ANSWERING REVIEWERS

24th of March, 2015

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 16237-review.doc).

Title: Prevalence and predictors of hospitalization in Crohn's disease in a prospective population-based inception cohort from 2000-2012

Authors: Petra A Golovics, Laszlo Lakatos, Michael D Mandel, Barbara D Lovasz, Zsuzsanna Vegh, Zsuzsanna Kurti, Istvan Szita, Lajos S Kiss, Tunde Pandur, Peter L Lakatos

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The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer:

(1) Reviewed by 00033010

The paper by Golovics et al entitled "Prevalence and predictors of hospitalization in Crohn's disease in a prospective population-based inception cohort from 2000-2012" analyzes the factors influencing hospitalization rates in a subset of patients affected by Crohn's disease. The paper is well written, inclusion/exclusion criteria and study protocol are appropriate; statistical analysis is proper and accurate.

Minor comments:

1. Authors claim that the aim was "to prospectively analyze prevalence…", but the present study seems to be rather a retrospective study. This aspect needs to be well clarified.

The data were collected prospectively, both in- and outpatient records were collected and comprehensively reviewed, and the analyses was performed after the completion of the data collection.

2. In tables 2 and 3, all p values may be reported, even if not significant.

We have entered the significant and also the not significant p-values in tables 2 and 3.

Table 2. Predictive factors for immunosuppressive use (A) and need for major IBD-related abdominal surgery (B)

A

	univariate analysis	**logistic regression**
early IBD-related hospitalization	**p=0.001, OR=2.08 95%CI: 1.33-3.26**	**p=0.01, OR: 2.03 95% CI: 1.18-3.49**
perianal disease	**p=0.01, OR=2.28 95%CI: 1.21-4.30**	**p=0.046, OR: 2.07 95% CI: 1.01-4.22**
age at diagnosis*	**p<0.001**	**p=0.002**
location	**p=0.016 for location**	**p=0.197**
smoking	**p=0.054**	**p=0.06**
non-inflammatory behavior	**p=0.06**	**p=0.173**
arthritis	**p=0.03, OR=1.76 95%CI: 1.05-2.98**	**p<0.001, OR=2.96 95%CI: 1.63-5.39**
steroid use (any time)	**p<0.001, OR=5.78 95%CI: 3.57-9.35**	**-**

B

	univariate analysis	**logistic regression**
early IBD-related hospitalization	**p<0.001, OR: 7.24 95% CI: 4.34-12.1**	**p<0.001, OR: 5.80 95% CI: 3.20-10.5**
non-inflammatory behavior	**p<0.001, OR: 5.38 95% CI: 3.30-8.76**	**p<0.001, OR: 2.15 95% CI: 1.56-2.94**
location	**p<0.001****	**p=0.02 for location, p=0.002, OR: 0.33 95% CI: 0.16-0.67 for colonic location**
smoking	**p=0.17**	**p=0.202**
perianal disease	**p=0.19**	**p=0.329**
anaemia at presentation	**p<0.001, OR: 2.79 95% CI: 1.73-4.51**	**p<0.001, OR: 4.39 95% CI: 2.37-8.11**

*according to Montreal classification, **if all locations were considered, OR= Odds ratio, 95% CI= 95 % Confidence interval, p value= significance level, NS, non-significant

3. Authors used Cox regression for survival analysis. This aspect has been reported in the "Results" section, but needs to be enclosed also in "Materials and methods".

We have enclosed Cox regression analysis also in the „Materials and methods" section.

4. Was an early use of biologic therapy (top-down) used in this study and associated to a lower risk of re-hospitalization? This aspect is hard to realize from the current text.

The use of biologics was low in this population-based cohort because the anti-TNF's became widespread available just after 2008 in Hungary. This prevented us from statistically meaningfully evaluating the association between anti-TNF exposure and risk of re-hospitalization.

5. Only the 8.2% of patients received anti-TNF alpha treatment. This low rate could have negatively influenced the hospitalization rate. This point needs to be discussed.

In the present study we report on changes in hospitalization rates in the era of the increasing use of biological therapy. Population-based studies before and from the biological era suggest unchanged/declining hospitalization rates, but the long-term impact of the biological therapy on hospitalization rates needs to be further evaluated.

6. Authors affirm that the need of steroids was associated to high risk of re-hospitalization. Have the Authors available data about the weight of steroids on major post-operative complications in this population? (see Nguyen et al, J Crohns Colitis, 2014).

We have not collected data about major post-operative complications in this population-based inception cohort, of note however need for steroids before surgery indicates also a more severe disease course, thus it may be the disease itself and not only steroids that lead to the negative outcome(s).

(2) Reviewed by 00052899

In this population-based cohort, the author prospectively analyzed the prevalence, length and predictors of hospitalization in Crohn's disease in the biological era. They concluded that non-inflammatory disease behavior at diagnosis was identified as the pivotal predictive factor of both hospitalization and re-hospitalization. Furthermore, early hospitalization requirement was independently associated with clinically significant outcomes. For my point of view, the manuscript is carefully prepared and the paper is well organized. However, a number of points need clarifying and certain statements require further justification. Just, I suggest minor revision. There are given below.

1.The author should explain the medical therapy for Crohn's disease in more detail.

In CD the treatment is comparable to that in West European and North American countries. In mild to moderately active cases of CD, especially in ileal disease, patients are treated with budesonide and/or mesalazine in the suggested doses. In contrast with the European and North American guidelines and findings by the Cochrane group, 5-ASA, and in some cases sulfasalazine, are still used for maintenance in CD. Short-term systemic corticosteroids, and less frequently, budesonide are the choice of drugs for

inducing remission in moderate to severe disease. Antibiotics (metronidazole and ciprofloxacin) are routinely used in active disease, and in perianal disease. Currently, immunomodulators, especially azathioprine are used earlier and in higher doses than some years ago for inducing and maintaining remission. Yet, overall, they are used less frequently compared with Western Europe or North America, with only about 15%–40% of CD patients being prescribed the drug. The percentage is highly variable between referral centers and primary care. The doses used also vary ranging from 1.0 to 2.5–3 mg/bw/kg. Thiopurine methyl transferase (TPMT) genotyping, or enzyme activity measurements, for the detection of patients with a higher risk for developing leucopenia, is not done routinely. The use of other drugs, such as methotrexate, is marginal and limited to selected, refractory CD patients in referral centers, as suggested. Also we have to note that most CD patients (including mild to moderate cases), are receiving maintenance treatment with 5-ASA or azathioprine, or both, which are more commonly used in referral centers. Biological agents for induction and maintenance therapy have become commercially available about five years ago, but the use is mainly restricted to specialized centers. The availability of this drug is limited however to specialized centers in most of Eastern Europe, thus ''step up'' approach is the current treatment of choice in most of these countries Surgery is mainly performed in selected centers and with almost the same frequency in Eastern Europe as in West European countries. The procedures performed are also similar. (Lakatos L, Lakatos PL. Management of inflammatory bowel diseases in Eastern Europe. Postgrad Med J. 2006 Apr;82(966):270-3.)

2. The author should explain the corresponding location of L1, L2, L3 and L4 in Table 1.

We have explained the corresponing location of L1, L2, L3 and L4 in Table 1:

L1: ileal, L2: colonic, L3: ileocolonic, L4: isolated upper disease

3. The format of the tables should be checked and corrected.

We have checked the format of the tables and corrected them in the manuscript.

4. The references in the manuscript should be corrected to the style for WJG.

We have corrected the references in the manuscript to the style for WJG.

5. There are several typographical errors.

We have corrected the typographical errors in the manuscript.

(3) Reviewed by 00029041

This is a retrospective study not a prospective one. In the era of biological therapy, the study of low percentage of anti-TNF alpha treatment has less research priority.

In the present population-based inception cohort of IBD patients, data regarding disease characteristics, medical therapy, hospitalizations and surgical procedures were captured prospectively from the time of the diagnosis. In referral patients, disease phenotype, course, and hospitalization events were captured retrospectively at the time of the referral visit and prospectively thereafter. In this study we report the change of hospitalization rates and indications of hospitalizations in the era of increasing biological use, and interestingly in this population-based cohort only a small proportion of CD patients received anti-TNF therapy. Of note, data from clinical trials on hospitalization rates do not reflect real life setting and may overestimate the overall effect of anti-TNFs. Thus data obtained in population-based setting are essential, more objectively assess disease outcomes and enable generalizability of the findings to real-life IBD populations. Therefore, the low prevalence of anti-TNF therapy rather reflects the population-based nature of the study and the real-life requirement of anti TNFs.

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,

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