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

El-Hussuna, Alaa; Open Source Research Collaborating Group

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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

*Open Source Research Collaborating Group (#OpenSourceResearch)**

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

Aim: We aimed to search and analyze 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.

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*Contributors: Alaa El-Hussuna (Department of Surgery, Aalborg University Hospital, Hobrovej 18-22, 9000, Aalborg, Denmark; Twitter: @AlaaEl_Hussuna), Pär Myrelid (Department of Clinical and Experimental Medicine, Linköping University, Linköping, Sweden; Twitter: @PMyrelid), Stefan D. Holubar (Director of Research, Department of Colon & Rectal Surgery, Cleveland, OH 44195; Twitter: @HolubarStefan), Paulo G. Kotze (Colorectal Surgery Unit, Catholic University of Parana (PUCPR), Curitiba; Brazil; Twitter: @pakotze), Graham Mackenzie (Public Health, NHS Lothian, 2-4 Waterloo Place, Edinburgh EH1 3EG, UK; Twitter: @gmacscotland), Gianluca Pellino (Department of Surgery, Università della Campania Luigi Vanvitelli, Aversa, Italy; Twitter: @GianlucaPellino), Des Winter (Centre for Colorectal Disease, St Vincent's University Hospital, Elm Park, Dublin 4, Ireland; Twitter: @des_winter), Justin Davies (Addenbrooke's Hospital, Cambridge University Hospitals NHS Foundation Trust, UK; Twitter: @jdcamcolorectal), Ionut Negoi (Carol Davila University of Medicine and Pharmacy Bucharest, Romania; Twitter: @IonutNegoi), Perbinder Grewal (Department of Cardiovascular, University Hospital Southampton, UK; Twitter: @perbinder), Gaetano Gallo (Department of General Surgery, "Magna Graecia" University, Catanzaro, Italy; Twitter: @Gae_Gallo), Kapil Sahnan (Imperial College Faculty of Medicine, Department of Surgery and St Marks Hospital, London, UK; Twitter: @KSahnan), Ines Rubio-Perez (General and Digestive Surgery Department, La Paz University Hospital, 28046 Madrid, Spain; Twitter: @InesRPsurg), Daniel Clerc (Department of Visceral Surgery, University Hospital CHUV, Lausanne, Switzerland; Twitter: @daclerc1), Nicolas Demartines (Department of Visceral Surgery, Lausanne University Hospital CHUV, Lausanne, Switzerland; Twitter: ProfDemartines), James Glasbey (Academic Department of Surgery, University of Birmingham Heritage Building, UK; Twitter: @DrJamesGlasbey), Miguel Regueiro (Department of Gastroenterology, Hepatology, and Nutrition, Cleveland Clinic, Cleveland, OH; Twitter: @MRegueiroMD), Ahmed E. Sherif (Department of Clinical Surgery, University of Edinburgh, UK; Twitter: @Asherief), Peter Neary (South East Cancer Governance Lead, University Hospital Waterford/Cork, Ireland; Twitter: @peterneary7), Francesco Pata (Department of Surgery, Sant'Antonio Abate Hospital, Gallarate, Italy.; Twitter: @drfrancescopata), Mark Silverberg (Mount Sinai Hospital Inflammatory Bowel Disease Centre, University of Toronto, ON, Canada; Twitter: @guthealthmd), Stefan Clermont, (Zuyderland medical center, Heerlen. the Netherlands; Twitter: @ClermontsStefan), Sami A. Chadi (Division of General Surgery, University Health Network, Toronto, Ontario, Canada; Twitter: @Schadi_CRS), Sameh Emile (General Surgery Department, Mansoura Faculty of Medicine, Mansoura City, Egypt; Twitter: @dr_samehhany81), Nicolas Buchs (Department of Surgery, University Hospitals of Geneva, Switzerland; Twitter: @nicolas_buchs), Monica Millan (Department of Surgery, Joan XXIII University Hospital, Tarragona, Spain; Twitter: @monicamillan72), Ana Minaya-Bravo (University Henares Hospital, Coslada. Madrid. Spain; Twitter: @minaya_bravo), Hossam Elfeki (Department of General Surgery, Mansoura Faculty of Medicine, Mansoura University, Egypt; Twitter: @hossamelfeki), Veronica De Simone (Proctology Unit, Catholic University, Fondazione Policlinico Universitario A. Gemelli, Rome, Italy; Twitter: @veronicaDeSim), Mostafa Shalaby (Department of General Surgery, Mansoura Faculty of Medicine, Mansoura University, Egypt; Twitter: @mostafashalaby), Celestino Gutierrez (Department of Suregry,,Centre Hospitalier de Redon Ille-et-Vilaine Bretagne-France; Twitter: @CelestinoGutirr), Cihan Ozen (Department of Surgery, Aalborg University Hospital, Hobrovej 18-22, 9000, Aalborg, Denmark; Twitter: @ismailisabel), Ali Yalçınkaya (Gazi University, Faculty of Medicine, Ankara, Turkey; Twitter: @aliykya), David Rivadeneira (Colorectal Surgery & Surgical Services, Northwell Health in Huntington, NY, USA; Twitter: @drivadeneiramd), Alssandro Sturiale (Proctological and Perineal Surgical Unit, Cisanello University Hospital, Pisa, Italy; Twitter: @Dr_A_Sturiale), Nuha Yassin (Department of surgery, Royal Wolverhampton Hoaspital, UK; Twitter: @NuhaZsurgeon), Antonino Spinelli (Humanitas Clinical and Research Center, Humanitas University, Milan, Italy; Twitter: @AntoninoSpin), Jay Warusavitarne (Imperial College London, London, UK; Twitter: @colorectal_jay), Argyrios Ioannidis (Department of General, Laparoscopic and Robotic Surgery, Athens Medical Center ; Twitter: @ArgIoannid), Steven Wexner (Department of Colorectal Surgery, Cleveland Clinic Florida, Weston, FL; Twitter: @SWexner), Julio Mayol (Hospital Clínico San C; Twitter: @julioma) Open source research article: Written with, and peer reviewed by, contributors on Twitter using online shared Google document.

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Address correspondence to: Alaa El-Hussuna, MBChB, MSc, PhD, Aalborg University Hospital, Hobrovej 22, 9000 Aalborg, Denmark (alaanewemail@gmail.com).

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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 preoperative 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, antidrug 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 article and was an effective method of collaboration.

Key Words: Crohn disease, inflammatory bowel disease, ulcerative colitis, biologic treatment, biologics, anti-TNF alpha, postoperative outcome, surgery.

WHAT DOES THIS ARTICLE 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 identified all the studies published until September 30, 2018, analyzed these studies, described the 106 studies, and attempted to answer these questions:

1. Why these 106 studies reported divergent results?
2. Why there are a large number of studies with severe 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 coauthors and paragraph-by-paragraph revision of the manuscript via the #OpenSourceResearch.

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 that 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), that is Crohn disease (CD) and ulcerative colitis (UC). Biologics, including antitumor necrosis factor-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 angiogenesis[1] and collagen synthesis.[2–4] 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-TNF.[5] 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 study,[6] and risk for second surgery is 28.7% based on meta-analysis of population-based studies.[7] Furthermore, up to 50% of CD patients have been exposed to an a-TNF at time of their first surgery.[8] In UC, the risk of colectomy seems to have decreased in the era of biologics.[9] 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 (A.E.).[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 a-TNF agents (eg, infliximab or adalimumab), integrin inhibitors (eg, vedolizumab), or IL-12/23 inhibitors (eg, 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 Material. 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 (European Society of ColoProctology [ESCP], European Crohn's and Colitis Organization [ECCO], Association of Coloproctology of Great Britain and Ireland, American Society of Colon and Rectal Surgeons [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 and Rectal Surgeons.
6. Contacting experts in the field using the Twitter #SoMe4Surgery hashtag. Many authors are expert in this subject (A.H., S.H., P.K., P.M., J.D., A.E., A.S., N.Y., S.W., see Supplementary Material 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 (A.E.) completed the final draft which was then edited for grammar by a native English-speaking author (S.H.).

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, short message service, 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 2 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 preoperative 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 cohorts[11–42] (CD with/without UC), in 16 retrospective cohorts (UC),[43–58] 3 prospective ones,[59–61] 4 experimental studies,[62–65] 3 population-based studies,[66–68] 10 narrative reviews,[69–78] and 14 meta-analyses[10, 79–89] making a total of 82 studies over the past 15 years (Tables 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 5501 (24%) were on preoperative biological treatment.

TABLE 1. Clinical Studies About Type of Preoperative Biological Treatment in Patients With Crohn Disease

Author/Publication's Year		Cohort/Treated (7895/2026)	Type of Biological Treatment	Weeks Before Surgery
Observational retrospective studies				
1	Tay[11] et al (2003)	100/22	IFX	8
2	Colombel[12] et al (2004)	270/52	IFX	8[a]
3	Marchal[23] et al (2004)	79/40	IFX	12[b] (8, 4, and less than 4 wk)
4	Appau[34] et al (2008)	389/60	IFX	12
5	Indar[37] et al (2009)	112/17	Anti-TNF	8
6	Nasir[38] et al (2010)	370/119	IFX, ADA, CZM	8[a]
7	Kasparek[39] et al (2011)	94/48	IFX	12
8	Canedo[40] et al (2011)	225/65	IFX	8
9	Regueiro[41] et al (2011)	24/11	IFX	2–4 wk after surgery[c]
10	El-Hussuna[42] et al (2012)	417/32	IFX, ADA, CZM	12
11	White[13] et al (2012)	338/59	IFX, ADA, CZM	12
12	Myrelid[14] et al (2013)	298/111	IFX, ADA	8
13	Serradori[15] et al (2013)	217/42	Anti-TNF	12 (and 8 wk)
14	Syed[16] et al (2013)	325/150	Anti-TNF	8
15	Uchino[36] et al (2013)	405/79	IFX	12
16	Bafford[17] et al (2013)	196/35	Anti-TNF	12
17	Kotze[18] et al (2016)	123/71	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[d]	IFX	12 (8 and 4 wk)
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 wk)
Nation-wide database study				
25	Nørgård[66] et al (2013)	2293/214	IFX, ADA, CZM	12 (2 and 4 wk)

The time interval between last administered dose of biological treatment and surgery varied among the studies.
[a]And 4 wk after surgery.
[b]Nine patients received anti-TNF-α more than 12 wk prior to surgery.
[c]Data were collected from a randomized clinical trial to investigate postoperative recurrence of CD.
[d]Pediatric patients.
IFX, infliximab; ADA, adalimumab; CZM, certolizumab; UST, ustekinumab; VDZ, vedolizumab; anti-TNF, antitumor necrosis factor agents.

TABLE 2. Clinical Studies About Type of Preoperative Biological Treatment in Patients With Crohn 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 wk)
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[a]
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

[a]About 65% of patients in this cohort received anti-TNF-α therapy before surgery.
IFX, infliximab; ADA, adalimumab; CZM, cemizia; VDZ, vedolizumab; anti-TNF, antitumor necrosis factor agents.

TABLE 3. Clinical Studies About Type of Preoperative Biological Treatment in Patients With Ulcerative Colitis

Author/Publication's Year		Cohort/Treated (11,965/2181)	Type of Biological Treatment	Weeks Before Surgery
Observational retrospective studies				
1	Selvasekar[43] et al (2007)	301/47	IFX	8[a]
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 (2012)[b]	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 wk)

[a]Only 49% of patients in the study cohort.
[b]Pediatric age cohort.
IFX, infliximab; ADA, adalimumab; CZM, cemizia; VDZ, vedolizumab; anti-TNF, antitumor necrosis factor agents.

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 internal between medication and surgery, drug concentration, presecence of antidrug 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 immunogenicity.[90] The IBDResponse[61] 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- to 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 first-order elimination

TABLE 4. Meta-analyses and Systematic Reviews That Investigated the Effect of Biological Treatment on Postoperative Outcome in Patients With Inflammatory Bowel Disease

Author/Publication's Year		Disease	Primary Outcome
Systematic/narrative reviews			
1	Subramanian[69] et al (2006)	CD and UC	Postoperative complications
2	Ali[70] et al (2012)	CD and 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[73] et al (2015)	CD and 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 and UC	Postoperative complications
Meta-analyses			
1	Yang[116] et al (2009)	UC	Postoperative complications
2	Ehteshami-Afshar[82] et al (2011)	CD and UC	Colectomy and hospitalization rates
3	Kopylov[81] et al (2012)	CD	Colectomy and hospitalization rates
4	El-Hussuna[10] et al (2013)	CD	Anastomotic complications
5	Billioud[84] et al (2013)	CD and UC	Postoperative complications
6	Narula[85] et al (2013)	CD and UC	Postoperative complications
7	Rosenfeld[86] et al (2013)	CD	Postoperative complications
8	Yang[116] et al (2014)	CD	Postoperative complications
9	Ahmed Ali[87] et al (2014)	CD	Overall/infectious complications
10	Selvaggi[120] et al (2015)	UC	Pouch-related postoperative complications
11	Waterland[88] et al (2016)	CD	Infectious complications
12	Law[89] et al (2018)	CD and UC	Overall/infectious complications
13	Xu[80] et al (2018)	CD	Postoperative complications
14	Yung[81] et al (2018)	CD and UC	Postoperative complications

It shows 12 reviews about CD, 9 about mixed population, and only 3 about UC.

TABLE 5. Clinical Studies About Risk Factors for Unfavorable Postoperative Outcome in Patients With Crohn Disease and Ulcerative Colitis

	Author/Publication's Year	Disease	Cohort/Treated (12,830/2881)	Type of Biological Treatment	Weeks Before Surgery
Observational retrospective studies					
1	Iesalnieks[121] et al (2008)	CD	282/4	IFX	8
2	Sampietro[122] et al (2009)	CD	393/13	Biological agents (not specified)	Not specified
3	Canedo[123] et al (2010)	CD and UC	213/61	IFX, ADA	8
4	Holubar[124] et al (2010)	CD	92/32	Biological agents (not specified)	Not specified
5	De Silva[125] et al (2011)	UC	666/58	IFX	Not specified
6	Mascarenhas[126] et al (2012)	CD	93/19	IFX, ADA and others (not specified)	12
7	Riss[127] et al (2012)	CD	182/3	IFX	1
8	Tzivanakis[128] et al (2012)	CD	207/not stated	IFX	Not specified
9	Bellolio[129] et al (2013)	CD	434/42	Biological agents (not specified)	Not specified
10	Gu[130] et al (2013)	UC	204/73	Anti-TNF-α (not specified)	Not specified
11	Bartels[131] et al (2013)	UC	71/16	Anti-TNF-α (not specified)	Not specified
12	Bewtra[132] et al (2013)	UC	830/65	IFX	Not specified
13	Hicks[133] et al (2014)	UC	179/43	IFX	Not specified
14	Morar[134] et al (2015)	CD	142/4	IFX, ADA	4
15	Zuo[135] et al (2015)	CD	344/8	IFX	Not specified
16	Feuerstein[136] et al (2015)	UC	209/24	Anti-TNF-α (not specified)	Not specified
17	Li[136] et al (2016)	CD	1461/190	Biological agents (not specified)	Not specified
18	Germain[137] et al (2016)	CD	137/13	Anti-TNF-α (not specified)	8
19	Yamamoto[138] et al (2016)	CD	231/79	IFX, ADA	8
20	Sahami[139] et al (2016)	UC	640/51	Anti-TNF-α (not specified)	12
21	Guo[140] 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	Diederen[141] 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[142] et al (2018)	CD and UC	1000/71	Biological agents (not specified)	6
Reviews					
26	Huang[143] et al (2015)	CD	3807/1833	Biological agents (not specified)	Not specified
27	Beddy[144] et al (2011)	CD and UC	Not stated	Biological agents (not specified)	Not specified

In these studies, biological treatment was analyzed as part of the risk factors in multivariate analysis.
IFX, infliximab; ADA, adalimumab; CZM, cemizia; anti-TNF-α, antitumor necrosis factor alpha agents.

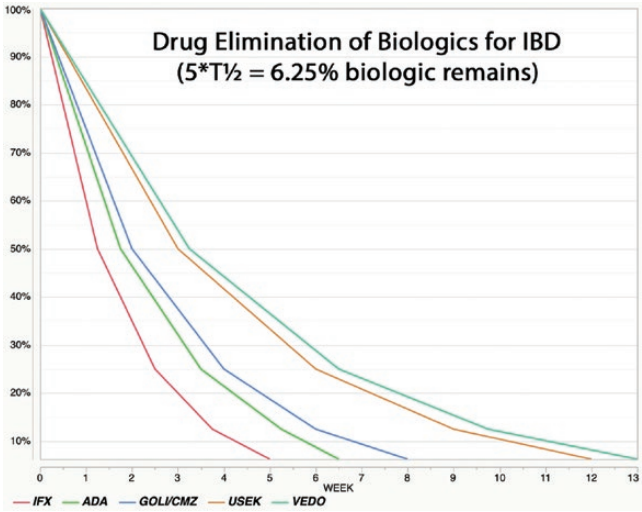

FIGURE 1. Graphical representation of the theoretical in vivo half-lives of biologic agents used to treat CUC. Note this graph assumes first-order elimination pharmacokinetics. With permission from Stefan Holubar.

kinetics (Fig. 1), which may or may not be applicable; of note, trace levels of infliximab can be found up to 12 weeks after administration.[90] 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 tissue[91] 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 (Fig. 1). Drug concentration is essential for drug action and for the stimulation of antidrug antibody formation.[90] 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, and these levels may be decreased by leakage of the antibodies through inflamed bowel mucosa into the stool[92] and/or deactivation by development of antibodies against the injected anti-TNF (antidrug 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 surgery.[60] Lau et al reported serum drug concentrations from samples drawn at varying preoperative time points in 143 patients with IBD treated with a-TNF.[30]

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 antidrug antibodies.[29] Analysis by Waterman et al included patients exposed to a-TNF treatment within 180 days of surgery. El-Hussuna[61] et al reported in IBDResponse study drug concentration and antidrug 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 antidrug antibodies in this group of patients.

Antidrug antibodies

The IBDResponse trial[61] showed that some patients develop antidrug antibodies to a-TNF agents regardless of the route of administration (IV or SC). These antidrug antibodies may reduce the efficacy of drugs. Misinterpretation of results in the studies where these antibodies were not measured cannot be dismissed. Only 2 studies[29, 61] measured and reported these antidrug antibodies. Concurrent administration of immunomodulators has been shown to reduce the formation of antidrug antibodies.[90]

How the Included Studies Adjusted for Potential Confounding Factors in Multivariate 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, whereas others are less studied such as preoperative 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 reversal.[26] In patients with UC most of the studies reported postoperative outcome after subtotal colectomy,[36, 43–46, 48, 55, 67, 68] completion prctectomy,[57] ileal pouch-anal anastomosis,[43–45, 48, 50, 51, 53, 54, 58, 98] and other procedures in addition to the above-mentioned.[49]

(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 American Society of Anesthesiology 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, 42, 53, 59, 96]

(h) Preoperative intra-abdominal sepsis (intra-abdominal abscess and/or enteric fistula) was reported in 9 studies.[13, 15, 16, 30, 34, 42, 59, 60, 96]

(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, 42, 45, 48, 50, 54, 59, 60, 68, 96, 97] 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 3 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 anastomosis.[14] Patients who received a diverting stoma were excluded in some studies,[38, 42] whereas other studies investigated these patients in subgroup analyses.[59]

(m) Other factors such as intra-operative blood loss,[37, 42] indication for surgery,[12, 23, 25, 27, 29, 30, 34, 40, 50] multicenter versus single centre,[27–30, 32, 33, 35, 39, 42, 54] leucocytosis[100] were reported but they appear to have minimum or no effect on the postoperative outcome. Close cooperation between surgeon and gastroenterologist in presurgical 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) Preoperative optimization: few studies reported interventions to optimize the patients prior to surgery, for example, 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 postopertative outcomes,[95, 94] it was only reported in some studies, whereas 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 trial[61] 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 infection[95] 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 were 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 Disease Activity Index (CDAI) was reported in 2 studies only,[60, 99] whereas Harvey–Bradshaw Index was reported in one study.[61] One study reported ACG severity of disease index,[38] whereas another one applied a local classification of disease activity.[28] In UC studies, one study used deprivation index,[68] whereas others used a local disease activity index[36, 48] or the Mayo score.[55] Regarding disease severity, there is a high likelihood that the most severely ill patients received anti-TNF, whereas 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 course,[14] either at time of surgery or prior to (but withheld) versus 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 nonseptic/noninfectious complications. A few studies used the classification of surgical complications versus medical complications,[18, 30, 44, 97] whereas 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 CD.[99]

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 level.[120] 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.[145]

How the Different Studies Conducted Statistical Analyses

Most of the statistical analyses were done in similar fashion, that is, univariate analyses with chi-square test, Student *t* test, or Fisher exact test 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 studies[37] to more recently low risk of bias studies[59]; nevertheless, the topical debate and controversy continues. There are 3 layers of complexity that made it difficult to reach definitive conclusions about the issue at hand:

1. Difficulty of conducting clinical research compared with basic science research. Clinical research is becoming more difficult due to the increased complexity of regulations and governance which can be far from patients' interests.[102] Up to half of the approved studies by ethics committees are never published.[103] It is well documented that clinical research attracts much less funding than basic science or translational research adding another challenge for outcomes research.[104]
2. Difficulty in conducting research in surgery compared with 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 preoperative and postoperative assessments. To this end, a number of groups have been working toward developed standardized outcome sets to facilitate comparison of data and effective meta-analysis.[105–108] Moreover, investigator-initiated trials often fail due to insufficient enrollment of patients with IBD,[100] and a priori power analyses are rarely reported. Only one third to half of patients with IBD need surgery during their lifetime (75% in CD[8]) 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 Disease

According to recently published guidelines,[109–111] surgery in patients with receiving a-TNF therapy may be associated with an increased risk of complications. Chronologically, the ASCRS 2015 clinical practice guideline on CD stated that patient receiving preoperative biologic treatment (ie, a-TNF or cyclosporine) should be considered for staged procedures because of postoperative complications risk.[109] 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 ECCO published its third evidence-based CD consensus in 2016,[110] 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 preoperative 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 readmissions.[111] 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 treatment.[109–111] 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 consensus.[112] For acute situations, performing staged procedures (ie, subtotal colectomy with end ileostomy as first stage)[119] was advised for patients receiving biologic treatment (a-TNF) and/or Prednisolone 20 mg daily or higher for >6 weeks. Regarding preoperative 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 recommended.[112] Guidelines from the ASCRS published in 2014[113] 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 noncomparable results and conclusions. Going forward, propensity-score matching or inclusion of the propesity

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 where 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, antidrug 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 randomized controlled trial 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 or meta-analysis; therefore, no statistical analysis was performed.

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

SUPPLEMENTARY DATA

Supplementary data are available at *Crohn's & Colitis 360* online.

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