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EDITORIAL

Surgical treatment of ulcerative colitis in the biologic therapy era

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Abstract

Recently introduced in the treatment algorithms and guidelines for the treatment of ulcerative colitis, biological therapy is an effective treatment option for patients with an acute severe flare not responsive to conventional treatments and for patients with steroid dependent disease. The reduction in hospitalization and surgical intervention for patients affected by ulcerative colitis after the introduction of biologic treatment remains to be proven. Furthermore, these agents seem to be associated with increase in cost of treatment and risk for serious postoperative complications. Restorative proctocolectomy with ileal pouch-anal anastomosis is the surgical treatment of choice in ulcerative colitis patients. Surgery is traditionally recommended as salvage therapy when medical management fails, and, despite advances in medical therapy, colectomy rates remain unchanged between 20% and 30%. To overcome the reported increase in postoperative complications in patients on biologic therapies, several surgical strategies have been developed to maintain long-term pouch failure rate around 10%, as previously reported. Surgical staging along with the development of minimally invasive surgery are among the most promising advances in this field.

Key words: Ulcerative colitis; Inflammatory bowel disease; Infliximab; Surgery; Laparoscopy; Single incision laparoscopy; Total abdominal colectomy; Ileal pouch anal anastomosis; Restorative proctocolectomy

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INTRODUCTION

Ulcerative colitis (UC) is a mucosal inflammatory process affecting the rectum and the colon. It is characterized by contiguous inflammation starting in the rectum and progressing for variable distance proximally[1]. Intermittent exacerbations are typical, with symptoms characterized by bloody diarrhea associated with urgency and tenesmus[2]. The activity of disease can range from complete remission to fulminant symptoms along with systemic toxic effects[3].

Although the exact pathogenesis of UC remains poorly

understood, the most credited model states that the intestinal flora triggers and drives an aberrant intestinal immune response and subsequent inflammation in a genetically susceptible host[4]. Medical therapy aims at the control of symptoms and the resolution of the underlying inflammatory process, classically by a variety of agents in combination, such as 5-aminosalicylates, corticosteroids, and immunosuppressants, including purine antimetabolites and cyclosporine[5]. Treatment schemes are based on disease severity, (defined as mild, moderate or severe based on clinical ad laboratory parameters) and on the extent of the disease (pancolitis, left-sided colitis, rectosigmoiditis or proctitis)[6]. However, about a quarter of patients with UC end up needing a colectomy because of failure of medical therapy, onset of unacceptable side effects of chronic therapy, occurrence of acute complication of UC (fulminant colitis, severe bleeding, toxic megacolon, perforation), or development of malignancy[7].

For all of these patients, the removal of the colon and rectum represents a definitive cure for their disease, with cessation of symptoms, withdrawal of morbid medical therapy, and avoidance of the risk of developing a malignancy associated with the persistence of inflammation[8].

However, surgery is not without risks and can significantly affect patients' lifestyle, therefore, is traditionally deemed as a salvage treatment when medical therapy is ineffective[1].

During the last three decades astounding progress has been accomplished both in medical and surgical treatments, which might lead to substantial changes in the traditional principles for the management of UC patients. Medical therapy of UC has recently entered the era of biologic treatments with the approval by Food and Drug Administration (FDA) in 2005 of Infliximab, a monoclonal antibody directed against tumor necrosis factor-alpha. The initial enthusiasm raised by the promise to reduce the colectomy rate in acute presentations, was subsequently partially dampened by conflicting reports regarding Infliximab's safety and impact on the need for surgery in urgent/emergent setting[9-13].

As the number of available medications increases, more and more often patients are referred for surgery severely malnourished, immunocompromised, and experiencing the side effects of corticosteroids, immunomodulators, and biological agents. Whether they are referred for colectomy in an acute or chronic setting, these patients represent a unique challenge for colorectal surgeons, given the compromised general conditions and poor nutritional status in the former, and the side effects of long term corticosteroid use in the latter[14-16].

Together with the advances in medical therapy, the surgical treatment and techniques in UC has evolved as well. Restorative proctocolectomy with ileal pouch-anal anastomosis (IPAA) is today considered the gold standard and, in experienced hands, can now be performed safely for UC with a low postoperative complication rate and a long-term pouch failure rate reported less than 10%[17-19]. Moreover, the introduction of minimally invasive techniques might further decrease postoperative morbidity and improve patients' satisfaction, with reduced impact on body image and better cosmesis[20-22].

The purpose of this report is to discuss the recent advances in medical and surgical treatment of UC patients addressing surgical concerns in the era of biologic therapy.

BIOLOGIC THERAPY IN UC: THE GASTROENTEROLOGIST'S VIEW

The primary goals of medical therapy in the treatment of UC are to induce remission of symptoms and maintain it on a long-term basis: by reducing the number of relapses, which occurs in 67% of patients and, at least, once over a 10-year period[23], medical therapy lowers the risk of long-term complications and improves patients' quality of life.

The majority of UC patients present with moderate- to severe disease (80%) rather than mild disease (20%)[24] and, during their illness, nearly 20% of patients afflicted with UC will experience a severe acute episode that requires hospitalization[25].

Despite the progress accomplished in medical therapy, which broadened the horizon of possible treatments after failure of corticosteroids[26,27], the need for surgery in this patient population seems to be unchanged or slightly decreased over time. Reported colectomy rates are steadily ranging between 20% and 30% in most of the epidemiological studies with additional risk for needing a resection as the extent and severity of the disease increase[8,28-31]. Beside a 10% who have surgery for cancer or pre-neoplastic degeneration, the vast majority of patients need an operation for acute colitis with severe complications not responsive to medical therapy[32,33]. The advantage of prolonged medical therapy *vs* surgery in patients with acute severe colitis failing initial high dose corticosteroids is still debated. About one third of these patients undergo a colectomy within one year, most likely in an emergency setting, and even if second-line medical therapy may reduce the need for immediate colectomy, most of them will require colectomy by 10 years[32,34]. In this setting, early subtotal colectomy and ileostomy combined with a late reconstructive surgery remains a safe alternative[19] since second-line medical therapy carries with it a not negligible mortality risk[35].

Additionally, about 20% of patients with UC have a persistent active disease often requiring several courses of systemic steroids, but followed by relapse of symptoms during steroid tapering or soon after their discontinuation, a condition known as steroid-dependency. Steroid dependency is associated with serious complications, which, for a significant proportion of patients, become an indication for surgery[36].

Although surgery is curative of the underlying inflammation and restorative proctocolectomy with IPAA preserves the normal anatomic route for defecation, the procedure may lead to new symptoms, such as diarrhea,

incontinence, nocturnal leakage, and in some patients does not obviate the need for medication. In several surgical series that follow patients a minimum of 5 years, up to 60% of patients are still having more than 8 bowel movements daily, with 55% of patients experiencing incontinence, and 50% nocturnal leakage[37-39]. Even if surgical techniques have dramatically evolved, surgery is still associated with significant early and late postoperative complications, e.g. anastomotic leak, pelvic sepsis, small bowel obstruction, pouchitis, sexual dysfunction, reduced fecundity in women and pouch failure[40,41]. Repeated surgery is sometimes necessary. A population-based study reported that approximately 20% of patients who had undergone IPAA required at least one additional surgery, and 15% of patients required at least two additional surgeries[42]. Pouch leak and the associated pelvic sepsis rate in large series have been reported to range from 5% to 15%[43]; incidence of late small-bowel resection after IPAA ranges from 12% to 35%. Pouchitis is the most frequent long-term complication of the IPAA[1]. It has been reported in 12% to 50% of patients postoperatively, and some patients (5%-19%) require chronic therapy. Finally, the risk of long-term pouch loss has been reported to range from 1% to 20% in different studies with an overall rate of pouch loss less than 10%, needing diverting ileostomy, pouch excision and end ileostomy, or pouch revision[17-19].

Acute severe ulcerative colitis

According to current treatment algorithms, in case of acute colitis, unless toxic megacolon, perforation or severe bleeding-which are absolute indication for surgery-occur, patients are started on high-dose iv steroids[44]. Response to treatment is assessed by objective measures (e.g., Oxford index or Sweden index) on day 3-4. Two different strategies have been developed in the attempt of avoiding surgery when a first course of steroids fails to control an acute flare. The standard approach in the '80s was to prolong the administration of steroids for other 7-10 d, which did not show any reduction in colectomy rates[45-47]. Ten years later, cyclosporine was found to be effective in patients with acute severe UC non responsive to steroids, and has been used as rescue therapy[44,48-51]. In a randomized controlled trial (RCT) 82% of patients on cyclosporine improved, while no patient improved in the placebo group[52]. However, as many as 50% of patients that responded to cyclosporine, required colectomy in subsequent studies with longer follow-up[35,53]. Moreover, the management of patients under cyclosporine can represent a real challenge, given the risk of severe and potentially fatal toxicities, which greatly limit the use of this medication.

Infliximab, an anti-tumor necrosis factor (TNF) antibody, has been approved recently by the United States FDA for the treatment of UC to reduce signs and symptoms, to induce clinical remission and healing of the intestinal mucosa, and to eliminate the use of corticosteroids in patients presenting with moderately-to-severely active UC without adequate response or who are intolerant or have medical contraindications to therapy with corticosteroids or immune modulators[54].

Response to infliximab has been assessed in RCTs with various endpoints such as clinical response, remission and colectomy rates. In patients with severe, steroid-refractory UC, the initial small trials demonstrated modest efficacy after single infusions when early clinical response was determined. The first published trial by Sands *et al*[55] in 2001 randomized 11 patients with steroid refractory UC to a single infliximab infusion or placebo, and noted a 50% (4/8) clinical response rate with infliximab at a week 2 evaluation. Subsequent studies by Probert *et al*[56] and Järnerot *et al*[51] also enrolled patients with steroid-refractory disease. The first study failed to show any significant difference between placebo and 2 infusions of infliximab 5 mg/kg in inducing remission as measured by endoscopy or clinical score. However, Järnerot *et al*[51] demonstrated in patients with moderate and severe steroid-refractory UC that only 7/24 (29%) patients who received a single infliximab infusion underwent colectomy within 90 d, compared with 14/21 (67%) who received placebo. The superiority of infliximab was only statistically significant in patients with moderate to severe disease, but not in those with more severe disease on the fulminant colitis score, although the study was not powered to detect differences between these two last groups. Even though a later report showed that at 2 years follow-up, the colectomy rate in patients who received infliximab had increased to 46%[57], these studies positioned infliximab as a therapeutic option for patients with steroid-refractory disease. The first controlled trial[58] involving patients who had moderate to severe disease that were neither steroid-dependent nor steroid-refractory, reported superior clinical response rates compared to those seen in steroid-refractory populations. These trials reported high response rates (100% and 83%, respectively), but follow-up was short (9.7 and 3 mo, respectively). The active ulcerative colitis trial (ACT) 1 and ACT 2 trials[59] each randomized 364 patients with moderate to severe UC who were failing conventional therapy (but did not require hospitalization) to either placebo or induction/maintenance infliximab 5 mg/kg or 10 mg/kg. Both in ACT 1 and ACT 2, eligible patients had moderate to severe UC despite concurrent treatment with corticosteroids, alone or in combination with azathioprine or mercaptopurine, but ACT 2 also required that the patient had failed 5-aminosalicylic acid (5-ASA) therapy. In ACT 1, both doses of infliximab (5 mg/kg and 10 mg/kg) resulted in a statistically significant clinical response at week 8 (68.4% and 61.5% respectively, $P < 0.01$, compared to a placebo response of 37.2%). This was similar in ACT 2, with clinical response at week 8 in 64.5% of patients in the infliximab 5 mg/kg group and 69.2% in the infliximab 10 mg/kg group, compared to a 29.3% response rate in the placebo group ($P < 0.001$). Clinical remission rates in the infliximab arms at week 8 ranged from 27.5% to 38.8% across both studies compared to

placebo-induced remission rates of 14.9% (ACT 1) and 5.7% (ACT 2). Mucosal healing and steroid-free remission rates were also superior in the infliximab arms of these studies. Sandborn *et al*[60] reported colectomy rates in ACT 1 and ACT 2 patients in a follow-up study. The cumulative colectomy rate at 54 wk was 10% in patients treated with infliximab, compared with 17% in those treated with placebo. These colectomy rates were not unexpected since the enrolled patients had moderate to severe disease, however in 13% of the enrolled patients the colectomy follow-up data was unavailable. The ACT 1 and ACT 2 studies were well-designed, large studies, with comprehensive assessment of clinical and secondary endpoints. They provided important data to support the use of infliximab in patients with moderate to severe UC who have failed other therapies such as steroids, immunomodulators and mesalamine. However, infliximab is not a panacea for all; the proportion of patients who started the study on steroids and were able to come off and remain in remission, was low (20%)[59].

In a recent study by Colombel *et al*[61], the association between early mucosal healing (defined as Mayo endoscopy subscore at week 8 endoscopy) and clinical outcomes in ACT-1 and ACT-2 patients was investigated. The authors observed that a low week 8 endoscopy subscore was significantly associated with a lower rate of colectomy at 54 wk follow-up ($P = 0.0004$; placebo $P = 0.47$) and better outcomes in terms of symptoms and need for steroids at weeks 30 and 54 ($P < 0.0001$, infliximab; $P < 0.01$, placebo), especially for those patients who did not achieve clinical remission at week 8[61].

A Cochrane meta-analysis of RCTs concluded that, when compared to placebo, treatment with infliximab is three-fold as effective in inducing clinical remission [relative risk (RR) 3.22; 95% CI: 2.18-4.76] and nearly twice as effective in inducing clinical response (RR: 1.99; 95% CI: 1.65-2.41) or endoscopic remission (RR: 1.88; 95% CI: 1.54-2.28) at week 8 in patients presenting with moderate-to-severe UC refractory to conventional treatment with corticosteroids and/or immune modulators[10].

Steroid dependent ulcerative colitis

Another specific pattern of UC disease is represented by steroid-dependent patients, in whom a response can be obtained with systemic steroids, but the relapse will occur as the dose is tapered or a few weeks or months after discontinuation, making it necessary to increase the dosage again or resume treatment to achieve control of symptoms[36]. As UC patients become dependent-upon or refractory to corticosteroids, the range of action from a medical standpoint become limited and a colectomy becomes a treatment option as the disease is deemed as refractory to medical treatment, or because of the occurrence of complications either related to the disease or associated with side effects of medications[1].

Often, immunomodulator therapies, such as azathioprine or mercaptopurine (6-mercaptopurine) are considered in these patients before surgery as a steroid-sparing treatment. However, the efficacy of azathioprine or mercaptopurine in UC is still debated[62]. Thiopurines are an effective maintenance therapy for patients who require repeated courses of steroids, however the quality of available data is quite poor, as stated in a recent Cochrane review[63]. Currently, the recommendation for using thiopurines in UC is based on the evidence shown by only one RCT of Ardizzone *et al*[64] which found steroid-free, clinical and endoscopic remission in 53% patients on azathioprine compared with 21% given only 5-ASA [odd ratio (OR) on intention to treat analysis 4.78, 95% CI: 1.57-14.5]. Azathioprine maintenance treatment of UC is beneficial for at least 2 years if patients have achieved remission while taking the drug, but not in those with chronic activity despite the drug[65].

When a steroid-dependent patient fails to benefit from thiopurines or shows intolerance to them, there are very few alternatives to conventional drugs, which lack of current definitive evidence of efficacy. Methotrexate has been tested and, although some uncontrolled studies suggested some benefit with its use[66-68], the only double-blind, placebo-controlled trial, showed no therapeutic benefit[69]. Therefore, current guidelines do not consider methotrexate as an evidence-based therapy in steroid-dependent UC.

After the demonstration of clinical efficacy of infliximab in the treatment of moderate-severe resistant UC, few small series have included steroid dependent patients. Only one study from Italy[70] specifically evaluated steroid dependent UC in an open-label study on 20 patients randomized to infliximab or methylprednisolone. This was the first RCT to implement a regimen of a triple infliximab infusion for induction followed by infusions to maintain remission. Even if this study was statistically underpowered, it demonstrated the benefit of infliximab therapy for responders, who were able to taper and then discontinue steroids during the maintenance phase (9 of 10 patients), as compared with the methylprednisolone group (8 of 10 patients), where responders required continued steroid therapy.

BIOLOGIC THERAPY IN UC: THE SURGEON'S VIEW

Biologic therapy has shown the ability to induce and maintain remission, but, as we stated above, its introduction in the therapeutic algorithm did not substantially affect the overall rate of colectomies, suggesting that it is effective only in delaying but not in avoiding surgery for a subgroup of patients who at some point will require an operation[54,59,60,71]. The clinical efficacy of infliximab in UC still remains unpredictable. Induction therapy is not always effective, and, to date, clinical and/or molecular predictors of response have not been identified. No RCT has been conducted comparing infliximab and cyclosporine in severe UC. Most of the current knowledge comes from the ACT 1 and ACT 2 trials. Those results are in part influenced by the heterogeneity of the sample (in-

Table 1 Literature-based comparison of postoperative complication risk associated with preoperative use of infliximab

Ref.	Year	Non-IFX/IFX patients	Infectious complication			Non-infectious complication		
			IFX group	Non-IFX group	OR (95% CI)	IFX group	Non-IFX group	OR (95% CI)
Selvasekar *et al*[13]	2007	254/47	13 (28%)	25 (10%)	3.50 (1.64-7.5)	16 (34%)	99 (39%)	0.81 (0.4-1.55)
Schluender *et al*[12]	2007	134/17	3 (18%)	11 (8%)	2.40 (0.6-9.63)	3 (18%)	26 (19%)	0.89 (0.24-3.33)
Kunitake *et al*[9]	2008	312/101	6 (6%)	32 (10%)	0.55 (0.22-1.36)	11 (11%)	17 (5%)	2.12 (0.96-4.69)
Mor *et al*[85]	2008	46/46	10 (22%)	1 (2%)	13.8 (1.82-105)	6 (13%)	6 (13%)	1.00 (0.3-3.37)
Ferrante *et al*[83]	2009	119/22	2 (9%)	29 (24%)	0.31 (0.07-1.141)	NR	NR	NR
Coquet-Reinier *et al*[84]	2010	13/13	NR	NR	NR	3 (23%)	4 (38%)	NR
Gainsbury *et al*[86]	2011	52/29	5 (17%)	14 (27%)	1.87 (0.46-7.57)	12 (41%)	16 (31%)	0.59 (0.19-1.87)

IFX: Infliximab; OR: Odd ratio; NR: Not reported; CI: Confidence interval.

cluding both steroid-dependent and/or immunomodulator-dependent and steroid responsive and/or immunomodulator-responsive patients). More studies are needed to assess the role of concomitant administration of immunosuppressants and infliximab[59]. Furthermore, data on maintenance therapy with infliximab in UC are scant and the benefits of continued maintenance therapy, as well as its long-term safety, are poorly known. The results of the ACT-1 and ACT-2 extension studies conducted on the 229 patients who achieved improvements with infliximab during the trials, showed that the benefits observed in the main studies are basically maintained up to 3 additional years, however an high drop-off rate was observed, due to adverse events (10.5%), lack of efficacy (4.8%), need for surgery (0.4%), or other reasons (14.8%)[72]. Furthermore, it is not clear to what extent postponing surgery by the means of a quite morbid medical therapy represents a safe and effective strategy.

Because of the early onset and chronic nature of inflammatory bowel diseases, patients can be expected to utilize considerable health care resources. Costs analysis are complicated, because they must calculate the impact that such therapies have on the direct costs of health care and the indirect costs for both the patient and their families and the health care system[73]. Surgeries and hospitalizations account for the majority of health care direct costs in inflammatory bowel disease (IBD), and medication costs, on the other hand, accounted for a quarter of total direct medical costs. Moreover, the cost data are right-skewed, with 25% of patients accounting for 80% of total costs[74]. This division of health care costs implies that the most effective cost-containment measure would be the one that reduces the number of hospitalizations and surgeries. With the improved response and remission rates seen with the use of infliximab for induction and maintenance treatment in IBD patients, the clinical benefits may likely translate into economic benefits as well[75]. Surprisingly, many of the cost-effectiveness and utility analyses suggested that infliximab use was associated with rather high incremental cost per quality adjusted year life[73] and the expanding use of infliximab has not significantly impacted the use of surgical procedures for patients with either UC or Crohn's disease, and rates of nonsurgical hospitalizations have actually increased[76,77]. This belief is supported by the observation that in the United States the hospitalization rates for IBD increased between 1998 and 2004, leading to a concurrent rise in the economic burden, with medical hospitalizations accounting for the largest proportion (58%) of inpatient services costs and biologic agents representing the most costly medications[78,79]. Further pharmaco-economic analyses are needed to accurately assess the impact of infliximab treatment on the costs associated with the treatment of UC.

Surgery in the biologic era: Treatment in evolution

The concept of pushing conservative treatment until surgery is strictly required may be risky, as it has been shown that mortality three years after elective colectomy for UC (3.7%) is significantly lower than that after admission without surgery (13.6%) or when an emergency operation is performed (13.2%)[80]. Moreover, a British study recently reported a significantly higher risk to develop major complications at a 5 year follow up for patients who received a longer course of medical therapy for acute severe UC before surgery, suggesting that the threshold for elective surgery may be too high in current practice[81].

While it's well known that high-dose systemic corticosteroid therapy (> 40 mg/d prednisolone-equivalent) is a widely recognized risk factor for pouch-related septic complications after restorative surgery[82], whether or not the preoperative administration of infliximab may increase the rates of septic complications is still controversial (Table 1)[9,12,13,83-86]. Nevertheless, the group from the Cleveland Clinic has found a covariate-adjusted risk of early complication for patients treated with infliximab 3.54 times higher, with the rate of sepsis increased by 13.8 folds, despite a significantly higher rate of three-stage procedures in the infliximab group[85]. Similar results have been shown in a paper by Mayo Clinic, where patients treated with infliximab prior to pouch surgery had a significantly higher incidence of anastomotic leaks, pouch specific and infectious complications, with the administration of anti-TNF-alpha as the only factor independently associated with septic complications (OR 3.5)[13]. In another study, a synergic interaction in increasing surgical morbidity was found between infliximab and cyclosporine A when administered together in the preoperative time[12]. These concerns are supported by a recent meta-analysis conducted including 5 studies and 706 patients, which revealed an

increased risk of short-term post-operative complications (OR 1.80, 95% CI: 1.12-2.87) associated with preoperative infliximab use, along with a trend towards increased post-operative infection[87].

Given the concern of increased rate of complications in patients on aggressive medical management, several different surgical approaches have been proposed. First described by Parks and Nichols in 1978, restorative proctocolectomy with IPAA has progressively gained acceptance to become the gold standard in the surgical treatment of UC for the last 25 years[88,89]. The introduction of this technique-most often fashioned as a J pouch created with the terminal ileum and anastomosed to the anal canal-was a real breakthrough, offering a curative treatment to these patients without the need for a permanent stoma, thus preserving their body image, achieving a quality of life comparable to that of the general population[38,90]. However, the procedure is technically demanding and is associated with a significant morbidity rate (around 30%), and an incidence of postoperative pelvic sepsis ranging between 5%-24%[91]. Since it has been shown that the occurrence of a pelvic infection can dramatically affect the functional outcome of the pouch, and considering that long-term steroid use and malnutrition are recognized risk factors for pelvic sepsis, surgical strategies have been developed in order to minimize the occurrence of infectious complications, especially in this subset of patients[92,93]. A total abdominal colectomy with end ileostomy is the operation of choice as first step of a restorative procedure, as it can be performed safely and quickly in the hands of an experienced colorectal surgeon, allowing the patient to overcome the colitis, wean off the medications, and return to an optimal health and nutritional status[94,95]. Moreover, as it is well known that a postoperative diagnosis of indeterminate colitis or Crohn's disease is not rare after colectomy in these patients[96], a multistep surgical procedure allows for selecting the most appropriate reconstructive surgery on the basis of the pathological findings of the colectomy specimen[19,94,97].

The removal of the rectum and the restoration of the bowel continuity with IPAA are performed as a second step when the patient has fully recovered, and the creation of a temporary ileostomy, although adding the need for one more operation, can further reduce the risk of local sepsis secondary to anastomotic leaks[98,99]. Albeit restorative surgery is not free from long term complications, such as incontinence and soiling (10%-60% of patients, depending on series and entity), pouchitis (about 50% of patients), and sexual dysfunction (20%-25% of cases), with a rate of pouch failure requiring excision ranging between 5%-15%, the majority of these conditions are manageable with medical and physical therapy, which explains the overall satisfaction in patients after IPAA, which exceeds the 90% in most series[40,98,100-105].

Indeed, most recent researches have shown that social and sexual function as well as overall quality of life is significantly improved after restorative surgery, when compared to the period with active UC or diverting ileostomy[106-109].

The application of minimally invasive techniques to the surgical treatment of UC at the beginning of the 1990s contributed in significantly improving the acceptance and tolerability of the procedure[110]. Numerous case series and, finally, two meta-analyses have been published since then, demonstrating the feasibility and safety of the laparoscopic approach, at the cost of longer operative times[110-117]. A subsequent RCT showed that operative time could be significantly reduced with the adoption of a hand-assisted technique, which at the same time allows for preserving the advantages of a minimal invasive approach[118]. Scant data is available so far regarding long-term outcomes, however the few series with adequate follow-up report laparoscopy pouch function results as good as the ones achieved with open surgery[21,119]. Laparoscopy has also been adopted with good results in the emergency setting[120,121], and similarly as for open surgery, a staged approach to a minimally invasive restorative procedure should be preferred which is as effective in significantly reducing the rate of post-operative pelvic sepsis[121-123]. Furthermore, when a staged procedure is planned, laparoscopy has been shown to decrease postoperative adhesion formation with less intraoperative adhesiolysis required during subsequent completion proctectomy and IPAA[124]. Similarly, a study by Indar and colleagues on 34 patients who underwent laparoscopic IPAA, where a laparoscopic exploration of the abdominal cavity was performed during the ileostomy closure, found that no patient had dense adhesion and only a minority of patients had filmy avascular adhesion to the abdominal wall (32%) and to the adnexa (29%), which represents a significant improvement compare to the rates reported for open surgery (as high as 90%)[125].

Despite the lack of strong evidence about the benefits attainable with laparoscopy in terms of short-term outcomes[21,126], it has been proven that patients treated laparoscopically are more satisfied with the cosmetic results and perceive a better body image-aspect anything but negligible in this usually young and socially active patient population-especially in the women's subset, as confirmed by the results of a RCT with a median follow-up of 2.7 years[21,119]. More recently, the quest for further minimizing surgical trauma and extent of incisions, has led to the development of single incision laparoscopy (SIL), which has already been applied in the field of colorectal diseases with proven benefits in terms of short-term outcomes over standard laparoscopy[127-131]. To date only few cases of SIL for UC has been reported, but preliminary results show that particularly for the total abdominal colectomy, this "no scar" approach have the potential for improving not only the cosmesis, but also the postoperative course, with less pain and reduced need for narcotics, which may translate in shorter hospital stay and faster return to normal activities[132-135]. Considering the excellent outcome of restorative surgery, heightened by the potentials of minimal invasive techniques, surgery should not be considered the last resort when everything has failed, but rather a valid alternative to an expensive and risky medical therapy[136].

CONCLUSION

Medical therapy in UC is rapidly evolving and the introduction of modern biological drugs has led to substantial changes in the traditional principles of management. Infliximab, the first biological agent used as rescue therapy after failure of steroids in UC, appears to be effective in reducing the need for urgent colectomy, although its efficacy in the long-term is not proven. In addition, concerns have been raised regarding the economic burden related to this drugs and the risk for serious postoperative complications.

Surgery continues to play an important role in UC treatment and its evolution keeps pace with the advance in medical therapy and the risk associated with it. Restorative proctocolectomy with IPAA, staged procedures, and minimally invasive surgery are important treatment tools to limit postoperative morbidity and achieve excellent long-term outcomes in these patients.

In an attempt at avoiding surgery, aggressive medical therapy is not without complications. A complex decision making process in a multidisciplinary fashion should take into consideration the excellent results of modern surgical therapies to avoid unnecessary morbidity.

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