Author’s response to reviews

Title: Healthcare Resource Utilization and Costs Associated with Inflammatory Bowel Disease among Patients with Chronic Inflammatory Diseases: A Retrospective Cohort Study

Authors:

David Hudesman (David.Hudesman@nyulangone.org)
Soumya Chakravarty (schakr66@its.jnj.com)
Bruno Emond (bruno.emond@analysisgroup.com)
Lorie Ellis (LEllis@its.jnj.com)
Patrick Lefebvre (Patrick.Lefebvre@analysisgroup.com)
Kay Sadik (KSadik@its.jnj.com)
Jose Scher (Jose.Scher@nyulangone.org)

Version: 1 Date: 27 Nov 2019

Author’s response to reviews:

From:
David P. Hudesman, MD
Associate Professor, Medical Director
NYU Langone Health
855-698-4232
David.Hudesman@nyulangone.org

And
Soumya D. Chakravarty, MD, PhD
Medical Director, Rheumatology
Janssen Scientific Affairs, LLC
215-325-2019
schakr66@ITS.JNJ.com

To: Ciarán Martin Fitzpatrick, PhD
Editor of BMC Rheumatology

Date: 27 November 2019

Subject: Manuscript BRHM-D-19-00065

Dear Dr. Fitzpatrick and the editorial board of BMC Rheumatology,

On behalf of our colleagues, we would like to thank you, the Reviewers, and the editorial staff for taking the time to review our manuscript titled “Healthcare Resource Utilization and Costs Associated with Inflammatory Bowel Disease among Patients with Chronic Inflammatory Diseases: A Retrospective Cohort Study”. Please find appended to this letter our responses to your comments as
well as those from the Reviewers, which were received on October 31, 2019. We have addressed each comment raised by the Reviewers and have also made the requested changes to the electronic version of the manuscript using the Track Changes feature. If there are any other materials you require in considering this re-submission, or if you have any other questions, please feel free to contact either of us, the co-corresponding authors, using the contact information at the top of the present letter. We look forward to receiving additional feedback on this revised version.

Sincerely,
Dr. David P. Hudesman, MD
Dr. Soumya D. Chakravarty, MD, PhD

Diederik de Cock (Reviewer 1)

Dear authors,

I want to thank you for this interesting read on the incidence of IBD in CID in this retrospective observational study of US claims databases. In general, the study is done adequately but I have some remarks.

-The biggest risk in interpreting these results is the major difference in age between the two population. Although I believe there was a basic adjustment for it in the poisson regression, a matched design would give a more valid estimate of the risk if IBD in CID if you want to compare it with the general population. Why did the authors not perform a propensity analysis to overcome this flaw?

Response: We thank the Reviewer for this and all subsequent comments. We agree with the Reviewer that our study cohorts differed with respect to age. The incidence rates were only reported descriptively, since the aim was to provide readers with an estimate of how many patients had IBD in each patient cohort. Our objective was not to compare these IBD incidence rates to those observed in the general population. However, when comparing HRU and costs between cohorts, we adjusted for confounding factors using multivariable regression models. We have clarified that the incidence rates were only reported descriptively and added a limitation related to the fact that these rates were unadjusted (underlined portions highlight additions; strikethrough highlights deletions):

Abstract, Background: “Given the increasing use of novel agents for the treatment of CIDs, including those that may increase the risk of IBD in patients with CIDs, the objective of the study was to describe estimate the incidence of IBD and to quantify healthcare resource utilization (HRU) and costs associated with IBD among patients with CIDs.”

Background, 4th paragraph: “The objectives of the current study were to describe estimate the incidence of IBD among patients with CIDs and compare HRU and costs among patients with CIDs who developed IBD versus patients with CIDs who did not develop IBD.”

Discussion, 6th paragraph: “Second, as with all observational studies, results from the current study may be affected by residual confounding from measured and unmeasured factors. In particular, since incidence rates of IBD were only reported descriptively for each patient cohort, confounding related to differences in patients’ baseline characteristics (such as age) may remain.”

Small remarks:
- Why were patients with cancer on certain drugs excluded? (also for transplants?)
Response: Patients receiving certain drugs were excluded because it was not possible to determine for which disease the drug had been prescribed. Rituximab, for instance, is approved to treat RA and multiple different malignancies. Therefore, patients with cancer and CID may have received this agent either to treat cancer or RA, and claims data do not contain information that could allow us to distinguish between these possibilities. Consequently, we chose to exclude these patients.

Patients who had a transplant procedure were also excluded because of the high costs usually associated with this procedure. Our concern was that these outliers might skew the results.

We have clarified as follows in the methods section (underlined portions highlight additions; strikethrough highlights deletions):

Methods, Study sample: “Patients with cancer treated with rituximab or ofatumumab, with a transplant procedure, or Patients with ≥2 claims with a diagnosis of IBD (i.e., Crohn’s disease [ICD-9 CM code 555.x; ICD-10 CM code K50.x] or ulcerative colitis [ICD-9 CM code 556.x; ICD-10 CM code K51.x]) during the 12-month baseline period were excluded. Moreover, patients with cancer treated with rituximab or ofatumumab during the baseline period were excluded because it could not be determined using claims data whether these agents were prescribed to treat cancer or CID. Patients with a transplant procedure were also excluded because of the high costs usually associated with this procedure, which may skew results.”

- There seems to be overlap in the different diagnoses of CID. Was a sensitivity analysis performed with patients receiving DMARDs/steroids to check if the numbers have face validity.

Response: We confirm that many of our study cohorts are indeed non-mutually exclusive (i.e., there is overlap). This is mentioned in the following sentence of the methods section:

Methods, Study cohorts: “Eligible patients with claims for more than one CID were classified into each eligible CID cohort (i.e., one patient could be present in more than one cohort). Each of the six cohorts mentioned above was analyzed separately.”

We would also like to point out that the overlap between cohorts is described in the following statement of the results section:

Results, Baseline characteristics: “Between the RA, PsO with PsA, PsO without PsA, and AS patient cohorts, 3,280 patients were both in the RA and PsO with PsA cohorts, 3,310 patients were both in the RA and PsO without PsA cohorts, 2,957 patients were both in the RA and AS cohorts, 276 patients were both in the PsO with PsA and AS cohorts, and 288 patients were both in the PsO without PsA and AS cohorts.”

We thank the Reviewer for the suggestion to conduct a sensitivity analysis among patients receiving DMARDs and/or steroids. We have conducted a sensitivity analysis on this subset of patients and have added these new results to the manuscript. The methods and results have been updated as follows (underlined portions highlight additions):

Methods, Statistical analysis: “In a sensitivity analysis, costs were evaluated in the subset of patients with AS, RA, PsA, or PsO who received DMARDs and/or corticosteroids.”

Results, Healthcare costs: “Among patients with CID who received DMARDs and/or corticosteroids,
those who developed IBD (N=2,020) incurred mean total all-cause healthcare costs of $44,192 compared with $25,472 for those who did not (N=320,561), resulting in an adjusted MYCD of $17,605 (P<0.0001). Similar to the main analysis, this difference was largely driven by higher hospitalization costs (adjusted MYCD: $7,755), outpatient costs (adjusted MYCD: $5,392), and pharmacy costs (adjusted MYCD: $3,612, all P<0.0001).”

- Were other comorbidities considered? This can be considered of importance in such a cost analysis

Response: We thank the Reviewer for the opportunity to clarify this important point. When assessing the difference in HRU and costs between patients with and without IBD, we adjusted for the Quan-Charlson Comorbidity Index score (i.e. a score that predicts 1-year in-hospital mortality based on a large number of comorbidities, such as hypertension, diabetes, and chronic pulmonary disease [1]). We have clarified this in the following statement (underlined portions highlight additions; strikethrough highlights deletions):

Methods, Statistical analysis, 2nd paragraph: “The rates of HRU between patients with and without IBD among the six cohorts were compared using generalized linear models (GLMs) with a Poisson distribution adjusting for age, gender, region, type of insurance plan, Quan-CCI score (i.e., a score derived from a number of comorbidities [e.g., hypertension, diabetes, chronic pulmonary disease] and their associated risk of in-hospital mortality), and type of CID (i.e., RA, PsA, PsO, or AS)”

Furthermore, please note that costs related to other comorbidities are included in all-cause healthcare costs. We have clarified as follows (underlined portions highlight additions; strikethrough highlights deletions):

Methods, Study measurements: “By definition, all-cause healthcare costs included any healthcare costs incurred during the follow-up period, regardless of whether they were related to CIDs, IBD (e.g., endoscopies, colonoscopies), or other comorbidities.”

Reference:


- US claims data is biased in types of patients who receive insurance. (eg Higher SES). This should be stated in the limitation section

Response: We agree with the Reviewer that our results may not be generalized to patients without insurance. However, our study population may still include individuals with a relatively low socioeconomic status who purchased a health insurance plan with limited coverage due to financial constraints. We have clarified as follows (underlined portions highlight additions; strikethrough highlights deletions):

Discussion, 6th paragraph: “Third, the data used in this study covered only commercially-insured patients who may have a higher socioeconomic status and may not be representative of the general US population. For example, uninsured individuals and Medicaid beneficiaries were not included in the current study.”
Is it surprising that patients with 2 comorbidities have higher costs than patients with 1 CM?

Response: We thank the Reviewer for the opportunity to clarify this important point. We agree that the costs of patients with both IBD and CID would be higher than those of patients with CID alone. However, the novelty of our study lies in the quantification of the incremental HRU and costs associated with IBD, which can be useful for not only health care providers, but insurers and policy makers as well.

We have clarified by adding the following paragraph in the discussion (underlined portions highlight additions; strikethrough highlights deletions):

Discussion, 3rd paragraph: “While it was anticipated that patients with IBD and CID would incur higher costs than patients with CID alone, this study is the first to quantify the incremental costs and HRU associated with IBD among patients with AS, PsO, PsA, or RA, stratified by type of CID. Of note, the difference in total all-cause healthcare costs found in our study ($18,500) is similar to that observed in recent analyses which assessed the incremental burden of patients with IBD versus non-IBD controls (IBD: $16,03127, CD only: $17,46335, UC only: $11,02936). Although comparisons with results from other analyses are prone to confounding, this suggests that the incremental burden associated with IBD in a population of patients with CID is similar to that observed in the general population.”

Rachel Knevel (Reviewer 2)

Hudesman et al. performed a study to the health care expenses from patient with both chronic inflammatory diseases (CID) and inflammatory bowel diseases (IBD, defined by m. Crohn and Ulcerative Colitis) versus CID alone. The reasoning to perform this study was that some of the treatments of CID can trigger IBDs.

The paper is well written. The authors describe very clearly what they did, and the methods and analyses are easy to understand. The conclusions are valid and supported by the data. The tables and figures are clear.

However, I wonder how informative the study is in general. It seems quite obvious that patients with both IBD and CID will have higher health care expenses. Also the expenses should not be the reason to adequately treat CID, so the authors reason to perform the study seems a bit farfetched. Still, also obvious conclusions are valuable to proof with data, particular when this was not done before or if you want to quantify the effect.

Response: We thank the Reviewer for this and all subsequent comments. We agree that the costs of patients with both IBD and CID would be higher than those of patients with CID alone. However, the novelty of our study lies in the quantification of the incremental HRU and costs associated with having IBD, which can be useful not only health care providers, but insurers and policy makers as well.

We have clarified by adding the following paragraph in the discussion (underlined portions highlight additions; strikethrough highlights deletions):

Discussion, 3rd paragraph: “While it was anticipated that patients with IBD and CID would incur
higher costs than patients with CID alone, this study is the first to quantify the incremental costs and HRU associated with IBD among patients with AS, PsA, PsO, or RA, stratified by type of CID. Of note, the difference in total all-cause healthcare costs found in our study ($18,500) is similar to that observed in recent analyses which assessed the incremental burden of patients with IBD versus non-IBD controls (IBD: $16,031, CD only: $17,463, UC only: $11,029). Although comparisons with results from other analyses are prone to confounding, this suggests that the incremental burden associated with IBD in a population of patients with CID is similar to that observed in the general population.”

Furthermore, although costs may not be the main consideration in treatment decisions, they are relevant for insurers and policy makers. Per the Reviewer’s comment, we have modified the introduction to reposition our study as follows (underlined portions highlight additions; strikethrough highlights deletions):

Background, 3rd paragraph: “Both CID and IBD are associated with substantial economic burden, but the relative increased costs among patients with CIDs and concomitant IBD compared to those without IBD remain an important consideration when deciding on the clinical management of patient symptoms. Given the increasing use of novel agents for the treatment of CIDs, including those that may increase the risk of IBD in patients with CIDs, it is important to evaluate the incremental healthcare resource utilization (HRU) and costs associated with IBD in these patients. While multiple previous studies have assessed the incremental costs of patients with IBD relative to controls without IBD, little is known on the burden of IBD in patients with pre-existing CID. A recent real-world analysis of the economic burden associated with IBD among patients with PsA and AS in the United States (US) showed that compared to patients without IBD, those with IBD had significantly higher total healthcare costs; up to 27% higher in patients with PsA, and 38% higher among patients with AS. However, this analysis exclusively focused on patients with PsA or AS; thus, it is unclear whether the conclusions of this study can be generalized to other patients with CID.”

However, the results of the study are not more than a gross estimate of the expenses because the diseases are not very well defined (2 ICD codes is a rather imprecise measure to identify patients with a particular disease) and gastro-and colonoscopies were not included in the expenses while I imagine they contribute to a substantial part of the expenses of patients with IBD.

Response: Thank you for the comments. Selecting the study population with ≥2 claims of a given condition is common in claims database analyses [1-9]. The reason to require ≥2 diagnoses is to eliminate possible rule-out diagnoses, in which case the diagnosis would only appear once and would never be confirmed later on. A recent study published by the Crohn’s and Colitis Foundation assessed healthcare costs associated with IBD and identified patients with IBD using ≥2 IBD diagnoses [9]. In claims data, diagnosis codes remain the most accurate mean to identify patients with CID and IBD.

We also wish to clarify that the costs associated with gastroscopies and colonoscopies, although not reported separately, were captured within all-cause healthcare costs. We believe this confusion may have arisen from a statement made in the discussion, which we have revised as follows (underlined portions highlight additions; strikethrough highlights deletions):

Discussion, 1st paragraph: “Another possible driver could be costs related to endoscopy/colonoscopy procedures, which were captured as part of all-cause healthcare costs, but were not reported separately although data for these procedures was not available in the current study.”
Methods, Study measurements: “By definition, all-cause healthcare costs included any healthcare costs incurred during the follow-up period, regardless of whether they were related to CIDs, IBD (e.g., endoscopies, colonoscopies), or other comorbidities.”

References:


In addition, as the authors acknowledge, other studies already showed that patients with IBD+CID have higher health care expenses. Though the authors have made some different selections of patients, the analyses and conclusions are basically similar to previous studies.

Response: We thank the Reviewer for the opportunity to clarify this important point. The main novelty of our study relative to others is that all patients had pre-existing CID. In contrast, most other studies focused on IBD versus non-IBD patients (regardless of pre-existing CIDs). Bergman et al. also focused on patients with CID, but only patients with PsA or AS were evaluated. We have clarified as follows (underlined portions highlight additions; strikethrough highlights deletions):

Background, 3rd paragraph: “While multiple previous studies have assessed the incremental burden of IBD relative to controls without IBD23-27, little is known on the burden of IBD in patients with pre-existing CID. A recent real-world analysis of the economic burden associated with IBD among patients with PsA and AS in the United States (US) showed that compared to patients without IBD, those with IBD had significantly higher total healthcare costs; up to 27% higher in patients with PsA, and 38% higher among patients with AS.26 However, this analysis exclusively focused on patients with PsA or AS; thus, it is unclear whether the conclusions of this study can be generalized to other patients with CID.”

Discussion, 4th paragraph: “Only one previous analysis from Bergman et al. compared HRU and costs
between patients with CID who subsequently developed IBD and controls who did not develop IBD. However, this study only included patients with PsA or AS, thereby precluding the generalization of findings to other CIDs. Indeed, CIDs show substantial heterogeneity in their incidence, prevalence, and the characteristics of affected patients (e.g., age, gender, associated comorbidities, etc.)33, which may impact HRU and costs. For this reason, all patients with CIDs were included in the present study and were classified into different cohorts based on the type of CID(s) diagnosis.”

Another noteworthy difference between our study and the analysis of Bergman et al. relates to the definition of IBD. Bergman et al. identified IBD cases using diagnoses of UC, CD, or gastrointestinal disturbances (i.e., gastroenteritis, colitis, and gastritis), while the present study only used diagnoses of UC and CD. As already mentioned in the discussion section, this difference likely explains why the incidence rates of IBD were much higher in Bergman et al.’s study (PsA: 2.5%, AS: 4.1%) relative to the present study (0.52%-1.73%).

Discussion, 2nd paragraph: “The one-year incidence of IBD varied among subsets of patients with different CIDs, ranging from 0.39% in patients with PsO but without PsA to 1.73% among patients with AS. A previous study based on similar data reported an IBD incidence of 2.5% in patients with PsA and 4.1% in patients with AS during the one-year period following the initial claim for PsA/AS. IRs were higher because the definition of IBD included Crohn’s disease, ulcerative colitis, and gastrointestinal disturbances (i.e., gastroenteritis, colitis, and gastritis) as opposed to only Crohn’s disease and ulcerative colitis in the current study.”

Minor comments:
- I would be curious to know the health costs of patients with only IBD

Response: In our study, the costs of patients with IBD and CID were compared to those of patients with CID alone. This enabled us to isolate the economic burden of IBD, as reported by the incremental costs of $18,500. This would be similar to the difference observed in previous studies that compared the costs of patients with versus without IBD in the general population, since the incremental cost of IBD is also isolated in these types of studies.

To address the Reviewer’s query, we compared the difference in total all-cause healthcare costs observed in our study ($18,500) with that observed in the three most recent studies that assessed the costs of patients with versus without IBD in the general population. One study that included patients with CD (no patients with UC) reported a cost difference of $17,463; another study that included patients with UC (no patients with CD) reported a cost difference of $11,029; and another study that included any patients with IBD reported a cost difference of $16,031. Therefore, the incremental burden associated with IBD in patients with CID is similar to that in the general population. We have clarified as follows (underlined portions highlight additions; strikethrough highlights deletions):

Discussion, 3rd paragraph: “Of note, the difference in total all-cause healthcare costs found in our study ($18,500) is similar to that observed in recent analyses which assessed the incremental burden of patients with IBD versus non-IBD controls (IBD: $16,03127, CD only: $17,46335, UC only: $11,02936). Although comparisons with results from other analyses are prone to confounding, this suggests that the incremental burden associated with IBD in a population of patients with CID is similar to that observed in the general population.”

- I would be curious to know the prevalence of patients with both IBD and CID codes irrespective of the longitudinal order of the codes.
Response: We have updated Figure 3 to provide data on the prevalence of IBD per the Reviewer’s comment. As shown in the figure, prevalence rates are approximately three times higher than incidence rates across all cohorts, but the trends observed across cohorts remain largely the same. We have modified the methods and results section as follows (underlined portions highlight additions):

Methods, Study measurements: “The one-year incidence rate (IR) of IBD was calculated for each cohort. The numerator was defined as the number of patients with ≥2 claims with an IBD diagnosis during the period of evaluation (i.e., one year), and the denominator was defined as the total number of patients in the cohort studied. As a sensitivity analysis, the one-year prevalence of IBD among patients with or without a prior IBD diagnosis was also reported for each cohort. The numerator and denominator definitions used were the same as the ones used to measure incidence, except that patients who had a prior IBD diagnosis were not excluded from the numerator and denominator.”

Results, One-year IR and prevalence of IBD: “The one-year IR of IBD by type of CID is depicted in Figure 3. Among all patients with CIDs, the IR of IBD was 0.52%. For patients in the AS cohort, the IR of IBD was numerically higher (1.73%), compared to other CID cohorts (IR range: 0.39% in the PsO without PsA cohort to 0.54% in the AS, PsA, or PsO cohort) and the non-CID cohort (0.25%). The prevalence of IBD was higher across all cohorts, but consistent trends were observed, with values ranging from 1.29% in patients with PsO without PsA to 6.05% in patients with AS. The prevalence of IBD was 0.60% in the non-CID cohort.”

- the analysis that patients with CID+IBD have more IBD related surgery compared to CID's patients without IBD is redundant.

Response: We agree that patients with CID and IBD would have more IBD-related surgeries than patients with CID alone. However, the aim was to quantify the occurrence and costs associated with these events in patients who developed IBD rather than to compare with patients who did not develop IBD.

- what a remarkable high opioid usage. Is this also found in other cohorts?

Response: We thank the Reviewer for the opportunity to clarify this point. The high rates of opioid use observed in our study reflect both the pain burden associated with CIDs as well as US-specific circumstances.

In our study, 38.8% of patients with CID and 24.0% of those without CID used opioids during the baseline period. This difference is likely driven by patients who were prescribed opioids to manage the pain associated with CIDs. Indeed, patients with CIDs are known to exhibit higher use of prescription opioids than the general population to manage their pain [1, 2]. Specifically, a study by Zhdanava et al. that included patients with PsO reported rates of opioid use that were very similar to ours (PsO cohort: 42.8%, matched non-PsO cohort: 30.7%) [2].

In absolute terms, the rate of opioid use in the non-CID cohort of our study (24.0%) was nonetheless high, and that reported by Zhdanava et al. (30.7%) was in the same range. This is likely due to the marked increase of opioid use across the US over the past few years [3]. We have added the following paragraph in the discussion to clarify:

Discussion, 7th paragraph: “The high rates of opioid use observed in the current study reflect both the
pain burden associated with CIDs as well as US-specific circumstances. Overall, 38.8% of patients with CID and 24.0% of those without CIDs used opioids during the baseline period. This difference is likely driven by patients who were prescribed opioids to manage the pain associated with CIDs. Patients with CIDs are known to exhibit higher use of prescription opioids than the general population for pain management [41,42]. A study by Zhdanava et al. that included patients with PsO reported rates of opioid use that were consistent with those of the present study (PsO cohort: 42.8%, matched non-PsO cohort: 30.7%) [42]. In absolute terms, the rate of opioid use in the non-CID cohort of our study (24.0%) was nonetheless high, and that reported by Zhdanava et al. (30.7%) was in the same range. This is likely due to the marked increase of opioid use across the US over the past few years [43].

References:


- page 8 line 11 what do the authors mean by "100 payers representing about 75 million covered individuals"? Do the included patients in this study concern real patient data or are the numbers inferred?

Response: We had access to real individual patient data via the MarketScan database, although we acknowledge that the wording of this statement may have caused confusion. We have clarified as follows:

Methods, Data source: “The databases comprise claims from approximately 75 million individuals covered by 100 payers representing about 75 million covered individuals.”