

Biological treatment and the potential risk of adverse postoperative outcome in patients with inflammatory bowel disease: An open source expert panel review of the current literature and future perspectives

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Abbreviations

ACPGBI - The Association of Coloproctology of Great Britain and Ireland

ASCRS – American Society of Colon and Rectal Surgeons

ASA – American Society of Anesthesiology

BMI – Body Mass Index

CCF- Crohn's & Colitis Foundation (formerly known as the Crohn's & Colitis Foundation of America [CCFA]).

CCI - Comprehensive Complication Index

CD – Crohn's Disease

CDAI - Crohn's Disease Activity Index

ECCO – European Crohn's and Colitis Organization

ESCP – European Society of ColoProctology

ELISA - Enzyme-Linked Immuno-Sorbent Assay

GRADE - Grading of Recommendations, Assessment, Development and Evaluations

HBI – Harvey Bradshaw Index

IBD – Inflammatory Bowel Disease

IL – Interleukin

IPAA – Ileal Pouch Anal Anastomosis

IV – Intravenous

LOS - Length of Stay

PRISMA - Preferred Reporting Items for Systematic Reviews and Meta-Analyses

SC – Subcutaneous

SoMe4Surgery – Social Media for Surgery

TNF – Tumor Necrosis Factor

a-TNF- Anti-Tumor Necrosis Factor alpha inhibitors

UC – Ulcerative Colitis

Abstract

Background: There is widespread concern that treatment with biologics agents may be associated with sub-optimal postoperative outcome after surgery for inflammatory bowel diseases (IBD).

Aim: We aimed to search and analyse the literature regarding the potential association of biologic treatment on adverse postoperative outcome in patients with IBD. We used the subject as a case in point for surgical research. The aim was not to conduct a new systematic review.

Method: This is an updated narrative review written in a collaborative method by authors invited through Twitter via the following hashtags (#OpenSourceResearch and #SoMe4Surgery). The manuscript was presented as slides on Twitter to allow discussion of each section of the paper sequentially. A Google document was created which was shared across social media and comments and edits were verified by the primary author to ensure accuracy and consistency.

Results: Forty-one collaborators responded to the invitation, and a total of 106 studies were identified that investigated the potential association of pre-operative biological treatment on postoperative outcome in patients with IBD. Most of these studies were retrospective observational cohorts, 3 were prospective, 4 experimental and 3 population-based studies. These studies were previously analyzed in 10 systematic/narrative reviews and 14 meta-analyses. Type of biologic agents, dose, drug concentration, anti-drug antibodies, interval between last dose and types of surgery varied widely among the studies. Adjustment for confounders and bias control ranged from good to very poor. Only 10 studies reported postoperative outcome according to Clavien-Dindo classification.

Conclusion: Although a large number of studies investigated the potential effect of biological treatment on postoperative outcomes, many reported divergent results. There is a need for randomized controlled trials. Future studies should focus on the avoiding the weakness of prior

studies we identified. Seeking collaborators and sharing information via Twitter was integral to widening the contributors/authors and peer review for this paper, and was an effective method of collaboration.

Keywords:

Inflammatory bowel disease, Crohn's disease, ulcerative colitis, biologic treatment, biologics, anti-TNF alpha, postoperative outcome, surgery.

What does this paper add to existing literature and what it does not add?

This study represents the most extensive literature review done on the subject using a unique, social media-based, methodology. It identifies all the studies published until 30th September 2018, analyses these studies, described the 106 studies and attempt to answer these questions:

1. Why these 106 studies reported divergent results?
2. Why there is a large number of studies with sever limitations in methodology? Is this not a waste of resources?
3. Can social media and internet connection improve research quality and facilitate optimal design of future studies?

To the best of our knowledge, this represents the first research project conducted using social media to recruit co-authors and paragraph-by-paragraph revision of the manuscript via the #OpenSourceResearch hashtag.

The authors would like to emphasize that:

1. This is not a systematic review or meta-analysis because there are already many systematic reviews and meta-analysis about the subject with divergent conclusions.

2. This is a case in point for surgical research. With such study, the authors hope, less temptation to conduct small series studies will be encountered and better cooperation in conducting larger scale studies will be encouraged to advance surgical science.

Introduction:

Biologic therapies have revolutionized the management of inflammatory bowel diseases (IBD), *i.e.* Crohn's disease (CD) and ulcerative colitis (UC). Biologics, including anti-TNF-alpha agents (a-TNF), and more recently anti-integrin and anti-IL-12/23 agents, are reserved for patients with moderate-to-severe disease activity, or for patients who are medically-refractory to conventional therapy such as azathioprine, mercaptopurine, methotrexate or corticosteroids. However, TNF is an important component of the immune defense mechanism and plays a role in wound healing through a dose-dependent effect on angiogenesis¹ and collagen synthesis²⁻⁴. Inhibition of TNF mediated pathways may impair wound healing after surgery thus theoretically increasing the risk of postoperative complications such as surgical site infection and anastomosis-related complications, although the latter has to date never been demonstrated in any clinical study or trial.

Despite having been used since 1998, the natural history of CD appears to be unaffected using a-TNF⁵. Hence, the risk of surgery to treat refractory CD may not have changed in the era of biologics. The overall risk of surgery was 22% in a recent European study⁶ and risk for second surgery is 28.7% based on meta-analysis of population-based studies⁷. Furthermore, up to 50% of CD patients have been exposed to an a-TNF at time of their first surgery⁸. In UC, the risk of colectomy seems to have decreased in the era of biologics⁹. It is not clear whether this change is related to the introduction of biologics or better preoperative optimization.

To date, there are 106 scientific papers assessing the effect of a-TNF therapy on postoperative outcome, with divergent conclusions. As such there is a need to assess the current evidence, and to assess each studies strength and weakness, so as to help plan future studies with

optimal design and methodology. Thus, the aim of this study was to assess the potential association between preoperative exposure to biologics with postoperative outcomes in IBD patients, and to make recommendations for the optimal design of future studies.

Method

This study is a narrative review based on a published systematic review by one of the authors (AE)¹⁰. In this update, all eligible studies were included. No statistical analyses or bias control analyses were conducted because of the wide heterogeneity of the included studies. Biologic treatment was defined as treatment with α -TNF agents (*e.g.* infliximab or adalimumab), integrin inhibitors (*e.g.* vedozulimab) or IL-12/23 inhibitors (*e.g.* ustekinumab).

Aim

The aim of this review is to PROVIDE a case in point about surgical research by examining one subject in MINTIOUS details to identify the limitations of REPORTED studies and attempt to lead the design of future studies.

Eligibility Criteria

Case-control and cohort studies were included irrespective of publication status, year of publication, or language. Included studies assessed patients with CD or UC undergoing laparoscopic or open abdominopelvic surgery. Based on pharmacokinetic studies, the intervention group included patients who received any type or dose of biologics within 3 months of surgery.

Outcome Measures

Outcome measures were assessed after 30 days of follow-up. The outcomes were assessed as defined by the authors of the included studies.

Search strategy and method of updating the review

The search strategy is attached as a supplementary on-line file. The search was prospectively updated by the authors using:

1. Alerts from PubMed.gov

2. Alerts from researchgate.com (any citation of articles by authors).
3. Alerts from relevant journals
4. Attending relevant conferences (ESCP, ECCO, ACPGBI, ASCRS).
5. Following topical developments in the subject as the authors are reviewers in many international journals and are, or have been, members of guidelines committees for UC and CD with the following organization: European Crohn's and Colitis Organization, Crohn's and Colitis Foundation, and the American Society of Colon & Rectal Surgeons.
6. Contacting experts in the field using the Twitter #SoMe4Surgery hashtag. Many authors are expert in this subject (AH, SH, PK, PM, JD, AE, AS, NY, SW, please see the supplementary files with list of all authors). All the contributors were asked to update the list of the included articles using their Twitter network to ensure that all relevant studies are included. Two additional papers were identified via this mechanism.

Open source research project

The paper was written in a collaborative method with authors invited personally and through Twitter via the following hashtags (#OpenSourceResearch and #SoMe4Surgery). A Google document was created which was shared across social media and comments and edits were verified by the primary author to ensure accuracy and consistency. The manuscript was presented on Twitter in sequential posts by section. Each post contained 1-2 paragraphs of the manuscript modified to fit the limited space in Twitter and include powerpoint slides and images. This collaboration allowed this research and paper to be unique in the way it was written and edited.

Twitter offered a platform to engage researchers, to broaden the search and to conduct scientific discussions.

The final draft was sent by email to all contributors for feedback prior to submission and the primary author (AE) completed the final draft which was then edited for grammar by a native English-speaking author (SH).

Twitter analysis of the #OpenSourceResearch

Twitter is an American-based yet international online news and social networking service to which users post and interact with messages known as "tweets". Tweets were originally restricted to 140 characters, but this limit was doubled for all languages except Chinese, Japanese, and Korean. Registered users may post, like, and "retweet" tweets, but unregistered users can only read them. Users access Twitter through its website interface, through Short Message Service (SMS) or its mobile-device application software ("app").

As this paper was written as a social-media based collaboration, it was important to capture social media activity as potential source material for the paper, and to assess the response to the idea of an open source research paper, as well as to document the main influencers of these discussions. Data were collected through two tools – "Followthehashtag" for geographical mapping and gender split of tweeters, and "NodeXL" to document the networking interactions between tweeters and describe the interactions between these tweeters (replies, retweets and mentions of other tweeters). Both tools can be used to quantify the number of tweeters, retweeters, and tweets. Both tools also provide information about individual tweets. Additional information is available at <http://analytics.followthehashtag.com/#!/?!id=dashboard> and at <https://www.smrfoundation.org/nodexl/>.

Results

We identified a total of 106 studies that investigated the impact of pre-operative biological treatment on postoperative outcome in patients with IBD. The relation of a-TNF therapy with postoperative outcomes in patients with IBD has been investigated in 32 retrospective CD cohorts¹¹⁻⁴² (CD with/without UC), in 16 retrospective cohorts (UC)⁴³⁻⁵⁸ three prospective ones⁵⁹⁻⁶¹,

four experimental^{62–65}, three population based studies^{66–68}, ten narrative reviews^{69–78} and 14 meta-analyses^{10,79–89} making a total of 82 studies over the past 15 years (Table 1-4). In addition, 27 studies investigated this relation as part of other risk factors of unfavorable postoperative outcome, as well as studies with a focus on rheumatoid arthritis (Table 5). The 54 clinical studies which included 32 retrospective cohorts of CD, 16 retrospective cohorts of UC, 3 prospective cohorts of CD and 3 nation-based studies are demonstrated in details in Tables 1-3. In total these clinical studies have included 22,923 patients of whom 5,501 (24%) were on pre-operative biological treatment.

How confounding factors were addressed in the different studies?

The included studies varied in the method in which they addressed potential confounding factors as type of medication, time interval between medication and surgery, drug concentration, presence of anti-drug antibodies. Here is an account of these confounding factors and how they were addressed in different studies.

Type of medication

Some studies defined the type of biological treatments (e.g. Infliximab); others reported a broad category of treatment (e.g. a-TNF, including certolizumab pegol and golimumab) while a few studies included all biological treatments without any definition (Tables 1-3). This may influence the results as these agents differ in their efficacy, half-life, mechanism of action, pharmacodynamics and pharmacokinetics including bioavailability and elimination/excretion (in stool for example). Infliximab, for instance, is administered intravenously (IV), while adalimumab, certolizumab pegol, and golimumab are administered subcutaneously (SC). Intravenous administration is associated with large volume, rapid central distribution with low variability in bioavailability. Absorption from SC administration is slow, and it may induce more immunogenicity⁹⁰. The IBDResponse⁶¹ trial has drawn attention to this problem and challenged the results obtained from previous studies where a mix of biological treatment agents were registered.

Time interval between medication and surgical intervention

Most of the studies chose a 8-12 week interval from the last dose of a-TNF to the date of surgical surgery (Tables 1-3). This is mainly based on pharmacokinetics of infliximab (the most commonly used drug), assuming 1st order elimination kinetics (Figure 1) which may or may not be applicable; of note trace levels of infliximab can be found up to 12 weeks after administration⁹⁰. However, during this time, drug concentration and its efficacy can vary from a peak at the time of administration to a trace level at the end of time interval (see the next section).

Drug concentration in the peripheral blood (serum levels of biological agents)

Drug concentration in the peripheral blood correlates with drug concentration in the inflamed tissue⁹¹ and it varies during the 12-week period prior to surgery with a peak at the time of administration and a fading to trace levels in the following weeks (Figure 1). Drug concentration is essential for drug action and for the stimulation of anti-drug antibody formation⁹⁰. Reporting biologic treatment at 12 weeks interval can therefore be misleading and interpretation of the results may differ. Only 4 studies investigated drug concentration in the peripheral blood^{29,30,60,61}. These 4 studies reported the drug concentration at different time intervals using trough levels in the serum. These trough levels are measured by using enzyme-linked immunosorbent assay (ELISA) and these levels may be decreased by leakage of the antibodies through inflamed bowel mucosa into the stool⁹² and/or deactivation by development of antibodies against the injected anti-TNF (anti-drug antibodies)⁹³. Fumery *et al*⁶⁰ reported drug concentration of 76 of the 93 patients who received a-TNF treatment within a period of 12 weeks before surgery. The measurement of trough level was done on the day of surgery⁶⁰. Lau *et al.* reported serum drug concentrations from samples drawn at varying pre-operative time points in 143 patients with IBD treated with a-TNF³⁰.

Waterman *et al.* reported drug concentration in a subset of 19 patients with UC exposed to a-TNF treatment within 8 weeks prior to surgery. The authors also reported anti-drug antibodies²⁹.

Waterman *et al.* analysis included patients exposed to a-TNF treatment within 180 days of surgery.

El-Hussuna⁶¹ *et al* reported in IBDResponse study drug concentration and anti-drug antibodies for 18 patients with IBD. Samples were collected within 24 hours before surgery as well as 6, 24 and 48 hours after surgery providing a unique chance to examine the drug and anti-drug antibodies in this group of patients.

Anti-drug antibodies

The IBDResponse trial⁶¹ showed that some patients develop anti-drug antibodies to a-TNF agents regardless of the route of administration (IV or SC). These anti-drug antibodies may reduce the efficacy of drugs. Misinterpretation of results in the studies where these antibodies were not measured cannot be dismissed. Only two studies^{29,61} measured and reported these anti-drug antibodies. Concurrent administration of immunomodulators has been shown to reduce the formation of anti-drug antibodies⁹⁰.

How the included studies adjusted for potential confounding factors in multi-variate analysis
Many researchers suspected confounding factors play a role and affect postoperative outcomes.

These factors have a varying degree of influence on the postoperative outcome and with increasing influence by the number of concurrent risk factors. Some of these factors are well-studied such as concurrent medications, while others are less studied such as pre-operative optimization, the latter which has been recently shown to have a strong influence on the postoperative outcome^{94,95}. Three categories of confounding factors can be identified and have been studied:

Factors with questionable impact as shown by the studies that adjusted for these factors:

a) Type of surgical intervention and access to abdominal cavity (studies of ileo-caecal resection^{15,19,34,60,96}, studies of different types of bowel resections with or without stricturoplasty^{11-14,16-18,22-25,27-33,36-40,42,59,66,97} and studies of ileostomy reversal²⁶. In patients with UC most of the studies reported postoperative outcome after subtotal colectomy^{36,43-46,48,55,67,68}, completion proctectomy⁵⁷, ileal pouch-anal anastomosis (IPAA)^{43-45,48,50,51,53,54,58,98} and other procedures in addition to the above-mentioned⁴⁹.

- b) One third of studies adjusted for BMI^{15,16,19,24,28,29,32,33,36,38–40,43,45,49,53,54,58–60,96}.
- c) Many studies adjusted for ASA score^{14,15,33,34,36,38,45,54,59,96}. However, many studies reported comorbidity,^{19,26–28,32,33,36,40,45,48,53,54,67} but few used Charlson comorbidity score^{16,25,66,68}.
- d) Previous intestinal resections reported/adjusted for in 14 studies^{12,14–16,19,23,27,28,36,39,40,60,96,99}.
- e) Disease phenotype reported was reported in many studies^{13–19,22,29,30,34,36,38,39,59,60,97,99}.
- f) The affected bowel segment/length or disease location was reported in 20 studies^{12–15,19,27,29,36,39,44–46,50,58–60,96,97,99}.
- g) Duration of operation was reported in some studies^{15,23,28,36,40,53,59,96,42}.
- h) Preoperative intra-abdominal sepsis (intra-abdominal abscess and/or enteric fistula) was reported in nine studies^{13,15,16,30,34,59,60,96,42}.
- i) Disease duration was reported in 15 studies^{12,16,18,22,27,28,35,36,38,39,46,58,66,67,99}.
- j) Urgency of surgical intervention was reported in one third of studies^{12,14–18,25,27,29,31,33,35–38,40,45,48,50,54,59,60,68,96,97,42}. Some studies excluded urgent/emergency operations to attain a homogenous group of elective surgical procedures^{28,38,61}.
- k) Surgeon's experience (trainee, general surgeon, or colorectal surgeon) was reported in only three studies^{30,31,96}.
- l) The type/configuration of anastomosis or stoma construction was reported in several studies^{14,15,19,33,45,50,54,59,96}. One study included stricturoplasty in addition to primary anastomosis¹⁴. Patients who received a diverting stoma were excluded in some studies^{38,42} while other studies investigated these patients in sub-group analyses⁵⁹.

m) Other factors like intra-operative blood loss^{37,42}, indication for surgery^{12,23,25,27,29,30,34,40,50}, multi-centre versus single centre^{27-30,32,33,35,39,42,5442}, leucocytosis¹⁰⁰ were reported but they appear to have minimum or no effect on the postoperative outcome. Close cooperation between surgeon and gastroenterologist in pre-surgical decision making may have an impact on postoperative outcome^{25,101} but this factor is difficult to measure and not reported.

Factors expected to have large impact but were less-well studied

- a) Pre-operative optimization: few studies reported interventions to optimize the patients prior to surgery e.g. nutritional support^{15,59,60,96}, correction of anemia, or prehabilitation.
- b) Use of a mechanical bowel preparation, which has been associated with anastomotic leaks rates, was reported in only one study.¹⁵

Factors which would be expected to have a large impact on postoperative outcome

- a) Concurrent medication was reported by almost all studies^{11-15,17-19,22-25,27-40,43-46,48-51,53-55,58-60,66,67,96-98} except one population-based study on UC.⁶⁸
- b) Although nutritional status is widely known to influence postoperative outcomes,^{95,102} it was only reported in some studies while others did not report it^{60,66,59,24,96,19}. Nutritional status was measured indirectly by assessment of serum albumin and/or haemoglobin^{11,16,18,24,25,27,29,30,32,33,35-37,39,40,45,49,50,55,59,60,96-98} in those studies that adjusted for nutritional status. The IBDResponse trial⁶¹ used a validated standard score (nutritional risk screening which included weight loss more 10% of body weight) to assess nutritional status.
- c) Smoking is well-documented risk factor of surgical site infection⁹⁵ however, with small sample size series (as in case of most studies) is it difficult to demonstrate statistical significance due to lack of power. Data on smoking was reported by some studies^{11,13-16,18,19,24,28,30,32-36,46,49,50,55,58-60,68,96,97}.

d) Crohn's disease activity index (CDAI) was reported in two studies only^{60,99} while Harvey-Bradshaw index (HBI) was reported in one study⁶¹. One study reported ACG severity of disease index³⁸ while another one applied a local classification of disease activity²⁸. In UC studies, one study used deprivation index⁶⁸, while others used a local disease activity index^{36,48} or the Mayo score⁵⁵. Regarding disease severity, there is a high likelihood that the most severely ill patients received anti-TNF, while the less ill patients did not. One study tried to compare similar groups where all patients received anti-TNF at any time during the disease course¹⁴, either at time of surgery or prior to (but withheld) vs. after surgery.

How the included studies reported outcomes

Different methods were used to report the postoperative outcome making the comparison of studies difficult. Some studies reported major and minor complications^{16,19,22,23,37,39}. Others reported short-term (early) and long-term (late) postoperative morbidity^{12,23,28}. A third category of studies reported septic/infectious^{11,12,14,17,19,27,31,32,35,40,43,46,54,58,59,99} and non-septic/non-infectious complications. A few studies used the classification of surgical versus medical complications^{18,30,44,97} while other studies presented postoperative complications without classification or grading.^{14,16,24,25,27,29,33,34,49,51,60,66,67,98} However, there was increasing tendency to report outcomes according to Clavien-Dindo classification of postoperative complications^{14,19,28,30,53,59,60,96,97}. One study reported outcome when biological treatment was used after surgical intervention in CD⁹⁹. To the best of our knowledge, one study has used the Comprehensive Complications Index, a relatively new composite outcome of any complication weighted by Clavien-Dindo level⁵⁰. Interestingly, no difference in the length of stay (LOS) postoperatively was shown between patients treated with biological agents and those who did not receive treatment in the studies where LOS was reported. This was unexpected in studies that reported increased complication rates in patients treated with biological agents, as LOS will be longer in patients with postoperative complications.

How the different studies conducted statistical analyses

Most of the statistical analyses were done in similar fashion *i.e.* univariate analyses with χ^2 ,

Student's t-test, or Fisher's exact tests for categorical and Mann-Whitney, Wilcoxon signed-rank tests for continuous variables. However, regarding multivariable analyses, many studies did not report what variables were entered in multivariate analyses, nor how these variables were chosen for the multivariate analyses^{23,38}. Errors in interpretation of statistical results were not uncommon for instance lack of adjustment for confounding factors^{26,37}.

Discussion

Despite the large number of studies available in the literature, the relationship between biologic treatment and postoperative outcome in IBD is still controversial. During the last 15 years there have been improvements in study design, statistical analyses and sample size; moving from high-risk of bias studies³⁷ to more recently low-risk of bias studies⁵⁹; nevertheless the topical debate and controversy continues. There are three layers of complexity that made it difficult to reach definitive conclusions about the issue at hand:

1. **Difficulty of conducting clinical research** compared to basic science research. Clinical research is becoming more difficult due to the increased complexity of regulations and governance which can be far from patients' interests¹⁰³. Up to half of the approved studies by ethics committees are never published¹⁰⁴. It is well documented that clinical research attracts much less funding than basic science or translational research adding another challenge for outcomes research¹⁰⁵.
2. **Difficulty in conducting research in surgery compared to medical specialties.** Variation in surgical practice affects postoperative outcome and leads to a strong confounding factor in surgical research. Few studies include surgeon experience or years from training.

3. Difficulty in conducting IBD research. There is no doubt IBD is complex and heterogeneous; the treatment is complex as are the pre-operative and postoperative assessments. To this end, a number of groups have been working towards developed standardized outcome sets to facilitate comparison of data and effective meta-analysis¹⁰⁶¹⁰⁷¹⁰⁸¹⁰⁹. Moreover, investigator-initiated trials often fail due to insufficient enrollment of patients with IBD¹⁰⁰, and *a priori* power analyses are rarely reported. Only one third to half of patients with IBD need surgery during their lifetime (75% in CD⁸) making it even harder to recruit patients. Funding is a general problem in research, but it is more prominent in investigator-initiated trials, especially in IBD. Having said this, it might be assumed that research in IBD surgery is very well planned to reduce poor quality and ensure best use of resources. However, as of today this is not the case which as this review demonstrates. Large amount of resources were used in repeating studies with minor variations in design.

Crohn's Disease

According to recently published guidelines¹¹⁰⁻¹¹², surgery in patients with receiving a-TNF therapy may be associated with an increased risk of complications. Chronologically, the American Society of Colon and Rectal Surgeons (ASCRS) 2015 clinical practice guideline on CD stated that patient receiving pre-operative biologic treatment (*i.e.* a-TNF or cyclosporine) should be considered for staged procedures because of postoperative complications risk¹¹⁰. The authors suggested final decision should be up to surgeon discretion using an individualized approach to each patient. A delay of at least 8 weeks was proposed for elective whenever possible. The recommendations were graded as weak, quality of evidence 2C.

The European Crohn's and Colitis Organization (ECCO) published its third evidence-based CD consensus in 2016¹¹¹, where the impact of biologic treatment for patients undergoing surgery was deemed unclear and controversial. The authors based their statement on controversial data and

advocated optimal pre-operative preparation. A joint statement of the ESCP and ECCO considered a-TNF to be associated with risk of postoperative complications, particularly sepsis (surgical site infections, abdominal abscesses, anastomotic leaks) and higher readmissions¹¹². Nevertheless, no recommendation was made regarding the interval of biological treatment withdrawal. All guidelines agree on the higher risk associated with long-term steroid therapy. Prednisolone 20 mg daily or higher for > 6 weeks was associated with higher postoperative surgical complications, especially when used in combination with biologic treatment¹¹⁰⁻¹¹². The American Gastroenterological Association (AGA) did not published specific recommendation on the clinical management of biological treatment prior to surgery.

Ulcerative colitis

Published guidelines on the surgical management of UC includes the ECCO consensus¹¹³. For acute situations, performing staged procedures (i.e. sub-total colectomy with end ileostomy as first stage) was advised for patients receiving biologic treatment (a-TNF) and/or Prednisolone 20 mg daily or higher for > 6 weeks. Regarding pre-operative management of biologic treatments, the increased risks of postoperative complications, although controversial, were outlined, and single stage procto-colectomy with ileo-anal pouch reconstruction, for patients under a-TNF therapy, was not recommended¹¹³. Guidelines from the ASCRS published in 2014¹¹⁴ lacked definitive consensus statement on the management of a-TNF prior to elective surgery for UC. According to the authors, literature was insufficient to assess the impact of biological treatment on postoperative outcomes and there was a claim for multi-institutional larger studies.

There is no statistical model to predict the effect of various confounding factors on the postoperative outcomes in patients with IBD. It is nevertheless believed that the weight of these confounding factors in the final model is certainly different, and no standard recommendations for which variables

to include in a multivariate model exists, thus there is wide heterogeneity in model building, thus leading to varying and potentially non-comparable results and conclusions. Going forward, propensity-score matching or inclusion of the propensity score in the multivariate model, and other novel methods such as the difference-in-difference and use of instrumental variables all may play a role in reducing both the measured, and unmeasured, bias and confounding in these studies.

Future perspectives

ESCP conducted a snapshot audit in 2015 in which patients with CD undergoing ileo-caecal resection and right side colectomy were included, but this snapshot study did not provide a definitive answer regarding the effect of biologic treatment on postoperative outcomes [101]. Clearly, there is a need for randomized controlled trials investigating the effect of biological treatment on postoperative outcome in patients with IBD. The Pre-operative Continuation versus Discontinuation of anti-TNF treatment in Patients with Crohn's Disease (PCDantiPCD) trial protocol was presented in the 16th Nordic postgraduate course in colorectal surgery and at the ESCP 2018 trial session, and integrates many of the points discussed above.

Measurement of drug concentration, anti-drug antibodies and application of a standardized validated scoring systems for disease activity, nutritional status and smoking will lead to better understanding of the effect/weight of different covariates in a model that describes how anti-TNF treatment influence the postoperative outcome. Meta-analysis of these RCT will provide a solid evidence to eliminate the uncertainty of previous observational studies.

Limitations

This narrative updated review has the limitations of the studies included. It was not planned as a new systematic review nor meta-analysis, therefore no statistical analysis was done.

Conclusion

Many studies have investigated the effect of biologic treatment on postoperative outcome using different methodological approaches (retrospective, prospective, population-based, experimental, snapshot audit and meta-analyses) with divergent results. Future studies should focus on the avoiding the above highlighted weakness of the studies we reviewed. Consensus guidelines by the invested societies, such as ECCO, CCF and ESCP are needed to guide future research. There is also a need for a randomized controlled trial to define the association, or lack thereof, between biological and adverse postoperative outcomes.

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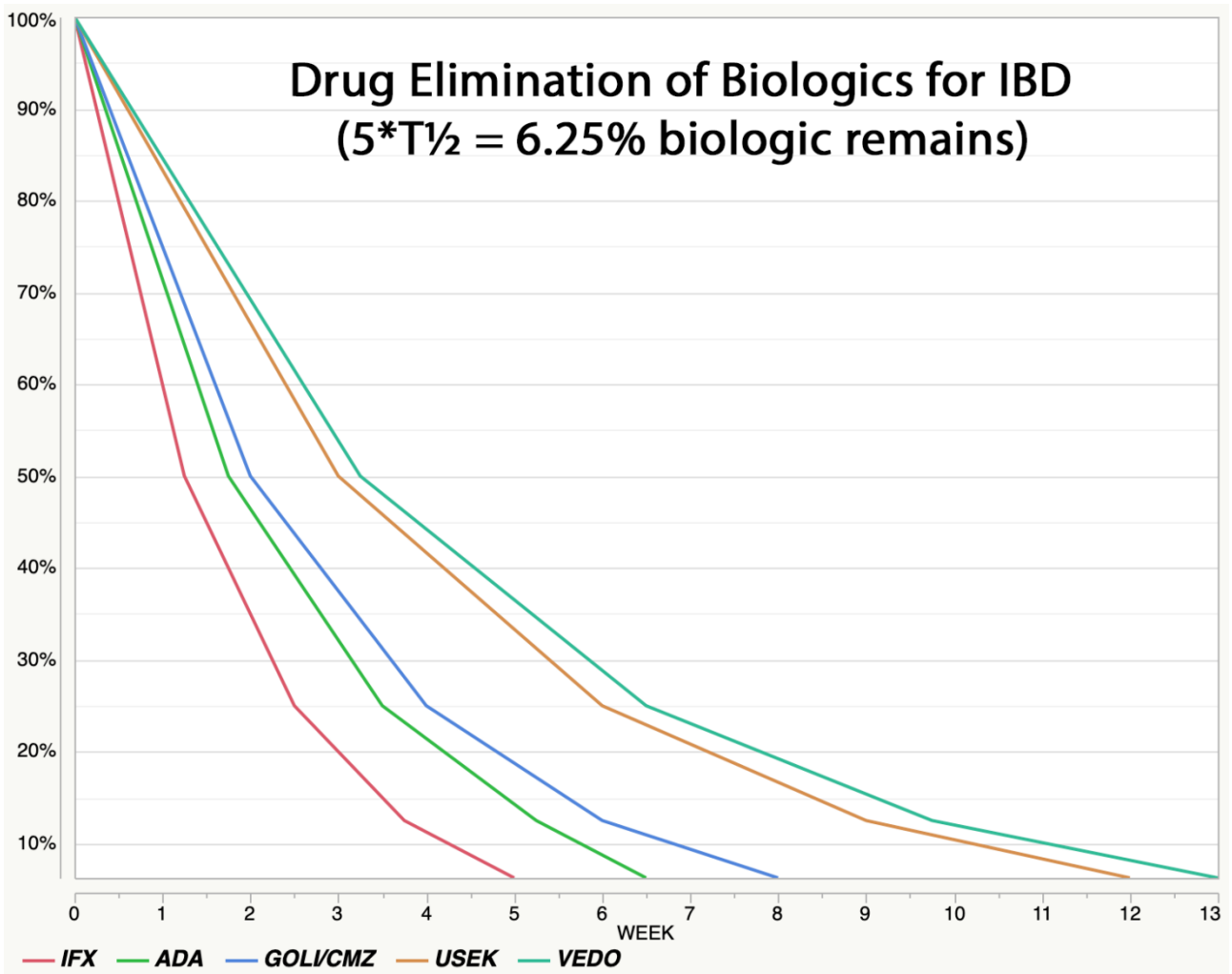
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Figure 1 Graphical representation of the theoretical in vivo half-lives of biologic agents used to treat CUC. Note this graph assumes first order elimination pharmacokinetics. With permission from Stefan Holubar



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Table 1

Clinical studies about type of pre-operative biological treatment in patients with Crohn's disease. The time interval between last administered dose of biological treatment and surgery varied among the studies.

Author/publication's year	Cohort/treated	Type of biological treatment	Weeks before surgery
7895/2026			
Observational retrospective studies			
1	Tay ¹¹ et al 2003	IFX	8
2	Colombel ¹² et al 2004	IFX	8*
3	Marchal ²³ et al 2004	IFX	12** (8,4 and less than 4 weeks)
4	Appau ³⁴ et al 2008	IFX	12
5	Indar ³⁷ et al 2009	Anti-TNF	8
6	Nasir ³⁸ et al 2010	IFX, ADA, CZM	8*
7	Kasperek ³⁹ et al 2011	IFX	12
8	Canedo ⁴⁰ et al 2011	IFX	8
9	Regueiro ⁴¹ et al 2011	IFX	2-4 weeks after surgery***
10	El-Hussuna ⁴² et al 2012	IFX, ADA,CZM	12
11	White ¹³ et al 2012	IFX, ADA,CZM	12
12	Myrelid ¹⁴ et al 2013	IFX, ADA	8
13	Serradori ¹⁵ et al 2013	Anti-TNF	12 (and 8 weeks)
14	Syed ¹⁶ et al 2013	Anti-TNF	8
15	Uchino ³⁶ et al 2013	IFX	12
16	Bafford ¹⁷ et al 2013	Anti-TNF	12
17	Kotze ¹⁸ et al 2016	IFX, ADA	8

18	Shim ²¹ et al 2016	60/60	Anti-TNF , UST	Up to 72
19	Zimmerman ²² et al 2016	123/24 _n	IFX	12 (8 and 4 weeks)
20	Kotze ⁹⁷ et al 2017	123/71	ADA	2
21	Jouvin ¹⁹ et al 2018	360/58	IFX, ADA,CZM	8
22	Lightner ³² et al 2018	213/213 (169 anti-TNF- α)	Anti-TNF- α and UST	12
Prospective studies				
23	Brouquet ⁵⁹ et al 2016	592/340	IFX, ADA,VDZ,other Anti-TNF	12
24	Fumery ⁶⁰ et al 2016	209/93	IFX, ADA	12 (and 4 weeks)
Nation-wide database study				
25	Nørgård ⁶⁶ et al 2013	2293/214	IFX, ADA,CZM	12 (2 & 4 weeks)

*and 4 weeks after surgery

**Nine patients received anti-TNF- α more than 12 weeks prior to surgery

***Data was collected from a randomised clinical trial to investigate postoperative recurrence of CD

n Paediatric patients

IFX: Infliximab, ADA:Adalimumab, CZM: Certolizumab, UST: Ustekinumab,VDZ: Vedolizumab, Anti-TNF: Anti-tumour necrosis factor agents

Table 2

Clinical studies about type of pre-operative biological treatment in patients with Crohn's disease, Ulcerative Colitis and indeterminate colitis (mixed population studies)

Author/publication's year	Cohort/treated 3003/1234	Type of biological treatment	Weeks before surgery	
Observational retrospective studies				
1	Kunitake ²⁵ et al 2008	413/101	IFX	12
2	Regadas ²⁶ et al 2010	249/28	IFX	8
3	Rizzo ²⁷ et al 2011	114/54	Anti-TNF	12 (and 4 weeks)
4	Krane ²⁸ et al 2013	518/142	IFX	12
5	Waterman ²⁹ et al 2013	282/73	IFX, ADA	25
6	Lau ³⁰ et al 2015	217/143	IFX, ADA, CZM	Not specified*
7	Alsaleh ³¹ et al 2016	47/47	IFX	12
8	Lightner ³² et al 2016	392/220	VDZ	12
9	Shwaartz ³³ et al 2016	282/73	IFX, ADA, CZM	8
10	Yamada ³⁵ et al 2017	443/193	IFX, ADA, VDZ	4
Prospective studies				
11	El-Hussuna ⁶¹ et al 2018	46/18	IFX, ADA, CZM	12

IFX: Infliximab, ADA: Adalimumab, CZM: Cemzia, VDZ: Vedolizumab Anti-TNF: Anti-tumour necrosis factor agents

*About 65% of patients in this cohort received Anti-TNF- α therapy before surgery.

Table 3

Clinical studies about type of pre-operative biological treatment in patients with Ulcerative Colitis

Author/publication's year	Cohort/treated 11965/2181	Type of biological treatment	Weeks before surgery	
Observational retrospective studies				
1	Selvasekar ⁴³ et al 2007	301/47	IFX	8*
2	Schluender ⁴⁴ et al 2007	151/17	IFX	Up to 54
3	Mor ⁵¹ et al 2008	523/85	IFX	Up to 37
4	Ferrante ⁵² et al 2009	141/22	IFX	Up 12
5	Coquet-Reinier ⁵³ et al 2010	26/13	IFX	Up to 23
6	Gainsbury ⁵⁴ et al 2011	81/29	IFX	12
7	Bregnbak ⁵⁵ et al 2012	71/20	IFX	12
8	Kennedy ⁹⁸ et al 2012π	38/11	IFX	8
9	Uchino ⁵⁷ et al 2013	196/22	IFX	12
10	Eshuis ⁵⁸ et al 2013	72/38	IFX	Up to 32
11	Gu ⁴⁵ et al 2013	181/25	IFX, ADA, CZM	12
12	Nelson ⁴⁶ et al 2014	78/28	IFX	1
13	Zittan ⁴⁷ et al 2016	562/196	Anti-TNF	Up to 24
14	Kulaylat ⁴⁸ et al 2017	2476/650	IFX, ADA, CZM	12
15	Lightner ⁴⁹ et al 2017	150/150	VDZ	12
16	Ferrante ⁵⁰ et al 2017	170/94	VDZ, Anti-TNF	8-16
Nation-wide database study				
17	Nørgård ⁶⁷ et al 2013	1226/199	Anti-TNF	12

18	Ward ⁶⁸ et al 2017	6225/753	Anti-TNF	12 (and 4 weeks)
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IFX: Infliximab, ADA: Adalimumab, CZM: Cemzia, VDZ: Vedolizumab Anti-TNF: Anti-tumour necrosis factor agents

* Only 49% of patients in the study cohort
n Paediatric age cohort

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Table 4

Meta-analyses and systematic reviews that investigated the effect of biological treatment on postoperative outcome in patients with inflammatory bowel disease. It shows 12 reviews about CD, 9 about mixed population and only 3 about UC.

Author/publication's year	Disease	Primary outcome	
Systematic/narrative reviews			
1	Subramanian ⁶⁹ et al 2006	CD & UC	Postoperative complications
2	Ali ⁷⁰ et al 2012	CD & UC	Postoperative complications
3	El-Hussuna ⁷¹ et al 2014	CD	Postoperative complications
4	Papaconstantinou ⁷² et al 2014	CD	Postoperative complications
5	Saab ⁷⁸ et al 2015	CD	Postoperative complications
6	Holubar ¹²¹ et al 2015	CD & UC	Overall/infectious complications
7	Alexakis ⁷⁴ et al 2015	UC	Colectomy and hospitalization rates
8	Chang ⁷⁵ et al 2015	CD	Surgical complications
9	Kotze ⁷⁶ et al 2017	CD	Postoperative complications
10	Engel ⁷⁷ et al 2017	CD & UC	Postoperative complications
Meta-analyses			
1	Yang ¹²² et al 2009	UC	Postoperative complications
2	Ehteshami-Afshar ⁸² et al 2011	CD & UC	Colectomy and hospitalization rates
3	Kopylov ⁸¹ et al 2012	CD	Colectomy and hospitalization rates
4	El-Hussuna ¹²³ et al 2013	CD	Anastomotic complications
5	Billioud ⁸⁴ et al 2013	CD & UC	Postoperative complications
6	Narula ⁸⁵ et al 2013	CD & UC	Postoperative complications
7	Rosenfeld ⁸⁶ et al 2013	CD	Postoperative complications

8	Yang ¹¹⁷ et al 2014	CD	Postoperative complications
9	Ahmed Ali ⁸⁷ et al 2014	CD	Overall/infectious complications
10	Selvaggi ¹²⁴ et al 2015	UC	Pouch-related postoperative complications
11	Waterland ⁸⁸ et al 2016	CD	Infectious complications
12	Law ⁸⁹ et al 2018	CD & UC	Overall/infectious complications
13	Xu ⁸⁰ et al 2018	CD	Postoperative complications
14	Yung ⁸¹ et al 2018	CD & UC	Postoperative complications

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Table 5

Clinical studies about risk factors for unfavorable postoperative outcome in patients with Crohn's disease and Ulcerative colitis. In these studies, biological treatment was analysed as part of the risk factors in multi-variate analysis.

Author/publication's year	Disease	Cohort/treated 12830/2881	Type of biological treatment	Weeks before surgery	
Observational retrospective studies					
1	Iesalnieks ¹²⁵ et al 2008	CD	282/4	IFX	8
2	Sampietro ¹²⁶ et al 2009	CD	393/13	Biological agents (not specified)	Not specified
3	Canedo ¹²⁷ et al 2010	CD & UC	213/61	IFX, ADA	8
4	Holubar ¹²⁸ et al 2010	CD	92/32	Biological agents (not specified)	Not specified
5	De Silva ¹²⁹ et al 2011	UC	666/58	IFX	Not specified
6	Mascarenhas ¹³⁰ et al 2012	CD	93/19	IFX, ADA and others (not specified)	12
7	Riss ¹³¹ et al 2012	CD	182/3	IFX	1
8	Tzivanakis ¹³² et al 2012	CD	207/not stated	IFX	Not specified
9	Bellolio ¹³³ et al 2013	CD	434/42	Biological agents (not specified)	Not specified
10	Gu ¹³⁴ et al 2013	UC	204/73	Anti-TNF- α (not specified)	Not specified
11	Bartels ¹³⁵ et al 2013	UC	71/16	Anti-TNF- α (not specified)	Not specified
12	Bewtra ¹³⁶ et al 2013	UC	830/65	IFX	Not specified
13	Hicks ¹³⁷ et al 2014	UC	179/43	IFX	Not specified
14	Morar ¹³⁸ et al 2015	CD	142/4	IFX, ADA	4
15	Zuo ¹³⁹ et al 2015	CD	344/8	IFX	Not specified

16	Feuerstein ¹³⁹ et al 2015	UC	209/24	Anti-TNF- α (not specified)	Not specified
17	Li ¹⁴⁰ et al 2016	CD	1461/190	Biological agents (not specified)	Not specified
18	Germain ¹⁴¹ et al 2016	CD	137/13	Anti-TNF- α (not specified)	8
19	Yamamoto ¹⁴² et al 2016	CD	231/79	IFX, ADA	8
20	Sahami ¹⁴³ et al 2016	UC	640/51	Anti-TNF- α (not specified)	12
21	Guo ¹⁴⁴ et al 2017	CD	118/11	Anti-TNF- α (not specified)	24
22	Collaborative ¹⁰¹ 2017	CD	375/82	IFX, ADA, CZM and others (not specified)	12
23	Diederer ¹⁴⁵ et al 2017	UC	422/14	Anti-TNF- α (not specified)	12
24	Galata ¹⁰⁰ et al 2018	CD	305/72	IFX, ADA, Golimumab, Vedozulimab and others	4
25	Heimann ¹⁴⁶ et al 2018	CD & UC	1000/71	Biological agents (not specified)	6
Reviews					
26	Huang ¹⁴⁷ et al 2015	CD	3807/1833	Biological agents (not specified)	Not specified
27	Beddy ¹⁴⁸ et al 2011	CD & UC	Not stated	Biological agents (not specified)	Not specified

IFX: Infliximab, ADA: Adalimumab, CZM: Cemzia, Anti-TNF- α : anti-tumour necrosis factor alpha agents