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TITLE PAGE

Efficacy of Tumor Necrosis Factor Antagonist Treatment in Patients With Refractory Ulcerative Proctitis

Running head: Anti-TNF for ulcerative proctitis

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[α]See appendix for the list of investigators of the PROTECT-GETAID study group

Abbreviations:

5-ASA, 5-aminosalycilic acids

ACT, active ulcerative colitis trials

ADA, adalimumab

AZA, azathioprine

CI, confidence interval at 95%

CRP, C reactive protein

GETAID, groupe d'études thérapeutiques des affections inflammatoire du tube digestif

GOL, golimumab

HR, Hazard Ratio

IBD, inflammatory bowel disease

IFX, infliximab

IQR, interquartile range

MH, mucosal healing

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OR, Odds Ratio

PGA, physician global assessment

SD, standard deviation

TNFα, tumor necrosis factor alpha

UC, ulcerative colitis

UCEIS, ulcerative colitis endoscopic index of severity

UP, ulcerative proctitis

Word count: 3 951

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CONFLICT OF INTEREST STATEMENT

Guillaume Pineton de Chambrun declares lecture fees from Pfizer, MSD, AbbVie, Takeda and Ferring; consulting fees from Takeda, Tillots Pharma and Janssen.

Aurélien Amiot declares consulting fees from Abbvie, Hospira, Takeda, Gilead and Biocodex; lecture fees and travel accommodations from Abbvie, Janssen, Biocodex, Ferring, Takeda and MSD; advisory board fees from Gilead, Takeda and Abbvie.

Guillaume Bouguen received lecture fees from Abbvie, Ferring, MSD, Takeda and Pfizer; consulting fees from Takeda and Janssen.

Stéphanie Viennot declares lecture fees from Pfizer, MSD, AbbVie, Takeda and Janssen; consulting fees from Takeda and Janssen.

Romain Altwegg declares lecture fees from MSD, Abbvie, Pfizer, Takeda, and Janssen.

Edouard Louis declares no conflict of interest.

Michael Collins declares lecture fees from Abbvie, Takeda, Celgene; consulting fees from AbbVie.

Mathurin Fumery declares financial support from Abbvie, MSD, Ferring, Boehringer, Pfizer, Takeda and Tillots Pharma.

Florian Poullenot declares lecture fees from MSD, Abbvie, Pfizer, Shire, Takeda, Janssen and Ferring.

Laura Armengol declares no conflict of interest.

Anthony Buisson declares no conflict of interest.

Vered Abitbol declares fees from Biogen, Abbvie, Takeda, Janssen, Amgen, Pfizer, Amgen, Vifor, Arkopharma, UCB.

David Laharie has received board or lectures fees from Abbvie, Celgene, Ferring, Janssen, MSD, Novartis, Pfizer, Roche and Takeda.

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Philippe Seksik declares consulting fees from Takeda, Abbvie, Merck-MSD, Biocodex and Ferring Pahrmaceuticals, grants from Biocodex, sponsored travel from Merck-MSD and Takeda.

Stéphane Nancey declares lecture fees from Pfizer, MSD, AbbVie, Takeda, Ferring, Janssen, Lilly and Novartis; consulting fees from Abbvie, Takeda, Tillots Pharma and Janssen.

Pierre Blanc declares lecture fees from Abbvie, Tillots Pharma and Pfizer.

Yoram Bouhnik declares no conflict of interest.

Benjamin Pariente declares no conflict of interest.

Laurent Peyrin-Biroulet declares fees from Abbvie, Janssen, MSD, Pfizer, Celltrion, Biogen and Takeda.

CONTRIBUTIONS

GPDC and LPB contributed to the development of study protocol, the collection of the data, the analysis of the dataset, the writing of the manuscript and the critical review of the manuscript. AA, GB, SV, RA, EL, MC, MF, FP, LA, AB, VA, DL, PS, SN, PB, YB and BP contributed to the development of the study protocol, the collection of the data and the critical review of the manuscript.

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ABSTRACT

Background & Aims: It is a challenge to manage patients with ulcerative proctitis (UP) refractory to standard therapy. We investigated the effectiveness of tumor necrosis factor (TNF) antagonists in a large cohort of patients with refractory UP.

Methods: We conducted a nationwide retrospective cohort study of 104 consecutive patients with active UP refractory to conventional therapies, treated at 1 of 15 centers in France or 1 center in Belgium (the GETAID cohort). Patients received at least 1 injection of anti-TNF (infliximab, adalimumab, golimumab) from October 2006 through February 2017. Clinical response was defined as significant improvement in UC-related symptoms, and remission as complete disappearance of UC-related symptoms, each determined by treating physicians. We collected demographic, clinical, and treatment data. The median duration of follow-up was 24 months (interquartile range, 13–51 months). The primary outcome was clinical response of UP to anti-TNF treatment.

Results: : Overall, 80 patients (77%) had a clinical response to anti-TNF therapy and 52 patients (50%) achieved clinical remission. Extra-intestinal manifestations (odds ratio [OR], 0.24; 95% CI, 0.08–0.7), ongoing treatment with topical steroids (OR, 0.14; 95% CI, 0.03–0.73), and ongoing treatment with topical 5-aminosalycilates (OR, 0.21; 95% CI, 0.07–0.62) were significantly associated with the absence of clinical remission. Sixty percent (38/63) of the patients who had endoscopic assessment during follow up had mucosal healing. Among the overall population (n=104), the cumulative probabilities of sustained clinical remission were 87.6%±3.4% at 1 year and 74.7%±4.8% at 2 years.

Conclusion: In a retrospective study of 104 patients with refractory UP, anti-TNF therapy induced clinical remission in 50% and mucosal healing in 60%. About two thirds of the patients were still receiving anti-TNF therapy at 2 years.

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Keywords: inflammatory bowel disease; second-line treatment; immune suppression; trial; proctitis

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INTRODUCTION

Ulcerative colitis (UC) is a chronic inflammatory bowel disease (IBD) characterized by intestinal inflammation limited to the colonic mucosa.[1] In population-based studies, 25–55% of patients had ulcerative proctitis (UP) at diagnosis.[2] UP defined as a disease limited to the rectum is classified as E1 according to the Montreal classification.[3] Although it is generally assumed that UP represents the benign end of the spectrum of UC, it is responsible for many distressing symptoms including increased stool frequency, tenesmus, urgency and bleeding, and clearly alters patients' quality of life.[2] Despite the significant benefits of aminosalicylates and corticosteroids, some patients with UP fail to improve and will require additional medical therapy.

Medical management of patients with UP refractory to standard therapies is challenging as there is very little evidence-based data regarding drug efficacy in this clinical situation.[4] Several medications have been tested to treat refractory UP.[5] In a randomized controlled trial, azathioprine (AZA) was more effective than oral 5-aminosaliylates (5-ASA) to achieve steroid-free clinical and endoscopic remission.[6] Cyclosporin enemas and oral methotrexate have not proven to be significantly effective in inducing and maintaining long-term clinical response and remission.[6-8] A recent randomized, placebo-controlled, trial demonstrated that tacrolimus rectal ointment was more effective than placebo for the induction of clinical remission and mucosal healing (MH) in patients with UP.[9] Appendectomy has also been proposed as a treatment for patients with refractory UP.[10] Overall, these results remain difficult to interpret because of small sample size and the lack of well-designed published studies supporting their efficacy for refractory UP.

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Furthermore, patients with UC limited to the rectum are systematically excluded from randomized clinical trials on biologics. Topical administration of infliximab was found to be effective in one patient with chronic refractory UP.[11] Only one French small retrospective observational study has investigated the efficacy of infliximab in patients with refractory UP.[12] Regarding short-term outcome, 69% (9/13) patients presented a complete response to infliximab. To date, there is no data regarding efficacy of adalimumab, golimumab or other biologics in patients with refractory UP.

The aim of this study was therefore to evaluate the effectiveness of anti-TNF therapy in a large nationwide retrospective cohort study from the GETAID.

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METHODS

Selection of patients

A retrospective observational study was performed in 15 French and one Belgium referral center affiliated with the Groupe d'Etude Thérapeutique des Affections Inflammatoires du tube Digestif (GETAID). All consecutive patients with a diagnosis of UC based on clinical, biological and morphological criteria according to European guidelines, and with an active UP according to treating physician (maximal extension of macroscopic endoscopic lesions <20 cm from the anal verge) refractory to conventional therapies (topical and oral 5-ASA, topical and systemic corticosteroids and/or thiopurines) who were treated with at least one injection of a monoclonal anti-TNFα antibody (infliximab, adalimumab, golimumab) from October 2006 to February 2017 were included in the study. The study protocol was approved by the Montpellier University institutional review board. All authors had access to the study data, reviewed and approved the final manuscript.

Data collection

The date of inclusion corresponded to the first administration of anti-TNF therapy. Patient files were retrospectively reviewed and demographic, biological, and endoscopic data were obtained from the medical records. The following characteristics were anonymously recorded for each included patient: gender, age at inclusion, date of diagnosis, duration of disease, smoking status, presence of extraintestinal manifestations, prior exposure to UC treatment including local and systemic steroids, local and oral 5-ASA, conventional immunosuppressants (thiopurines, methotrexate and cyclosporin), UP clinical activity before the start of anti-TNF based on Mayo clinical subscore (from 0 to 9) and endoscopic findings (Mayo endoscopic subscore and UCEIS) when available, main indication for introducing anti-TNF, type of anti-TNF (infliximab, adalimumab, golimumab), anti-TNF induction and

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maintenance doses, type of response (no response, partial response and complete response), concomitant treatment with thiopurines, other ongoing drugs at commencement of anti-TNF, duration of anti-TNF treatment, optimization of the treatment, C-reactive protein levels (CRP) and endoscopic findings at inclusion and during follow-up. All data were encoded in an Excel® electronic database which was anonymized with attribution of a nonsignificant number for each patient.

Outcomes

The primary objective was to assess the primary clinical response of UP to anti-TNF treatment. Evaluation of the global clinical response to anti-TNF was based on the judgement of the referring physician and was graded as follows: no response, clinical response, and clinical remission. Clinical response was defined as significant improvement in UC-related symptoms as judged by the treating physician. Remission was defined as the complete disappearance of UC-related symptoms as judged by the treating physician. Clinical outcomes were collected by each local investigators from retrospective notes in each patient chart. Definitions of primary outcomes were clearly defined in study protocol and explained to each local investigator before data collection. Secondary outcomes were: (1) clinical response and remission during the induction phase (first 3 months), (2) changes in the Mayo clinical subscore (retrospectively calculated from physician notes) between anti-TNF therapy initiation and week 12, (3) Mucosa healing during follow-up (defined as a Mayo endoscopic subscore of 0 or 1) among patients who underwent endoscopic assessment, (4) changes in the Mayo endoscopic subscore or UCEIS index prospectively assessed before anti-TNF initiation and during the first follow-up colonoscopy, (5) coloproctectomy during follow-up, (6) the identification of predictive factors of anti-TNF efficacy, (6) the cumulative

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probability of anti-TNF retention among primary responders, and (7) the safety of anti-TNF treatment. The rate of anti-TNF optimization was also recorded, but was not considered to be a loss of clinical benefit. To determine safety, all adverse events, defined as any significant event that occurred from the date of inclusion to the last follow-up, were recorded in patients receiving at least one injection of any anti-TNF agents. Severe adverse events were defined as any adverse event that resulted in hospitalization or extension of the hospital stay, was fatal or life threatening, or led to a significant disability.

Statistical analysis

Descriptive statistics were used to analyze baseline characteristics. Medians with interquartile ranges (IQR) or means with standard deviations (SD) were calculated for continuous data, and percentages were computed for discrete data. Univariate and multivariate logistic regression were performed to identify predictive factors associated to clinical remission with anti-TNF treatment, expressed as odds ratios (OR) with 95% confidence intervals (CI). Variables with a p value below 0.1 were used for multivariate analysis. For multivariate analysis adjusted for sex and age at diagnosis, variables included were extraintestinal manifestations, the type of anti-TNF (subcutaneous vs intravenous), concomitant thiopurines, ongoing treatment with topical 5-ASA and topical steroids. Proportion of patients with sustained clinical remission and anti-TNF failure (defined as the occurrence of anti-TNF withdrawal for loss of response or intolerance and/or colectomy) over time were described using Kaplan-Meier survival analysis. A p value of < 0.05 was considered to be significant.

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RESULTS

Patient characteristics

One-hundred and four patients (51 female and 53 male) with refractory UP treated with anti-TNFα from 16 GETAID centers were included in the study, with a median follow-up of 24 (IQR: 12.9-51.2) months. The baseline demographic and clinical characteristics of the patients are presented in **table 1**. Mean age at diagnosis was 34±11.9 years. Anti-TNF therapy was started after a median follow-up of 46 (IQR:19.8-110.5) months from the diagnosis of UP.

Fifty percent (52/104) of the patients were treated with infliximab, 39% (41/104) with adalimumab and 11% (11/104) with golimumab. Fifty-three (55/104) percent of patients were concomitantly treated with topical or oral 5-ASA or steroids at the start of anti-TNF therapy. Anti-TNF was associated with a thiopurine in 38 % (40/104) of the patients. Patients were initially treated with the recommended dose of anti-TNF for induction. Following initiation of anti-TNF, 47% (49/104) of patients had an intensification of the anti-TNF agent after a median duration of follow-up of 6 (IQR: 3-13.6) months; 17 patients had a dose increase, 24 a shortening of the injection interval, and 8 both dose increase and interval shortening.

Short-term outcomes

Following a median duration of follow-up of 3 (IQR:1.6-7.0) months between anti-TNF initiation and clinical evaluation, 77% (80/104) of patients had a primary clinical response to the anti-TNF agent and 50% (52/104) achieved clinical remission (**Figure 1**). Corticosteroid-free remission was achieved in 45% (n=47/104) of the patients. The mean Mayo clinical subscore before the start of anti-TNFα was of 5.9 ± 1.9 points (n=99). At 3 months after anti-

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TNF start 42% (33/78) of the patients had a MAYO clinical subscore < 2. In patients with clinical scores available at baseline and 3 months after anti-TNFα start (n = 76), we observed a significant decrease in the Mayo clinical subscore (5.9 ± 1.9 vs. 2.5 ± 2.6, $p < 0.001$) between baseline and week 12 evaluation and 58% of the patients presented at least a clinical response defined by a decreased in the Mayo clinical subscore of 3 or more points with bleeding score of 0 or 1. Among patients with an available CRP at baseline and 3 months after anti-TNF treatment initiation (n=49), there was a significant decrease in the mean CRP level (11.6±21.4 at inclusion vs. 4.7±4.6 at the end of the anti-TNF induction period, p=0.028) (**Supplementary Table 1**).

Factors associated with short-term outcomes

In univariate analysis, extraintestinal manifestations, ongoing topical steroids at baseline and ongoing topical 5-ASA at baseline were significantly associated with the absence of primary clinical remission (**Table 2**). Concomitant treatment with thiopurines at baseline was significantly associated with primary clinical remission (**Table 2**). In a multivariate analysis adjusted for sex and age at diagnosis and including as variables extraintestinal manifestations, the type of anti-TNF (subcutaneous vs intravenous), concomitant thiopurines, ongoing treatment with topical 5-ASA and topical steroids, extraintestinal manifestations (OR=0.24; 95%CI:0.08-0.7; p=0.009), ongoing topical steroids at baseline (OR=0.14; 95%CI:0.03-0.73; p=0.019) and ongoing topical 5-ASA at baseline (OR=0.21; 95%CI:0.07-0.62; p=0.007) were independently associated with the absence of primary clinical remission (**Table 2**).

Endoscopic findings

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A baseline colonoscopy was available in 82% (85/104) patients with a median delay before anti-TNF start of 0.9 (IQR: 0.1-2.16) months. A follow-up colonoscopy was available in 61% (63/104) of patients after a median follow-up of 11.7 (IQR: 5.5-17.4) months. Among these patients, 60% (38/63) had mucosal healing (Mayo endoscopic subscore of 0 or 1) (**Figure 1**). Among these patients, there was a significant decrease in the Mayo endoscopic subscore (2.4±0.6 vs. 1.3±1.1, n=46, $p<0.001$) and in the UCEIS index (4.9±1.4 vs. 2.3±2.3, n=42, $p<0.001$), between baseline and follow-up colonoscopies (**Supplementary Table 1**).

Long-term outcomes

Among the overall population (n=104), after a median follow-up of 23.6 months (IQR:12.9-57.9), 64% (67/104) were in clinical remission at last follow up. Among these 104 patients, the cumulative probability of sustained clinical remission was 87.6%±3.4% at one year, 74.7%±4.8% at two years, and 56.4%±6.2% at 5 years (**Figure 2a**). When considering only patients with an initial response to anti-TNF therapy (n=80), the cumulative probability of sustained clinical remission, irrespective of the treatment given, was 90.5%±3.4% at one year, 77.9%±5.3% at two years, and 55.8%±7.4% at five years (**Figure 2b**). During follow-up, 9% (9/104) of patients were hospitalized for a flare of their UP and 4% (4/104) underwent a coloproctectomy with ileal pouch-anal anastomosis.

Among the 24 patients with primary non response to anti-TNFα, 75% (18/24) of the patients were switch to another ant-TNFα agent and 46% (11/24) were eventually treated with vedolizumab with achievement of clinical remission in 22% (4/18) and 82% (9/11) of the cases, respectively. Among patients with an initial response to anti-TNFα, 19% (15/80) had a switch to another anti-TNFα and 11% (9/80) were eventually treated with vedolizumab

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during follow-up with achievement of clinical remission in 53% (8/15) and 56% (5/9) of the cases, respectively.

At the end of the follow-up period, 61% (63/104) of the patients were still on anti-TNF at last follow up. Among the 80 patients with a primary clinical response to anti-TNF, 34% (27/80) stopped the first anti-TNF agent for secondary loss of response, intolerance or surgery. In these patients (n=80), the cumulative probability of first anti-TNF failure-free survival (no withdrawal for secondary loss of response, intolerance and/or surgery) was 94.6%±2.6% at 6 months, 80.6%±4.9% at one year, and 69.6%±5.9% at two years. Optimization of anti-TNF therapy during follow-up was performed in 43.7% of the patients (35/80). Failure of first anti-TNF therapy defined as optimization, intolerance, loss of response or surgery was observed in 57.5% (46/80) of the patients during follow-up.

Safety of anti-TNF therapy

There were missing data for 8 patients. Overall, 22% (21/96) of the patients presented side effects after starting anti-TNF therapy (**Table 3**). Three patients had an infusion reaction leading to anti-TNF withdrawal, five patients had skin manifestations, four patients had an infection, one patient presented alopecia, and 9 patients had other side effects such as arthralgia, headache, abnormal liver enzymes or weight gain.

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DISCUSSION

The management of refractory UP remains challenging in the era of biologics. These patients are excluded from clinical trials on biologics and available studies on the effectiveness of anti-TNF therapy in a real-life setting are of small sample size.[12] As UP represents about one third of all cases of UC, 5-ASA treatment is often insufficient in moderate to severe UC and azathioprine has modest efficacy in this indication.[13] Further evidence regarding the potential of anti-TNF therapy in treating these patients is eagerly awaited.

We first demonstrated that anti-TNF therapy, either intravenously or subcutaneously, can induce a clinical response in 77% of patients. These results are in line with previous reports. Indeed, in a small retrospective study on infliximab efficacy in patients with UP, 85% of patients experienced clinical improvement.[12] The ACT (infliximab), ULTRA (adalimumab), and golimumab (PURSUIT) trials in patients with pancolitis or left-sided colitis treated with infliximab demonstrated short-term clinical response in about 63%–69% of patients whatever disease extension.[14-16] Moreover, in our study, clinical response was accompanied by a significant drop in CRP levels. Similar changes were in CRP levels were reported in the previous retrospective study on infliximab in patients with UP.[12]

Interestingly, no difference in clinical efficacy was observed in our study between the three anti-TNF for patients with UP, as it has already been demonstrated in population-based studies and network meta-analysis for patients with UC.[17] Importantly, UP patients treated with anti-TNF in our study are truly refractory patients with previous use of topical and oral 5-ASA and corticosteroids in a large majority of patients and previous failure of thiopurines in almost two thirds of them.

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Few studies have investigated other immunosuppressants to treat patient with UP. A recent retrospective multicenter study assessing the efficacy of AZA in patients with refractory UP demonstrated that 71% (10/14) of patients achieved short term response and 21% (3/14) steroid-free clinical remission. Also, In this study, after a median follow-up of 46.2 (26.4–47.8) months, only 5 patients receiving AZA out of 25 had treatment success at the end of follow-up.[13] Another multicenter, randomized, double-blind, placebo-controlled, induction trial compared the efficacy of a tacrolimus rectal ointment (3ml of tacrolimus at 0.5mg/ml) administrated twice a day for 8 weeks with rectal placebo in patients (n=21) with refractory UP. In this study, 73% (8/11) of the patients treated with tacrolimus achieved clinical response. Clinical remission and mucosal healing were achieved in 45% and 73% of the patients treated with tacrolimus.[9]

It is well established that anti-TNF agents are able to induce mucosal healing in patients with UC.[18] Mucosal healing is associated with better outcomes and is now a therapeutic goal in our practice.[18] In our study, we observed mucosal healing (Mayo endoscopic subscore of 0 or 1) in 60% of the patients with available endoscopic assessment. Moreover, there was a significant decrease in the Mayo endoscopic subscore and UCEIS from baseline to follow-up colonoscopies. ACT 1 and 2 studies reported the same rate of mucosal healing at week 8 in patents with UC treated with infliximab 5mg/kg (62% and 60%, respectively).[14] The previous retrospective study on infliximab in 13 patients with UP reported mucosal healing in only two of the seven patients (28%) with follow-up colonoscopies.[12]

Long-term follow-up is required to assess the sustained efficacy of medical treatment in refractory UP. The median follow-up in our study was 24 months. In patients with an initial response to anti-TNF, the probability of first anti-TNF failure-free survival at two years was

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70%. More importantly, among the whole cohort, at the end of the follow-up, 64% of the patients with refractory UP were in clinical remission, with 61% still receiving an anti-TNF agent. These data are in accordance with previous studies on the long-term outcome of patients treated with infliximab for refractory UC, with a sustained clinical response rate of 68% after a median follow-up of 33 months.[19]

Previous studies have identified several clinical or biological factors influencing response to anti-TNF in UC, such as severity of the disease, younger age, duration of colitis or extensive colitis.[20] In our study, we found that extraintestinal manifestations, ongoing topical steroids and 5-ASA at baseline were significantly associated with the absence of clinical remission in patients with refractory UP. Another recent study also identified extraintestinal manifestation as a risk factors for colectomy in patients with UC on thiopurine treatment.[21] In our cohort combination therapy with thiopurines was associated with clinical remission in univariate analysis only, probably because of lack of statistical power. Regarding ongoing treatment with topical 5-ASA or steroids, this may emphasize that the fact that patients on topical treatments at anti-TNF initiation might present more refractory UP.

In the first retrospective study on UP, only one patient relapsed after infliximab induction and underwent proctocolectomy.[12] In our cohort, 4% of patients underwent proctocolectomy with ileo-anal anastomosis. This colectomy rate is lower than those reported in patients with left-sided or extensive UC (17%), as expected given the limited disease extent.[19] Very little is known about the switch to another anti-TNF agent in patients with refractory UP. Our cohort provides interesting data showing that more than two thirds of the patients with anti-TNF primary non-response were switched to a second

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anti-TNF during follow-up with achievement of clinical remission in 22% of the cases. Moreover, half of these patients eventually received vedolizumab during follow-up with achievement of clinical remission in 82% of patients.

The strengths of our study are the large number of patients included, the nationwide character of the study and the duration of follow-up which allowed us to look at predictors of short and long-term efficacy. Moreover, the availability of data on CRP, an objective biomarker of intestinal inflammation, improved the strength of the assessment of anti-TNF efficacy in these patients. Limitations of our study are its retrospective character with absence of comparator group and the absence of systematic assessment of mucosal healing. Moreover, we were not able to collect data on fecal calprotectin, anti-TNF trough level or disease extension during follow-up.

In conclusion, our data support the use of anti-TNF monoclonal antibodies in patients with refractory UP with 50% of patients achieving clinical remission and 64% showing sustained clinical remission at the end of follow-up. Moreover, our study also demonstrated that anti-TNF agents are able to induce mucosal healing in 60% of patients with refractory UP. Regarding follow-up, about half of the patients were still on anti-TNF therapy at 2 years.

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TABLES AND FIGURE LEGENDS

Table 1: Baseline characteristics of patients with refractory ulcerative proctitis	
	n = 104
Gender, n, %	
Female	51 (49)
Mean age at diagnosis, years ± SD	34 ± 11.9
Median duration of disease prior to anti-TNF, years (IQR:1-3)	46 (19.8 – 110.5)
Active smokers, n, %	6 (6)
Extraintestinal manifestations, n, %	
Arthralgia and ankylosing spondylitis	24 (23)
Skin or mucosal lesions	3 (3)
Uveitis	1 (0.9)
UC treatment prior to anti-TNF, n, %	
Topical 5-ASA	100 (96)
Oral 5-ASA	99 (95)
Topical corticosteroids	85 (82)
Oral corticosteroids	89 (86)
Thiopurines	63 (62)
Methotrexate	9 (9)
Cyclosporine	5 (5)
Tacrolimus	0 (0)
Mean Mayo clinical subscore prior to anti-TNF, ± SD	5.9 ± 1.9
Mayo endoscopic subscore prior to anti-TNF, n, % (n=88)	
Mayo 1	6 (7)
Mayo 2	45 (51)
Mayo 3	36 (41)
Mean UCEIS endoscopic index prior to anti-TNF, ± SD	4.9 ± 1.4
Type of anti-TNF n, %	
IFX	52 (50)
ADA	41 (39)
GOL	11 (11)
Reasons for anti-TNF, n, %	
Steroid-dependency	23 (22)
Failure of corticosteroids	27 (26)
Failure of immunosuppressant drugs	49 (47)
Other reasons	7 (7)
Concomitant therapies, n, %	
Thiopurines	40 (38)
Methotrexate	7 (7)
Topical 5-ASA	26 (25)
Oral 5-ASA	16 (15)
Topical corticosteroids	15 (14)
Oral corticosteroids	26 (25)
Abbreviations: 5-ASA, 5-aminosalycilates; ADA, adalimumab ; Anti-TNF, anti-tumor necrosis factor alpha monoclonal antibodies; GOL, golimumab ; IFX, infliximab ; IQR, interquartile range; n, number of patients; UC, ulcerative colitis; UCEIS, ulcerative colitis endoscopic index of severity.	

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Table 2: Predictive factors associated with primary clinical remission in patients with ulcerative proctitis treated with anti-TNF (n=104)

		Univariate analysis				Multivariate analysis[α]			
Variables		OR	95% CI		P-value	OR	95% CI		P-value
Sex	*F vs M*	**1.471**	0.679	3.185	0.327				
Age at diagnosis	*Years*	**0.977**	0.945	1.011	0.181				
Smoking	*Yes vs No*	**0.458**	0.080	2.627	0.381				
Extraintestinal manifestations	*Yes vs No*	**0.316**	**0.123**	**0.809**	**0.016**	**0.235**	**0.079**	**0.701**	**0.009**
Previous treatments									
Local steroids	*Yes vs No*	**1.341**	0.483	3.729	0.573				
Systemic steroids	*Yes vs No*	**0.838**	0.261	2.692	0.767				
Local 5-ASA	*Yes vs No*	**3.187**	0.320	31.705	0.323				
Oral 5-ASA	*Yes vs No*	**0.327**	0.033	3.249	0.340				
Thiopurines	*Yes vs No*	**1.158**	0.521	2.575	0.719				
Methotrexate	*Yes vs No*	**0.783**	0.198	3.098	0.728				
Cyclosporine	*Yes vs No*	**4.167**	0.449	38.626	0.209				
Mayo clinical subscore at baseline		**1.016**	0.821	1.258	0.883				
Type of anti-TNF	*SC vs IV*	**0.538**	0.247	1.171	0.118				
	ADA vs IFX	**0.633**	0.278	1.444	0.277				
	GOL vs IFX	**0.275**	0.065	1.157	0.078				
Duration of disease prior to anti-TNF	*Months*	**1.000**	0.997	1.002	0.908				
Combination therapy with thiopurines	*Yes vs No*	**2.284**	**1.016**	**5.133**	**0.046**				
Ongoing drugs at anti-TNF start									
Local steroids	*Yes vs No*	**0.115**	**0.024**	**0.541**	**0.006**	**0.142**	**0.028**	**0.729**	**0.019**
Oral steroids	*Yes vs No*	**0.410**	0.161	1.044	0.062				
Local 5-ASA	*Yes vs No*	**0.195**	**0.070**	**0.547**	**0.002**	**0.211**	**0.069**	**0.648**	**0.007**
Oral 5-ASA	*Yes vs No*	**0.722**	0.245	2.126	0.555				

[α] Variables included in the multivariate analysis are sex, age at diagnosis, extraintestinal manifestations, type of anti-TNF (subcutaneous vs intravenous), concomitant thiopurines, ongoing treatment with topical 5-ASA, ongoing treatment with Topical steroids and ongoing treatment with oral steroids.

Abbreviations: 5-ASA, 5-aminosalycilic acid; ADA, adalimumab; Anti-TNF, anti-tumor necrosis factor alpha monoclonal antibodies; CI, confidence interval; GOL, golimumab; IFX, infliximab; IV, intravenous; OR, odds ratio; SC, subcutaneous.

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Table 3: Adverse events in patients with ulcerative proctitis treated with anti-TNF	
	n=104
Infusion reaction	3
Skin lesions	5
Alopecia	1
Infections	4
Arthralgia	4
Delayed hypersensitivity	1
Headache	1
Abnormal liver enzymes	1
Weight gain	1
Muscle weakness	1

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Figure 1: Efficacy of anti-TNFα therapy in patients with refractory ulcerative proctitis.

Figure 2: Sustained clinical remission during follow-up in patients with ulcerative proctitis treated with anti-TNF. a, proportion of patients with sustained clinical remission during follow-up in the overall population (n=104). **b,** proportion of patients with sustained clinical remission during follow-up among anti-TNFα primary responders (n=80).

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APPENDIX

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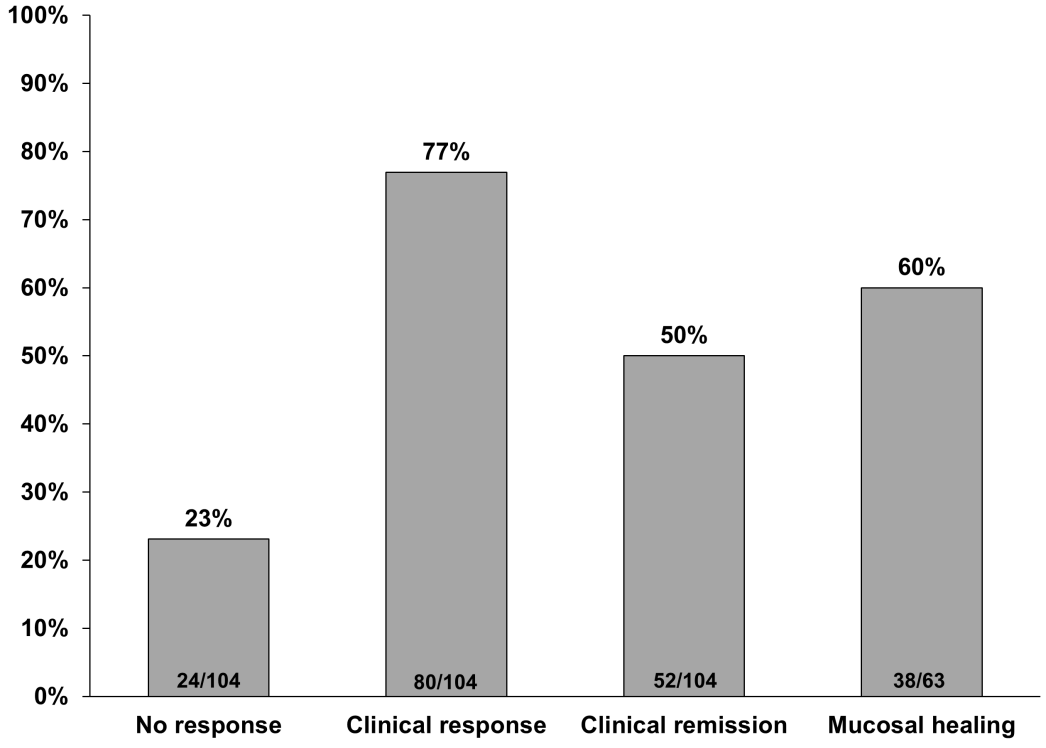
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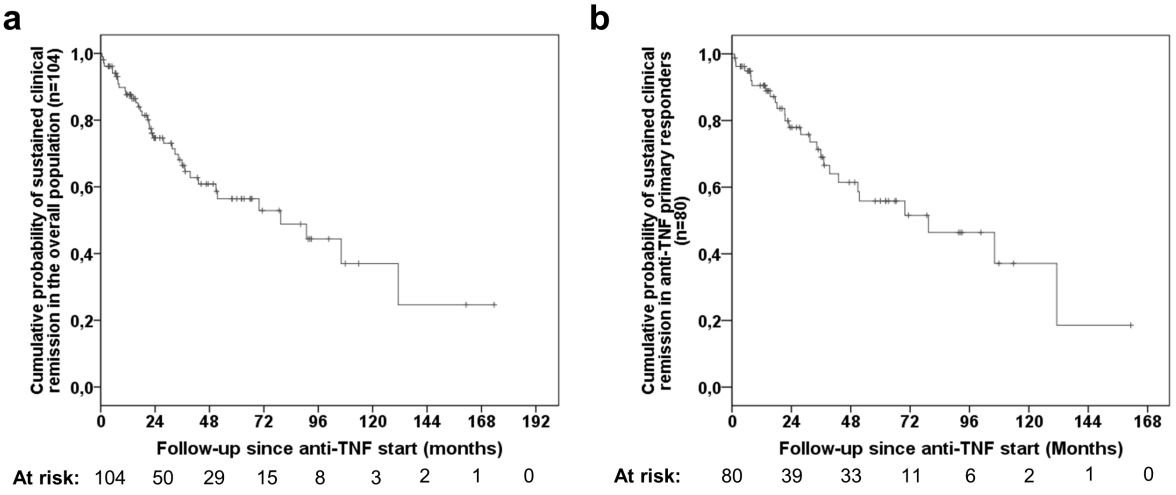

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WHAT YOU NEED TO KNOW

Background:

- Management of refractory ulcerative proctitis is challenging as patients with ulcerative colitis limited to the rectum are systematically excluded from randomized clinical trials investigating efficacy of biologics.
- We investigated the effectiveness of tumor necrosis factor (TNF) antagonists in a large cohort of patients with refractory ulcerative proctitis.

Findings:

- In a retrospective study of 104 patients with refractory ulcerative proctitis, anti-TNF therapy induced clinical remission in 50% and mucosal healing in 60%.
- About two thirds of the patients were still receiving anti-TNF therapy at 2 years.

Implications for patient care:

- Anti-TNF agents might be a good therapeutic option for patients with ulcerative proctitis.

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Supplementary Table 1: Changes in biological and endoscopic parameters with anti-TNF therapy

Biological parameter	***Baseline***	***At 3 months***	***p-value***
Mean CRP level (mg/l, n=49)	11.6 ± 21.4	4.7 ± 4.6	0.028
Endoscopic parameters*	***Baseline***	***Follow-up***	***p-value***
Mayo endoscopic subscore (from 0 to 3, n=46)	2.4 ± 0.6	1.3 ± 1.1	< 0.001
UCEIS index (from 0 to 8, n=42)	4.9 ± 1.4	2.3 ± 2.3	< 0.001

*Follow-up colonoscopies were performed after a median delay from anti-TNF initiation of 11.7 (IQR: 5.5 - 17.4) months.

Abbreviations: Anti-TNF, anti-tumor necrosis factor alpha monoclonal antibodies; CRP, C reactive protein; IQR, interquartile range; n, number of patients; UCEIS, ulcerative colitis endoscopic index of severity;

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