologicals per 100000 population), the economic situation of the country or the financing of the health care system."

Furthermore, we extended the correlation analysis with two new variables, namely the share of public expenditure in total health expenditure and the share of governmental expenditure in public health expenditure (See the Result section and Table 5), in order to explore the relationship between the health care system financing method and access. According to the results, we found no significant correlations between these variables and the access. Thus, we can conclude it is rather the wealth of the country than the organization or financing of the health care system which influences access.

3. Is there any regulation for maintaining biologics? Are there any countries in the study that require patients to satisfy criteria for maintaining for biologics?

We thank the reviewer for this question. We indeed asked the experts about the criteria of maintaining biological therapy in the questionnaire, but we did not mention these in the manuscript.

According to the experts, in most of the countries there were no specific criteria to satisfy for maintaining biological therapy, but maintenance was based on the clinicians' judgement. Only in Hungary and in Sweden, it was recommended to evaluate maintenance on the CDAI scale. We added this information to the Results section.

Minor Comments 1. On page 7, misspelling (last sentence of Introduction)

We thank the reviewer for the remark. We have corrected the misspelling.

Reviewer #2

The aim of this study was to examine the access to biological therapies of the patients with Crohn's disease in 10 European countries. This is a questionnaire-based survey among 10 gastroenterology experts (one in each country). The results are thoroughly analyzed and discussed. The manuscript is well-written. The only concern is that it would be convenient to include some details about the most commonly used biological therapies in CD (their mechanisms of action, efficacy, etc.)

We thank the reviewer the valuable suggestion. We have added briefly the mechanism of action and data on efficacy and safety with references to the Introduction section. Similar efficacy and safety profiles of these biologicals were found in our meta-analysis carried out in 2013 based on 11 original RCTs [4], which results were confirmed by recent literature as well [5, 6].

*"*These drugs are monoclonal antibodies with different mechanisms of action (infliximab and adalimumab are anti-tumor necrosis agents, vedolizumab is an anti-integrin drug and ustekinumab is an interleukin-12 and -23 inhibitor) but with similar safety profile and comparable efficacy [4-6]."

References

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