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The impact of biologics in surgical outcomes in ulcerative colitis

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ABSTRACT

Ulcerative Colitis (UC) is an immune mediated condition characterized by inflammation of colonic mucosa, associated with progressive damage of the colon and possible complications, such as hemorrhage, perforation and cancer. It is strongly advocated a treat to target approach in patients with UC consisting in an early and aggressive inflammatory control. Some patients can require colectomy for medically refractory disease or to treat colonic neoplasia. Even though the first line biologic therapy targeting the tumor necrosis factor-alfa (TNF-α) is associated with improvement of the inflammation in some patients, others do not respond at first or lose response over time. Novel drugs targeting different inflammatory pathways have been studied in UC, however, it remains unclear whether surgical rates have been reduced in the biological era. Controversy also exists if biological agents impair surgical postoperative complication rates in UC. The aim of this review is to describe all relevant data available and briefly summarize the real impact of biologics in surgical outcomes in ulcerative colitis.

1. Introduction

Ulcerative colitis (UC) is a chronic immune mediated inflammatory disease affecting the colon, characterized by a relapsing and remitting course, and commonly associated with irreversible tissue damage, acute and long term complications, ultimately resulting in an impaired quality of life and disability [1,2]. Its incidence is rising worldwide [3]. The pathogenesis is multifactorial, involving genetic predisposition, epithelial barrier defects, dysregulated immune responses, and environmental factors [4,5].

Early and aggressive medical intervention in the management of the disease, could alter its natural course, and aim to induce and then maintain steroid-free remission, defined as resolution of symptoms, normalization of biomarkers and endoscopic healing [6–8].

The traditional step-up approach consists of first-line therapy with "conventional" or standard of care treatment such as 5-aminosalicylic acid drugs, corticosteroids, and immunomodulators (azathioprine and 6-mercaptopurine) [9].

Across various cohorts, between 14 and 47% of adults with UC will develop pancolitis and 12–15% will develop severe disease requiring hospitalization [10]. Approximately 20% of patients with UC will require surgery during the course of their disease. The rate of colectomy after a disease duration of 10 years is approximately 16% [11]. Possibly, the cumulative risk of surgery among patients with UC has changed over time, with recent advances in medical therapy.

Since their introduction in the therapeutic armamentarium in late 1990s, biological therapy (anti-tumor necrosis alpha [TNFα] and more recently anti-integrin agents) have demonstrated clear efficacy in inducing and maintaining clinical and endoscopic remission, but it is still debated whether the use of these agents leads to fewer hospitalizations and surgeries, or merely delays surgical interventions [12–14].

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Surgery for UC should be indicated by interdisciplinary means and failure to medical therapy is considered to be the most common indication, followed by dysplasia or neoplasia. Perforation, fulminant bleeding, and toxic megacolon represent the emergency indications for surgery in patients with UC [15].

The aim of this review is to present current evidence regarding surgical trends in UC after introduction of biological therapy in the management of the disease, as well as to describe and discuss the impact of biological drugs in postoperative outcomes.

2. Ulcerative colitis, surgery and anti-TNF agents

Over the last two decades, five TNF-targeting agents were studied in autoimmune inflammatory diseases [16], but only infliximab (IFX) [17], adalimumab (ADA) [18,19], and golimumab (GOLI) [20,21] are currently approved for the management of UC.

2.1. Infliximab (IFX)

IFX is the first anti-TNF agent approved for UC and continues to be a mainstay for the treatment of moderate-to-severe disease refractory to conventional therapy [9,17,22]. It is a chimeric murinic IgG1 monoclonal antibody that binds with great affinity to soluble TNF-α, thus, it prevents this cytokine from binding to their respective cellular receptors. Moreover, IFX is also responsible for inducing apoptosis of inflammatory cells while binding to its membrane-bound TNF [23].

Pivotal prospective, randomized, placebo-controlled trials (ACT 1 and ACT 2), aimed to evaluate the safety and efficacy of IFX for the management of moderate-to-severe UC. Data showed superior clinical response/remission and mucosal healing rates over both, induction and maintenance phase, as compared to placebo [17]. A total of 728 patients were allocated into 3 groups in each protocol to either receive placebo, IFX 5 mg/kg or IFX 10 mg/kg of body weight administered intravenously at weeks 0, 2 and 6 (induction phase) and then every eight weeks (maintenance phase) through week 46 (in ACT 1) or week 22 (in ACT 2). Results from both ACT 1 and ACT 2 trials, showed a superiority of IFX (5 or 10 mg/kg) in clinical response (61.5–69.4% *vs.* 29.3–37.2%, $p < 0.001$), clinical remission (27.5–38.8% *vs.* 5.7–14.9%, $p < 0.001$) and mucosal healing (59–62% *vs.* 30.9–33.9%, $p \leq 0.002$) rates at week 8, as compared to placebo (primary endpoint). Furthermore, drug exposed patients were more likely to have a clinical response at week 30 ($p = 0.002$) and at week 54 (45% *vs.* 20%; $p < 0.001$), when compared to placebo [17].

Despite positive results over clinical response/remission and mucosal healing rates, data regarding surgical outcomes, hospitalization and postoperative outcomes in UC patients under biologic therapy are conflicting. Moreover, available data from colectomy rates and postoperative complications derived from randomized controlled trials are limited, and most of the studies are from observational or retrospective cohorts. Therefore, it is a challenge to distinguish the influence of possible confounders in each study population, such as disease duration and severity along with nutritional status, that could be considerate as predictive factors for developing post-surgical complications [24].

Some studies suggested that IFX might reduce the short-term need for surgery and UC related hospitalizations [25,26]. Pivotal trials (ACT 1 and 2) evaluated surgical outcomes in 87% of the enrolled population (total of 630 patients) after 54 weeks of follow-up. The cumulative incidence for colectomy was 10% in IFX-exposed patients *vs.* 17% in the placebo group ($p = 0.02$). Fewer UC related hospitalizations and surgical procedures per 100 patient-years of treatment occurred in patients under IFX therapy [26]. Reich et al. conducted a retrospective chart review of 657 UC patients who were submitted to colectomy from 1998 to 2011. Their results showed that urgent colectomy rates declined after 2005, with an annual percent change of 18.6%, along with elective colectomy rates with an annual percent change of 14.9% [27]. Thus, a suggestion of decreased surgical rates in the biological era, after the approval of IFX in 2005 could be observed.

In contrast, some studies suggested that colectomy rates in UC patients under biologics remained unchanged throughout the years. Moore et al. retrospectively reviewed 7.227 individuals from 2001 to 2010 and found that there were a slightly reduction in colectomy rates after incorporation of biological agents in the management of the disease (from 9.97% to 8.88%, $p = 0.03$). However, colectomy rates remained stable when considering only severe cases of UC (9.97% *vs* 11.14%; $p = 0.18$) [28].

Abelson and colleagues reviewed data from 9.244 UC patients submitted to related-disease surgery between 1995 and 2013 (2.174 excluded for several reasons: diagnosis of cancer, partial colectomy, proctectomy, or colostomy, or had unreasonable reoperation sequences). Subsequently, they allocated the remaining population into 2 period-groups: 1995–2005 and 2006–2013 (pre and post-IFX, respectively). Their results showed that UC-related surgery after 2005 was more likely to require multiple procedures and had worse postoperative morbidity during the index hospitalization, at 90-day and 1-year follow up. Possibly, a worse clinical scenario with a more aggressive refratrory disease, described in the latter group-period, was associated with a multistage surgery approach. Moreover, a refractory disease profile could have higher adverse surgical outcomes when compared to patients presenting with mild disease, submitted to previous early surgical intervention. The current study did not consider previous medication, disease activity or nutritional status [29].

Surgical complications after preoperative IFX therapy remain a major concern and controversial issue in the surgical management of UC. TNF is a critical component of the immune response and wound healing [30]. Inhibition of TNF could, theoretically lead to some postoperative complications, such as infections, anastomotic leaks, and intra-abdominal abscesses [31]. A systematic review of 7 different studies ($n = 162$) under IFX treatment submitted to primary ileal pouch-anal anastomosis (IPAA) showed higher rates of early pouch-specific complications occurring after ileostomy closure when compared to patients not using preoperative IFX [32].

Conversely, Zittan et al. conducted a retrospective analysis of 773 UC patients who underwent IPAA, of whom 196 were exposed to IFX preoperatively. Their results showed that IFX was not associated with an increased risk of infectious and noninfectious complications after IPAA, including pelvic abscesses, leaks, and wound infections [33].

Yang et al. published a meta-analysis in 2010 that demonstrated an increased risk of short-term postoperative complications in patients who were exposed to IFX previous to surgery [34]. However, later in 2012, the same authors, reproduced a different meta-analysis with more consistent data, and concluded that preoperative IFX use does not increase the risk of early postoperative complications in UC patients undergoing abdominal surgery [24]. These two different meta-analysis from the same authors represent the controversy over the topic.

Lau and colleagues, in the first prospective study over the topic, assessed preoperative IFX levels of 217 patients submitted to abdominal surgery (123 CD and 94 UC) and correlated these findings with early postoperative outcomes. In the UC group, there were no significant differences in adverse postoperative complications, morbidity and hospital readmissions between detectable and undetectable serum IFX level groups, even when stratified into types of index surgery (IPAA and subtotal colectomy or total proctocolectomy/end-ileostomy). This study showed that