Increased risk of post-operative complications in patients with Crohn's disease treated with anti-tumour necrosis factor α agents – a systematic review

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ABSTRACT

INTRODUCTION: Tumour necrosis factor α (TNF-α) plays a role in the immune defence, angiogenesis and collagen synthesis. Inhibition of these pathways may increase the risk of infections and impair wound healing in patients after surgery. Biologic treatments including anti-TNF-α agents are increasingly used in the treatment of inflammatory bowel disease. Taking into consideration the biologics' mechanism of action, fears have been expressed that they might increase the rate of post-operative complications. Results from 18 retrospective studies were conflicting, and meta-analyses based on these studies did not agree. The objective of this study was to review data from present reviews and meta-analyses in an attempt to come to conclusions for the use of anti-TNF-α in Crohn's disease patients in clinical practice.

METHODS: Literature search using both electronic and manual searches was conducted according to a pre-defined protocol. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were applied.

RESULTS: Two systematic reviews and six meta-analyses were found. Meta-analyses that included a large number of patients and applied quality assessment showed an increased risk of overall post-operative complications and an increased rate of infectious or anastomosis-related complications in patients receiving anti-TNF-α.

CONCLUSION: The use of anti-TNF-α agents in Crohn's disease patients is associated with an increased risk of post-operative complications after abdominal surgery.

Surgeons and gastroenterologists taking care of patients with inflammatory bowel diseases are faced with conflicting results regarding the effect of anti-TNF-α agents on post-operative complications. In this paper, we analyse the present evidence and draw conclusions to be used in daily practice.

Biological treatments with anti-tumour necrosis factor alpha agents (anti-TNF-α) are effective in Crohn's disease (CD). Despite this, population-based studies have not been able to demonstrate a reduction in the need for surgical treatment [1]. Surgical treatment is still required in approximately 70% of CD patients, and 30-70% of all patients require repeated operations [2]. Early and aggressive anti-TNF-α therapy has proven beneficial and is widely used. Consequently, more patients who require surgery have recently been exposed to these agents [3-5]. Furthermore, CD patients exposed to anti-TNF-α may undergo abdominal surgery for other indications.

TNF-α has been termed the body's sentinel cytokine or "fire alarm" as it initiates the defence response to local injury. As a result of innate and adaptive immune responses, the level of TNF-α is increased in the serum and mucosa of patients with CD and is a trigger for and a mediator of positive and negative feedback loops which influence the chronicity of inflammation [6]. Anti-TNF-α are monoclonal antibodies directed against this key cytokine for inflammation and immune defence and acts in two ways: Firstly, by scavenging soluble TNF-α, thereby preventing activation of immune cells via TNF-α receptors; and, secondly, by ''reverse signalling'' acting on membrane-bound TNF-α receptors on monocytes and T-cells inducing apoptosis and inhibition of further cytokine release [7].

Besides being an important actor in the immune defence, TNF-α plays a role in angiogenesis and collagen synthesis. Inhibition of these pathways may increase the risk of infection and impair wound healing after surgery. Taking into consideration the biologics' mechanism of action, fears have been expressed that they alone or in combination with steroids and immunomodulators may increase the rate of post-operative complications, especially infectious complications and those related to wound healing and anastomoses.

We evaluate the present evidence as expressed in reviews and meta-analyses in an attempt to attain evidence-based recommendations.

METHODS

The literature search applied was the same as in the recent meta-analysis by El-Hussuna et al [8]. It was conducted based on a protocol developed and reported according to the recommendations in the Cochrane Handbook for Reviews of Interventions and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.

SYSTEMATIC REVIEW

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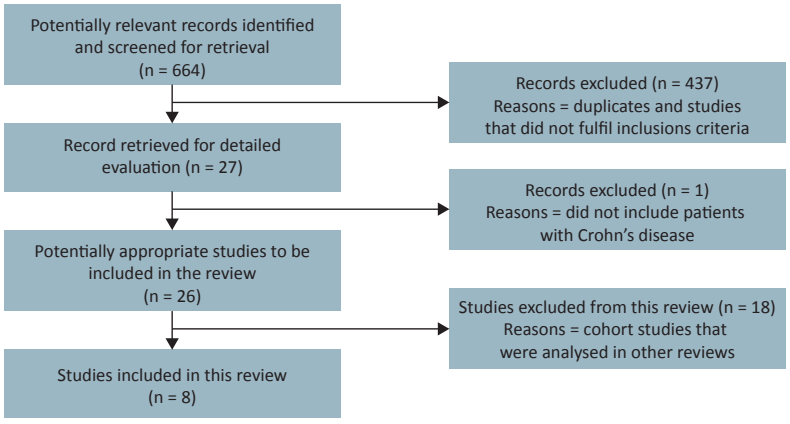
FIGURE 1

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram.



Search strategy

Studies were identified through electronic and manual searches. The electronic searches were performed in MEDLINE, Embase and the Cochrane Library. All databases were searched from their date of inception to 04th July 2014. The search strategy for MEDLINE included the following terms: ("Antibodies, Monoclonal"[Mesh] OR "PEG-modified tumour necrosis factor-alpha"[Supplementary Concept] OR "Tumour Necrosis Factor-alpha/antagonists and inhibitors"[Mesh] OR anti-TNFs OR anti-TNF OR adalimumab OR Infliximab) AND (Crohn disease OR Crohn* disease) AND ("General Surgery/adverse effects"[Mesh] OR "General Surgery/complications"-[Mesh] OR "Surgical Procedures, Operative/adverse effects"[Mesh] OR "Surgical Procedures, Operative/complications"[Mesh] OR "Postoperative Complications"[Mesh] OR postoperative complication* OR postoperative infection*) Limits: Humans AND (("biological agents"[MeSH Terms] OR ("biological"[All Fields] AND "agents"[All Fields]) OR "biological agents"[All Fields] OR "biologics"[All Fields]) OR (("biology"[MeSH Terms] OR "biology"[All Fields] OR "biologic"[All Fields]) AND agents[All Fields])) AND ("Crohn disease"[MeSH Terms] OR ("Crohn"[All Fields] AND "disease"[All Fields]) OR "Crohn disease"[All Fields]) AND ((("General Surgery/adverse effects"[Mesh] OR "General Surgery/complications"[Mesh]) OR ("Surgical Procedures, Operative/adverse effects"[Mesh] OR "Surgical Procedures, Operative/complications"[Mesh])) OR "Postoperative Complications"[Mesh]) Limits: Humans.

Manual searches included scanning of reference lists in relevant papers and conference proceedings and searches in the WHO search portal.

Data extraction

One author (AE) performed the literature searches and listed eligible studies. The search was independently repeated by a research specialist at the University of Copenhagen's Library to make sure that no relevant studies were missed. All authors participated in the final selection of studies for inclusion.

Eligibility criteria

Reviews or meta-analyses were included irrespective of their publication status, year of publication or language. Included studies assessed patients with CD undergoing laparoscopic or open abdominal surgery. No review was excluded.

Outcome measures

The primary outcome measure was 30-day post-operative complications.

RESULTS

There are 18 retrospective studies on the effect of anti-TNF-α on post-operative complications in CD patients undergoing abdominal surgery (as per 4 July 2013) [9-26]. These studies have been the subject of two systemic reviews [27, 28] and six meta-analyses [8, 29-33]. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were applied (**Figure 1**). The first narrative review by Subramanian et al was limited to three studies, which included 425 CD patients of whom 108 were preoperatively treated. The authors concluded that available evidence does not suggest an increased rate of post-operative complications. Ali et al [28] reviewed eight studies; three on CD patients, four on ulcerative colitis (UC) patients and one with a mixed IBD population. In total, there were 1,372 CD patients of whom 199 were treated with anti-TNF-α. The authors claimed that it was not possible to reach definite conclusions because "The stud¬ies are limited by small numbers of patients, disparate comparison groups, different definitions of measured outcomes and varying timeframes of drug exposure and follow-up".

FACT BOX

The mechanism of action of anti-tumour necrosis factor alpha agents (biologics) may lead to a suppression of cell-mediated immunity increasing the risk of post-operative complications.

The effect of anti-tumour necrosis factor alpha agents (biologics) on post-operative complications remains a controversial issue after more than two decades of using these drugs.

There are 18 retrospective studies with divergent results due to heterogeneous outcome measures.

Two systemic reviews and six meta-analyses arrived at different conclusions.

This article investigates the published systemic reviews and meta-analyses on the subject.

The authors conclude that anti-tumour necrosis factor alpha agents (biologics) increase the risk of post-operative infectious complications in patients with Crohn's disease undergoing abdominal operation.

TABLE 1

Meta-analyses on anti-TNF-α and post-operative complications in Crohn's disease.

Reference	Disease studied: aim of the study	Studies, n	Medication	Treated/total CD patients, n/N	Quality assessment: method	Results after applying quality assessment when applicable[a]
Ehteshami-Afshar et al, 2011 [29]	CD and UC	3 CD, 8 UC and 1 mixed	Infliximab	253/1,151	Jadad	All: OR = 2.11 (CI: 1.02-4.36) Anastomotic: OR = 1.71 (CI: 1.02-2.87) Infectious: OR = 1.56 (CI:0.71-3.44)[b]
Kopylov et al, 2012 [30]	CD	8	Anti-TNF-α agents	423/1,641	NOS (excluded studies are not mentioned)	All: OR = 2.2 (CI: 0.96-5.04) Anastomotic: OR = 1.18 (0.61-2.30) Infectious: OR = 1.62 (CI: 0.92-2.86)
Rosenfeld et al, 2013 [31]	CD	6	Infliximab	257/1,159	–	Major: OR = 1.59 (CI: 0.89-2.86) Minor: OR = 1.8 (CI: 0.87-3.71)
Billioud et al, 2013 [32]	CD, UC and IC	9 CD, 9 UC and 3 mixed	Anti-TNF-α agents	977/4,251 (pure CD patients: 549/1,907)	–	All: OR = 1.31 (CI: 0.96-1.77) Anastomotic: – Infectious: OR = 1.45 (CI: 1.03-2.05)
Narula et al, 2013 [33]	CD and UC	7 CD, 8 UC and 3 mixed	–	1,146/4,659	NOS	All: OR = 2.19 (CI: 1.69-2.84) Anastomotic: – Infectious: OR = 1.93 (CI: 1.28-2.89)
El-Hussuna et al, 2013 [8]	CD	11 CD and 3 mixed	Anti-TNF-α agents	679/3,042	NOS	All: RR = 1.77 (CI: 1.46-2.15) Anastomotic: RR = 1.63 (CI: 1.03-2.60) Infectious: RR = 1.15 (CI: 0.86-1.53)

CD = Crohn's disease; CI = confidence interval; IC = indeterminate colitis; NOS = Newcastle-Ottawa Scale; OR = odds ratio; RR = relative risk; TNF = tumour necrosis factor; UC = ulcerative colitis.
a) Results are expressed as overall complications (all), anastomosis-related complications (anastomotic) and unfectious complications (infectious).
b) Complications presented for both CD & UC.

The major findings from the six meta-analyses are presented in **Table 1**. The first analysis by Efthasami et al [29] focused on colectomy rates and post-operative complications in UC as well as in CD patients. The method for quality assessment used in this study was basically designed for randomised controlled clinical trials. No sensitivity analysis was conducted for studies with high risk of bias. The study had many crucial drawbacks such as mixing of retrospective and randomised studies, mixing studies about the recurrence of disease with those that examine the post-operative complications and reporting the results in a non- systematic way. The study results are difficult to interpret. This study revealed an increased risk for overt anastomotic leak, pouch-related complications, infections and thrombotic events after anti-TNF-α treatment. Not all the relevant studies were included. No sub-group analysis was performed for CD patients, and the results are not applicable to these patients.

Two meta-analyses from 2012 and 2013, respectively, included more than 1,000 patients. Many of the limitations of the previous reviews were addressed in the meta-analysis by Kopylov et al [30]. However, the authors did exclude abstracts and three relevant studies with a mixed population of CD, UC and indeterminate colitis. The authors did not report results after applying quality assessment. Nevertheless, they reported an increase in infectious complications in addition to trends for increased overall and non-infectious complications. No increase in the risk of anastomotic complications was reported in a subgroup analysis. The authors pointed out that discrepancy in the classification of complications influenced the statistical analysis.

Rosenfeld et al [31] found no difference in the rate of major complication, minor complication, re-operation or 30-day mortality rates between the infliximab group and control groups. Sensitivity analyses performed by excluding individual studies had no influence on the results. The study excluded some studies that reported the use of other relevant anti-TNF-α agents than infliximab. The study excluded abstracts from the analysis, but included them in the results section, which might be confusing. No quality assessment was performed. Moreover, grouping the complications into major and minor ones made the results of this study incomparable with other meta-analyses. In addition to the above mentioned drawbacks, the authors admit that the small number of included studies means a low power to detect bias.

There are three up-to-date meta-analysis including more than 3,000 operations. Billioud et al [32] examined several studies on CD and UC. They did not apply quality assessment or sensitivity analysis. They found an increased risk of infectious complications in CD patients. There was no subgroup analysis on anastomotic complications. Narula et al [33] performed a meticulous sensitivity analysis and applied quality assessment by excluding studies with a high risk of bias. They found that

TABLE 2

Studies included in the 6 meta-analyses on anti-TNF-α and post-operative complications.

	Meta-analysis					
Study	Ehteshami-Afshar et al, 2011 [29]	Kopylov et al, 2012 [30]	Rosenfeld et al, 2013 [31]	Billioud et al, 2013 [32]	Narula et al, 2013 [33]	El-Hussuna et al, 2013 [8]
Brzezinski et al, 2002 [19]	–	–	–	–	–	+
Colombel et al, 2004 [11]	+	+	+	+	–	+
Tay et al, 2003 [18]	–	+	+	+	–	+
Marchal et al, 2004 [21]	+	+	+	+	+	+
Appau et al, 2008 [9]	+	+	+	+	+	+
Kunitake et al, 2008 [23]	+	–	+	+	+	+
Indar et al, 2009 [22]	–	–	+	+	–	+
Nasir et al, 2010 [14]	–	–	+	+	+	+
Regadas et al, 2011 [15]	–	–	+	+	–	+
Rizzo et al, 2011 [16]	–	–	+	+	+	+
Kotze et al, 2011 [20]	–	–	+	–	–	+
Canedo et al, 2011 [10]	–	+	+	+	+	+
Kasparek et al, 2012 [13]	–	+	+	+	+	+
El-Hussuna et al, 2012 [12]	–	–	–	–	–	+
Waterman et al, 2013 [24]	–	–	–	–	+	–
Syed et al, 2013 [17]	–	–	–	+	+	–
Mascarenhas, 2012[a]	–	–	–	–	+	–
Selvasekar, 2007[a]	+	–	–	+	+	–
Schluender, 2007[a]	+	–	–	+	+	–
Mor, 2008[a]	+	–	–	+	+	–
Ferrante, 2009[a]	+	–	–	+	+	–
Coquet-Reinier, 2010[a]	–	–	–	+	+	–
Gainsbury, 2011[a]	–	–	–	+	–	–
Bordeianou, 2010[a]	+	–	–	–	–	–
De Silva, 2011[a]	–	–	–	+	–	–
Bregnbak, 2012[a]	–	–	–	+	+	–
Nørgård et al, 2012 [36]	–	–	–	–	+	–
Eshuis, 2013[a]	–	–	–	+	+	–
Sandborn, 2009[a]	+	–	–	–	–	–
Gustavsson, 2010[a]	+	–	–	–	-	–
Järnerot, 2005[a]	+	–	–	–	–	–

a) Please contact the corresponding author for further information.

treatment with anti-TNF-α agents was associated with an increased risk of overall and infectious complications. A trend for increase in non-infectious complications was reported. They did not analyse anastomosis-related complications.

The most recent meta-analysis by El-Hussuna et al [8] did apply quality assessment in addition to a sensitivity analysis excluding studies with a mixed population. After excluding studies with high risk of bias, the authors found an increase in the risk of overall post-operative complications and anastomotic related complications.

DISCUSSION

Larger meta-analyses that applied quality assessment of the included studies, demonstrated increased risks after anti-TNF-α treatment, not only for all complications, but also in subgroup analysis for infectious and anastomotic complications.

Early observational retrospective studies yielded conflicting results due to small samples and variations in methodology [8]. The major shortcoming of most of these studies is the lack of adjustment for confounders such as disease severity, smoking, nutritional state and concomitant use of other medications like corticosteroids. It was hypothesised that a pooled estimate of all the odds ratios from several retrospective studies would reduce the influence of confounders and thus have sufficient power to detect previously unrecognised associations. This hypothesis gave birth to two systemic reviews and six meta-analyses.

The six meta-analyses reached divergent conclusions. It was not possible to make a statistical analysis of these six meta-analyses in our review due to differences in their methodology, e.g. inclusion of studies with mixed CD and UC populations, inclusion of abstracts, inclusion of low quality studies and of studies exploring

one or several anti-TNF-α agents (**Table 2**). There were also differences in the outcome measures, for instance in the definition of infectious/septic complications.

Despite this, it is possible to recognise a pattern of relations between anti-TNF-α and post-operative complications. The recent large meta-analyses, which applied quality assessment and sensitivity analyses reducing the influence of confounders, suggest an association between anti-TNF-α and post-operative complications, particularly infectious complications. This was also supported by another recent meta-analysis [34], which was published after the last literature search. The associations between anti-TNF-α agents and post-operative infectious complications seem to be related both to an impaired immune defence and to an impaired healing capacity resulting in infections and anastomotic complications. Anastomotic complications represent the most serious complications that are related to an impaired healing. Despite the significance of these complications, anastomotic complications were included in only one of the three recent meta-analyses, demonstrating an almost doubled risk. It could be speculated that the increased infectious complications in the other two meta-analyses harboured also anastomotic complications.

Meta-analysis carries inherited risks, and the findings should therefore be interpreted with caution. Even after quality analysis and sensitivity analysis, it is not possible to control for confounders. Moreover, if all included studies have similar confounders, this might enhance a false result.

Whether this association between preoperative use of anti-TNF-α and post-operative complications in Crohn's disease is causal remains uncertain. Two recent Danish population-based cohort studies have even challenged this association [35, 36]. There is, indeed, a need for more well-designed studies. Randomised controlled studies on this subject are too difficult to perform. Prospective data, including confounding factors, collected for instance in national quality data bases, are most likely the way to sol ve these issues [17, 28, 30, 32, 33].

Until this issue is settled through larger prospective studies, it is recommended to carefully use biologic treatments in patients expected to be candidates for an abdominal operation.

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