The impact of pre-operative biologic therapy on post-operative surgical outcomes in ulcerative colitis: a systematic review and meta-analysis

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Abstract

Background and aims: Biologic therapy has emerged as an effective modality amongst the medical treatment options available for ulcerative colitis (UC). However, its impact on post-operative care in patients with UC is still debatable. This review evaluates the risk of post-operative complications following biologic treatment in patients with UC.

Methods: A systematic search of the relevant databases was conducted with the aim of identifying studies that compared the post-operative complication rates of UC patients who were either exposed or not exposed to a biologic therapy prior to their surgery. Outcomes of interest included both infection-related complications and overall surgical morbidity. Pooled odds-ratio (OR) and 95% confidence intervals (CI) were calculated using Review Manager 5.3.

Results: In all, 20 studies, reviewing a total of 12,494 patients with UC, were included in the meta-analysis. Of these, 2254 patients were exposed to a biologic therapy prior to surgery. The pooled ORs for infection-related complications (n = 8067) and overall complications (n = 11,869) were 0.98 (95% CI 0.66–1.45) and 1.14 (95% CI 1.04–1.28), respectively, which suggested that there was no significant association between the use of pre-operative biologic therapy and post-operative complications. Interestingly, the interval between the last dose of biologic therapy and surgery did not influence the risk of having a post-operative infection.

Conclusions: This meta-analysis suggests that pre-operative biologic therapy does not increase the overall risk of having post-operative infection-related or other complications.

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Keywords: biologic therapy, postoperative complications, ulcerative colitis

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subsequently require surgery during the course of their disease.5,7,8

Whilst surgery can be curative, it does carry significant morbidity, including the risk of pouch leakage, pelvic abscess, wound infection and bleeding. Due to the immunosuppressive nature of biological therapy, there has always been a concern regarding the impact of pre-operative exposure to biologics on post-operative complication rates.

So far, studies have shown conflicting evidence with regards to different biologics and also between UC and Crohn’s populations. Interestingly, the meta-analyses looking at the entire IBD population (Crohn’s and UC together) have produced different results, in comparison with meta-analyses addressing the UC population alone. The systematic reviews available on UC population are underpowered due to the lack of larger studies.

In their study, Appau et al. observed that the use of Infliximab within 3 months of surgery increased the risk of post-operative sepsis, abscess and readmissions in the Crohn’s population.9 One of the initial meta-analyses by Yang et al. within the UC population found that there was no significant relationship between Infliximab treatment and infectious complications,10 but the overall complication rate was increased. The same research team published an updated review in 2012, which arrived at a similar conclusion regarding post-operative infections.11 Following this, a meta-analysis by Billioud and colleagues showed no difference between biologic and non-biologic therapy groups with regards to both infections and any complications within the UC population.12 Another systematic review in 2018, compared the post-operative complication rates in IBD patients following their pre-operative exposure to Vedolizumab, an anti-tumour necrosis factor (anti-TNF) and no biologic therapy.13 This review had also found that there was no significant difference in the overall post-operative outcomes between the Vedolizumab and no biologic therapy groups. Further to these, a very recent systematic review by Law et al. showed that infectious complications were increased in IBD patients who were exposed to anti-TNF therapy pre-operatively.14

In light of the above, we set out to conduct a systematic review and meta-analysis in order to provide a more up-to-date and comprehensive analysis on the pre-operative use of biologics and their post-operative complication rates in patients with UC.

Materials and methods
This systematic review and meta-analysis followed the guidance laid out in the Cochrane Handbook and is reported in accordance with the Preferred Reporting Items for Systematic Reviews and meta-analyses (PRISMA) guidelines. It was also registered with PROSPERO (id-CRD42019141827).

Search strategy
Literature search strategies were developed using medical subject headings (MeSH) and text words related to the title. The search was performed in Medline, EMBASE, Scopus, Cochrane and Pubmed, using a various combination of keywords and subject headings:

- Inflammatory bowel disease OR ulcerative colitis OR crohn*;
- AND *Umb OR biologic OR anti-TNF OR TNF antagonist OR TNF inhibitor OR Infliximab;
- AND Surgery OR surgical outcome OR postoperative complication;
- AND Infect* OR wound infection OR mortality OR morbidity OR death OR length of admission OR non-infectious.

Study selection and eligibility criteria
Studies were included based on the following inclusion criteria: (1) prospective and retrospective comparative cohort studies, case controlled studies, nested case-control studies, cross sectional studies and randomised controlled trials; (2) examined general adult human population of 18 years or older; (3) published in English and were available as full texts in the medical database between January 1997 and December 2019; (4) follow up period should be at least 30 days following surgery for both control and intervention group (maximum period can be up to 1 year). The exclusion criteria were as follows: (1) studies that did not have a control group; (2) studies that were published as reviews or abstracts.

All types of IBD were included at the search stage, to ensure the maximum capture of the articles,
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even though the focus was on UC. The first article on biologics was published in the year 1997 by Baert et al.15 Hence this year was chosen as the upper time limit for the literature search.

Any studies not meeting the inclusion criteria were excluded. The reference lists of the included papers were also checked manually for potential studies. The resulting articles were exported to the Rayyan software and were screened by two independent reviewers.

Definitions

Outcomes of interest included infectious complications, which were defined as any infection that occurs within 30 days of surgery, which may or may not be the direct result of surgery. Such complications included pelvic sepsis, anastomotic leak, fever, surgical site infection (SSI), incisional SSI, organ space SSI, pneumonia, gastrointestinal infection, urinary tract infection and sepsis. Non-infectious complications were also considered, which were defined as any complications that did not meet the criteria of infectious complication including ileus, obstruction, DVT, thromboembolism, readmission, reoperation, urinary retention, dehydration or electrolyte disturbances. A surgical procedure is considered as a one-stage procedure, if proctocolectomy and pouch formation (IPAA) are performed at the same time. In a two-stage procedure, the colectomy is performed, which is then followed by a completion proctectomy and pouch creation in the second stage. If a defunctioning loop ileostomy is created during the second stage, it is reversed in a third operation, and this is referred to as a three-stage procedure.

Quality assessment and risk of bias assessment

The Newcastle Ottawa Scale (NOS) was used for critical appraisal of the quality of the selected papers.16 This is a valid scale of choice due to its application for observational type studies. The study selection process, comparability of controls to cases in terms of baseline characteristics and outcome measures, including the length of follow up and their quality, were assessed. An article with a score of more than 7 is considered as of good quality. The heterogeneity of the studies was established using the $I^2$ test while the publication bias was assessed through a visual inspection of funnel plots. $I^2 > 50\%$ was considered as significant heterogeneity.

Data synthesis and analysis

Data extracted from the selected articles included: authors, the year of publication, study years, country where the study took place, whether there were any disparity between the baseline characteristics of exposed and unexposed groups (and the characteristics in which there were a disparity), type of biologic studied, the time between use of biologic and surgery, number of patients, the number who received biologics and the number who did not receive biologics, other medications used by patients, type of surgery performed, duration of follow up, infectious complication rates, non-infectious complication rates and the overall complication rates. All statistical analyses were carried out on Review Manager 5.3 software. Pooled odds ratio (OR) for infectious complications and overall complications were calculated using the random or fixed effects models in accordance with the heterogeneity of the studies. The OR for each study and the pooled OR were summarised in a forest plot.

Results

A total of 1340 studies were retrieved, of which 1318 were excluded on review of title and abstract. Of the remaining 22 articles, 2 were excluded after reviewing the full text as they did not meet the eligibility criteria (Abelson et al. and Lightner et al.).17,18 The other 20 full text articles were considered for quality assessment and data extraction. The search process is shown as a PRISMA diagram in Figure 1. The study characteristics are summarised in Table 1. The funnel plots are shown in the supplemental file, Figures S1–S5.

Analysis of infectious complications (n=8067)

Meta-analysis was performed on 14 studies that looked at post-operative infectious complications and pre-operative biologic use.19–22,25,26,28–31,34–36 Amongst them, 13 studies used anti-TNF therapy, two studies looked at Vedolizumab and one study analysed both anti-TNF and Vedolizumab. All of these studies looked at 30-day post-operative infectious complications, which included both surgical site and non-surgical site infections. In 10 studies, the last biologic dose was given within 12 weeks prior to surgery. The types of surgery varied across the studies, which included laparoscopy or open surgery, total or subtotal colectomy, combined total proctocolectomy and ileal pouch-anal anastomosis as
1-stage, 2-stage or 3-stage procedure. No publication bias was detected.

**Overall risk of infectious complications.** The occurrence of post-operative infections within 30 days of surgery in 1348 patients with UC was compared with 6717 controls. The pooled OR was 0.98 [95% confidence interval (CI) 0.66–1.45; test of heterogeneity $I^2 = 57\%$, $p = 0.004$] (Figure 2). This suggests that there was no significant association between the pre-operative biologic use and the overall risk of having a post-operative infection.

**Anti-TNF and infectious complications.** A total of 1259 patients, in 13 studies, had anti-TNF as a biologic therapy; 128 infectious complications in biologic group were compared with 471 events in the control group. The pooled OR for the infectious complication was 0.97 (95% CI 0.63–1.87) ($I^2 = 59\%$, $p = 0.004$) (Figure 3). This suggests that there was no increased risk of having an infection post-operatively in patients who have had pre-operative exposure to anti-TNF.

**Vedolizumab and infectious complications.** Only two studies looked at the post-operative infectious rates in a total of 258 patients, who were exposed to Vedolizumab pre-operatively; amongst them 9 patients had infections. The pooled OR was 0.80 (95% CI 0.15–4.31) ($I^2 = 57\%$, $p = 0.13$) (Figure 4). This may suggest that there was no increased risk of having an infection post-operatively. However, the number of studies and the total study population were small in this group; hence, it is difficult to arrive at a valid conclusion.

**Biologic to surgery duration and infections.** A further subgroup analysis was performed to
Table 1. The baseline characteristics, type of biologic therapy used and post-operative complications of the studies included in the meta-analysis.

| Paper | Country | Study years | Drug studied | Last dose (weeks) | Duration of follow up | No. of patients in cohorts | Exposed | Unexposed | Infectious complications | Overall complication |
|-------|---------|-------------|--------------|------------------|-----------------------|--------------------------|---------|-----------|------------------------|---------------------|
| Bregnbak et al. | Denmark | 2005–2010 | Infliximab | <12 | 30 days | 71 | 20 | 51 | Exposed: 4 | Unexposed: 21 |
| Eshuis et al. | Netherlands | 2006–2010 | Infliximab | 10–32 | 30 days | 72 | 38 | 34 | Exposed: 11 | Unexposed: 7 |
| Ferrante et al. | Belgium | 1998–2008 | Infliximab | <12 | 30 days | 141 | 22 | 119 | Exposed: 2 | Unexposed: 29 |
| Ferrante et al. | Belgium | 2006–2016 | Infliximab, Vedolizumab | <16 | 30 days | 165 | 94 | 71 | Exposed: 24 | Unexposed: 22 |
| Gu et al. | US | 2006–2010 | Anti-TNF | <12 | 30 days & 1 year | 588 | 167 | 421 | n/a | |
| Kulaylat et al. | US | 2005–2013 | Infliximab, Adalimumab, Certolizumab | <12 | 90 days | 1172 | 303 | 869 | n/a | |
| Mor et al. | US | 2000–2006 | Infliximab | 4–37 | 30 days + late complications | 92 | 46 | 46 | Exposed: 10 | Unexposed: 1 |
| Nelson et al. | US | 2006–2012 | Infliximab | <5 | 30 days | 74 | 24 | 50 | Exposed: 6 | Unexposed: 12 |
| Norgard et al. | Denmark | 2003–2010 | Infliximab, Adalimumab, other anti-TNF | <12 | 60 days | 1226 | 199 | 1027 | n/a | |
| Selvasekar et al. | US | 2002–2005 | Infliximab | <8 | 30 days | 301 | 47 | 254 | Exposed: 13 | Unexposed: 25 |
| Uchino et al. | Japan | 2012–2014 | Infliximab | <12 | 30 days | 181 | 44 | 137 | Exposed: 5 | Unexposed: 32 |
| Uchino et al. | Japan | 2015–2018 | Infliximab, Adalimumab, Golimumab | <12 | 30 days | 301 | 146 | 155 | Exposed: 16 | Unexposed: 25 |
| Ward et al. | UK | 2006–2015 | Infliximab, Adalimumab, Golimumab | <12 | 30 days | 6225 | 753 | 5472 | Exposed: 35 | Unexposed: 270 |
| Zittan et al. | Canada | 2002–2013 | Infliximab | <24 | Up to 1 year | 758 | 196 | 562 | n/a | |
| Jarnerot et al. | Sweden & Denmark | 2001–2004 | Infliximab | n/a | n/a | 21 | 7 | 14 | n/a | |
| Schluender et al. | US | 2000–2005 | Infliximab | n/a | 30 days | 151 | 17 | 134 | Exposed: 3 | Unexposed: 11 |
| Coquet-Reinier et al. | France | 1999–2008 | Infliximab | <12 | 30 days | 26 | 13 | 13 | Exposed: 1 | Unexposed: 2 |
| Gainsbury et al. | US | 2005–2009 | Infliximab | <12 | 30 days | 81 | 29 | 52 | Exposed: 5 | Unexposed: 14 |
| de Silva et al. | Canada | 1996–2009 | Infliximab | n/a | n/a | 662 | 34 | 628 | n/a | |
| Yamada et al. | US | 2014–2016 | Infliximab, Adalimumab, Vedolizumab | <8 | 30 days | 186 | 55 | 129 | Exposed: 10 | Unexposed: 18 |

n/a, not applicable; TNF, tumor necrosis factor.
look at whether a biologic therapy within 12 weeks prior to surgery increased the risk of post-operative infection. Of the 14 studies, 10 fulfilled the criteria, and a total of 1153 patients received biologics within 12 weeks prior to their surgery.19,21,26,28–31,35,36,38 The pooled OR for infectious complications was 0.83 (95% CI 0.53–1.30; \(I^2 = 58\%\), \(p = 0.01\)) (Figure 5). This suggests that the time lag between the surgery and the last dose of biologic therapy did not influence the risk of having a post-operative infection.

Figure 2. Forest plot for pre-operative biologic therapy and the overall post-operative infectious complications within 30 days. CI, confidence interval.

Figure 3. Forest plot for pre-operative anti-TNF therapy and post-operative infectious complications. CI, confidence interval.

Figure 4. Forest plot for pre-operative Vedolizumab therapy and post-operative infectious complications. CI, confidence interval.
A total of 17 studies assessed the overall post-operative complication rates (infectious and non-infectious) in patients with UC who had biologics prior to their surgery (Figure 6). The number of participants in each study ranged from 21 to 6225. The duration of follow up following surgery varied from 30 days to 1 year across the studies; 12 articles studied the overall complication rates within 30 days of surgery. No publication bias was detected among the studies.

The overall pooled OR for the occurrence of any post-operative complication was 1.14 (95% CI 1.01–1.28; \( I^2 = 34\% \); \( p = 0.09 \)). This suggests that there was no significant association between the pre-operative biologic therapy and the overall risk of having a post-operative complication.

**Discussion**

To date, numerous meta-analyses have been produced on biologics and their effects on post-operative outcomes in the IBD population; however, the resulting evidence is still conflicting. Previous meta-analyses examining the effects of pre-operative biologics on post-operative outcome in Crohn’s disease have reported increased post-operative complication rates compared with patients who have not had biologic therapy. A systematic review by Yang et al. in 2012 looked at pre-operative Infliximab therapy and post-operative complications within the UC population. This review,
which included 13 articles, showed that there was no significant association between the pre-operative use of Infliximab and post-operative infectious or overall complications. When Crohn’s and UC populations were considered together, the meta-analyses so far have reported increased risk of having post-operative complications. As such, a recently published systematic review by Law et al. investigated post-operative infectious complications in the IBD population following pre-operative immunosuppressive medical therapy. This review showed that the overall risk of having a post-operative infection was increased in the anti-TNF group in comparison with the group that had not had anti-TNF therapy (OR 1.26, 95% CI, 1.07–1.50). However, when the subgroup analysis was performed for UC and Crohn’s disease separately, the results were significant only for Crohn’s disease (for UC OR 1.05, 95% CI, 0.79–1.41 and for Crohn’s OR 1.48, 95% CI, 1.11–1.97). Although the exact mechanisms for this finding are so far unclear, it is likely due to the differing molecular pathophysiology and disease severity between UC and Crohn’s disease. Hence, the overall results from the IBD population cannot be applied to patients with UC and, hence, we sought to summarise the evidence for the UC population only in the present systematic review.

The examination of the funnel plots (supplemental file, Figures S1–S4) showed that there was moderate heterogeneity amongst the studies that looked at infectious complications. This was due largely to the two outlying studies, which were Mor et al. and Selvasekar et al. The high heterogeneity was likely due to the variations in the surgical procedure these studies described. The study population in both of these studies also comprised a larger number of participants who had proctocolectomy and IPAA as the primary surgery, although the terminology used in these studies to describe this procedure was two-stage.

The results from our meta-analysis suggest that there was no significant association between the pre-operative use of biologic therapy and the overall risk of having infections post-operatively, with low heterogeneity between studies. The findings remained true when anti-TNF was considered separately. However, 3 of those 14 studies, namely, Selvasekar et al., Mor et al. and Eshuis et al. (one-stage group), reported increased post-operative infection rates. This could be explained in that, firstly, all of these studies looked at the post-operative infections in study populations where the majority of patients underwent proctocolectomy and IPAA as their primary surgery. The impact of the type of surgery in post-operative outcome is discussed below in detail. Secondly, in these studies, the Infliximab group had higher proportion of patients with severe disease. For example, in the study by Eshuis and colleagues, all of the five patients who developed pelvic sepsis in the Infliximab/one-stage group had pancolitis. Patients who have advanced disease are generally more unwell and their nutritional status tends to be poor. In their study, Nakamura and colleagues clearly showed that the pre-operative nutritional status predicts the post-operative complications. It is also worth noting that, although the body mass index was matched between the study groups in those studies, the precise markers for nutritional status were not assessed. Thirdly, a higher proportion of patients in those study populations were on multiple concomitant medications, including steroids. In the study by Selvasekar et al., there was a significant difference between the Infliximab and non-Infliximab groups with regards to concomitant corticosteroids (p < 0.001). In their study, Bregnbak et al. reported that the post-operative infectious complications were increased in patients who had corticosteroids, regardless of their pre-operative exposure to Infliximab (45.8% in steroid group versus 13.0%, p = 0.028). This was further supported in a paediatric population by Markel and colleagues, who clearly showed that steroids and poor nutritional status were independent risk factors for post-surgical wound infection. A similar finding was also noted by Ferrante et al. in patients who had moderate to high dose of corticosteroids for more than 8 weeks. Hence, it is possible that these factors might have contributed to a different outcome of those aforementioned studies.

In the present systematic review, it is difficult to draw any firm conclusions regarding Vedolizumab as only a small number of studies could be included and therefore the results are underpowered. Our subgroup analysis, however, found similar results to those reported previously.

We found that there was no significant association between the interval from last dose of biologic therapy to surgery (<12 weeks) and post-operative infections in UC. This differs from the recent systematic review by Law et al., which showed that
the post-operative infections were increased in IBD patients who received anti-TNF within 8 weeks of surgery. In this latter meta-analysis, the study population largely comprised patients with Crohn’s disease, which, in turn, most likely have influenced the outcome.

Several factors could have influenced the outcome of this meta-analysis. For example, the duration of the disease prior to surgery. Trialling biologics as a rescue therapy after corticosteroid failure might have posed some delay in pursuing surgery. Randall et al. showed longer duration of medical therapy prior to surgery in patients with acute severe colitis was associated with increased rate of post-operative complications. Another larger, multicentre study demonstrated a strong association between the disease course of more than 5 years and anastomotic leakage in IBD patients who underwent proctocolectomy and IPAA in an elective setting. Therefore, it is of utmost important that these patients are cared for in a multidisciplinary setting, and that decisions are made in timely manner to avoid unnecessary delays to improve the overall disease outcome.

In addition to the above, surgical-related factors such as the type of surgery, timing and indication for surgery also might have influenced post-operative outcomes. Eshuis et al. looked at pre-operative Infliximab exposure and post-operative outcomes in one-stage and two-stage restorative proctocolectomies separately. This showed a higher incidence of pelvic sepsis (risk difference 24%; 95% CI: 6–42) and non-infectious complications (risk difference 30%; 95% CI: 4–56) in the one-stage group. In their prospective study on patients with severe IBD, Hyman and colleagues showed that subtotal colectomy and ileostomy was a safe and effective procedure of choice. The British Society of Gastroenterology (BSG) guidelines recommend subtotal colectomy with ileostomy and rectal stump as a surgery of choice in patients with severe colitis in an emergency setting. It also strongly suggests that the completion proctectomy and pouch formation should not be undertaken in an acute setting. A subgroup of analysis for one and two-stage procedures could not be performed in our meta-analysis, owing to the fact that the number of studies that looked at this were small, and it was not possible to calculate or retrieve the data for different types of surgery separately. Moreover, as stated above, there was a considerable overlap in the terms used to describe the surgical procedures.

Finally, the major limiting factor of this meta-analysis was the observational nature of the included studies. Ideally, larger, prospectively designed studies looking at various combinations of medications as well as different types of surgical interventions are required. These studies should also attempt to measure the drug levels at the time of surgery, which could help determine the degree of immunosuppression present amongst patients undergoing surgery.

In summary, the pre-operative use of biologics does not increase the risk of post-operative infections or surgical morbidity in patients undergoing surgery for UC. Furthermore, the duration between the last dose of biologic therapy and surgery does not appear to have an effect on the risk of having a post-operative infection; hence, it should not preclude patients from having emergency surgery.

Author contributions
JZ, SC & RPA: literature review, data collection, preparation of manuscript, manuscript editing. RA: design and concept, literature review, critical revision of the manuscript for important intellectual content. AP provided critical revision of the manuscript for important intellectual content.

Authorship statement
All authors have made substantial contributions to: (1) the concept of this literature review, or acquisition of data, or analysis and interpretation of data; (2) the drafting the paper or revising it critically for important intellectual content; and (3) provide final approval of the submitted paper.

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