Author's response to reviews

Title: Medication adherence and persistence in the treatment of Canadian ulcerative colitis patients: analyses with the RAMQ database

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Author's response to reviews: see over
We thank you for considering publishing our manuscript to BMC Gastroenterology. We are pleased to submit our revised manuscript entitled “Medication adherence and persistence in the treatment of Canadian ulcerative colitis patients: analyses with the RAMQ database” (MS:4277462417513547).

As presented below, we have addressed all peer review comments. Moreover, all changes were made to fulfill the editorial requirements.

Editorial Requirements

1) Please have a separate Conclusions Section aside from the one which is included in the Abstract Section. In the manuscript file, the conclusion has been separated from the Discussion Section. In addition, several changes have been made to the manuscript file structure, according to the online author’s instructions.

2) All figures must have a figure title listed after the references in the manuscript file. The figure file should not include the title or number. Figure titles have been replaced after the references. Moreover, all figure numbers have been removed for the figure files.

3) It is important for the final layout of the manuscript that the figures are cropped as closely as possible to minimise white space around the image. Figures have been re-cropped to minimise white space around the image.

Reviewer’s comments

Minor revision

1) Did you exclude 5-ASA prescriptions for microscopic colitis? No, only patients with a diagnosis of Crohn’s disease (ICD-9) diagnostic codes 555.0–555.9 were excluded. The majority of patients who are
using 5-ASA are UC or CD patients. The proportion of 5-ASA users with other diagnosis, such as microscopic colitis, were considered minimal in this study.

2) **How did you account for cessation of therapy because the patient was given a new prescription for another drug if 5-ASA was ineffective? Eg. initiation of imuran or remicade**

In these circumstances, patients were considered has having cease their 5-ASA medication, which impacted their treatment adherence and persistence.

3) **How do the results of your study add to the literature?**

Adherence and persistence data in UC reported in the literature mainly come from clinical trials. As mentioned in the Discussion section (p.13, line 1), because this present study used data from an administrative claims database, it enables the inclusion of a large number of subjects that are assumed to accurately represent a general population in a real-world setting, contrary to a clinical trial, with relatively small sample size and controlled clinical environment. Specifically in contrast to this study, clinical trials reported excellent rates of adherence with 5-ASA therapy, in the order of 80% of patients or more. As participants are generally better motivated and under close medical supervision compared with those receiving therapy outside the clinical trial setting, these rates do not necessarily reflect real-world use and from this point of view, the RAMQ database allows a more accurate estimation of adherence and persistence.

To focus on the main strength of the present study, the following sentence was modified in the Conclusion section (p.13, line 24): The overall findings demonstrated that, in a real-life setting, adherence and persistence were poor in 5-ASA patients…

4) **I don’t think it is possible to calculate a mean age as RAMQ provides information on age categories.** We agree that RAMQ provides information on age categories only. However, it is possible to estimate the mean age of a RAMQ population. For example, for patients who are in the age category 15-19 years, a mean age of 17 years will be attributed. The estimated reported in the present study was considered to be representative of the of the mean age of the study population.

The following precision was added in the Results section (p.9, line 13): the mean age of the study population was estimated at 55.3 years…

5) **No data on dose used, and dose frequency. This data may not be available from the database. If not this should be made clear.**
The estimation of adherence and compliance was based on patients renewal of their 5-ASA medication, without considering dose and dose frequency, which are not readily available from the RAMQ database.

6) In the background, p.4 2nd paragraph the authors state that Mezavant multimatrix pH-dependent and gastro-resistant coating is the reason the drug can be taken once daily. It should be made clear that the Eudragit-S coating delays release until the distal ileum/caecum is reached, and the hydrophilic and lipophilic matrix core allows gradual release of drug as it passes through the colon. The design is intended to allow more mucosal contact with the native drug before N-acetylation, The manufacturers had the foresight to use trial designs to demonstrate once-daily therapy was as effective as divided dose, and the same has now been shown for most other delayed release mesalamine preparations. This should be clarified.

We agree that this sentence need to be clarified. The intial sentence was modified according to the reviewer’s comment: « Compared to the other 5-ASA treatments, which need to be taken as 2 to 4 times per day, Mezavant was designed to allow delayed and gradual release of 5-ASA in the colon due to its Multi Matrix hydrophilic and lipophilic coating, thus it can be taken only once daily and was shown in clinical trials to be as effective as twice daily mesalamine formulations [16, 17] ».

Major revision

1) First is the possibility for selection bias, as there was no information on the diagnostic codes used to define ulcerative colitis (UC). Persons with a diagnostic code of Crohn’s disease (CD) (the International Classification of Diseases, Ninth Revision [ICD-9] diagnostic codes 555.0–555.9) were excluded. But patients are often given both diagnostic codes in these databases; what was the algorithm used to include/exclude patients? It is noteworthy that other investigators have used validated algorithms to identify persons with UC and/or CD, implying difficulty in this area.

We agree this is a limitation of our study. Some patients with UC may have been excluded if they also carry a diagnosis of CD. Also, some patients with CD may have been kept if they were never given a CD diagnosis. This limitation is inherent to this kind of database, but is also a reflection of the difficulties of distinguishing between these two diagnoses in clinical practice. Nevertheless, this would have had a limited impact on the relative adherence and persistence of one medication compared to another.
To answer to the reviewer’s comment, the following limitation was added in the Discussion Section (p.13, line 20): Furthermore, some patients with UC may have been excluded if they also carry a diagnosis of CD. Also, some patients with CD may have been kept if they were never given a CD diagnosis. This limitation is inherent to this kind of database, but is also a reflection of the difficulties of distinguishing between these two diagnoses in clinical practice. Nevertheless, this would have had a limited impact on the relative adherence and persistence of one medication compared to another.

2) The possibility for selection bias is also increased because the definition of new users of medication was problematic. New users were operationalized as having no prescription claim in the 3 months prior to the date of the first prescription fill’[index date] of a mesalamine treatment (Asacol® or generics, Pentasa®, Salofalk®, or Mezavant®). However, these individuals may be poor adherers or not persistent with medication; a longer time interval such as not having a prescription fill in a 6–month or 1–year period is suggested.

We agree that for some patients the 3-month period could be insufficient to consider them as new users. It is a tradeoff between a longer time interval and the number of patients that could be included in the analysis. One major reason to select naïve patients, is to avoid estimating adherence and persistence of experienced patients who have more chance to be adherent and persistent than real naïve patients. Therefore in this case, a shorter time interval (i.e. 3 months) would have a limited impact, because even though these patients could be experienced patients they would not have adequate adherence or persistence.

3) Second, the definition of persistence was missing.

In the Methods Section, the following sentence can be found (p.7, line 13): Adherence was defined as the consistency of medication consumption as detailed in the recommended treatment regimen while persistence was defined as the long-term continuation of treatment.

4) Third, is the possibility for confounding by indication, as patients who switched to another mesalamine treatment were considered as non-persistent to the initial medication. That the authors observed significantly better adherence and persistence with Mezavant®, which is a new once daily oral treatment, seems to confirm this suspicion. So does the observation that there were fewer users of Mezavant compared to the other medications. Moreover, whereas the RAMQ data for this study covered the years January 1, 2004 to December 31, 2009, Mezavant only became available to Canadian...
UC patients for maintenance of remission in June 2011. It should be noted that the authors and the study were funded by Shire, the manufacturer of Mezavant.

Although confounding by indication could be considered, we need to point out that Mezavant was fully reimbursed by the RAMQ since February 2008 (not June 2011). Therefore, although it is a relatively new agent, there was sufficient time to also allow switching from Mezavant to another 5-ASA formulation.

Should you have any question, do not hesitate to contact me.

Yours sincerely,

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