

Do anti-TNF agents and combination treatment increase postoperative complication risk?

Anti-TNF ajanlar ve kombinasyon tedavisi postoperatif komplikasyon riskini artırır mı?

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INTRODUCTION

Ulcerative colitis (UC) is a chronic inflammatory disease with unknown etiology. 5-aminosalicylic acid (5-ASA), corticosteroids and immunomodulators like 6-mercaptopurine and azathioprine are used in the treatment. Recently, infliximab, an anti-tumor necrosis factor (TNF) agent, has also begun to be used in the treatment of UC. Although infliximab was generally a safe agent, side effects such as infusion reactions, anaphylaxis, opportunistic infections, tuberculosis reactivation, and sepsis were reported (1). Despite optimal medical treatment, 50% of the patients with UC are reactivated in the first year and 30% of them undergo surgery (2). Studies regarding postoperative complication risk among patients undergoing operation under infliximab treatment and/or combination treatments are contradictory and limited. This study was performed to offer suggestions by reviewing all the literature to clarify this important subject in daily practice.

MATERIALS AND METHODS

A search in Medline was performed with the following key words by using systematic literature scan method: "infliximab AND postoperative complication", "infliximab AND ulcerative colitis AND postoperative complication", "infliximab" [Substance Name] AND "Postoperative Complications", "infliximab AND postoperative outcome", "steroid OR infliximab AND ulcerative colitis AND postoperative complication", "steroids"

[Mesh] OR "infliximab" [Substance Name] AND "Colitis, Ulcerative" [Mesh] AND "Postoperative Complications" [Mesh], "azathioprine OR infliximab AND ulcerative colitis AND postoperative complication", "azathioprine" [Substance Name] OR "infliximab" [Substance Name] AND "Colitis, Ulcerative" [Mesh] AND "Postoperative Complications", "azathioprine OR steroid OR infliximab AND ulcerative colitis AND postoperative complication", "azathioprine" [Substance Name] OR "Steroids" [Mesh] OR "infliximab" [Substance Name] AND "Colitis, Ulcerative" [Mesh] AND "Postoperative Complications" [Mesh], "Colitis, Ulcerative" [Mesh] AND (infliximab OR adalimumab anti TNF OR TNF-alpha antagonists)", and "Crohn's disease AND infliximab AND postoperative complication". All of the studies performed in adult groups were included into the assessment. Additionally, other studies were attained by scanning literature references. After scanning 1062 literatures, 11 studies were attained in consequence of a 3e literature scan for determining whether or not anti-TNF agents and combination treatment increased postoperative complications. All of the 11 studies analyzed were retrospective studies. Analysis and evaluation criteria used in the studies are shown in Table 1.

RESULTS

Meta-analysis studies regarding anti-TNF agents and combination treatment (Anti-TNF+steroid,

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Table 1. Analysis and evaluation criteria**Postoperative complications**

Mortality
Anastomotic leak
Pelvic abscess
Pouch related complications
Surgical site infections
Nonsurgical site infections

Anti-TNF+azathioprine, Anti-TNF+azathioprine + steroid) increasing postoperative complications were not found. Eleven retrospective studies were found, and statistical analyses of these studies were performed.

Ferrante et al. (3) screened 141 UC patients retrospectively. Twenty-two of them were using infliximab treatment. All of them received an average of 2.5 infusions within the last 3 months. They concluded that infliximab did not increase postoperative complications but corticosteroid use and proctocolectomy without ileostomy did increase short-term postoperative complications.

Another study analyzed 26 UC patients. Thirteen of the patients were using infliximab treatment, and they received infusion treatment within the last 44 days on average. The final analysis showed that infliximab did not increase postoperative complications (4).

Kunitake et al. (5) screened a larger group of patients retrospectively. One hundred and eighty-eight Crohn patients, 156 UC patients and 69 indeterminate colitis patients were evaluated. One hundred and one patients were using infliximab treatment. Infliximab treatment was administered within the last 3 months. In this study, it was seen that neither infliximab nor steroid treatments increased postoperative complication risk.

In another study including 241 patients (Crohn, UC, indeterminate colitis), 28 of the patients were using infliximab treatment. In that study, it was shown that use of infliximab and other immunosuppressive agents did not increase postoperative complications (6).

Mor et al. (7) reported 523 UC patients who underwent surgery. Twenty-eight of the patients used infliximab treatment. An average of 3 infusions were administered within last the 3 months of surgery. Contrary to the findings in other studies, this study reported increased postoperative complications in both the short and long term.

Another similar study reported increased postoperative complications with infliximab use. Three hundred and one UC patients were screened retrospectively. Forty-seven of the patients were using infliximab treatment; infliximab treatment was administered within the last 2-6 months on average. In this study, it was seen that infliximab increased both pouch-related complications and postoperative infectious complications (8).

Postoperative complications and surgical indications of the patients receiving and not receiving infliximab are shown in Tables 2, 3, 4, and 5.

The literature for combination treatment is scarcer. Only two retrospective studies were found regarding combination treatment.

Schluender et al. (9) screened 151 UC patients retrospectively. Seventeen of the patients were using infliximab treatment. An average of 2 infusions were administered in an average of 2 months before operation during infliximab treatment. After analysis, it was shown that infliximab treatment did not increase postoperative complication risk, but sequential infliximab-cyclosporine treatment increased postoperative complication risk significantly.

Table 2. Postoperative complications of the patients receiving infliximab

Author, year	Total	Mortality	Anastomotic leak	Infection	Sepsis
Ferrante M, 2008	141 UC, 22 IFX	0	0	5	0
Selvasekar C, 2006	301 UC, 47 IFX	0	4	23	0
Reiner B, 2010	26 UC, 13 IFX	0	0	1	0
Kunitake H, 2008	413 CD, UC, IC, 101 IFX	2	3	6	0
Schluender S, 2007	151 UC, 17 IFX	0	0	0	0
Mor IJ, 2007	523 UC, 85 IFX	0	8	0	10
Regadas F, 2009	241 CD, UC, IC, 28 IFX	0	0	0	0
Total	IFX: 313	2	15	35	10

UC: Ulcerative colitis. CD: Crohn disease. IC: Indeterminate colitis. IFX: Infliximab.

Table 3. Postoperative complications of the patients not receiving infliximab

Author, Year	Total	Mortality	Anastomotic leak	Infection	Sepsis
Ferrante M, 2008	141 UC, 119 IFX (-)	0	15	78	0
Selvasekar C, 2006	301 UC, 254 IFX (-)	0	2	19	0
Reiner B, 2010	26 UC, 13 IFX (-)	0	1	0	0
Kunitake H, 2008	413 CD, UC, IC, 312 IFX (-)	1	9	31	0
Schluender S, 2007	151 UC, 134 IFX (-)	0	0	0	0
Mor IJ, 2007	523 UC, 438 IFX (-)	0	1	0	1
Regadas F, 2009	241 CD, UC, IC, 221 IFX (-)	0	3	15	2
Total	Total: 1491	1	31	143	3

UC: Ulcerative colitis. CD: Crohn disease. IC: Indeterminate colitis. IFX: Infliximab.

Table 4. Surgical indications of the patients receiving infliximab

Author, Year	Fulminant colitis (UC)	Intractable Disease (UC, CD)	Dysplasia/Neoplasia (UC)
Ferrante M, 2008	0	22/22	0
Selvasekar C, 2006	0	43/47	0
Reiner B, 2010	0	5/13	0
Kunitake H, 2008	1/101	69/101	0
Schluender S, 2007	x	x	x
Mor I.J, 2007	1/46	0	2/46
Regadas F, 2009	0	0	0

UC: Ulcerative colitis. CD: Crohn disease.

Table 5. Surgical indications of the patients not receiving infliximab

Author, Year	Fulminant colitis (UC)	Intractable disease (UC, CD)	Dysplasia/Neoplasia (UC)
Ferrante M, 2008	0	106/119	13/119
Selvasekar C, 2006	24/254	188/254	0
Reiner B, 2010	0	6/13	0
Kunitake H, 2008	2/312	199/312	12/312
Schluender S, 2007	x	x	x
Mor I.J, 2007	1/46	0	2/46
Regadas F, 2009	0	0	0

UC: Ulcerative colitis. CD: Crohn disease.

Aberra et al. (10) investigated the correlation between corticosteroid -azathioprine combination and postoperative complications. A total 159 patients with inflammatory bowel disease who underwent elective operation were screened retrospectively. While azathioprine treatment or addition of azathioprine treatment to steroid therapy did not increase postoperative complication risk, steroid therapy alone increased postoperative complication risk.

CONCLUSION

There is a disparity in the literature about postoperative complications and use of biologics. When 11 retrospective studies were evaluated, while some studies showed that infliximab did not increase postoperative complications (3- 6), others showed

that infliximab increased postoperative complications significantly (7,8).

There are many parameters influencing postoperative complication risk other than infliximab use. Parameters such as last infusion time, number of infusions, surgical indication (fulminant colitis, intractable disease, dysplasia, neoplasia), and surgical technique (total colectomy + ileostomy, ileal pouch-anal anastomosis (IPAA) + ileostomy, IPAA without ileostomy) influence complication risk (Tables 4, 5, 6). When the studies were evaluated, the most frequent indication of surgery was found to be intractable disease. Ferrante et al. (3) showed that proctocolectomy without ileostomy increased short-term postoperative infectious complications.

Table 6. Surgical technique

Author	Surgical Technique
Ferrante	Total colectomy+ileostomy, IPAA+ileostomy, IPAA without ileostomy
Reiner	Laparoscopic IPAA
Mor	Restorative proctocolectomy
Selvasekar	IPAA

IPAA: Ileal pouch - anal anastomosis

Table 7. Analysis results related with postoperative complication risk of patients

	IFX (N=184)	Plasebo (N=958)
Postop complication (+)	146 (A)	245 (B)
Postop complication (-)	38 (C)	713 (D)

OR: (AxD/BxC)= 146x713 /245x38= 11.18 (%95 CI:7.6-16.4) IFX: Infliximab

Table 8. Analysis results related with postoperative mortality risk of patients

	IFX (N=184)	Plasebo (N=958)
Postop mortality (+)	0 (A)	0 (B)
Postop mortality (-)	184 (C)	958 (D)

OR: (AxD/BxC)= 0x958/0x184=0 IFX: Infliximab

When we analyzed all of the UC studies evaluating infliximab and placebo arms for postoperative complications, the odds ratio (OR) was found to be 11.18 (95% confidence interval [CI]: 7.6-16.4) in the infliximab arm (Table 7). This shows infliximab increases postoperative complications significantly.

The infliximab and placebo arms of UC patients were evaluated regarding postoperative mortality, and the OR was found to be 0 in the infliximab

arm (Table 8). Infliximab fortunately does not increase postoperative mortality risk.

When two retrospective studies regarding combination treatment were evaluated, it was shown that infliximab + cyclosporine treatment and steroid therapy alone increased postoperative complication risk, but addition of azathioprine therapy to infliximab treatment did not increase postoperative complication risk (9,10).

Recommendation:

While infliximab use among ulcerative colitis patients increases postoperative complication risk, it does not increase the mortality rate. (EL 2b, RG B)

Addition of AZA/6-MP to infliximab treatment does not increase postoperative complication risk. (EL 2b, RG B)

Since cyclosporine therapy together with infliximab treatment increases postoperative complication risk, it is not recommended. (EL 2b, RG B)

Steroid therapy may increase postoperative complication risk. (EL 2b, RG B)

Not performing ileostomy as a surgical technique increases postoperative complication risk. (EL 2b, RG B)

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