Original Article

Anti-Tumour Necrosis Factor Therapy for Inflammatory Bowel Diseases Do Not Impact Serious Infections after Arthroplasty

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Abstract

Background and Aims: There is a paucity of data on the safety of joint replacement surgery in patients with inflammatory bowel disease [IBD], including those on tumour necrosis factor- α inhibitors [anti-TNF]. We explored the risk of serious infections in this population.

Methods: A retrospective case-control study [2006–2014] was performed using the MarketScan Database. All patients aged 18–64 years with an International Classification of Diseases code for IBD and an IBD-specific medication, with ≥ 6 months of enrollment prior to hip, knee or shoulder replacement surgery, were included. Ten non-IBD controls were frequency-matched to each case on length of enrollment, year and the joint replaced. Primary outcome was serious infection [composite of joint infection, surgical site infection, pneumonia, sepsis] within 90 days of the operation. Cox proportional hazards models were used to assess the association of IBD and IBD medications with serious infection.

Results: More patients with IBD [$N = 1455$] had serious infections than controls [3.2% vs 2.3%, $p = 0.04$], but not after controlling for comorbidities (hazard ratio [HR], 1.3; 95% confidence interval [CI], 0.95–1.76). Among IBD patients, corticosteroids were associated with increased risk of serious infection [HR, 4.6; 95% CI, 2.2–9.8; $p < 0.01$] while anti-TNFs were not. Opioids were also associated with increased risk of infection [HR, 1.5; 95% CI, 1.2–1.8; $p < 0.01$].

Conclusions: After controlling for comorbidities, IBD patients were not at increased risk of serious infection following joint replacement. Corticosteroids, but not anti-TNFs or immunomodulators, were associated with increased risk of serious infections in IBD patients.

Key Words: TNF α inhibitors; joint replacement; serious infections; inflammatory bowel disease

1. Introduction

The inflammatory bowel diseases [IBD] are lifelong conditions, and patients often require surgery for conditions unrelated to their IBD. It is common for gastroenterologists to be consulted about the risk of infections and managing peri-operative tumour necrosis factor alpha inhibitor [anti-TNF] and immunomodulator therapy in their patients with IBD undergoing surgical procedures. Treatments for IBD, namely corticosteroids, immunomodulators and anti-TNFs, suppress the body's immune response and may increase the risk of infection. Animal models suggest anti-TNFs also impair wound healing.¹ Stopping these agents, however, may increase the risk of an IBD flare. Most studies examining the risk of infections in the post-operative period related to anti-TNF exposure in IBD patients have focused on abdominal surgeries for complications of IBD.^{2,3} The literature is conflicting, with one meta-analysis suggesting anti-TNF therapy is associated with increased risk of infection after surgery for Crohn's disease [CD],² while another showed no increased risk following surgery for ulcerative colitis [UC].³ Only a few studies have addressed complications among IBD patients undergoing surgery for non-IBD-related conditions.^{4,5}

Joint replacement surgery is an ideal procedure to study the safety of non-abdominal surgery in IBD patients because it is a commonly performed, often elective, procedure. The prevalence of IBD is increasing,⁶ and chronic corticosteroid use can predispose patients with IBD to fractures and avascular necrosis.⁷ As the IBD population ages, the number of patients with IBD undergoing joint replacement surgery is likely to increase. Our aim here was to explore the risk of serious infections and other complications in IBD patients undergoing joint replacement surgery compared to patients without IBD, and to examine the effect of anti-TNFs, immunomodulators and corticosteroid therapies on the risk of infection.

2. Materials and Methods

2.1. Study design

We designed a retrospective case-control study using the Truven Health Analytics MarketScan Commercial Claims and Encounters Database from 2006 to 2014. This database includes private health insurance claims across the continuum of care [e.g. inpatient, outpatient, pharmacy] as well as enrollment data from participating employers and health plans across the United States, and includes data for more than 150 million employees and their dependents. The database includes a variety of fee-for-service, preferred provider organizations, and capped health plans.

We identified all patients aged 18–64 years with an International Classification of Diseases [ICD-9-CM] procedure or Current Procedural Terminology [CPT-4] code for hip, knee or shoulder replacement. To limit our analyses to those undergoing elective surgery, we excluded patients coded for a related fracture during the index admission, admission through the emergency room, and septic arthritis or active malignancy in the 6 months prior to joint replacement [Supplementary Table S1, Appendix]. We then identified all patients with an ICD-9-CM diagnosis code for CD or UC in the 6 months prior to surgery [Table S1, Appendix]. Patients with an ICD-9-CM code for both UC and CD were classified as having indeterminate colitis. IBD patients were required to have at least one claim for an IBD medication in the 6 months prior to joint replacement. IBD-specific medications included corticosteroids [oral or intravenous], 5-aminosalicylates, immunomodulators [azathioprine, 6-mercaptopurine, methotrexate], anti-TNFs [infliximab, adalimumab, certolizumab pegol, golimumab] and/or natalizumab.

Patients were required to have at least 6 months of enrollment prior to surgery to identify baseline comorbidities, medication utilization and exclusion conditions.

We excluded patients with an ICD-9-CM diagnosis code in the 6 months before surgery for another condition for which anti-TNFs are an approved treatment [Table S1, Appendix], to restrict the population to patients receiving these medications for IBD. There was no minimum requirement for follow-up after surgery, and patients were censored at the time of loss of insurance, death or the end of the study period [December 31, 2014]. For each case, ten non-IBD control patients were frequency-matched on type of joint replacement, year of surgery and duration of insurance enrollment.

Baseline comorbidities were assessed in the 6 months prior to surgery using the Elixhauser method.^{8,9} The Elixhauser algorithm includes a set of 30 chronic conditions defined by ICD-9-CM diagnosis codes found to be predictors of mortality in administrative data.⁹ It outperforms other comorbidity measures in predicting reoperation and mortality after hip replacement surgery.¹⁰ Additional conditions identified included smoking status and use of opioids in the 6 months prior to surgery.

The Human Resources Protection Office at Washington University exempted this study from oversight by the Institutional Review Board.

2.2. Outcomes

The primary outcome measure was new serious infection within 90 days of surgery. Serious infection was defined as a composite of prosthetic joint infection, osteomyelitis, septic arthritis, surgical site infection [SSI] requiring intervention, pneumonia or sepsis. Patients who experienced one of the outcomes in the 30 days prior to surgery were not considered to have a new infection. Patients with an ICD-9-CM code for SSI and a CPT-4 or ICD-9-CM procedure code for surgical drainage [Table S1, Appendix] within 7 days were considered to have SSI requiring intervention. Secondary outcome measures included *Clostridium difficile* infection [CDI], urinary tract infection [UTI], venous thromboembolism [VTE], haemorrhage/haematoma, mechanical complications, index length of stay, total charges for the index admission, and readmission. UTI was not included in the primary outcome because these infections are often not life-threatening and can be asymptomatic. Sepsis from a urinary source, however, would be included in the primary outcome, because ICD-9-CM diagnosis codes for sepsis of any source were included. CDI was not included in the primary outcome because it is well established that IBD patients are at increased risk of such infection.¹¹ We also captured prosthetic joint failure through the end of follow-up, defined as a subsequent joint revision surgery identified by ICD-9-CM procedure or CPT-4 codes.

For patients with IBD, we identified IBD-related hospitalizations, emergency department visits, surgery, bowel obstruction or a new prescription for an IBD-specific medication that the patient was not on prior to surgery. IBD-related hospitalizations were defined as having UC or CD as the primary discharge diagnosis or UC or CD as a secondary diagnosis plus a code for an IBD-related complication [intestinal obstruction, perforation, abdominal abscess, pouchitis, fistula, IBD surgery] during that hospitalization. All diagnosis and procedure codes used are listed in the Supplementary Appendix [Table S1].

2.3. Statistical analysis

2.3.1. IBD cases compared to controls

We performed univariate analyses using chi-square or Fisher's exact tests [where appropriate] for categorical variables, and Student's *t*-test for normally distributed or the Mann–Whitney *U* test for

non-normally distributed continuous variables. We examined hip, knee and shoulder replacement surgeries together and separately.

We developed Cox proportional hazards models using backwards stepwise elimination, after confirming the proportional hazards assumption was satisfied, to determine if IBD was a significant predictor of serious infection. Variables with $p < 0.2$ in univariate analysis or with clinical/biological plausibility for association with serious infection were eligible for inclusion. Because of its skewed nature in the population, age was categorized in four groups [< 50 years, 51–55 years, 56–60 years and 60–64 years]. Variables with $p < 0.1$ were retained in the final model.

Due to unequal follow-up time, we calculated the rate of joint re-operation per person-year of follow-up. We used Kaplan–Meier plots and the log-rank test to determine if there was a difference in joint survival between IBD patients and controls for each type of surgery. Patients were censored at loss of health insurance enrollment, death or the end of the study period.

2.3.2. Analyses restricted to IBD patients

In subset analyses we compared the proportion of patients with the primary and secondary outcomes measures restricted to those patients with IBD. We constructed a Cox proportional hazards model for serious infection using backwards stepwise elimination. The following IBD medication classes were used as independent variables in the model: 5-aminosalicylate with or without corticosteroids, immunomodulators with or without corticosteroids, any anti-TNF use [and/or immunomodulator and/or corticosteroids] and corticosteroid monotherapy. Only two patients were on natalizumab so they were excluded from this analysis. Current anti-TNF use was defined as any infusion for infliximab within 4 months prior to surgery or any prescription for adalimumab or certolizumab pegol within 3 months prior to surgery, as described previously.¹² A golimumab prescription within 3 months was also considered current. Current immunomodulator use was defined as in a previous study as any prescription that would run out within 30 days of surgery.^{13,14} Current corticosteroid use was defined as any corticosteroid prescription with daily supply extending up to at least 30 days before surgery. A similar definition has been used previously.¹⁵ A patient with any prescription for an aminosalicylate in the previous 6 months prior to surgery was included in the aminosalicylate group. In addition to Elixhauser comorbidities, IBD hospitalization during the 6-month baseline period, IBD surgery during the baseline period, IBD subtype, perianal disease and extra-intestinal manifestations were tested in the Cox model. Variables with $p < 0.05$ were retained in the final model.

As sensitivity analysis, we used any prescription in the 6 months prior to surgery to define the medication categories. To explore the effect of corticosteroids further, we constructed a model with the following categories: any corticosteroid use, aminosalicylate therapy without corticosteroids, immunomodulators without corticosteroids and anti-TNF [with or without an immunomodulator] without corticosteroids. We also examined the number of infections in patients on infliximab who had an infusion within 8 weeks prior to surgery and in those who had their last infusion more than 8 weeks prior to surgery.

A value of $p < 0.05$ was considered statistically significant in all analyses. All analyses were performed using SAS version 9.4.

3. Results

3.1. Baseline characteristics

We identified 1455 patients with IBD [Figure 1] and frequency-matched 14550 control patients who underwent joint replacement

surgery. A majority of IBD patients were female [54.6%], with a mean age of 56 years [SD 7.0] [Table 1]. CD was coded in 631 patients [43.4%], UC in 727 [50.0%] and indeterminate colitis in 97 [6.7%] [Table 2]. Patients with IBD were significantly more likely to have been prescribed an opioid analgesic in the 6 months prior to surgery compared to controls [Table 1]. The comorbidities that differed between IBD patients and controls are listed in Table 1 while IBD-specific medication exposure is listed in Table 2 and Table S2.

3.2. IBD cases compared to controls

More patients with IBD had a serious infection than controls within 90 days after surgery [3.2% vs 2.3%, $p = 0.04$] [Table 3]. CDI, UTI and readmission within 90 days were also more frequent in IBD compared to control patients. IBD patients had longer hospital stay during the surgical admission, although this difference was not clinically significant [2.9 vs 2.7 days, Table 3]. There was no difference in joint failure among IBD patients and controls after hip, knee or shoulder replacement [Figures S1–S3, Appendix]. When the analysis was stratified by individual procedures, a larger percentage of IBD patients had serious infection after knee replacement compared to controls [3.7% vs 2.4%, $p = 0.02$], but this was not the case for hip [2.8% vs 2.2%, $p = 0.37$] or shoulder replacement [3.0% vs 1.3%, $p = 0.29$] [Table S3].

After controlling for baseline comorbidities, IBD was not associated with increased risk of serious infection (hazard ratio [HR], 1.3; 95% confidence interval [CI], 0.95–1.76) [Table 4]. Opioid use was associated with a significantly increased risk of serious infection [HR, 1.5; 95% CI, 1.2–1.8]. The individual comorbidities chronic pulmonary disease, diabetes, liver disease and obesity were independently associated with increased risk of serious infections. In a separate multivariate model, opioid analgesic use, cigarette smoking, diabetes and chronic pulmonary disease were associated with increased risk of pneumonia [Table S4, Appendix]. Opioid analgesic use, diabetes and liver disease were associated with joint infection or SSI requiring intervention [Table S5, Appendix].

3.3. Analyses restricted to IBD patients

The number of serious infections was similar in patients with CD and UC [Table S6, Appendix]. The percentage of patients who experienced IBD complications was higher in patients with CD as compared to UC [3.7% vs 1.7%, $p = 0.02$], and a greater proportion of patients with CD were readmitted within 90 days than patients with UC [14.1% vs 7.6%, $p < .01$] [Table S6, Appendix].

After adjusting for comorbidities, and using 5-aminosalicylate therapy as the reference, corticosteroid monotherapy was associated with a significantly increased risk of serious infection [HR, 4.6; 95% CI, 2.2–9.8; $p < 0.01$], while immunomodulator [HR, 0.4; 95% CI, 0.1–1.3] and anti-TNF therapy [HR, 0.7; 95% CI, 0.2–2.5] were not [Table 5]. Diabetes and renal failure were also associated with increased risk of serious infection. Similar results were seen in a sensitivity analysis in which medications were defined as any prescription within the 6 months prior to surgery [HR, 2.5; 95% CI, 1.3–4.7, $p < 0.01$] [Table S7]. When corticosteroids in any combination were compared to the other medication classes without corticosteroids, corticosteroids were associated with an increased risk of infection [HR, 3.0; 95% CI, 1.5–5.9, $p < 0.01$] [Table S8]. IBD-hospitalization or IBD-related surgery in the 6 months before joint replacement were not associated with serious infection.

Of the 117 patients on infliximab, 97 [82.9%] received an infusion within 8 weeks prior to surgery compared to 20 patients [17.1%] who had their last infusion more than 8 weeks prior to surgery. One patient in each group had a serious infection after surgery.

Figure 1. Case selection flow chart.

Table 1. Baseline characteristics of IBD and control patients undergoing elective joint replacement surgery.

	IBD cases N = 1455	Controls N = 14 550	<i>p</i>
Age, mean [±SD]	56.02 [7.00]	56.20 [6.40]	0.87
Female, <i>n</i> [%]	795 [54.64]	7922 [54.45]	0.89
Knee replacement, <i>n</i> [%]	888 [61.03]	8880 [61.03]	1.00
Hip replacement, <i>n</i> [%]	500 [34.36]	5007 [34.41]	0.97
Shoulder replacement, <i>n</i> [%]	67 [4.60]	670 [4.60]	1.00
Median follow-up, years[±IQR]	1.25 [1.09–3.26]	1.30 [1.07–3.22]	0.59
Opioid prescription, <i>n</i> [%]	803 [55.19]	6248 [42.94]	<0.01
Smoker, <i>n</i> [%]	108 [7.42]	1102 [7.57]	0.84
Elixhauser comorbidities, <i>n</i> [%]			
Congestive heart failure	21 [1.44]	116 [0.80]	0.01
Pulmonary circulation disease	15 [1.03]	76 [0.52]	0.01
Peripheral vascular disease	18 [1.24]	93 [0.64]	<0.01
Other neurological disorders	46 [3.16]	281 [1.93]	<0.01
Chronic pulmonary disease	178 [12.23]	1246 [8.56]	<0.01
Hypertension	587 [40.34]	6451 [44.34]	<0.01
Renal failure	27 [1.86]	180 [1.24]	0.05
Liver disease	26 [1.79]	115 [0.79]	<0.01
Obesity	177 [12.16]	2588 [17.79]	<0.01
Weight loss	13 [0.89]	30 [0.21]	<0.01
Fluid and electrolyte disorders	84 [5.77]	635 [4.36]	0.01
Chronic blood loss anaemia	24 [1.65]	117 [0.80]	<0.01
Other deficiency anaemia	167 [11.48]	958 [6.58]	<0.01

IBD, inflammatory bowel disease; IQR, interquartile range; SD, standard deviation. Significant *p* values are in bold type.

Table 2. Baseline medication exposure and disease characteristics of IBD patients undergoing elective joint replacement surgery.

	IBD cases N = 1259
IBD subtype, <i>n</i> [%]	
Crohn's disease	631 [43.37]
Ulcerative colitis	727 [49.97]
Indeterminate colitis	97 [6.67]
Medications at the time of surgery, <i>n</i> [%]	
ASA ^a	773 [61.40]
Immunomodulators ^a	263 [20.89]
Any anti-TNF ^b	142 [11.28]
Corticosteroids only	81 [6.43]
IBD hospitalization, previous 6 months, <i>n</i> [%]	46 [3.16]
IBD surgery, previous 6 months, <i>n</i> [%]	14 [0.96]
Fistula, <i>n</i> [%]	3 [0.21]
Perianal abscess, <i>n</i> [%]	7 [0.48]
Anal fistula, <i>n</i> [%]	10 [0.69]
Intra-abdominal abscess, <i>n</i> [%]	7 [0.48]
Perforation, <i>n</i> [%]	1 [0.07]
Obstruction, <i>n</i> [%]	28 [1.92]
Extra-intestinal manifestations, <i>n</i> [%]	
Oral aphthous ulcers	1 [0.07]
Scleritis or episcleritis	7 [0.48]
Uveitis or iritis	7 [0.48]
Pyoderma gangrenosum	4 [0.27]
Erythema nodosum	2 [0.14]
Enteropathic arthritis	10 [0.69]
Other inflammatory spondylopathies ^c	18 [1.24]

Anti-TNF, tumor necrosis factor alpha inhibitor; ASA, aminosaliclates; IBD, inflammatory bowel disease.

^aWith or without corticosteroids.

^bWith or without immunomodulators and with or without corticosteroids.

^cIncludes spinal enthesopathy, sacroiliitis not otherwise specified, other inflammatory spondylopathies and unspecified spondylopathy.

4. Discussion

In a large administrative health claims database, we found that patients with IBD had a significantly higher incidence of composite serious infection following joint replacement surgery compared to control patients, but not after controlling for comorbidities. There was no difference in joint infections, mechanical complications or joint survival between IBD and control patients. The use of corticosteroids, but not immunomodulators or anti-TNFs, was associated with increased risk of serious infection. Few patients suffered an IBD complication after joint replacement surgery.

This is the largest study to examine outcomes of joint replacement surgery in the IBD population. The only other study was a case-control study with 17 IBD patients that found IBD patients had more complications and lower implant survival than controls.⁵ A case of enteric-articular fistula causing implant infection after hip replacement surgery has been reported.¹⁶ It is reassuring that in our much larger study, we observed no clinically meaningful increase in the number of joint infections in patients with IBD.

Much of the literature on orthopaedic surgery in immunosuppressed patients is in those with rheumatoid arthritis [RA]; however, only a few studies have specifically examined joint replacement.^{17,18} A recent study of RA patients undergoing joint replacement found that the use of corticosteroids, but not biological or non-biological disease-modifying anti-rheumatic drugs, was associated with increased risk of joint infection, similar to our findings for a wider range of infections.¹⁷ A recent meta-analysis found that anti-TNF therapy was associated with increased risk of SSI after orthopaedic surgery, but this association was no longer statistically significant when only hip or knee replacement were examined.¹⁸

The increased risk of serious infection with the use of corticosteroids that we observed is consistent with previous literature in the general IBD population.^{19–21} Our finding that anti-TNF inhibitors were not associated with increased risk of serious infection is consistent with some,²⁰ but not all, previous studies.^{19,21,22} It was surprising

Table 3. Complications within 90 days after joint replacement surgery.

	IBD cases N = 1455	Controls N = 14 550	<i>p</i>
Serious infection, <i>n</i> [%] ^a	46 [3.16]	344 [2.30]	0.04
Pneumonia	17 [1.17]	124 [0.85]	0.22
Joint infection ^b	22 [1.51]	178 [1.22]	0.35
SSI requiring intervention	3 [0.21]	26 [0.18]	0.74
Sepsis	7 [0.48]	35 [0.24]	0.09
<i>Clostridium difficile</i> infection	11 [0.76]	18 [0.12]	<0.01
Urinary tract infection	89 [6.12]	691 [4.75]	0.03
Venous thromboembolism	68 [4.67]	584 [4.01]	0.23
Haemorrhage or haematoma, <i>n</i> [%]	19 [1.31]	144 [0.99]	0.25
Prosthesis malfunction, <i>n</i> [%] ^c	52 [3.57]	473 [3.25]	0.51
Mechanical complications after knee replacement, <i>n</i> [%] ^d	56 [3.85]	460 [3.16]	0.16
Index length of stay [mean, days]	2.89	2.70	<0.01
Index total charges [mean, \$]	30 220	29 894	0.93
90-day readmission, <i>n</i> [%]	152 [10.45]	1052 [7.23]	<0.01
Joint reoperation [per 1000 patient-years] ^e			
Knee	19.74	17.60	0.58
Hip	19.22	14.52	0.34
Shoulder	16.18	22.71	0.95

IBD, inflammatory bowel disease; SSI, surgical site infection. Significant *p* values are in bold type.

^aIncludes pneumonia, postoperative joint infection, sepsis and surgical site infection requiring intervention.

^bIncludes infected prosthesis, septic arthritis and osteomyelitis.

^cIncludes loosening, dislocation and fracture.

^dIncludes tendon rupture, arthrofibrosis and instability.

^eNot limited to 90 days.

Table 4. Cox proportional hazards model for risk of serious infections within 90 days after joint replacement surgery.

Variable	HR	CI	<i>p</i>
IBD	1.29	0.95–1.76	0.11
Opioid analgesic use	1.47	1.20–1.80	<0.01
Chronic pulmonary disease	1.33	0.98–1.80	0.07
Diabetes mellitus	1.54	1.20–1.98	<0.01
Liver disease	2.85	1.55–5.25	<0.01
Coagulopathy	1.85	0.98–3.50	0.06
Obesity	1.34	1.05–1.71	0.02
Fluid and electrolyte disorders	1.46	0.98–2.16	0.06

CI, 95% confidence interval; HR, hazards ratio; IBD, inflammatory bowel diseases. Significant *p* values are in bold type.

Table 5. Association of IBD medications with risk of serious infections within 90 days after surgery in the IBD population.

Variable	HR	CI	<i>p</i>
IBD therapy			
Aminosaliculates ^a	Ref		
Immunomodulators ^a	0.39	0.12–1.29	0.13
Any anti-TNF ^b	0.74	0.22–2.45	0.62
Corticosteroids only	4.60	2.16–9.79	<0.01
Diabetes mellitus	3.09	1.52–6.25	<0.01
Renal failure	3.32	1.01–10.91	0.05

ASA, aminosaliculates; anti-TNF, tumour necrosis factor alpha inhibitor; CI, 95% confidence interval; IBD, inflammatory bowel disease; HR, hazards ratio. Significant *p* values are in bold type.

^aWith or without corticosteroids.

^bWith or without immunomodulators and with or without corticosteroids.

that 6% of patients were treated with only corticosteroids, despite clinical guidelines recommending against corticosteroids as maintenance therapy.^{23,24} Other administrative studies have found that it is not uncommon for patients to be treated with prolonged courses of corticosteroids instead of adding corticosteroid-sparing agents – an immunomodulator or anti-TNF inhibitor.^{25,26} Our results re-emphasize the importance of managing steroid-dependent patients with corticosteroid-sparing agents.

Our finding that the incidence of CDI was higher in IBD patients than in controls is not surprising given that IBD patients are known to be at increased risk of CDI.¹¹ Hospitalization and antibiotic use, both of which occur with joint replacement procedures, are established risk factors for CDI.¹¹

Our finding that opioid use was associated with increased risk of infection is clinically relevant, because opioid use is more common in IBD patients than in the general population.²⁷ Although the increased risk of infection we observed may be due to residual confounding effects, it is consistent with other literature in IBD and joint replacement.^{19,21,28} Preoperative and prolonged opioid use has been shown to be associated with increased risk of re-admission, revision and infections after total knee arthroplasty.²⁸ Opioid analgesic use in IBD has previously been found to be associated with increased risk of infection^{19,21} and mortality.^{21,27} Another study found that the use of narcotics was associated with increased risk of complications after ostomy creation in patients with IBD.²⁹ Opioid analgesic use is another potentially modifiable risk factor to decrease adverse effects in the IBD population. In addition to opioids and corticosteroids, medical comorbidities such as diabetes and obesity were also potentially modifiable risk factors that were predictors of serious infection.

The major strength of our study is the use of a large data set that captures patients in both academic and community settings, including information from inpatient and outpatient encounters as well as pharmacy data. One advantage of the use of claims data is the ability to capture complications even for patients readmitted to a different health system.

Our study has limitations typical of administrative database studies. We did not have details regarding IBD activity and symptoms or laboratory data. However, including enough centres to provide adequate power to answer our question is probably not feasible with clinical data. Miscoding can be a problem with administrative data, but we mitigated this risk by requiring patients to have a prescription for an IBD medication, an ICD-9-CM diagnosis code for IBD and additional definitions for current use varying by drug class. Although not all infections may have been coded, there is no reason to suspect this would be different between IBD patients and controls. For oral medications, we could not be certain that a patient actually took a medication that was prescribed. However, we can be confident that infusions [e.g. infliximab] were administered because they had an associated Healthcare Common Procedure Coding System code for administration at a facility. Because we limited our analysis to elective joint replacement surgery, our results cannot be generalized to other orthopaedic procedures in patients with IBD or to emergency orthopaedic procedures. Because the MarketScan data only include patients with private insurance under the age of 65 years, our results may not be generalizable to patients with Medicaid, Medicare or without insurance. While no difference in VTE was shown in the study, we could not evaluate whether this was due to consistent prescription of anticoagulants due to an absence of guidelines suggesting optimal durations of anticoagulation after joint replacements and absence of patient-level compliance data.

One unresolved question we hoped to address was whether interrupting anti-TNF therapy was associated with decreased risk of infection and/or increased risk of IBD flare. Unfortunately, our sample size was too small to address this question with sufficient power. It is reassuring, however, that over 80% of patients on infliximab had an infusion within 8 weeks prior to surgery and only one patient had a serious infection. Similarly, we were unable to evaluate the risks of all individual drug combinations due to small numbers. For example, we could not evaluate whether the risk of infection with methotrexate or azathioprine differed or whether combination therapy with an anti-TNF increased the risk of infection more than anti-TNF monotherapy. To determine the association of all medication combinations, a much larger study would be needed. To have enough patients, a much larger spectrum of non-abdominal surgeries may be required.

In conclusion, we found that patients with IBD have a significantly higher incidence of serious infection after joint replacement surgery but not after controlling for coexisting comorbidities. Anti-TNFs were not associated with increased risk of serious infection after joint replacement procedures. Larger studies are needed to determine the effect of interrupting anti-TNF therapy in patients with IBD. Future studies are also needed to examine the safety of other non-abdominal surgeries in IBD patients.

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Conflict of Interest

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Author Contributions

MHG: Study concept and design, obtained funding, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content. AM, DS: acquisition of data, analysis and interpretation of data, critical revision of the manuscript for important intellectual content. KJH: Study concept and design, critical revision of the manuscript for important intellectual content. EVL: Study concept and design, critical revision of the manuscript for important intellectual content. MAC: Study concept and design, obtained funding, critical revision of the manuscript for important intellectual content. MAO: Study concept and design, obtained funding, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content. PD: Study concept and design, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Supplementary Data

Supplementary data are available at ECCO-JCC online.

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