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Original Article

Preoperative Ustekinumab Treatment Is Not Associated With Increased Postoperative Complications in Crohn's Disease: A Canadian Multi-Centre Observational Cohort Study

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Abstract

Background: Ustekinumab (UST), an anti-IL12/23 inhibitor is indicated for moderate-to-severe Crohn's disease (CD). However, it is unclear if patients treated with UST are at increased risk for postoperative complications.

Aim: To evaluate the postoperative safety outcomes in UST-treated CD patients.

Methods: A multicentre cohort study of UST-treated CD patients at two tertiary care centres (University of Calgary, University of Alberta, Canada) undergoing abdominal surgery between 2009 and 2016 was performed. Postoperative outcomes were compared against a control cohort of anti-TNF-treated patients over the same time-period. The primary outcome was occurrence of postoperative complications up to six months postoperatively, stratified by timing (early <30 days vs. late complications ≥30 days).

Results: Twenty UST-treated patients and 40 anti-TNF-treated patients were included with a median preoperative treatment exposure of 6.5 months and 18 months, respectively (p=0.01). Bowel obstruction was the most common surgical indication in both cohorts. UST-treated patients were more likely to require an ostomy (70.0% vs. 12.5%, p<0.001) and be on combination therapy with either systemic corticosteroids or concurrent immunomodulators (azathioprine or methotrexate) (25.0% vs. 2.5%, p=0.01). Despite the increased concomitant use of immunosuppression in the UST-treated cohort, there were no significant differences in early or late postoperative wound infections (1/20 in UST-cohort, 2/40 in anti-TNF cohort, p=1.00), anastomotic leak (0/20 in UST-cohort, 3/40 in anti-TNF cohort, p=0.54), or postoperative ileus/obstruction (3/20 in UST-cohort, 4/40 in anti-TNF cohort, p=0.67).

Conclusions: CD patients receiving preoperative UST did not experience an increase in postoperative complications, despite increased use of concurrent immunosuppression.

Keywords: *Ustekinumab, Crohn's disease, Surgery, Postoperative complications*

INTRODUCTION

Crohn's disease (CD) is a chronic progressive inflammatory condition of the gastrointestinal tract.(1–3) In the pre-biologic era before the approval of infliximab in 1998, up to 80% of patients required surgical intervention for management of disease-related complications including strictures, fistulae, and abscesses.(4,5) Since the introduction of biologic agents targeting tumor necrosis factor (TNF) alpha into the therapeutic armamentarium, there has been a paradigm shift in the natural history of CD with reduced need for surgery and hospitalization when treatment is used early, prior to the development of irreversible bowel damage and fibrostenotic disease.(6–10) In the Randomised Evaluation of an Algorithm for Crohn's Treatment (REACT 1) cluster randomised controlled trial, early anti-TNF initiation in combination with an immunomodulator was superior to conventional therapy for reducing surgical rate, hospitalization, or serious disease related complication (27.7% vs. 35.1%, p=0.0003) at 24 months.(6) However, one third of patients do not respond to anti-TNF agents due to non-TNF mediated pathways of inflammation and among responders, another third subsequently lose response due to insufficient drug levels or the development of anti-drug antibodies.(11,12)

Non-anti-TNF biologic therapies for the treatment of CD have been limited until 2014, when the United States Food and Drug Administration (FDA) approved vedolizumab, an $\alpha_4\beta_7$ integrin inhibitor. Subsequently, ustekinumab (UST), a monoclonal antibody targeting IL-12 and IL-23 through the common p40 subunit, was approved in 2016 by the FDA, the European Medicines Agency (EMA), and Health Canada. UST has been available since 2009 for use in patients with psoriasis. Prior to its approval in 2016 for the treatment of moderate-to-severe CD, UST had been available off-label for the compassionate treatment of CD patients failing anti-TNF therapy in view of the favourable therapeutic response in clinical trials.(13)

Approximately 30–50% of CD patients are likely to be on concurrent biologics at the time of surgery.(14) Data on the risk of perioperative infections and complications with the use of anti-TNF agents are conflicting, largely related to the significant heterogeneity of individual studies, patient cohorts, and nature of surgery.(15–22) A meta-analysis of eight studies reported a trend towards an increased risk of total complications with preoperative anti-TNF use.(23) No strong recommendations with regards to perioperative use of anti-TNF therapy have been made in either the 2015 Crohn's and Colitis Foundation of America (CCFA) position statement or the 2016 European Crohn's and Colitis Organization (ECCO) consensus.(24,25) While it is often a joint decision with the surgeon, unnecessary suspension of anti-TNF therapy and then subsequently restarting treatment after surgery may predispose patients to anti-drug antibody formation, infusion reactions, and loss of clinical response.

Perioperative outcomes among UST-treated CD patients is unclear. This is of paramount clinical relevance in view of the expected increasing use of UST for the treatment of refractory CD. Therefore, we report our clinical experience with the use of UST in CD patients preoperatively and compare the postoperative outcomes to those treated with anti-TNF therapy.

METHODS

Study Design and Patient Population

A retrospective observational cohort study of CD patients treated with UST from two tertiary academic care centres (University of Calgary, Calgary, Canada and University of Alberta, Edmonton, Canada) was performed. Adult (≥18 years) CD patients were eligible for inclusion if they met the following criteria: (i) had a confirmed diagnosis of CD by standard endoscopic, radiologic, and histologic parameters; (ii) received UST therapy within four months of abdominal surgery, and (iii) subsequently underwent abdominal surgery between January 1, 2009 and August 1, 2016. Abdominal surgery was defined as any surgery that was performed within the intra-abdominal compartment, but did not have to be specifically for CD management. Patients undergoing exclusive perianal surgery, including incision and drainage, examination under anesthesia, or seton placement, were excluded. Minimum UST exposure time was not an inclusion criterion.

UST-treated patients were then compared in a 1:2 ratio to a control group of CD patients treated with anti-TNF agents undergoing abdominal surgery over the same time period. Control patients were identified using the University of Calgary Gastrointestinal Research Group (GIRG) database and the University of Alberta Centre of Excellence for Gastrointestinal Inflammation and Immunity Research (CEGIIR) database. Matching on baseline covariates was not performed due to the small sample size; however, we restricted the selection of control patients to those undergoing surgery during the same time-period to control for potential temporal differences in surgical and nursing-related care.

Data were collected independently by authors (HHS and CM) from a provincial electronic medical record system and via chart review. Patient demographics including age, gender, disease phenotype as defined by the Montreal classification,(26) tobacco exposure, body mass index (BMI) at time of surgery, serum albumin level (g/L) within one month preoperatively, date of surgery, nature of surgery (emergency vs. elective, laparotomy vs. laparoscopic, types and indications for surgery) were collected. Medication history including biologic exposure and perioperative immunosuppression (corticosteroids, azathioprine, or methotrexate) were recorded. Systemic corticosteroid exposure was defined as a dose of ≥ 20mg per day of prednisone (or equivalent) given within four weeks perioperatively.

Outcomes

The primary outcome of interest was the occurrence of postoperative complications, up to six months after surgery. Postoperative complications were defined by the following events: (a) wound infection; (b) anastomotic leak; (c) intra-abdominal abscess; (d) non-surgical site infection; (e) delayed wound healing at one month post-surgery; (f) need for readmission or reoperation; (g) median duration of hospital admission; and (h) postoperative mortality. Outcomes of interest were defined by clinical assessment and where appropriate, supplemented by diagnostic imaging. Postsurgical outcomes for both cohorts were stratified by time to occurrence: early (<30 days post-surgery) and late (≥30 days and up to six months post-surgery).

Statistical analysis

Baseline patient characteristics were analysed using standard descriptive statistics; medians with interquartile ranges (IQR) were calculated for continuous data and percentage were calculated for categorical data. Comparisons between baseline characteristics and postoperative outcomes between UST-treated and anti-TNF-treated patients were performed using the Mann-Whitney U test for non-parametric continuous variables and Fisher exact test for categorical data. A *p*-value <0.05 was considered to be statistically significant. Statistical analysis was performed using SPSS 24.0 (Armonk, NY: IBM Corporation).

Ethical Considerations

This study was approved by the Human Research Ethics Board at both the University of Calgary and the University of Alberta.

RESULTS

Patient Population

Twenty-one UST-treated CD patients who underwent abdominal surgery between January 1, 2009 and August 1, 2016 were identified. One patient required emergency abdominal surgery outside of the study centres and due to incomplete data was excluded from the cohort. Forty anti-TNF treated CD patients who underwent abdominal surgery during the same time period were included in the control group. Half of these patients (20/40) received adalimumab, 18/40 (45%) received infliximab, and 2/40 (5%) received golimumab as their most immediate pre-operative anti-TNF agent. Although golimumab is not listed for the treatment of CD in Canada, it was used off-label for both the patients as salvage therapy after they lost response to infliximab and adalimumab. Baseline patient demographics are summarized in Table 1. There were no significant differences between both cohorts based on age, gender, BMI, coexistent diabetes mellitus, or pre-operative serum albumin level. UST-treated patients were nominally more likely to be treated with systemic corticosteroids (35% vs. 15%, p=0.10), have stricturing disease phenotype (50% vs. 27.5%, p=0.13), and have disease affecting the upper gastrointestinal tract (35% vs. 10%, p=0.53), although these associations were not statistically significant.

All patients from the UST cohort were infliximab-experienced (either intolerant, primary non-responders, or developed secondary loss of response to maintenance anti-TNF therapy). Seventy percent (14/20) were intolerant or had lost response to at least two anti-TNF therapies. In comparison, the majority of anti-TNF-treated patients (77.5%, 31/40) were previously biologic naïve and were on their first biologic at the time of surgery. Disease duration was numerically but not statistically longer in the UST-treated cohort compared to the anti-TNF-treated cohort (median disease duration 14.5 years [IQR 8.5–19.5] vs. 7.0 [IQR 3.0–15.5] years, p=0.07). UST-treated patients were also more likely to be smokers (50% vs. 5%, p<0.001) and had a higher burden of concomitant methotrexate (45% vs. 15%, p=0.02) and combination corticosteroid with immunomodulator (either azathioprine or methotrexate) (25% vs. 2.5%, p=0.01). Previous treatment history of both cohorts is summarized in Table 2.

Surgical Details

Surgical details, including surgical indication, nature of surgery, and surgical type are summarized in Table 3. The predominant indication for surgery in both cohorts was bowel obstruction (12/20 for UST and 26/40 for anti-TNF cohort, p=0.19). However, UST-treated patients were more likely to undergo surgery in the emergent setting (55% vs. 25%, p=0.04) and require a postoperative ostomy (70.0% vs. 12.5%, p<0.001). Although not statistically significant, UST-treated patients were also more likely to have undergone either proctocolectomy (10% vs. 0%, p=0.10) or subtotal colectomy (20.0% vs. 7.5%, p=0.21). A similar proportion of patients treated with UST and anti-TNF required ileal and ileocolonic resections (30.0% vs. 22.5%, p=0.54 and 35.0% vs. 42.5%, p=0.78, respectively).

Postoperative Outcomes

There were no significant differences across both cohorts for all postoperative complications, followed out to six months after surgery (Table 4). There were no significant differences in the rate of anastomotic leak, intra-abdominal abscess, non-surgical site infection, delayed wound heaing, need for readmission or reoperation, or median days of total hospital stay for both cohorts. No deaths were reported in both cohorts at six months. Only a single postoperative wound infection was reported in the UST-treated cohort.

UST was continued in 13 patients (65%) and anti-TNF therapy was continued in 28 patients (70%) postoperatively. Immunomodulator therapy with methotrexate or azathioprine

Table 1. Baseline patient demographics

	Ustekinumab cohort (n=20)	Anti-TNF cohort (n=40)	P value
Median age (years, IQR)	34.5 (26.3–51.5)	32.5 (22–42.5)	0.34
Male gender (n, %)	5 (25%)	15 (37.5%)	0.39
Current smoker (n, %)	10 (50%)	2 (5%)	<0.001
Median BMI (IQR)	23.6 (19.6–27.6)	23.6 (20.2–25.7)	1.00
Median duration of postsurgical follow up (months, IQR)	14.5 (6.3–21.8)	39.5 (22–56.8)	<0.001
Median duration of CD prior to surgery (years, IQR)	14.5 (8.5–19.5)	7 (3–15.5)	0.07
Median duration of biologics prior to surgery (months, IQR)	6.5 (3–12)	18 (5–33)	0.007
Montreal classification			
Age:	10 (50%)	13 (32.5%)	0.26
A1			
A2	7 (35%)	23 (57.5%)	
A3	3 (15%)	4 (10%)	
Behaviour:	2 (10%)	2 (5%)	0.13
B1			
B2	10 (50%)	11 (27.5%)	
B3	8 (40%)	27 (67.5%)	
P	7 (35%)	12 (30%)	0.77
Location:	5 (25%)	17 (42.5%)	0.53
L1			
L2	3 (15%)	3 (7.5%)	
L3	9 (45%)	16 (40%)	
L3+ L4	3 (35%)	4 (10%)	
Previous history of intestinal resection (%, range)	60% (0–3)	47.5% (0–9)	0.36
Median preoperative serum albumin (g/L, IQR)	34.0 (28–42.2)	34.0 (30.5–38)	0.53
Concomitant diabetes mellitus	0%	0%	-
Perioperative immunosuppression (n, %)			
Corticosteroid ≥ 20mg/day	7 (35%)	6 (15%)	0.10
Azathioprine	4 (20%)	10 (25%)	0.75
Methotrexate	9 (45%)	6 (15%)	0.02
Combination corticosteroid and azathioprine/ methotrexate	5 (25%)	1 (2.5%)	0.01

was added in 5 patients in the UST group (25%) and 11 patients in the anti-TNF group (27.5%). Therapy was changed in two patients (10%) in UST group to vedolizumab postoperatively; therapy was changed in three patients (7.5%) in the anti-TNF group to UST postoperatively. All medical therapy was discontinued after surgery in two patients (10%) in the UST-treated group and seven patients (17.5%) in the anti-TNF group.

DISCUSSION

Although the introduction of biologic therapy has ushered in a new era in the management of CD, surgery continues to hold a fundamental role in the treatment paradigm for patients with medically refractory or complicated CD. Indeed, approximately half of CD patients will require bowel resection within 10 years of diagnosis.(9) With the increasing adoption of UST for CD, we anticipate an increase in the number of patients who are on UST preoperatively. A fundamental question with any biologic therapy is whether exposure adversely influences post-operative outcomes. In this multicenter cohort study, we demonstrate no increased risk of either early or late postoperative complications in UST-treated patients undergoing intra-abdominal surgery as compared to patients treated with anti-TNF agents. This is despite UST-treated patients experiencing a significantly greater burden of immunosuppression preoperatively but may also be confounded by a significantly higher proportion requiring postoperative ostomy creation.

The impact of preoperative biologic therapy on postoperative outcomes and in particular, postoperative infections, remains controversial.(27–29) Previous meta-analyses have demonstrated a modestly increased risk of postoperative infectious complications associated with preoperative anti-TNF exposure

Table 2. Treatment exposure history

	Ustekinumab cohort (n=20)	Anti-TNF cohort (n=40)
Immunomodulators		
Azathioprine	11 (55%)	11 (27.5%)
Methotrexate	6 (30%)	9 (22.5%)
Previous anti-TNF therapy		
Infliximab	20 (100%)	7 (17.5)
Adalimumab	13 (65%)	4 (10%)
Certolizumab	1 (5%)	0
Golimumab	3 (15%)	0
Previously biologic naive	0	31 (77.5%)
Failed 1 anti-TNF therapies	6 (30%)	7 (17.5%)
Failed 2 anti-TNF therapies	11 (55%)	2 (5%)
Failed 3 anti-TNF therapies	3 (15%)	0
Other previous biologics exposure (commercial/clinical trials)		
Vedolizumab	1 (5%)	0
Ustekinumab	-	1 (2.5%)
Briakinumab (ABT-894)	0	1 (2.5%)
CCR-9 inhibitor	1 (5%)	0

Table 3. Surgical details

	Ustekinumab cohort (n=20)	Anti-TNF cohort (n=40)	P value
Indication of surgery:			
Medical refractory disease	^5 (25%)	^^3 (7.5%)	0.19
Obstruction	12 (60%)	26 (65%)	
Free bowel perforation	2 (10%)	2 (5%)	
Intraabdominal abscess	0	2 (5%)	
Closure of ostomy	0	3 (7.5%)	
Others	*1 (5%)	**4 (10%)	
Nature of surgery:			
Emergency	11 (55%)	10 (25%)	0.04
Open laparotomy	13 (65%)	20 (50%)	0.40
Type of surgery (n,%): Ileal resection	6 (30%)	9 (22.5%)	0.54
Ileocolonic resection	7 (35%)	17 (42.5%)	0.78
Subtotal colectomy	4 (20%)	3 (7.5%)	0.21
Proctocolectomy	2 (10%)	0	0.10
Ostomy	14 (70%)	5 (12.5%)	<0.001
Primary anastomosis	9 (45%)	26 (65%)	0.17
Stricturoplasty	1 (5%)	2 (5%)	1.00
Fistula repair	2 (10%)	3 (7.5%)	1.99
Hernia repair	1 (5%)	1 (2.5%)	1.00
Cholecystectomy	1 (5%)	4 (10%)	0.66
Appendectomy	0	1 (2.5%)	1.00
Adhesiolysis	0	7 (17.5%)	0.08

^inflammatory (ileo)colitis refractory to treatment x5

^^ inflammatory colitis refractory to treatment x 2, defunctioning loop ileostomy for refractory perianal disease x1

*cholecystectomy for cholecystitis

**cholecystectomy for porcelain gallbladder; cholecystectomy for gall bladder cancer; cholecystectomy for biliary colic x2

Table 4. Postoperative outcomes

	Ustekinumab cohort (n=20)	Anti-TNF cohort (n=40)	P value
Postoperative complications:			
Wound infection ≤ 30 days	1 (5%)	2 (5%)	1.00
Wound infection > 30 days	0	0	-
Anastomotic leakage ≤ 30 days	0	3 (7.5%)	0.54
Anastomotic leakage > 30 days	0	0	-
Abscess ≤ 30 days	0	4 (10%)	0.29
Abscess > 30 days	0	2 (5%)	0.54
Nonsurgical site infection ≤ 30 days	0	3 (7.5%)	0.54
Nonsurgical site infection > 30 days	0	0	-
Postoperative ileus /bowel obstruction	3 (15%)	4 (10%)	0.67
Delayed wound healing	0	5 (12.5%)	0.16
Need for reoperation/readmission	2 (10%)	6 (15%)	0.59
Median preoperative hospital stay (days, IQR)	0 (0–4)	0 (0–2)	0.59
Median total hospital stay (days, IQR)	7 (5–14)	7 (4–9)	0.45
Mortality at 6 months	0	0	-

(OR 1.45–1.56), with a magnitude of associated risk similar to that of systemic corticosteroids.(30–32) Furthermore, it has been shown in animal models that TNF inhibition reduces angiogenesis and collagen production. It has therefore been hypothesized to potentially inhibit wound healing in postoperative patients.(33) Biologically, UST blocks upstream Th1 and Th17 cytokine signalling involved in the proinflammatory response, and does not directly disrupt TNF pathways.

In the clinical trial development programs, there were no increased risks of serious adverse events or infections in patients who received UST when compared to placebo.(13,34) Although there is no direct head-to-head comparison, a systematic review with network meta-analysis of 10 RCT reported no significant difference in the safety profile between UST, anti-TNF agents and vedolizumab.(35) Fabiano *et al.* have also reported the perioperative outcomes of a cohort of 131 patients with psoriasis treated with various biologics (infliximab, adalimumab, UST and etanercept)(36). UST-treated patients were however a minority (13/131, 10%) of the cohort and most surgeries in this study (73/131, 56%) were performed for minor procedures (dermatologic and dental). There was no increased risk of wound infection for those who continued with biologic therapy compared to patients electively discontinuing therapy prior to surgery.

From our cohort of CD patients treated with UST, we did not observe an increased risk of adverse perioperative outcomes compared to CD patients treated with anti-TNF agents. This was despite a greater exposure to immunosuppressants and more complicated disease phenotype in the UST-treated cohort. Our UST-treated cohort was comprised of patients who were nominally more likely to have upper GI involvement, stricturing disease phenotype, and were unsuccessfully treated with conventional biologics including various anti-TNF agents and vedolizumab. Not unexpectedly, there was greater use of corticosteroids, methotrexate, and combination corticosteroid and immunomodulator in UST-treated patients. While perioperative use of immunomodulators appears to be safe, perioperative corticosteroid use has previously been associated with increased total complications.(32,37,38) UST-treated patients in this cohort also tended to be smokers, have a significantly longer CD duration, require emergent surgery, and have medical refractory disease: all are predictors of poor postoperative outcomes, but despite these poor prognostics factors, our pilot data did not appear to have biased findings towards increased risk in UST-treated patients. Our findings correlate with a recently published retrospective cohort of 44 UST-treated patients undergoing abdominal surgery: Lightner *et al.* also found no increased risk of surgical site infections or hospital readmission when comparing UST and anti-TNF treated patients.(39)

Of note, we observed a higher proportion of patients in the UST cohort who received an ostomy (70% vs. 12.5%, $p<0.001$). We postulate there are multiple reasons for this difference in ostomy creation, including: 1) possible hesitancy from surgeons to create a primary anastomosis in patients on UST; 2) a greater need for emergency rather than elective surgery among patients on UST; and 3) more complex disease phenotype and longer disease duration among UST-treated patients compared to anti-TNF-treated patients precluding primary anastomosis. The difference in ostomy creation introduces a potential source of bias in interpreting post-operative complication rates: ostomy creation may partially mitigate the risk of early post-surgical complications, such as wound dehiscence, especially in complex CD patients with greater preoperative immunosuppressant burden. However, if the decision for

ostomy creation was driven by more aggressive CD phenotype, this population would inherently be at increased risk for postoperative complications.

Other confounders that we have considered, including patient comorbidities such as age and diabetes mellitus, were comparable in both cohorts. To explore the effect of malnutrition as a confounder for occurrence of adverse perioperative outcomes, we compared preoperative BMI and serum albumin levels in both cohorts as surrogate measures of overall nutritional status, recognizing the inherent limitations that serum albumin is a negative phase reactant in acute inflammation and obese patients are not precluded from malnturtion.(40,41) Regardless, these markers were comparable for both cohorts. Elderly age and longer preoperative hospital stay were noted to be potential risk factors for post-colectomy complications in a study by Bartels *et al.*(42) However, these factors were not confirmed to be significant predictors in our cohort. For the single UST-treated patient who developed an early wound infection, there were multiple potential confounders, including presentation with a perforated viscus, operation in an emergency setting, open laparotomy, and significant corticosteroid exposure (≥ 20mg/day).(32,43)

Interestingly, we observed a relatively low rate of postoperative complications in this cohort, especially in comparison to previous reports where complication rates approached 20% on anti-TNF therapy.(44) Possible explanations of our low complication rates may include the selection of a relatively young patient cohort without a substantial burden of comorbid illness predisposing to postoperative complications, improvements in surgical technique (particularly less invasive surgical approaches) over time, and optimized post-surgical care and nursing support. However, our low postoperative event rate in the anti-TNF cohort may limit our ability to detect true differences from the UST-treated group.

There are some limitations to our study. Due to the retrospective nature, there are inherent limitations with respect to recall bias and incomplete data reporting. For example, perioperative drug level testing was not routinely available for analysis. Furthermore, exact quantification of preoperative UST exposure is challenging: UST and adalimumab are self-administered and we could not ensure compliance with medical therapy prior to surgery. Therefore, reliable confirmation of last dose of biologic preoperatively to determine the washout period and date of restarting biologic therapy postoperatively were only partially available and not included in the analysis to minimize observation bias. They are however, unlikely to be significant confounders in view of the long half-life of biologics.(45) Further, up to 55% of surgeries were performed in the emergency setting for UST-treated patients, limiting the washout period. Due to small sample size, our UST-treated cohort was compared with a randomly selected anti-TNF-treated cohort rather than a control group that was matched for covariates. Therefore, any comparisons may be confounded by potentially important differences in clinical characteristics between the two groups, such as preoperative medication use and disease phenotype. Finally, we present a multicentre experience with UST-treated patients requiring intra-abdominal surgery, but the study is underpowered due to 1) small total cohort size and 2) small number of postoperative complications. However, this study represents the first uniquely Canadian experience with UST in a clinically important and understudied setting and we hope to stimulate collaborative efforts from other authors to confirm these findings.

In conclusion, in this multicentre cohort study, we found preoperative UST exposure to be associated with an increased risk of requiring postoperative ostomy but not associated with an increased risk of early or late perioperative complications compared to preoperative anti-TNF therapy. However, larger prospective studies will be needed to confirm these findings.

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Conflict of Interest

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CM, HA, AKA, JXQP: nil
PGK: Consulting (Abbvie, Takeda, Pfizer), speaker's bureau (Janssen, Abbvie, Takeda, Ferring, Pfizer, UCB)
CHS: Advisory board (Janssen, Abbvie, Shire, Takeda, Actavis), speaker's bureau (Janssen, Abbvie)
RNF: Advisory board (Abbott/AbbVie, Celltrion, Ferring, Janssen, Shire, VSL#3), consulting fees (Abbott/AbbVie, Celltrion, Ferring, Janssen, Shire, VSL#3), research grants (Abbott/AbbVie, Alba Therapeutics, BMS, Celltrion, Centocor, Genentech, GSK, Janssen, Merck, Millennium, Novartis, Pfizer, Proctor & Gamble, Roche, VSL#3)
SMD: Advisory board (Takeda, Shire, AbbVie, Janssen, Ferring, Hospira), speaker's bureau (AbbVie, Janssen, Shire, Ferring, Takeda)
LAD: Consulting fees (AbbVie, Janssen), speaker's bureau (AbbVie, Janssen)
GGK: Advisory board (Janssen, Abbott, Merck, Schering-Plough, Shire, UCB Pharma), research support (Merck, Abbott, GlaxoSmith Kline, Shire), speaker's bureau (Janssen, Merck, Schering-Plough, Abbott, UCB Pharma)
KLN: Advisory board (AbbVie, Janssen, Pfizer, Ferring), research support (AbbVie, Janssen), speaker's bureau (Abbvie, Janssen)
KIK: Consulting fees (AbbVie, Janssen, Takeda, Ferring), speaker's bureau (AbbVie, Janssen)
BPH: Consulting fees (AbbVie, Janssen), speaker's bureau (AbbVie, Janssen, Shire, Pendopharm)
RP: Advisory board (Abbott/AbbVie, Amgen, Janssen, Merck, Pfizer, Prometheus Laboratories, Salix Pharma, Shire, Takeda, Warner Chilcott), consulting fees (Abbott/AbbVie, Amgen, Aptalis, Astra

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Authorship Statement

Guarantor of article: Remo Panaccione

Author Contributions

HHS and CM contributed to study design, data collection, data analysis, manuscript drafting and editing. PGK, HA, AKA, JXQP, CHS, RNF, SMD, LAD, GGK, KLN, KIK, BPH contributed to manuscript editing. RNF and RP contributed to study design, data analysis, and manuscript editing. All authors have approved the final version of the manuscript, including the authorship list.

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