that therapy with IFX significantly reduces the colectomy rate. Moreover, pre-operative treatment with IFX doesn’t seem to increase post-operative infectious complications. By an economic point of view, the cost-effectiveness of IFX-therapy was demonstrated for UC patients suffering from moderate to severe UC in a study based on a cost estimation of the National Health Service of England and Wales. However, the argument is debated.

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Key words: Ulcerative colitis; Infliximab; Colectomy; Post-operative complications; Cost-effectiveness; Inflammatory bowel disease

Abstract
Ulcerative colitis (UC) is an inflammatory bowel disease affecting large bowel with variable clinical course. The history of disease has been modified by the introduction of biologic therapy, in particular Infliximab (IFX), that has demonstrated efficacy in inducing fast symptoms remission, promoting mucosal healing and maintaining long-term remission. However, surgery is still needed for UC patients: in case of failure of medical therapy and if acute complications or a malignancy occurred. Surgical treatment is associated with a short-term post-operative mortality and morbidity respectively of 0%-4% and 30%. In this study we systematically analyzed: the role of IFX in reducing the colectomy rate, the risk of post-operative morbidity in pre-operatively IFX-treated patients and the cost-effectiveness of IFX therapy. Four of 5 analyzed randomized controlled trials demonstrated that therapy with IFX significantly reduces the colectomy rate. Moreover, pre-operative treatment with IFX doesn’t seem to increase post-operative infectious complications. By an economic point of view, the cost-effectiveness of IFX-therapy was demonstrated for UC patients suffering from moderate to severe UC in a study based on a cost estimation of the National Health Service of England and Wales. However, the argument is debated.

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Core tip: The introduction of biologic therapy with Infliximab (IFX) has significantly modified the clinical course of ulcerative colitis. In this study we systematically analyzed the role of IFX in reducing the colectomy rate, the risk of post-operative morbidity in pre-operatively IFX-treated patients and the cost-effectiveness of IFX therapy.
starting in the rectum and proximally progressing in continuity in the colon for a different distance. According to the Montreal Classification, which describes the maximal macroscopic extent of the disease at colonoscopy, the distribution of UC is commonly classified as: proctitis, left-sided and extensive colitis\textsuperscript{[1-4]}. Disease activity is grouped into remission, mild, moderate, or severe but the clinical course of UC is variable and can range from a long-standing remitting to a refractory or fulminant disease\textsuperscript{[5-11]}. Solberg et al.\textsuperscript{[11]}, in a population-based cohort study of 843 patients with inflammatory bowel disease, enrolled in South-Eastern Norway and systematically followed-up at 1, 5 and 10 years after diagnosis, identified 4 different clinical patterns: (1) initial high activity to remission or mild severity (55%); (2) chronic intermittent symptoms (37%); (3) continuous symptoms (6%); and (4) initial low activity to increased severity (1%)\textsuperscript{[12]}. The main symptoms of UC are bloody diarrhea and abdominal pain, associated with urgency and tenesmus. UC is conventionally treated with a step-up approach, based on the severity and extent of the disease, including various agents such as 5-aminosalicylates, corticosteroids and immunosuppressants (including thiopurines and cyclosporine). The primary aims of medical therapy in UC should be inducing and maintaining long-term remission, achieving mucosal healing, minimizing steroid-dependence, avoiding serious complications (hospitalization and surgery) and improving patients’ quality of life\textsuperscript{[13-17]}. However, standard therapy is not always able to achieve these goals and patients become steroid-dependent or experience frequent or severe relapse, with consequent increased risk of hospitalization and surgery. The history of disease has been partially modified by the introduction of biologic therapies. Infliximab (IFX) has demonstrated efficacy in inducing fast symptoms-remission, promoting mucosal healing and maintaining long-term remission\textsuperscript{[17-20]}. It is currently approved for patients with moderate to severe UC who have incomplete response, are intolerant or have any medical contraindications to corticosteroids and/or immunomodulators\textsuperscript{[21-24]}. It is also recommended as rescue therapy in severe steroid-refractory disease\textsuperscript{[20-27]} and in steroid-dependent patients\textsuperscript{[28,29]}. Surgery is still needed for UC patients, in case of failure of medical therapy, occurrence of acute complications (such as fulminant colitis, toxic megacolon and bowel perforation) or development of malignancy. Since its first description (1978), restorative proctocolectomy with ileal pouch anal anastomosis (IPAA) represents the gold standard of surgical treatment of UC: all the bowel for a different distance. According to the Montreal Classification, which describes the maximal macroscopic extent of the disease at colonoscopy, the distribution of UC is commonly classified as: proctitis, left-sided and extensive colitis\textsuperscript{[1-4]}. 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This restorative operation, avoiding a permanent stoma, maintains intestinal continuity and preserves the patient’s body image\textsuperscript{[30-33]}. Moreover, the introduction of minimally invasive approach significantly contributed in improving the acceptance and tolerability of this procedure\textsuperscript{[34-37]}, reducing the rate of post-operative adhesions and post-operative hospital stay and improving cosmetic results\textsuperscript{[38-41]}. However, even if in skilled hands, proctocolectomy with IPAA is not without risk and is associated with an estimated short-term mortality ranged between 0% and 4% and a morbidity rate of about 30%, with an incidence of pelvic sepsis ranging from 5% to 24% and a re-surgery risk of about 16%\textsuperscript{[42-45]}. If surgery represents a definitive solution for cessation of symptoms, withdrawing medical therapies and reducing the cancer-risk, it is not free of long-term post-operative morbidity (as pouchitis, fecal incontinence, female fecundity or fertility) with a relevant impact on patients’ quality of life\textsuperscript{[46-49]}. Population-based studies have reported a 10-years cumulative risk of colectomy ranging between 9%-30%, with some differences among countries. Approximately, 4% to 9% of UC patients will require colectomy within the first year of diagnosis and, subsequently, the risk of colectomy increases of 1% per year\textsuperscript{[50-52]}. It is still under debate whether, in the long-term, the biological therapies could be a valid approach for organ-sparing, rather than an expensive option to delay surgery. Aim of this review was to evaluate the real impact of biological therapy on the rate of colectomy in UC patients. A review of the literature searching for the terms “anti-tumor necrosis factor-α (TNF-α)”, “infliximab” matched with the terms “ulcerative colitis” and “surgery” was performed, using PubMed, MEDLINE, EMBASE and Cochrane databases. All relevant articles (both experimental and observational studies) in English between January 2000 and July 2013 were reviewed. Therapy with infliximab and rate of colectomy We identified five randomized controlled trials\textsuperscript{[53-54]}, one meta-analysis\textsuperscript{[55]} and six observational studies\textsuperscript{[56-61]} following literature search. Characteristics of the studies are summarized in Table 1.

### RANDOMIZED CONTROLLED TRIALS AND META-ANALYSIS

Two randomized, double-blind, placebo-controlled trials, ACT 1 and ACT 2, demonstrated the efficacy of IFX for induction (week 8) and maintenance (week 30 and week 54 for ACT1) of clinical response and remission in patients with moderate-to-severe UC, despite the use of conventional therapy\textsuperscript{[31]}. Further analysis, from ACT 1-2 open-label extension phase, focused on colectomy and hospitalization rates during follow-up to 54 wk. Compared with placebo, the cumulative incidence of colectomy through 54 wk for IFX was significantly lower (10% vs 17%, \( P = 0.02 \)), with an absolute risk reduction of 7% (95%CI: 0.01-0.12, HR \( = 0.59 \)). Moreover, in IFX-treated patients were recorded fewer (compared to placebo) UC-related hospitalizations and surgical procedures per 100 patient-years of treatment (40 vs 20, \( P = 0.003 \); 34 vs 21, \( P = 0.03 \) respectively)\textsuperscript{[58]}. Previous controlled smaller studies have addressed the risk of colectomy in patients with severe UC treated...
with IFX as rescue therapy. In 2001 Sands reported data on 11 patients with severe steroid-refractory disease, of whom 8 treated with IFX and 3 with placebo. After 2 wk, all patients treated with placebo underwent to surgery, while only 50% of patients receiving IFX needed surgery; however, the sample size was too small to detect a statistically significant benefit\(^6\). Later, 45 patients with moderate to severe UC were randomized to IFX or placebo (24 vs 21 respectively) both after four day from the start of corticosteroid treatment. In the placebo group more patients (14/21, 66.7%) than IFX group (7/24, 29.2%) had a colectomy (\(P = 0.017\); OR = 4.9; 95%CI: 1.4-17) within 3 mo after randomization\(^3\). After a follow-up of 3 years, 50% of patients in the IFX group and 76% in the placebo group had a colectomy (\(P = 0.012\))\(^4\).

Recently, Costa et al\(^5\) presented data from a meta-analysis on the benefit of IFX in reducing hospitalization and/or major surgeries in patients with inflammatory bowel disease. They analyzed 11 studies: 5 randomized controlled trials (RCTs) and 6 observational studies. In the RCTs, IFX treatment was associated with a significant 43% odds reduction of overall major surgery risk (OR = 0.57; 95%CI: 0.37-0.88) with a number-to-treat to avoid colectomy of 11 (95%CI: 6-51) for 1.2 years. However, a not significant increase was found in pooled results from observational studies (OR = 1.43; 95%CI: 0.65-3.13). The authors concluded that this discrepancy could be explained by the heterogeneity of observational studies, including patients at high risk of colectomy due to more severe disease and refractoriness to previous treatment.

**OBSERVATIONAL STUDY**

The first data on the long-term risk of colectomy were reported in a study of 314 UC patients from Italy. Among them, 52 (16.5%) patients had severe UC and were treated with intravenous corticosteroids for a median of 7 days. Of 15 patients who did not respond, 11 received IFX with short-term clinical benefit and 4 underwent urgent colectomy. In the long-term follow-up, another 6 patients underwent elective colectomy for a disease relapse, with a total colectomy rate, following the acute flare-up, of 19%. The long-term colectomy risk was not different between patients treated with IFX and steroid-responsive patients (18% vs 11%, respectively), as IFX was able to avoid urgent colectomy, but not to reduce the risk of elective surgery\(^3\). The risk of long-term colectomy in severe UC was also evaluated in a smaller Danish study of 52 UC patients. Nineteen (37%) patients had severe UC and 7 of them (37%) underwent colectomy after a median follow-up of 22 mo (range 4-57 mo).

Among the remaining patients with a chronic refractory UC, the colectomy rate was 21%. The authors concluded that IFX can avoid colectomy in two-thirds of the patients with acute, severe UC, but the beneficial effect on colectomy rate in chronic, refractory UC seems less convincing\(^5\). Long-term data on colectomy in UC patients treated with IFX come from referral centers studies. In the Leuven's cohort of 121 refractory UC patients (patients with acute severe attack, refractory to intravenous steroids were excluded), 21 patients (17%) came to colectomy and 68% of initial responders achieved a sustained clinical response during a median follow-up of 33 mo (IQR 17-49.8). Lack of short-term clinical benefit, high values of baseline C-reactive protein (CRP) and previous intravenous steroid or cyclosporine treatment were identified as independent predictors of colectomy\(^3\). These results are similar to those reported in a French multicenter study, in which, among 191 patients who received at least one IFX infusion, 36 patients (18.8%) underwent colectomy during a median follow-up of 18 mo (IQR 8-32).

### Table 1  Rate of colectomy after therapy with Infliximab

| Ref. | RCT |Pts (w)| Type of disease | FU | Rate of colectomy in IFX Pts | Rate of colectomy in control Pts | \(P\) value |
|------|-----|------|-----------------|----|-----------------------------|---------------------------------|-----------|
| Rutgeerts et al\(^5\) | Y | 364 (IFX) | Moderate to severe UC | 54 wk (ACT1) | 9.5% | 14.7% | < 0.05 |
| Sandborn et al\(^3\) | Y | 364 (control) | Severe active steroid-refractory | 30 wk (ACT2) | 50% | 100% | NS |
| Sands et al\(^4\) | Y | 8 (IFX) | Severe to moderate UC not responding to conventional therapy | 2 wk | 3 mo | 29.2% | 66.7% | 0.017 |
| Järnerot et al\(^5\) | Y | 24 (IFX) | Severe to moderate UC not responding to conventional therapy | 24 (control) | 36 mo | 50% | 76% | 0.012 |
| Teisner et al\(^7\) | N | 15 (IFX) | Severe steroid-refractory UC | 21 (control) | 26 mo | 18% | - | - |
| Ferrante et al\(^6\) | N | 52 (IFX) | Acute severe and chronic refractory UC | 21 (control) | 22 mo | 27% | - | - |
| Oussalah et al\(^8\) | N | 121 (IFX) | Acute severe refractory UC | 21 (control) | 33 mo | 17% | - | - |
| Multicenter | N | 191 (IFX) | UC | 21 (control) | 18 mo | 18.8% | - | - |
| Desmond et al\(^9\) | N | 21 (IFX) | UC | 21 (control) | 14 mo | 9.5% | - | - |
| Garcia-Planella et al\(^10\) | N | 22 (IFX) | UC | 22 (control) | 84 mo | 27.3% | - | - |

RCT: Randomized controlled trial; Pts: Patients; FU: Follow-up; IFX: Infliximab; UC: Ulcerative colitis; Y: Yes; N: Not.
Peri-operative infliximab and post-operative outcome

An increasing number of patients undergo to surgery after experienced biologic therapy. There is an emerging concern on the safety profile of IFX in the peri-operative setting in potentially pre-surgical patients. Many groups have reported their experiences for UC patients and there is not an agreement on the impact of these drugs on post-operative complications. The main characteristics of the studies are summarized in Table 2. Recently, Yang et al. performed a high quality meta-analysis based on five studies, including 706 patients, who were treated with IFX before restorative procto-colectomy with IPAA. The authors did not find a strong association between pre-operative treatment with IFX and short-term infectious complications (OR = 1.80). However, these results need to be interpreted with caution. The subgroup analysis was underpowered to assess the nature of these complications because of the small sample size and heterogeneity of the included studies (end-points, patients’ characteristics and indication, type and timing of surgery).

Infliximab and surgery: Cost-effectiveness

An important issue of IFX therapy is its cost-effectiveness. IFX is often perceived to be an expensive treatment option for patients with IBD. Tsai et al. made a cost-effectiveness analysis in UC patients based on a cost estimation of the National Health Service of England and Wales for the year 2006-07. At analysis of responders patients only, therapy with IFX was associated at an additional 0.753 quality-adjusted life year (QALYs) at an additional cost of £20662 compared to standard care without IFX; the estimated incremental cost per QALY gained for IFX against standard care was £27424. At analysis of remission patients, therapy with IFX derived an additional 0.387 QALYs at an additional cost of £7615 compared with standard care without IFX. The estimated incremental cost per QALY gained for IFX against standard care was £19696. The authors conclude that therapy with IFX appears to be a cost-effective treatment option for adult patients suffering from moderate to severe UC. In a recent study, Park et al. created a Markov model simulating 2 cohorts of 21-year-old patients with severe UC, following them until 100 years of age or death, comparing early colectomy with IPAA strategy to the standard medical therapy strategy (including IFX). In this study standard medical therapy accrued a discounted lifetime cost of $236370 per patient; in contrast, early colectomy with IPAA accrued a discounted lifetime cost of $147763 per patient. QALY-gained for standard medical therapy was 20.78, while QALY-gained for early colectomy with IPAA was 20.72; the resulting incremental cost-effectiveness ratio was approximately $1.5 million per QALY-gained. So, the authors concluded that early colectomy with IPAA after diagnosis of severe UC reduce health care expenditures and provides comparable quality of life compared exhaustive standard medical therapy. Only an extremely low quality of life after IPAA could maintain the standard medical therapy strategy as the optimal management strategy in severe UC.

CONCLUSION

IFX has demonstrated efficacy in inducing and maintaining clinical and endoscopic remission in the long run. IFX can also avoid urgent colectomy in patients with severe acute UC refractory to intravenous steroids. The real impact of biological therapy on the natural history of UC is still controversial, whereas it is not clear if it allows avoidance of colectomy or rather than a delay. The median colectomy risk for UC patients treated with IFX is about 10%-20% in both RCTs and observational studies, with higher rate for patients with severe acute attack. Data from RCTs support the efficacy of IFX in reducing the risk of surgeries in the long-term, but none was designed to assess IFX effects on surgeries. Real life data from referral centers do not confirm this issue, but each study includes patients with different baseline characteristics and risks of colectomy. From these evidences, it seems that patients with more severe disease, high inflammation burden, refractoriness to intravenous steroids and/or cyclosporine and history of hospitalizations, have higher risk of colectomy. So, it is necessary for physicians taking in account the risks and the benefits of medical

| Ref. | RCT | Pts (IFX vs control) | PO morbidity (IFX vs control) | P value | PO infectious complications (IFX vs control) | P value |
|------|-----|---------------------|-----------------------------|---------|---------------------------------------------|---------|
| Schluender et al. | N | 17 vs 134 | 36% vs 28% | > 0.05 | 18% vs 8% | > 0.05 |
| Selvaeskar et al. | N | 47 vs 254 | 62% vs 49% | 0.10 | 28% vs 10% | < 0.01 |
| Mor et al. | N | 46 vs 46 | 34.8% vs 15.2% | 0.004 | 21.7% vs 2.2% | 0.011 |
| Ferrante et al. | N | 22 vs 119 | 11.1% vs 28.6% | > 0.05 | 9% vs 24% | 0.161 |
| Gainbury et al. | N | 29 vs 52 | 44.8% vs 44.2% | 0.96 | 17.2% vs 26.9% | 0.32 |
| Rizzo et al. | N | 16 vs 22 | 37.5% vs 22.7% | > 0.05 | 18.7% vs 18.2% | > 0.05 |

RCT: Randomized controlled trial; Pts: Patients; PO: Post-operative; IFX: Infliximab; Y: Yes.
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