Journal of Coloproctology

www.jcol.org.br

Review Article

Impact of anti-TNF agents in postoperative complications in Crohn's disease: a review

Mansur Saab[a], *Bárbara Saab*[a], *Márcia Olandoski*[b], *Cláudio Saddy Rodrigues Coy*[c], *Paulo Gustavo Kotze*[a,*]

[a] *Colorectal Surgery Unit, Pontifícia Universidade Católica do Paraná (PUC-PR), Curitiba, PR, Brazil*
[b] *Biostatistics Department, Pontifícia Universidade Católica do Paraná (PUC-PR), Curitiba, PR, Brazil*
[c] *Colorectal Surgery Unit, Universidade Estadual de Campinas (UNICAMP), Campinas, SP, Brazil*

ARTICLE INFO

Article history:
Received 9 January 2015
Accepted 20 February 2015
Available online 8 April 2015

Keywords:
Crohn disease
Tumor-necrosis factor alpha
Colorectal surgery

ABSTRACT

The real impact of biological therapy (anti-TNF agents) in abdominal operations secondary to Crohn's disease is a matter of debate in the international literature. Several studies demonstrated that there can be an increase in postoperative complications in patients previously treated with these agents. On the other hand, the majority of studies published over the last years question this effect, and did not demonstrate any relationship between biologics and outcomes related to surgical postoperative complications. Some meta-analyses were published, with different outcomes and different conclusions. Experimental studies in animals were also recently published, with opposite results, despite similar methodology. In this review, the authors resume all the relevant papers in the international literature with respect to the theme, and demonstrate the heterogeneity of the studies, as well as the disparity of their results and outcomes. The real impact of anti-TNF agents on postoperative complications in Crohn's disease is still controversial, and needs to be better elucidated. Controlled trials must be performed to better address this issue.

Impacto dos anti-TNF nas complicações pós-operatórias na doença de Crohn: uma revisão

Palavras-chave:
Doença de Crohn
Fator de necrose tumoral-alfa
Cirurgia colorretal

RESUMO

O real e verdadeiro impacto da terapia biológica, constituída por inibidores do fator de necrose tumoral (TNF) alfa, em operações abdominais na doença de Crohn, ainda é extensamente debatido na literatura. Há muitos estudos que referem aumento da possibilidade de complicações em pacientes tratados previamente com esses agentes. Por outro lado, há uma série maior de trabalhos que questionam esse aumento, não demonstrando qualquer impacto dessas drogas nos desfechos pós-operatórios. Algumas metanálises foram publicadas, com resultados ligeiramente diversos. Trabalhos experimentais em animais foram

* *Corresponding author.*
E-mail: pgkotze@hotmail.com (P.G. Kotze).
http://dx.doi.org/10.1016/j.jcol.2015.02.003

recentemente realizados, igualmente com resultados opostos, apesar de metodologia semelhante. Nessa revisão, os autores discorrem sobre todos os trabalhos relevantes na literatura nacional e internacional sobre o tema, e demonstram a heterogenicidade dos mesmos, bem como a disparidade dos resultados e desfechos. O real impacto dos agentes anti-TNF sobre operações abdominais na doença de Crohn ainda é controverso, e precisa ser melhor elucidado. Estudos controlados devem ser realizados para melhor elucidação dessa questão.

Introduction

In recent years, remarkable progress in the medical treatment of Crohn's disease (CD) was achieved, particularly with the advent of tumor necrosis factor (TNF) inhibitors.[1,2] The clinical response to these drugs has been demonstrated in some randomized trials and, subsequently, other studies have shown reduction in hospitalizations and surgeries and a consequent change in the natural history of the disease, with the possibility of preventing complications in some subgroups of responders.[3,4] Infliximab (IFX) was the first anti-TNF drug approved for CD, and knowledge on this drug in the management of patients was consolidated by more than 14 years of clinical experience.[5] Subsequently, in 2007, a second biological agent of TNF-inhibitor class was approved by regulatory agencies for CD therapy, adalimumab (ADA). More recently, a third biologic drug, certolizumab pegol (CTZ), was approved as an option for CD therapy. These agents constitute what is known today as biological therapy in the management of CD. Its use is growing exponentially, and currently, these biologicals are considered the most effective drugs in the medical management of moderate to severe disease.[5]

The indications for biological treatment in CD are directed mainly for severe forms of this disease,[3,4] and frequently a surgical treatment will be indicated during the use of these drugs.[5] As these drugs are potent immunosuppressants, there is an obvious concern, if this reduction in the defenses somente, retirar body's could lead to greater possibilities of surgical and infectious complications in the postoperative period of a bowel resection in CD patients. There is also controversy on the effects of these agents at tissue level, in bowel anastomosis healing process. Data from the literature are conflicting, and retrospective studies of case series showed equally conflicting conclusions.

Against this scenario of doubt, where there really exists insecurity of surgeons in operating patients previously exposed to biological agents, it is critical to elucidate the relationship between these drugs and the rates of surgical and medical complications in the postoperative period after intestinal resections in CD. There is a notable lack of solid and consistent data on the subject. Hence, this scenario justifies the conduction of this review, in order to verify, through a full search of the literature, information on the actual outcome related to complications after abdominal surgery in CD patients with prior exposure to biological therapy.

Clinical studies with a trend for further postoperative complications with the use of biologicals

A study conducted at the Cleveland Clinic in Ohio (United States), published in 2008, compared the effects of IFX in patients undergoing ileocolectomy for CD into 3 groups: operated patients without IFX in pre-biological era, patients in the era after drug commercialization, and patients previously exposed to IFX before surgery. Retrospectively, 60 patients operated with prior exposure to IFX within 3 months before the procedure showed higher risk of sepsis, abdominal abscesses, re-admissions and anastomotic dehiscence. The authors also suggested that proximal diversion stomas were protective factors in relation to these higher risks, and could be recommended in patients with previous use of this medication.[6]

Rizzo et al., in an Italian single-center retrospective study, analyzed the surgical outcomes in 114 patients with CD and ulcerative colitis, with prior exposure to anti-TNF agents ($n = 54$) compared to a control group without use of these drugs ($n = 60$). With no distinction between the type of inflammatory disease, the authors concluded, in an univariate analysis, that infectious complications were more frequent in individuals previously treated with biologicals (60% *versus* 13%; $p = 0.023$). However, in a multivariate analysis, an increase in postoperative complications related to previous use of biologicals were not found. Only high doses of corticosteroids have been linked to higher rates of infection.[7]

In a meta-analysis published in 2012, Kopylov et al. analyzed eight studies on the subject, all included in this review, with a total of 1641 patients. After the pooled analysis of data from these studies, the authors concluded that there was a greater risk of infectious complication rates in patients previously treated with IFX, predominantly not related to the surgical site. They also found a tendency (not statistically confirmed) toward an increase in the rates of overall and non-infectious complications.[8]

In a French multicenter retrospective study, Serradori et al. analyzed the levels of postoperative infections after 217 major abdominal operations secondary to CD. In a univariate analysis, the authors found that patients older than 25 years and with previous use of corticosteroids, of anti-TNF agents, and of biologicals together with corticosteroids were risk factors for infections. On the other hand, in the multivariate analysis only the concomitant preoperative use of biologicals with corticosteroids was considered as a risk factor for

infectious complications (odds ratio [OR] = 8.03, 95% confidence interval [CI] = 1.93–33,43; $p = 0.035$).[9]

Syed et al., in 2013, published a study including patients undergoing various types of abdominal operations, even not related to CD. 325 operative procedures were studied in 211 patients, and 150 of these procedures were performed in subjects with prior exposure to biological agents. In the multivariate analysis, the authors found that previous use of TNF-alpha inhibitors (including IFX, ADA and CTZ) was a risk factor for overall higher rates of infectious complications (OR = 2.43; 95% CI = 1.18–5.03) and surgical site infections (OR = 1.96; 95% CI = 1.02–3.77).[10]

Four meta-analyses on the possible impact of anti-TNF agents on postoperative complications in CD patients have recently been published. Interestingly, all meta-analyzes include virtually the same studies (all included in this literature review), and through slightly different methods, these studies came to only slightly different conclusions. From these meta-analyses, only one, which pooled eight studies, pointed to a non-influence of biological therapy on postoperative outcomes; this will be discussed at the next session.[11] The other three meta-analyzes concluded that a negative influence of the use of these drugs in postoperative complications in CD may exist. Narula et al. reported, after inclusion of 18 studies and 4659 patients, that biological agents may slightly the risk of postoperative complications, and, above all, this can signify an analysis bias, and not the biological effect of these drugs *per se*.[12] El-Hussuna et al., after including 14 studies with 679 patients exposed to biologicals *versus* 2363 controls, concluded that, in studies with less potential for bias, previous use of these agents increased the risk of anastomotic dehiscence.[13] Finally, Yang et al., in their meta-analysis analyzing 18 studies and 5769 patients, showed an association between previous use of biologicals and complications (OR = 1.45, 95% CI = 1.04–2.02) and infectious (OR = 1.47 95% CI = 1.08–1.99) and non-infectious (OR = 2.29, 95% CI = 1.14–4.61) complications, respectively, in the postoperative period. The authors suggest a modest increase in the risk of complications in patients previously exposed to anti-TNF agents.[14]

The first prospective study on the theme "biologicals *versus* surgical complications" in the management of CD was published by Lau et al. in 2014. In this study, the authors measured IFX serum levels 7 days before the surgical procedure, in an attempt to relate higher serum levels with higher rates of complications. From a total sample of 217 patients, 123 were CD patients. Using an IFX serum level of 3 μg/ml as a cutoff point, overall (OR = 2.5, $p = 0.03$) and infectious (OR = 3.0, $p = 0.03$) complications in the postoperative phase were more frequent in patients with serum levels above this above this level. Higher rates of postoperative overall complications and of re-admissions in patients with IFX levels ≥8 μg/ml also were noted, compared to those subjects with IFX levels <3 μg/ml. These changes have not been confirmed in patients with ulcerative colitis submitted to surgical procedures, probably due to a more rapid washout of the drug in these patients.[15]

The studies described in this review session are summarized with their respective methodologies and key findings in Table 1.

Clinical studies with no trend for further complications with postoperative use of biologicals

The first study on the subject "biologicals and surgical complications in CD" in the literature was carried out in the United States in 2003. In this article, Tay et al. retrospectively demonstrated that patients with previous use of immunosuppressants in its various forms and undergoing abdominal operations secondary to CD did not show higher rates of intra-abdominal septic complications (abscesses, dehiscence, enterocutaneous fistulas) *versus* subjects without associated immunosuppression (5.6% in immunocompromised patients *versus* 25% in those untreated, $p < 0.01$). In a multivariate analysis, the authors also questioned a possible protective effect of immunosuppression (with some patients using biological agents), with reduced rates of complications compared to the control group.[16]

Colombel et al., in 2004, published a study reporting the first experience of the Mayo Clinic in Minnesota, United States, for possible consequences of perioperative use of IFX in postoperative complications. From a total of 270 patients undergoing abdominal operations for CD over the time period considered (all with intestinal resections), 52 were exposed to IFX. These authors found no increased risk of septic complications in patients who received IFX in the perioperative period.[17]

Marchal et al., in 2004, reported the experience of a Belgian referral centre, where 40 patients previously exposed to IFX undergoing intestinal resection had their outcomes compared to 39 matched patients according to age and type of procedure. The objective was to evaluate, between groups, the occurrence of early and late major and minor complications. These authors did not found higher rates of complications between groups and no difference between in in-hospital length of stay for these patients. A trend toward a higher incidence of infections in general in the group previously exposed to IFX was found, but without statistical significance.[18]

In 2008, an american study conducted by Kunitake et al. reported the isolated experience of an US referral center in the management of IBD in relation to possible changes in postoperative complication rates in patients who have previously used IFX. From a total of 413 patients studied, only 188 had CD. In that study, patients with ulcerative colitis and indeterminate inflammatory bowel disease were included. In their paper, the authors did not clarify the exact number of CD patients with prior use of IFX. However, they concluded that there were no overall differences (without distinguishing the type of inflammatory bowel disease) in clinical and surgical complication rates (16.8% in the group with IFX *vs.* 15.7% in control group; $p = 1.0$). Nevertheless, there was a higher mean of in-hospital length of stay for the group of operated patients who had been previously treated with IFX *versus* control group (12.2 *vs.* 10.2 days, $p < 0.0001$).[19]

In 2009, a series of 112 CD patients operated at the Mayo Clinic in Arizona, United States, was retrospectively described, and possible changes caused by corticosteroids, immunosuppressants and biologicals on postoperative outcomes were evaluated. Of these 112 patients, only 17 used IFX prior to their surgical procedure. Major complications were not found

Table 1 – Major studies showing a possible negative impact of the use of biologicals in postoperative complications in CD, with higher rates of complications.

Author	Journal	Year	Study type	Number of patients exposed to biologicals	Observations
Appau et al.	J Gastrointest Surg	2008	Single-center retrospective	60	Higher rates of sepsis, abdominal abscesses, readmissions and anastomotic dehiscence.
Rizzo et al.	Int J Colorect Dis	2011	Single-center retrospective	54 (Ulcerative colitis included)	Higher rates of infectious complications in univariate analysis
Kopylov et al.	Inflamm Bowel Dis	2012	Meta-analysis	423	Higher rates of infectious complications not related to the surgical site
Serradori et al.	Br J Surg	2013	Multicenter retrospective	42	Concomitant use of biologicals with corticosteroids increased infectious complications in multivariate analysis
Syed et al.	Am J Gastroenterol	2013	Single-center retrospective	150	Higher rates of infections in general and of surgical site infections
Narula et al.	Alim Pharmacol Ther	2013	Meta-analysis	987 (Ulcerative colitis included)	Higher rates of complications in general and of infectious complications
El-Hussuna et al.	Dis Colon Rectum	2013	Meta-analysis	Not defined	Higher rates of anastomotic complications in low bias studies
Yang et al.	Int J Surg	2014	Meta-analysis	Not defined	Higher rates of complications in general and of infectious complications
Lau et al.	Ann Surg	2014	Single-center prospective	123	Higher rates of complications in general and of infectious complications in patients with detectable serum IFX

in users of IFX. However, the authors did found that blood loss >400 ml ($p < 0.003$) and emergency surgery ($p < 0.005$) were the only risk factors for increased postoperative complications.[20]

Nasir et al. published in 2010 an update of the experience of the Mayo Clinic in Minnesota (United States) on the subject, this being the first study to include patients using ADA and CTZ in a series. The authors included patients presenting any intra-abdominal suture line, as a result of the surgical procedure for CD. The results of 119 patients previously exposed to anti-TNF agents, compared to 251 who did not use biologicals, were similar with respect to postoperative complications (27.9% *vs.* 30.1%, $p = 0.63$), showing no higher rates of complications in patients using anti-TNF agents prior to surgery.[21]

In Brazil, Kotze et al. presented in 2011, during the Crohn's and Colitis Foundation of America (CCFA–USA) meeting, the results of a pilot sample of patients, with lack of association between surgical complications and previous use of biologicals in CD patients. 76 patients were studied, 19 of them with prior exposure to biological agents (12 to IFX and 7 to ADA). The rates of overall postoperative complications, anastomotic dehiscence, urinary tract infection and pneumonia were similar between these two groups. This was the first study on the subject in Brazilian patients, and although published in abstract form, showed interesting results, compatible with those found in most papers from the international literature.[22]

Canedo et al. published the results of a retrospective study from the Cleveland Clinic, Weston, Florida, United States. The study included 225 patients undergoing bowel resection for CD divided into 3 groups: those with previous IFX, those on immunosuppressants and corticosteroids, and finally those on aminosalicylates only. In this series, there were no differences between the groups regarding pneumonia ($p = 0.14$), surgical site infection ($p = 0.35$), abscess ($p = 0.34$) and anastomotic dehiscence ($p = 0.44$) rates. Thus, the authors concluded that the previous use of IFX was not related to changes in postoperative outcomes in patients with DC in need of major abdominal surgery.[23]

El-Hussuna et al., in a Danish study that included 417 patients operated in four different hospitals, compared the postoperative outcomes of 32 patients operated with previous use of biologicals *versus* 385 patients without previous use of this agents. No higher rates of anastomotic postoperative complications were found in the group previously exposed to biological agents *versus* non-exposed group (9% *vs.* 12%; $p = 0.581$). In this study, a multivariate analysis showed that prior use of corticosteroids in daily doses >20 mg and colon-colonic anastomoses were main risk factors for anastomotic dehiscence in CD patients.[24]

In a German study, Kasparek et al. analyzed the impact of prior use of IFX in abdominal operations secondary to CD. As methodology, these authors matched their patients with control-cases. In each group, 48 patients with similar demographic characteristics and minor complications were included. No major postoperative morbidity in terms of sepsis

and anastomotic complications was found between groups, besides in-hospital length of stay. The authors suggested that there is no need for a change in surgical strategy in CD patients only in face of the use of IFX *per se*.[25]

Mascarenhas et al. studied possible complications secondary to ileocolic resection from a different perspective, but also retrospectively. These authors compared the complications in 93 CD patients (19 with previous use of biological therapy) *versus* 698 patients undergoing ileocolectomy for other causes. In a subanalysis of their study, these authors found no increase in the overall complication rate in patients with CD with or without previous use of biologicals.[26]

Norgard et al., in Denmark, reported their findings in a full-country database with over 2000 patients. The postoperative outcomes after major abdominal surgery for CD in 214 patients with previous use of biological agents were compared with the outcomes from 2079 patients without exposure to these drugs, in the largest study on the subject ever published in literature. The authors concluded that there was no difference in complications between the time of previous use of IFX (less than two weeks from the date of the operation and 2–12 weeks from the date of the procedure) *versus* control group. These authors also concluded that no higher rates of reoperation, anastomotic dehiscence and bacteremia occurred in patients with prior use of anti-TNF agents.[27]

In an interesting Canadian study, Waterman et al. also compared the effects of prior exposure to biological agents in abdominal operations secondary to CD. In this series, 195 patients had previously used IFX or ADA (or both) in a population of 473 patients, including patients with ulcerative colitis and indeterminate IBD. In patients with a combination of biologicals with immunosuppressive drugs prior to their surgery, higher rates of urinary tract and surgical site infection were found. The time elapsed since the last dose of the biological agent to surgery (less than 2 weeks, 2–4 weeks and 30–180 days) did not influence postoperative complication rates. One of the novelties of this study was the determination of serum levels of IFX previously to the procedure, and patients with detectable levels of the drug had early complications in similar numbers to those with undetectable levels.[28]

Bafford et al. published in 2013 the Mount Sinai Hospital experience for surgical complications in 196 CD patients, divided into 2 groups – with and without use of immunosuppressive drugs (including biological agents). Like many studies in the literature, the authors identified a higher risk of complications in users of biological agents. Additionally, these authors have not concluded in favor of an increased risk of postoperative complications in patients previously medicated with corticosteroids, thiopurines, or with a combination of more than one immunosuppressive agent.[29]

A meta-analysis published in 2013 by Billioud et al. included 21 studies on the effect of biologicals in abdominal surgery for IBD in general (CD and ulcerative colitis analyzed together). The authors concluded that there was an increased risk of infections in general in the postoperative period in CD patients (OR = 1.45; 95% CI = 1.03–2.05), but emphasized that potential influencing factors, mainly concomitant therapies, might not be adequately studied.[30] These results were similar to those in a meta-analysis published by Rosenfeld et al. in 2013, who found no influence of biological therapy on complications in patients from almost the same studies.[11]

Also retrospectively, Krane et al. studied possible consequences of IFX use in operations conducted solely by laparoscopy. This US sample included CD and ulcerative colitis patients, and 65 CD patients were operated with previous use of IFX, and their results in terms of complications were compared to 194 patients with the same disease and without prior biological treatment. There was no difference between groups regarding the conversion rates to laparotomy, overall complications, anastomotic dehiscence, thromboembolic events and infections. The authors concluded, through a multivariate analysis, that there is no influence of IFX on surgical outcomes after laparoscopic operations.[31]

In a Scandinavian study, Myrelid et al. studied 298 patients from six referral centers, 111 of whom previously exposed to the use of biologicals before surgery. The primary objective of the study was to analyze comparatively the two groups in relation to the previous use of these drugs and anastomotic complications. Infections in general were secondarily analyzed. The authors demonstrated that there was no difference between groups for anastomotic complications (7.2% *versus* 8%; $p = 0.976$), postoperative complications and infections in general. Similarly, differences in terms of anastomotic dehiscence between groups were not found in a multivariate analysis (OR = 0.89; 95% CI = 0.37–2.17), revealing no relationship between previous use of biologicals and worse postoperative outcomes.[32]

In a more recent critical review, Papaconstantinou et al., through a systematic literature review, carefully analyzed the most important studies discussed in this session, and using scores of studies by MINORS criteria, were unable to reach firm conclusions about the real impact of biological agents on postoperative outcomes in Crohn's disease.[33] The results of the main studies that didn't show a possible effect of biological agents on postoperative outcomes in CD patients are summarized in Table 2.

Experimental studies

An interesting experimental study on the "surgery and biologicals" theme was published by Lopes et al. in 2008.[34] Wistar rats, allocated into, with and without a single subcutaneous dose of 5 mg/kg of IFX, were operated. A median laparotomy was performed in these animals and, after euthanasia, the tensile force required for opening the suture line in the abdominal wall was measured. It was observed in this study that rats with prior IFX needed less tensile strength to open the suture line *versus* control group on days 3 and 7 after laparotomy. This study suggested a potential effect of IFX on changes in inflammatory and proliferative phases of wound healing, which could have an impact on a possible increase on the rates of anastomotic dehiscence.[34]

More recently, the international literature has been concerned with an understanding, at the physiological and cellular level, on the effects of anti-TNF agents in the process of anastomosis healing, and consequently on a possible impact on the success of the surgical outcome. Thus, some experimental studies have recently been published.

Table 2 – Main studies showing no difference in the rate of postoperative complications in patients with CD using biologicals.

Author	Journal	Year	Study type	Number of patients exposed to biologicals	Observations
Tay et al.	Surgery	2003	Single-center retrospective	72	Higher rates of intra-abdominal septic complications not reported
Colombel et al.	Am J Gastroenterol	2004	Single-center retrospective	52	Increased risk of complications in general or septic complications not found
Marchal et al.	Alim Pharmacol Ther	2004	Single-center retrospective	40	Higher rates of complications and differences in in-hospital length of stay were not found
Kunitake et al.	J Gastrointest Surg	2008	Single-center retrospective	101	Overall, no differences in rates of medical and surgical complications. However, a longer mean in-hospital length of stay was found
Indar et al.	World J Surg	2009	Single-center retrospective	17	No major complications were identified
Nasir et al.	J Gastrointest Surg	2010	Meta-analysis	119	No higher rates of complications were found
Kotze et al.	Inflamm Bowel Dis	2011	Multicenter retrospective	19	No differences in rates of postoperative complications in general, anastomotic dehiscence, urinary tract infection and pneumonia
Canedo et al.	Colorectal Dis	2011	Single-center retrospective	65	No differences in pneumonia, surgical site infections, abscesses and anastomotic dehiscence rates
El-Hussuna et al.	Scand J Gastroenterol	2012	Multicenter retrospective	32	No higher rates of postoperative anastomotic complications were observed
Kasparek et al.	Inflamm Bowel Dis	2012	Single-center retrospective	48	There were no major postoperative morbidity in terms of sepsis and anastomotic complications, besides in-hospital length of stay
Mascarenhas et al.	Am J Surg	2012	Retrospective	19	No increase in overall complication rate in a subanalysis of the study
Norgard et al.	Aliment Pharmacol Ther	2013	Multicenter retrospective	214	There were no differences in complications, or higher rates of reoperation, anastomotic dehiscence and bacteremia
Waterman et al.	Gut	2013	Single-center retrospective	195 (Ulcerative colitis e undetermined IBD included)	Higher rates of urinary tract infections and in the surgical site. Time since the last dose of biological agent and surgery did not influence postoperative complications.
Bafford et al.	J Clin Gastroenterol	2013	Single-center retrospective	63	No increased risk of complications identified.
Billioud et al.	J Crohns Colitis	2013	Meta-analysis	977	Increased risk of postoperative infections overall, but the authors could not properly study the influence of concomitant therapies.
Rosenfeld et al.	J Crohns Colitis	2013	Meta-analysis	344	There was no influence on complications.
Krane et al.	Dis Colon Rectum	2013	Single-center retrospective	65	Increased risk of postoperative infections overall, but the authors could not properly study the influence of concomitant therapies.
Myrelid et al.	Br J Surg	2014	Multicenter retrospective	111	There was no difference in anastomotic complications, postoperative complications and general infections.
Papaconstantinou et al.	J Gastrointest Surg	2014	Meta-analysis	1554	The authors did not reach, consistent conclusions

Table 3 – Main experimental studies analyzing the impact of the use of biologicals in postoperative complications in CD.

Author	Journal	Year	Study type	Number of animals exposed to biologicals	Observations
Lopes et al.	Acta Cir Bras	2008	Experimental prospective	30	Lower tensile strength to break suture lines; changes in inflammatory and proliferative phases of wound healing, and may increase anastomotic dehiscence
Papaconstantinou et al.	Int J Surg	2014	Experimental prospective	28	No difference in bursting pressure of anastomoses and in septic complications. Less inflammatory activity and increased tissue remodeling, without clinical consequences
Frostberg et al.	BMC Surg	2014	Experimental prospective	15	No difference in tensile strength to break suture lines
Jensen et al.	Surg Res	2014	Experimental prospective	21	Lower tensile strength to break anastomoses

A study from Greece sought possible effects of IFX in intestinal anastomoses in rats. After resection of the terminal ileum in their animals, the authors proceeded with a macro and microscopic analysis of anastomoses, besides dosing some cytokines by immunohistochemistry. In this study, there was no difference in anastomosis bursting pressure, as well as in septic complications in animals exposed to IFX *versus* controls. Additionally, the authors found an increased expression of TGF-beta1, MMP2 and collagen V in those animals previously exposed to IFX, showing less inflammatory activity and increased tissue remodeling, but without clinical consequences for the animals.[35]

Two recent studies have tried to analyze similar aspects, but in rabbit experimental models. Frostberg et al., in anastomoses performed in 30 rabbits (15 with a single dose of IFX 10 mg/kg) found no difference between groups in terms of tensile strength to break the suture lines.[36] In another experimental study from Denmark, Jensen et al. showed opposite results. In 32 operated rabbits, these authors verified that less tensile strength would be used to break the anastomoses in rabbits previously exposed to IFX (1.94 ± 0.44 N in IFX group *versus* 3.33 ± 0.39 N in placebo group, $p < 0.001$).[37] The results of the main experimental studies on this subject are detailed in Table 3.

Final considerations

In short, the controversy about the real impact of biological agents *per se* on the postoperative outcomes of abdominal surgery with resection in CD patients still persists.[38] There is a significant diversity in methodologies used in reviewed retrospective studies and in meta-analyses published. The only prospective study on the subject suggests that patients with higher serum levels of IFX could present higher rates of postoperative complications, but the sample of patients in each subgroup was small. Many studies intermingled CD with ulcerative colitis patients; this may also have implied some bias to their respective results. Some studies focused on overall complications, others only in infectious complications, and even others exclusively on surgical complications, which prevent a detailed conclusion on the subject. A controlled, multicenter, prospective study called PUCCINI trial is currently being conducted in the United States.[39] It is expected that more solid answers will be obtained in a study like this, more robust and with a higher level of evidence. Associated factors such as previous use of corticosteroids and malnutrition should always be considered in patients using biological therapy before abdominal surgical procedures in CD patients. An individualized decision on the type of procedure and on the best timing for its execution should be taken; the surgeon must study the situation as a whole, not considering only the type of medication used by the patient.

Conflicts of interest

The authors declare no conflicts of interest.

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