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Original research

Withdrawal of antitumour necrosis factor in inflammatory bowel disease patients in remission: a randomised placebo-controlled clinical trial of GETECCU

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ABSTRACT

Background and objectives Primary objectives: to compare the rates of sustained clinical remission at 12 months in patients treated with antitumour necrosis factor (anti-TNF) and immunomodulators who withdraw anti-TNF treatment versus those who maintain it. Secondary objectives: to evaluate the effect of anti-TNF withdrawal on relapse-free time, endoscopic and radiological activity, safety, quality of life and work productivity; and to identify predictive factors for relapse.

Design Prospective, quadruple-blind, multicentre, randomised, controlled trial. Patients with ulcerative colitis or Crohn's disease in clinical remission for >6 months and absence of severe endoscopic (and radiological in Crohn's disease) lesions were randomised to maintain anti-TNF treatment (maintenance arm (MA)) or to withdraw it (withdrawal arm (WA)). All patients maintained immunomodulators. Patients were followed-up until month 12 or up to clinical relapse.

Results One-hundred forty patients were randomised: 70 were allocated to the MA and 70 to the WA. The proportion of patients with sustained clinical remission at 12 months was similar in the MA and WA: 59/70 (84%), 95% CI=74% to 92% versus 53/70 (76%), 95% CI=64% to 85%. The proportion of patients with significant endoscopic lesions at the end of follow-up was 8.5% in the MA and 19% in the WA (p=0.1); a higher proportion of patients had faecal calprotectin >250 µg/g at the end of follow-up in the WA

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ It is not clear whether it is possible to withdraw antitumour necrosis factor (anti-TNF) treatment in some patients with IBD in remission.

WHAT THIS STUDY ADDS

⇒ Patients with IBD were randomised to withdraw anti-TNF agents or to maintain it (all patients maintained immunomodulators).

⇒ At 12 months, the proportion of patients with sustained clinical remission was similar between patients who withdrew the anti-TNF agent and those who maintained it.

⇒ Faecal calprotectin >250 µg/g at baseline was the only factor associated with lower likelihood of sustained clinical remission.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The discontinuation of anti-TNF agents in patients with IBD in clinical remission, under immunomodulators, and without significant endoscopic or radiological lesions, is feasible without a significant impact on sustained clinical remission at 12 months. In this population, faecal calprotectin could be used as a predictive factor of relapse (independently of anti-TNF withdrawal).

(p=0.01). The same percentage of patients in both groups had at least one adverse event (69%). The proportion of patients with serious adverse events was also similar in both groups (4% in MA vs 7% in WA).

Conclusion Anti-TNF withdrawal in selected patients with IBD in clinical, endoscopic and radiological remission has no impact on sustained clinical remission at 1 year although objective markers of activity were higher in patients who withdrew treatment.

Trial registration number https://www.clinicaltrialsregister.eu/ctr-search/search?query=2015-001410-10
https://clinicaltrials.gov/study/NCT02994836

INTRODUCTION

Antitumour necrosis factor (anti-TNF) drugs have changed the natural history of IBD, allowing for the achievement of more ambitious therapeutic goals in these patients.[1 2] Long-term therapy with anti-TNF agents is associated with safety concerns, such as a possible increased risk of opportunistic infections and malignancies, and a substantial cost.[3] It has been suggested that, after a period of stable remission, anti-TNF maintenance therapy could be discontinued in some patients.[3] Therefore, a cyclic treatment approach could be currently considered in certain cases.[3]

On the other hand, withdrawal of anti-TNF therapy seems to be associated with an increased risk of relapse.[4–9] A meta-analysis of 27 studies found that the overall risk of relapse following discontinuation of anti-TNF treatment was 44% for patients with Crohn's disease (CD) and 38% for those with UC.[10] However, the results of this meta-analysis were heterogeneous, and most of the studies were retrospective, with a low number of patients enrolled and without a control group to compare with.

To date, three clinical trials have been published assessing the risk of relapse after discontinuation of anti-TNF treatment.[11–13] These trials have provided controversial results, although overall, they indicate that the risk of relapse is higher in patients who discontinue anti-TNF treatment compared with those who continue it. However, these studies have relevant limitations that may affect the results.

The primary aim of the EXIT study was to compare the rates of sustained clinical remission at 1 year in patients who discontinue anti-TNF treatment versus those who continue treatment. As secondary objectives, we aimed to evaluate the proportion of patients in endoscopic remission among those who maintain anti-TNF treatment in comparison with those who discontinue it; to identify predictive factors of clinical relapse; and to compare the impact of both strategies on patients' quality of life (QoL), work productivity and safety.

METHODS

Study design

The EXIT trial is a prospective, quadruple-blind (neither patients, physicians, data managers, nor statisticians were aware of patients' allocation), multicentre, randomised (1:1), parallel controlled study in patients with IBD who had achieved clinical remission with an anti-TNF treatment and who were in clinical remission for at least 6 months with the standard dose. Intensified doses of anti-TNF therapy were defined as ≥10 mg/kg/8 weeks or 5 mg/kg/≤4 weeks for infliximab, and 40 mg/week for adalimumab.[14] The study was conducted at 33 IBD units across Spain. The study protocol was reviewed by Grupo Español de Trabajo en Enfermedad de Crohn y Colitis Ulcerosa (GETECCU), and it was previously published (online supplemental file 1).[14] Patients or the public were not involved in the design, or conduct, or reporting or dissemination plans of our research. The study protocol was registered in both European and United States clinical trial registers (EudraCT number 2015-001410-10 and ClinicalTrials.gov identifier NCT02994836). The first patient was included in June 2016. Written, informed consent was obtained from all patients. Coauthors had access to the study data and have reviewed and approved the final manuscript.

Treatment arms

Maintenance arm (MA): Continuation of the anti-TNF treatment (infliximab or adalimumab).

Withdrawal arm (WA): discontinuation of the anti-TNF treatment (infliximab or adalimumab). Patients were given a placebo matched to the drug they had been previously receiving. That is, patients who were on infliximab received an intravenous placebo, while patients who were receiving adalimumab received a placebo administered subcutaneously.

Infliximab/infliximab placebo was administered every 8 weeks, while adalimumab/adalimumab placebo was administered every 2 weeks.

Eligibility criteria

Patients eligible for enrolment in this study were those aged over 18 years with IBD (either CD or UC) diagnosed by the European Crohn's and Colitis Organisation criteria.[1 2] At the time of inclusion, patients had to be in clinical remission (see definition below in the Endpoints section) and receiving concomitant immunomodulators at stable doses for at least 3 months prior to inclusion in the study and maintain the treatment throughout the study period. For patients with CD, the indication for anti-TNF treatment had to be for luminal involvement only (not perianal). The required duration of clinical remission was ≥6 months, at a non-intensified dose of anti-TNF. The baseline colonoscopy performed within 3 months prior to inclusion had to rule out significant lesions (defined in Assessments section). For patients with ileal or ileocolic CD, the magnetic resonance enterography (MRE) performed within 3 months prior to inclusion should not show significant lesions (defined in Assessments section).

Exclusion criteria were the following: age <18 years; anti-TNF therapy for a non-IBD indication; CD treated with anti-TNF agents for perianal involvement (or both perianal and luminal), or with active perianal disease at enrolment; no concomitant treatment with immunosuppressants (thiopurine or methotrexate) at the time of enrolment and within the prior 3 months; history of bowel resection surgery; presence of significant endoscopic or radiological lesions 3 months prior to randomisation (see Assessments section); advanced chronic disease or any other condition that results in an inability to attend the clinic for monitoring or follow-up; pregnancy or breastfeeding, or intention to become pregnant during the study period; and refusal to consent to study participation.

Randomisation and blinding

The randomisation was performed in a decision-tree type format by an interactive web response system, where patient allocation to each strategy was stratified by the type of IBD (CD or UC), and the anti-TNF agent taken at the time of study inclusion (infliximab or adalimumab).

The quadruple-blind study design rendered the patient, physician, data manager and statistician blind to the study treatment. Only the pharmacy staff and the nurse responsible for study drug administration knew the treatment assigned to any given patient.

Endpoints

The primary endpoint of the study was 'sustained clinical remission at 12 months' (at every visit) after randomisation to anti-TNF maintenance or withdrawal. Clinical remission was defined for patients with CD as a Crohn's Disease Activity Index (CDAI) score <150 points, while for patients with UC remission was defined as a Partial Mayo Score (PMS) ≤2, with all subscores from the partial score being ≤1, and a rectal bleeding subscore of 0.[15] Clinical relapse was defined as a CDAI >150 points or a PMS >2 (as applicable) in two consecutive visits separated by at least 1 week. Other endpoints included clinical activity, endoscopic activity, radiological activity, patient-reported outcomes, and safety.

Any modification of concomitant treatment, or therapy addition to maintain remission was not allowed during the study period. If any of these changes occurred, the patient was pulled out from the study (early termination) by medical decision, and it was considered a failure.

Assessments

The timeline for study visits and the assessments conducted at each study visit are presented in online supplemental table 1. Detailed definitions of patient-reported outcome and laboratory assessments are described in online supplemental file 2. Endoscopic activity in patients with CD was assessed using the Simplified Endoscopic Activity Score for Crohn's Disease (SES-CD).[16] For patients with UC, endoscopic activity was assessed using the Mayo Endoscopic Subscore (MES).[17] Assessment of QoL was undertaken using the shortened Spanish version of the Inflammatory Bowel Disease Questionnaire 9 (CCVEII-9 QoL Questionnaire),[18] and work productivity and activity was assessed using the Spanish Work Productivity and Activity Impairment (WPAI) Questionnaire.[19 20]

Endoscopic assessment

All patients participating in the study had to undergo a colonoscopy within 3 months prior to the randomisation visit. Endoscopic activity in patients with CD was assessed using the SES-CD, with significant endoscopic lesions defined as the presence of any of the following: a SES-CD score ≥5, or any deep ulcer, or any superficial ulcers covering >10% of the surface of at least one intestinal segment. For patients with UC, endoscopic activity was assessed using the MES; a MES subscore of 3 was considered as having significant endoscopic lesions for the purpose of this study. The assessment of endoscopic activity was performed by the investigator and by a central reading by the group coordinator.

Radiological assessment

Radiological activity was assessed in patients with ileal or ileocolic CD by MRE within 3 months before the randomisation visit. Absence of activity in the small bowel or colon was defined as the absence of contrast enhancement, oedema or ulcers. A thickening of the wall without enhancement was not considered lack of remission. The definition of significant radiological lesions by MRE was the presence of oedema in T2 or ulcers in two or more intestinal segments (rectum, descending colon, transverse colon, ascending colon, ileum). Patients with ileal or ileocolic CD with an MRE showing significant radiological lesions were excluded from the study. The assessment for radiological activity was performed locally at each participating site.

Safety endpoints

AEs, adverse drug reactions and reports of pregnancy were collected during the study, from informed consent until up to 30 days after the last dose of study drug and/or the last visit. Serious AEs (SAEs) or serious adverse drug reactions were defined as any adverse event or adverse drug reaction that resulted in death, was life-threatening, required hospitalisation or prolongation of existing hospitalisation, resulted in persistent or significant disability or incapacity, or caused a congenital anomaly/birth defect. Clinically important AEs or adverse drug reactions were also considered serious regardless of whether they met the defined criteria and included important medical events requiring intervention to prevent one of the outcomes defined as serious.

Withdrawal criteria

Patients were allowed to withdraw from the study at any time, and a patient could be pulled out from the study at the investigator's discretion (ie, patients with clinical relapse but who did not meet the relapse criteria according to the protocol). At early termination, patients had to undergo the assessments outlined in online supplemental table 1.

Management of relapse

In case of clinical relapse after randomisation, the patient terminated the study follow-up; the treatment was selected at the discretion of the physician responsible for the patient. The patient experiencing the relapse had to undergo the assessments outlined in online supplemental table 1.

Data collection

Study data were collected and managed using an electronic data capture tool (Research Electronic Data Capture (REDCap)),[21] which is hosted at Asociación Española de Gastroenterología (AEG; www.aegastro.es), a non-profit medical society. AEG provided this service free of charge, with the aim of promoting investigator-driven research.

Statistical analysis

Sample size

Originally, assuming that 10% of patients continuing anti-TNF treatment longer than 12 months would experience a loss of efficacy[22] and an incidence of recurrence at 12 months of 25% after anti-TNF withdrawal,[4] the estimated sample size required to achieve a 5% significance level and a power of 80% was 200 patients (100 patients in each study arm). The sample size calculation was made by Sealed Envelope Ltd 2012 (Power calculator for binary outcome superiority trial; available from: https://www.sealedenvelope.com/power/binary-superiority/). However, because of slower than anticipated recruitment, the inclusion period was closed when 140 patients were included. Neither the steering committee of the trial nor the statistician had access to the database until it was locked. The new sample size had 80% power, with a 5% significance level, to detect an 18% difference

between groups (90% vs 72%), instead of the initially planned 15% difference (90% vs 75%).

Description of intention-to-treat and per-protocol populations and missing data

Patients who met the inclusion criteria and had been randomised were included in the intention-to-treat (ITT) analysis irrespective of whether they strictly adhered to the protocol; patients with early termination for any reason were considered failures ('not in sustained clinical remission at 12 months'). The per-protocol (PP) analysis included only those patients who had completed treatment and follow-up according to the protocol. Regarding the secondary outcomes (such as endoscopy, radiology or laboratory tests), the results were given as observed values.

Data presentation and analyses

Qualitative variables were presented as percentages with 95% CIs, while quantitative variables were presented as means and SDs (normal distribution) or medians and IQRs (non-normal distribution). Categorical variables were compared using the χ^2 test, and quantitative variables by the appropriate test for their distribution. The main outcome was the presence of sustained clinical remission at 12 months. Variables associated with the likelihood of sustained clinical remission at 12 months were identified by logistic regression analysis, where sustained clinical remission at 12 months was the dependent variable. Variables significantly differently distributed between patients who had sustained clinical remission at 12 months and those who did not, and those which were clinically relevant (such as anti-TNF withdrawal, type of IBD and type of anti-TNF agents), were included in the model. The multivariate analysis was performed using a stepwise model.

The Kaplan-Meier method was used to evaluate relapse-free time, and the log-rank test was used to assess differences between the anti-TNF maintenance or withdrawal curves. The variables associated with IBD clinical relapse were analysed using a Cox regression model, including treatment strategy (anti-TNF maintenance vs withdrawal) as an independent variable, and other factors that had been significantly associated with the risk of relapse in the univariate analysis as well as those who were clinically relevant.

RESULTS

Study population

A total of 159 patients were screened and 140 patients were randomised in the trial. Seventy patients were randomised to the MA cohort and 70 to the WA cohort, which comprised the ITT population. The flowchart of the patients included in the study is shown in figure 1. The group of patients who completed the study PP was considered the cohort for the PP analysis, which consisted of 63 patients in the MA cohort and 61 in the WA cohort.

Main characteristics of the study populations are presented in table 1. All baseline characteristics were similar in the MA and the WA, as shown in table 1. Most patients (96% in the MA and 99% in the WA) were under thiopurines, and a minority under methotrexate (table 1). A total of 129 patients were receiving treatment with azathioprine, with a median dose of 2.05 mg/kg (IQR=1.6–2.3), 7 patients were on mercaptopurine, with a median dose of 1.1 mg/kg (IQR=0.9–1.3); and 4 patients were on methotrexate: 2 at a dose of 25 mg/week, 1 at 20 mg/week and 1 at 12.5 mg/week.

Sustained clinical remission at month 12

In the ITT analysis, the proportion of patients in sustained clinical remission was similar in the two groups: 59/70 patients (84%, 95% CI=74% to 92%) in the MA versus 53/70 patients (76%, 95% CI=64% to 85%) in the WA (p=0.2) were in sustained clinical remission at the end of follow-up (figure 2).

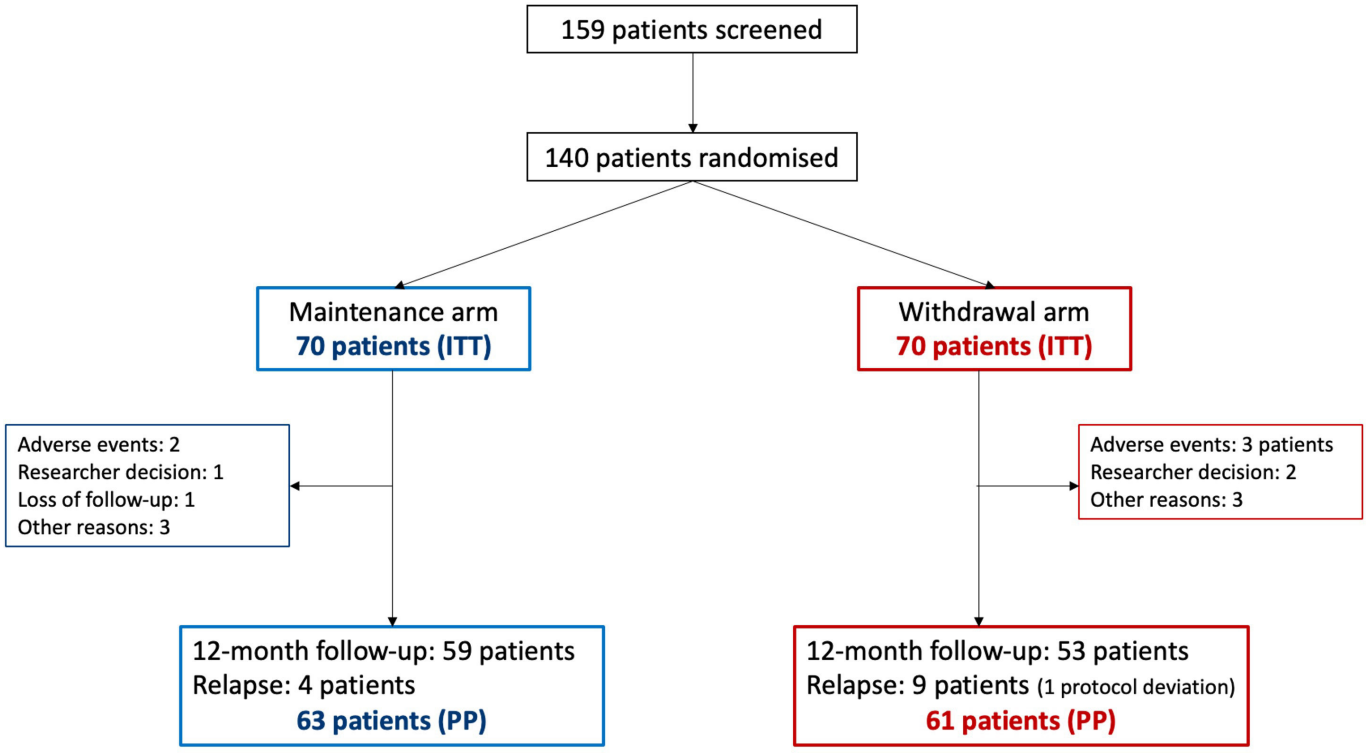


Figure 1 Flowchart of patients included in the study. ITT, intention-to-treat; PP, per-protocol.

Table 1 Characteristics of the study population at baseline

	Maintenance arm	Withdrawal arm
Mean age at inclusion (years), SD	41 (13)	41 (12)
Median time under current anti-TNF (years), IQR	2.9 (1.7–4.8)	2.6 (1.2–5.7)
Median time in remission with current anti-TNF at standard dose (months), IQR	22 (13–41)	20.9 (9.8–38.8)
Median time under immunomodulators (months), SD	31 (17–59)	25.6 (12.4–68.5)
Male gender, n (%)	40 (57)	48 (69)
Crohn's disease, n (%)	39 (56)	39 (56)
L1, n (%)	10 (32)	7 (23)
L2, n (%)	10 (32)	7 (23)
L3, n (%)	11 (35)	17 (55)
L4, n (%)	1 (3)	1 (3)
B1, n (%)	22 (71)	27 (87)
B2, n (%)	7 (23)	4 (13)
B3, n (%)	2 (6)	0 (0)
Perianal, n (%)	2 (6)	2 (6)
Ulcerative colitis, n (%)	39 (56)	39 (56)
Extensive, n (%)	29 (74)	21 (54)
Left-sided, n (%)	9 (23)	17 (44)
Proctitis, n (%)	1 (3)	1 (3)
Type of anti-TNF, n (%)		
Adalimumab, n (%)	9 (13)	10 (14)
Infliximab, n (%)	61 (87)	60 (86)
Indication for the anti-TNF, n (%)		
Refractoriness to immunomodulators, n (%)	10 (29)	21 (30)
Steroid-dependency, n (%)	25 (36)	24 (34)
Steroid-refractoriness, n (%)	14 (20)	14 (20)
Top-down strategy, n (%)	2 (3)	4 (6)
Others, n (%)	9 (13)	7 (10)
Prior intensification of current anti-TNF, n (%)	13 (19)	11 (16)
Type of immunomodulator		
Thiopurines	67 (96)	69 (99)
Methotrexate	3 (4)	1 (1)
Median CDAI, IQR	9.2 (0–29)	16.7 (0–32.4)
Median Partial Mayo Score, IQR	0 (0–0)	0 (0–0)
Median SES-CD, IQR	0 (0–0)	0 (0–0)
SES-CD values, n (%)		
0	25 (89)	23 (74)
1	2 (7)	3 (10)
2	0 (0)	0 (0)
3	1 (4)	2 (6)
4	0 (0)	3 (10)
Median Mayo endoscopic subscore, IQR	0 (0–0)	0 (0–0)
0	35 (90)	33 (85)
1	4 (10)	4 (10)
2	0 (0)	2 (5)
Median C reactive protein (mg/dL), IQR	0.1 (0.1–0.3)	0.1 (0.1–0.4)
Mean haemoglobin (g/dL), SD	14.3 (1.2)	14.6 (1.2)
Mean albumin (g/dL), SD	4.4 (0.3)	4.5 (0.3)
Faecal calprotectin >250 µg/g, n (%)	6 (10)	9 (15)
Mean adalimumab serum level (µg/mL), SD	12 (5.5)	13.7 (6.4)
Median infliximab serum level (µg/mL), IQR	4.6 (2.2–7.9)	5.3 (3.2–9.3)

CDAI, Crohn's Disease Activity Index; SES-CD, Simplified Endoscopic Score Crohn's Disease; TNF, tumour necrosis factor.

The proportion of patients who had a clinical relapse was also similar in both groups: 4/70 (6%, 95% CI=1.6% to 14%) in the MA vs 9/70 (13%, 95% CI=6% to 23%) in the WA (p=0.1) (figure 3).

These results were also confirmed in the PP analysis (figures 2 and 3).

The time to relapse was similar in both groups, as it is represented in the Kaplan-Meier curve (figure 4).

Endoscopic relapse at 12 months

A total of 59 patients out of 70 in each group underwent an ileocolonoscopy at the end of follow-up (either PP end of follow-up or due to early withdrawal). Mainly due to COVID-19 pandemic, several patients in each group refused the follow-up colonoscopy. As observed values, the proportion of patients with significant endoscopic lesions at the end of the study (either 12 months or early termination) was similar in both groups: 5/59 (8.5%, 95% CI=2.8% to 19%) in the MA versus 11/59 (19%, 95% CI=9.6% to 31%) in the WA (p=0.1). These results were confirmed in the PP analysis (online supplemental figure 1).

Radiological worsening at 12 months

A total of 20/21 patients with ileal involvement in the MA and 20/24 patients in the WA underwent an MRE at the end of follow-up (either 12 months or early termination). The proportion of patients with CD with significant radiological activity in MRI was also similar in the MA and the WA groups: 4 (20%) vs 7 (35%) (p=0.2), respectively.

Biochemical relapse at 12 months

A total of 59 patients in the MA and 52 patients in the WA had a faecal calprotectin determination at the end of follow-up (either 12 months or early termination). As observed values, the proportion of patients with faecal calprotectin >250 µg/g was significantly higher in the WA compared with the MA (17/52 (33%, 95% CI=20% to 47%) vs 8/59 (13%, 95% CI=6% to 25%) (p=0.01)) (online supplemental figure 2).

Predictive factors of sustained clinical remission at 12 months

A total of 112 patients were in sustained clinical remission at the end of follow-up: 59 in the MA and 53 in the WA. The characteristics of patients based on whether they were in sustained clinical remission at 12 months of the study or not are shown in online supplemental table 2. Only faecal calprotectin concentration at baseline was significantly higher in patients who were not in sustained clinical remission at 12 months compared with those who maintained it. In the multivariate analysis, having a faecal calprotectin >250 µg/g at baseline was the only variable associated with lower likelihood of sustained clinical remission at 12 months (OR=0.2, 95% CI=0.07 to 0.7). Of note, withdrawal of anti-TNF treatment had no impact on sustained clinical remission (OR=0.6, 95% CI=0.2 to 1.6). Other factors such as the type of IBD (CD vs UC) or the type of anti-TNF (adalimumab vs infliximab) were not associated with the likelihood of sustained clinical remission at month 12.

Regarding relapse-free survival, in the multivariate analysis, having a faecal calprotectin >250 µg/g at baseline was the only variable associated with higher risk of loss of clinical remission at the end of follow-up (HR=5.2, 95% CI=1.5 to 18). Of note, withdrawal of anti-TNF treatment was not associated with higher risk of losing remission (HR=2.9, 95% CI=0.7 to 11).

Safety

The proportion of patients with at least one AE was similar in both groups: 48 patients (68.5%) in each group. The proportion of patients with SAEs was also similar in both groups: 3 (4.2%) patients in the MA versus 5 (7.1%) patients in the WA.

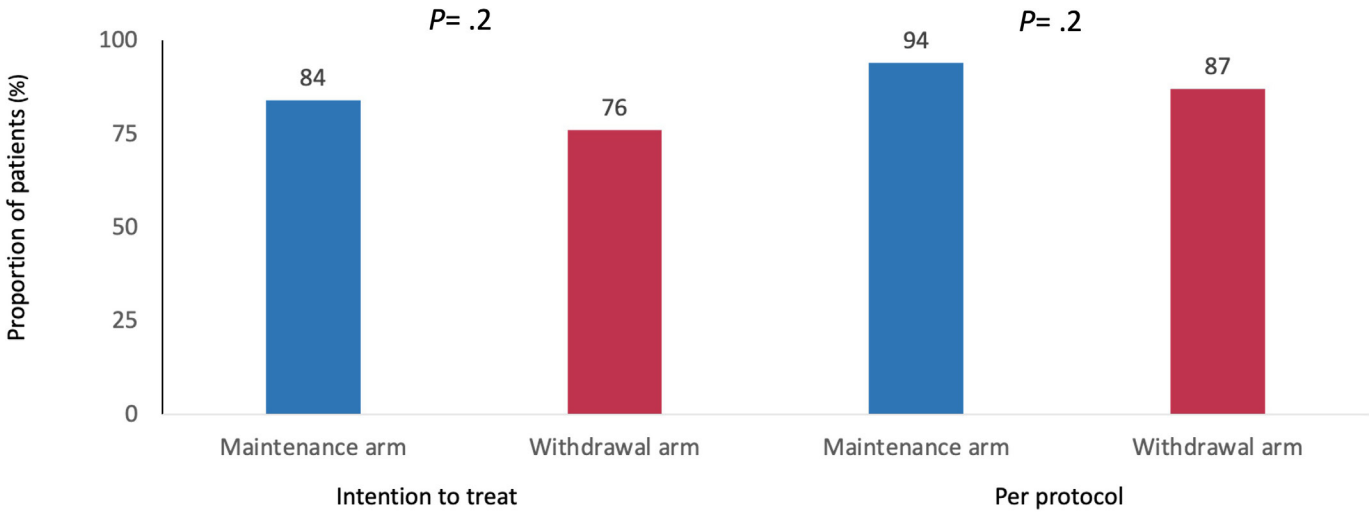


Figure 2 Proportion of patients in clinical remission at the end of follow-up.

Specifically, 9 (12.8%) patients in the MA and 7 (10%) patients in the WA had adverse events 'possibly related' to the study treatment (anti-TNF or placebo) according to the investigators' judgement; no AE was considered as certainly or probably related to the study treatment. AEs possibly related to the study drug are listed according to study arm in table 2.

Quality of life

Score in the CCVEII-9 Questionnaire was similar in the MA and the WA at baseline. This score remained stable in both groups throughout the follow-up. There was no observed decrease in the QoL Questionnaire score in patients who discontinued the anti-TNF treatment compared with those who continued it, as can be seen in online supplemental figure 3.

Work productivity

The proportion of patients who reported having paid employment was similar between the groups at baseline and during the follow-up, as shown in online supplemental table 3. The same pattern was observed for the proportion of patients who indicated that health issues had not affected their usual activities (online supplemental table 4). For those patients with paid employment, the CCVEII-9 Questionnaire was used to inquire about hours of work missed due to health problems, hours of work missed for other reasons, and total hours worked. As demonstrated in online supplemental table 5, no differences were observed in these parameters between the MA and WA throughout the study.

DISCUSSION

To our knowledge, this is the first randomised placebo-controlled trial evaluating the probability of maintaining clinical remission in both patients with CD and UC on anti-TNF therapy (both adalimumab and infliximab) in comparison with those who withdrew it (maintaining the immunomodulators). We did not observe a statistically significant difference in the proportion of patients maintaining clinical remission at the end of follow-up (1 year) in patients who maintained anti-TNF and in those who discontinued it. In addition, time to relapse and the presence of relevant endoscopic lesions were not statistically different in

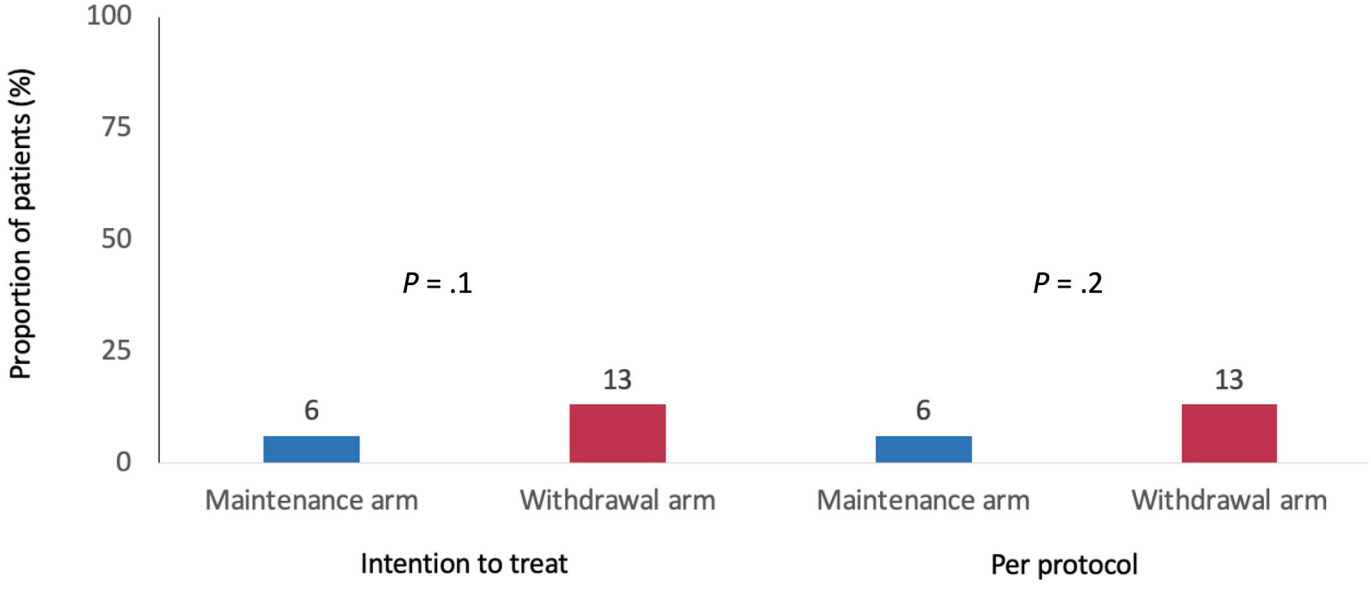
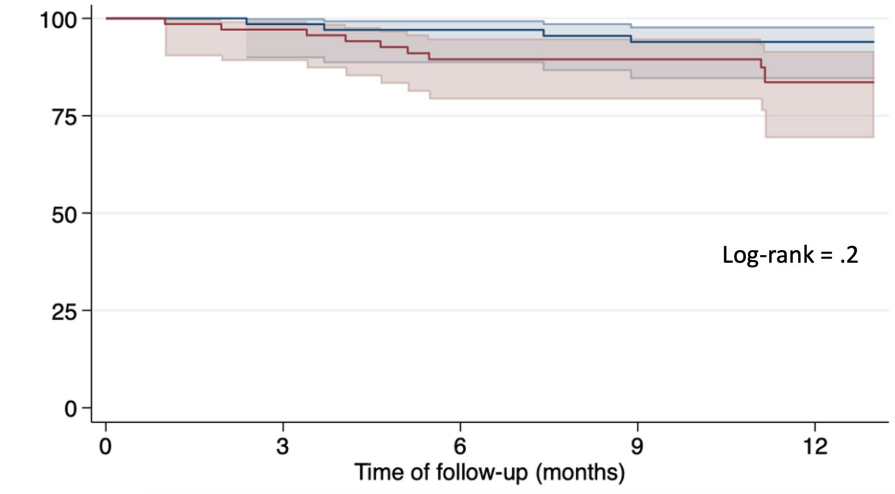


Figure 3 Relapse at the end of follow-up.



Patients at risk (n)	Maintenance arm	67	64	60	54
	Withdrawal arm	66	57	55	43
Patients in clinical remission (%)	Maintenance arm	97	97	94	94
	Withdrawal arm	94	89	89	82

Figure 4 Survival curve of clinical remission during follow-up (12 months).

both groups. Nevertheless, the proportion of patients with faecal calprotectin >250 µg/g at the end of follow-up was significantly higher among those who withdrew the treatment; in addition, percentage of patients with significant endoscopic lesions at the end of follow-up was more than double in those who discontinued treatment compared with those who continued it, the lack of statistical significance might be due to sample size limitations.

To date, three clinical trials have been conducted to assess the risk of relapse after discontinuation of anti-TNF treatment in patients with IBD, with controversial results. The first one was the HAYABUSA study published in 2021 by Kobayashi *et al*.[11] It was an open-label randomised trial including patients with UC treated with infliximab; 46 patients were allocated to maintain the treatment and 46 to discontinue it. At the end of follow-up (48 weeks), the proportion of patients in clinical remission was significantly higher among those who maintained the treatment in comparison with those who withdrew it (80.4 vs 54.3%, p<0.05). Of note, patients were eligible for this trial if they were in clinical and endoscopic remission (MES 0 or 1), and they had to have received infliximab for a minimum of only 14 weeks (although the median duration of previous infliximab treatment was 166 weeks). In addition, only 59% in the maintenance group and 65% in the discontinuation group were under concomitant immunomodulators; therefore, as many as 35% of patients in the discontinuation group were maintained off immunosuppressive treatment.

Table 2 Adverse events possibly related to the study drug

	Maintenance arm	Withdrawal arm
Infections, n (%)	4 (6)	1 (1)
Skin lesions, n (%)	2 (3)	2 (3)
Abdominal pain/diarrhoea, n (%)	1 (1)	1 (1)
Anaemia and elevated CRP, n (%)	0 (0)	1 (1)
Arthralgia, n (%)	1 (1)	0 (0)
Herpes zoster, n (%)	1 (1)	0 (0)
Odontogenic cyst, n (%)	0 (0)	1 (1)
Tuberculosis, n (%)	0 (0)	1 (1)

CRP, C reactive protein; n.s., not statistically significant.

The STOP-IT trial, published in 2022, was a multicentre, randomised, double-blind, placebo-controlled trial including patients with CD in clinical, biochemical and endoscopic remission after standard infliximab treatment for at least 1 year.[12] A total of 59 patients were randomised to continue infliximab therapy, and 56 to receive placebo for 48 weeks. The main endpoint was time to relapse. In this study, no relapses were observed in the maintenance group, whereas 49% of patients discontinuing infliximab experienced a flare. Various factors could have influenced the (high) risk of recurrence in these patients. First, patients may have been receiving intensified doses of infliximab prior to study inclusion, and it was only necessary for them to be in remission during two consecutive infliximab infusions. Second, 32% of patients in the maintenance group and 21% in the discontinuation group had previously undergone intestinal resection due to CD. Third, only 54% of patients in the maintenance group and 52% in the discontinuation group had concurrent treatment with immunosuppressants, leaving approximately half of the patients in the infliximab withdrawal group without any immunomodulatory treatment during the study follow-up. The authors noted a trend towards a higher risk of recurrence in the subset of patients within the infliximab discontinuation group who were not under concurrent immunomodulator treatment. Lastly, concerning the study design, in case of recurrence, the blind was broken to reveal the patient's treatment in the study, which might have impacted the interpretation of symptoms in subsequent patients.

Finally, Louis *et al* recently published the results of the SPARE trial. The primary aim of this trial was to compare the relapse rate and the time spent in remission over 2 years between patients in combo therapy (infliximab plus immunomodulators), and those stopping infliximab or immunomodulators.[13] An open-label randomised controlled trial was performed, in which adult patients with CD in steroid-free clinical remission on combination therapy with infliximab and immunomodulators were included and randomly assigned 1:1:1 either to

continue combination, discontinue infliximab or discontinue immunomodulators. Of note, the presence of ulcers in the baseline colonoscopy was not an exclusion criterion; in fact, about 10% of patients in each group had ulcerations at baseline. In case of relapse, treatment could be optimised or resumed. In addition, about 20% of patients in each group had a prior intestinal resection due to CD. Participants, those assessing outcomes and those analysing the data were not blinded to group assignments. A total of 67 patients were allocated in the combination group, 71 in the infliximab withdrawal group and 69 in the immunomodulator withdrawal group. The 2-year relapse rate was 14% in the combination, 36% in the infliximab withdrawal and 10% in the immunomodulator withdrawal groups. Thus, the risk of relapse was significantly higher in the infliximab discontinuation group than in the other groups. However, as treatment optimisation was allowed after relapsing and the success rates of these interventions were high, time spent in remission was similar in the three groups. Authors found that, in addition to infliximab discontinuation, other variables significantly associated with the risk of relapse were younger age at diagnosis, C reactive protein (CRP) in serum at baseline, faecal calprotectin over 300 µg/g at baseline and the endoscopic activity based on the Crohn's Disease Endoscopic Activity Index (CDEIS). On the contrary, infliximab serum level at baseline was not associated with the risk or relapse.

The proportion of patients who remained in clinical remission after discontinuation of infliximab treatment at the end of the follow-up in our study was higher (76%) than that reported in previously conducted studies (both clinical trials and observational studies). This difference could be attributed to the study design (blinded treatment assignment for all participating researchers and the patient), the maintenance of immunomodulators in all patients and the inclusion of a population of highly stable patients—without the relapse risk factors described in previously conducted observational studies. In this respect, a recently published topical review commissioned by the European Crohn's and Colitis Organisation identified several factors associated with the risk of relapse after anti-TNF discontinuation.[3] For instance, receiving escalated anti-TNF doses, the indication for the prevention of postsurgical recurrence or previous surgical resection, have been associated with the risk of relapse; while the maintenance of immunosuppressants after anti-TNF discontinuation has been suggested to have a protective effect against relapse. With respect to laboratory markers, the presence of anaemia, elevated CRP, high faecal calprotectin concentration or elevated serum infliximab level at the time of anti-TNF discontinuation have been associated with a higher risk of relapse. There are conflicting data on the predictive value of endoscopy lesions for disease relapse following biologic discontinuation.[23 24] We observed that faecal calprotectin >250 µg/g at baseline was associated with higher risk of relapse, which highlights that it could be useful for monitoring patients after treatment discontinuation; while anti-TNF serum level was not a predictive biomarker of relapse.

In agreement with the previous trials, both maintenance and withdrawal of anti-TNF seem to be equally safe in patients in clinical remission.[11–13] In addition, we observed no impact of anti-TNF withdrawal on patients' QoL or work productivity.

Data show that retreatment with the same medication after relapse following elective anti-TNF discontinuation in patients with CD in remission is generally safe and effective.[3] Taking this into account, along with the low likelihood of recurrence in patients without risk factors that we observed in our study, discontinuation of anti-TNF treatment could be considered as an option for a selected group of patients.

Our study has some limitations. First, due to slower than expected recruitment, partly attributed to the COVID-19 pandemic, the initially calculated sample size could not be achieved even with an extended inclusion period. Nevertheless, with the attained sample size, there was sufficient power to detect an 18% difference in the proportion of patients in clinical remission at the end of the follow-up, which is smaller than the differences detected in most studies. Second, for the same reason, some of the endoscopies and biological samples were not available (as patients were not allowed to go to the hospital during the pandemic for clinical trial procedures). Third, although the percentage of patients with significant endoscopic lesions at the end of follow-up was more than double in those who discontinued treatment compared with those who continued it, the lack of statistical significance is probably due to sample size limitations. Since endoscopy activity was not the primary outcome of the study, it lacks the statistical power to detect this effect. Fourth, although we included both types of IBD and two types of anti-TNF (adalimumab and infliximab), assuming they can be analysed together and adjusting the analysis for these variables, we do not have sufficient statistical power to analyse these factors separately. Therefore, we cannot conclude that the effect of discontinuation is similar across both pathologies or with both anti-TNFs. In addition, patients had to come to the hospital to receive the anti-TNF or placebo, without the benefit of fewer visits for drug administration in cases of treatment withdrawal. Additionally, patients on adalimumab/placebo had to come every 2 weeks, which differs considerably from clinical practice; for this reason, it is difficult to evaluate the benefit of treatment withdrawal in patients' reported outcomes such as work productivity. However, at least we could suggest that there is not an impair in QoL (due to disease worsening) in patients who withdraw the treatment. Finally, the observation period of our study was only 12 months after randomisation or at disease relapse; therefore, data on the response to restart of the treatment in the case of clinical relapse were not available. A post-hoc analysis for long-term outcomes is warranted.

Our study also has several strengths. It is a quadruple-blind study for both study investigators and patients, which mitigates potential biases in analysis and prevents the nocebo effect. Despite recruitment challenges, our study, along with the SPARE study, includes the largest number of patients per group, allowing for the identification of predictive factors for recurrence. To our knowledge, the present study is the first to analyse the impact of anti-TNF withdrawal on crucial outcomes to patients, such as QoL and work productivity. Finally, we believe that our study best replicates the characteristics of the population for whom treatment withdrawal would be considered: long-standing sustained remission, standard anti-TNF dosage, absence of significant endoscopic/radiological lesions, no previous IBD-related surgery and ongoing immunomodulator treatment. Therefore, the results could be readily extrapolated to clinical practice.

In conclusion, based on the EXIT trial, the discontinuation of anti-TNF agents in patients with IBD in clinical remission, under immunomodulators, and without significant endoscopic or radiological lesions, is not associated with lower sustained clinical remission at 12 months; however, the presence of a higher proportion of patients with elevated faecal calprotectin and significant endoscopic lesions at the end of follow-up calls for caution and should be considered when discontinuing treatment in patients. In this population

without significant endoscopic lesions, faecal calprotectin could be used as a predictive factor of relapse (independently of anti-TNF withdrawal). On the contrary, anti-TNF serum level at baseline is not associated with the risk of relapse. The lower relapse rate compared with other studies could be attributed to the EXIT study design (blinded allocation for all participants), cotreatment with immunomodulators (in all cases) and the included population (at least 6 months in remission, standard drug dosage, absence of significant endoscopic/radiological lesions, no prior surgery and exclusion of patients with anti-TNF indication for perianal disease). Finally, both approaches (maintenance and withdrawal of anti-TNF) demonstrate equal safety, showing no effects on either QoL or work productivity.

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