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## OP37
## Is the withdrawal of anti-tumour necrosis factor in inflammatory bowel disease patients in remission feasible without increasing the risk of relapse? Results from the randomised clinical trial of GETECCU (EXIT)

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Figure 1.a. Inclusion and exclusion criteria.

**INCLUSION CRITERIA**

- Over 18 years of age.
- Diagnosed with IBD (either Crohn's disease or ulcerative colitis) by the ECCO criteria.
- Concomitant immunosuppressants (thiopurine or methotrexate) at stable doses for at least 3 months prior to the inclusion.
- In Crohn's disease, the indication for anti-TNF treatment must have been for luminal involvement only (not perianal).
- Duration of clinical remission ≥6 months, at a non-intensified dose of anti-TNF.
- Absence of significant lesions at baseline colonoscopy (within 3 months of inclusion).
- For patients with ileal or ileocolic Crohn's disease, the magnetic resonance enterography performed within 3 months of inclusion must not show significant lesions.

**EXCLUSION CRITERIA**

- Anti-TNF therapy for a non-IBD indication.
- Crohn's disease treated with anti-TNF agents for perianal involvement.
- Active perianal disease at enrolment.
- History of bowel resection surgery.
- Advanced chronic disease or any other condition that results in an inability to attend the clinic for monitoring or follow-up.
- Women who are pregnant or breastfeeding, or who intend to become pregnant during the study period.
- Refusal to consent to study participation.

Figure 1.b. Clinical trial scheme.

| Visits | - 30 days | Baseline | Month 1 | Month 2 | Month 4 | Month 6 | Month 8 | Month 10 | Month 12 or clinical relapse |
|---|---|---|---|---|---|---|---|---|---|
| Informed consent | | X | | | | | | | |
| Anamnesis | | X | | | | | | | |
| Physical examination[a] | | X | X | X | X | X | X | X | X |
| CDAI (CD) | | X | X | X | X | X | X | X | X |
| Partial Mayo Score (UC) | | X | X | X | X | X | X | X | X |
| Colonoscopy | X | | | | | | | | X |
| SES-CD | X | | | | | | | | X |
| Score endoscópico de Mayo | X | | | | | | | | X |
| MRI enterography | X | | | | | | | | X |
| Quality of life (CCVEII-9) | | X | X | X | X | X | X | X | X |
| Productivity and working activity (Spanish-WPAI) | | X | X | X | X | X | X | X | X |
| Lab tests | | X | X | X | X | X | X | X | X |
| Anti-TNF and antibodies against anti-TNF serum levels | | X | | | | | | | |
| Faecal calprotectin | | X | X | X | X | X | X | X | X |
| Pregnancy test | | X | | | | | | | |
| Adverse events | | X | X | X | X | X | X | X | X |
| Concommitant medications | | X | X | X | X | X | X | X | X |

Figure 1.c. Clinical trial definitions.

| | |
|---|---|
| Clinical remission | Crohn's disease: CDAI <150 points.<br>Ulcerative colitis: partial Mayo index 2, with all scores (of the partial index) of 1 or less and with a rectal bleeding subscore of 0. |
| Significant endoscopic lesions | Crohn's disease: presence of any of the following: SES-CD ≥ 5, or any deep ulcer or superficial ulcers covering >10% of the surface of at least one intestinal segment.<br>Ulcerative colitis: endoscopic subscore of the Mayo index = 3. |
| Significant radolologic activity | Presence of oedema on T2 or identification of ulcers, in 2 or more intestinal segments (rectum, descending colon, transverse colon, ascending colon, ileum) in the magnetic resonance imaging. |

Evaluation of the endoscopic activity was carried out by the researcher and also centrally, by sending anonymous endoscopic images of the ileum (in patients with Crohn's disease) and of each of the colonic segments explored.

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**Background:** Background: The feasibility of anti-TNF discontinuation in inflammatory bowel disease (IBD) must be proven in clinical trials including patients in clinical, endoscopic, and radiologic remission at

**Figure 2. Baseline patients´ characteristics.**

| | Maintenance arm N=70 | Withdrawal arm N=70 | p |
|---|---|---|---|
| Age at inclusion (years), mean (SD) | 41 (13) | 41 (12) | 0.7 |
| Age at diagnosis (years), median (IQR) | 34 (21 – 42) | 29 (22 – 39) | 0.4 |
| Time with the anti-TNF at inclusion (years), median (IQR) | 2.9 (1.7 – 4.8) | 2.6 (1.2 - 6) | 0.7 |
| Time in remission before inclusion (months), median (IQR) | 22 (13.3 – 41) | 20.9 (9.8 – 39) | 0.6 |
| Time under immunomodulators at inclusion (months), median (IQR) | 31 (17 – 59) | 25.69 (12 – 68) | 0.7 |
| Age at anti-TNF start (years), mean (SD) | 38.4 (13) | 37.5 (13) | 0.6 |
| Male gender, n (%) | 40 (57) | 48 (69) | 0.2 |
| Smoking, n (%) | 10 (14) | 10 (14) | 1 |
| Previous biologic treatment, n (%) | 5 (7) | 5 (7) | 1 |
| Same biologic treatment, n (%) | 1 (7) | 1 (7) | 1 |
| Time from previous anti-TNF discontinuation to the current one median (IQR) | 0.78 (0 – 2.5) | 4 (1.5 - 8) | |
| Indication of previous biological treatment, n (%) | | | |
| Refractoriness to immunomodulators, n (%) | 2 (40) | 1 (20) | |
| Steroid dependency, n (%) | 1 (20) | 0 (0) | 0.3 |
| Steroid refractoriness, n (%) | 2 (40) | 2 (40) | |
| Others, n (%) | 0 (0) | 2 (40) | |
| Intensification of the previous biologic, n (%) | 4 (80) | 2 (40) | 0.2 |
| Reasons for discontinuation of the previous biologic | | | |
| Loss of response, n (%) | 4 (80) | 3 (60) | |
| Clinician's decision, n (%) | 1 (20) | 1 (20) | 0.6 |
| Others, n (%) | 0 (0) | 1 (20) | |
| Ulcerative colitis, n (%) | 39 (56) | 39 (56) | 1 |
| Extensive, n (%) | 29 (74) | 21 (54) | |
| Left-sided, n (%) | 9 (23) | 17 (44) | 0.2 |
| Proctitis, n (%) | 1 (3) | 1 (3) | |
| Crohn's disease, n (%) | 31 (44) | 31 (44) | 1 |
| Age at diagnosis | | | |
| A1, n (%) | 8 (20) | 5 (16) | |
| A2, n (%) | 15 (48) | 23 (74) | 0.09 |
| A3, n (%) | 8 (26) | 3 (10) | |
| Location, n (%) | | | |
| L1, n (%) | 10 (32) | 7 (23) | |
| L2, n (%) | 10 (32) | 7 (23) | 0.3 |
| L3, n (%) | 11 (35) | 17 (55) | |
| L4, n (%) | 1 (3) | 5 (10) | 0.3 |
| Behaviour | | | |
| B1, n (%) | 22 (71) | 27 (87) | |
| B2, n (%) | 7 (23) | 4 (13) | 0.2 |
| B3, n (%) | 2 (6 ) | 0 (0) | |
| Perianal, n (%) | 2 (6) | 2 (6 ) | 1 |
| Family history, n (%) | 11 (16) | 14 (29) | 0.5 |
| Surgery due to inflammatory bowel disease, n (%) | 0 (0) | 0 (0) | 1 |
| Extraintestinal manifestations, n (%) | 16 (23) | 9 (13) | 0.1 |
| Concomitant immunomodulators | | | |
| Thiopurines, n (%) | 67 (96) | 68 (99) | 0.3 |
| Methotrexate, n (%) | 3 (4) | 1 (1) | |
| Anti-TNF type | | | |
| Adalimumab, n (%) | 9 (13) | 10 (14) | 0.8 |
| Infliximab , n (%) | 61 (87) | 60 (86) | |
| Anti-TNF indication | | | |
| Refractoriness to immunomodulators, n (%) | 20 (29) | 21 (30) | |
| Steroid dependency, n (%) | 25 (36) | 24 (34) | |
| Steroid refractoriness, n (%) | 14 (20) | 14 (20) | 0.9 |
| Top-down strategy, n (%) | 2 (3) | 4 (6) | |
| Other, n (%) | 9 (13) | 7 (10) | |
| Previous intensification of the current anti-TNF, n (%) | 13 (19) | 11 (16) | 0.6 |
| CDAI, median (IQR) | 9.2 (0 -29) | 16.7 (0 – 32) | 0.5 |
| Partial Mayo Score, median (IQR) | 0 (0 – 0) | 0 (0 – 0) | 0.3 |
| SES-CD, median (IQR) | 0 (0 – 0) | 0 (0 – 1) | 0.1 |
| Mayo endoscopic subscore | | | |
| 0 | 35 (90) | 33 (85) | |
| 1 | 4 (10) | 4 (10) | 0.3 |
| 2 | 0 (0) | 2 (5) | |
| Haemoglobin (g/dL) at baseline, mean (SD) | 14.3 (1.25) | 14.6 (1.2) | 0.1 |
| Albumin (g/dL) at baseline, mean (SD) | 4.4 (0.38) | 4.5 (0.37) | 0.2 |
| C-reactive protein (mg/dL) at baseline, median (IQR) | 0.1 (0.1 – 0.3) | 0.1 (0.1 – 0.4) | 0.2 |
| Faecal calprotectin (μg/g) at baseline, median (IQR) | 26 (0-68) | 19 (1-76) | 0.8 |
| Faecal calprotectin >250 μg/g, n (%) | 6 (10) | 9 (15) | 0.4 |
| Adalimumab trough serum levels at baseline (IU/mL), mean (SD) | 12 (5.5) | 13.7 (6.4) | 0.5 |

SD, standar deviation; IQR, interquartile range; CDAI, Crohn's Disease Activity Index; SES-CD, Simplified Endoscopic Score for Crohn's Disease.

Figure 3.a. Clinical remission at the end of follow-up.

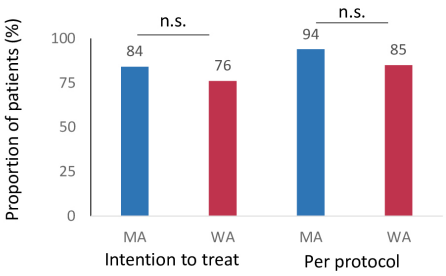



Figure 3.b. Relapse during follow-up.

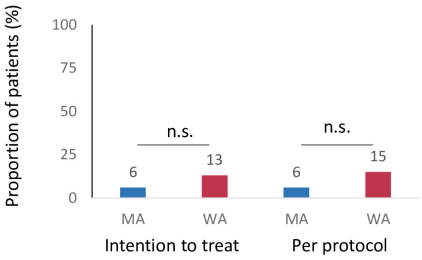



Figure 3.c. Significant endoscopic lesions at the end of follow-up.

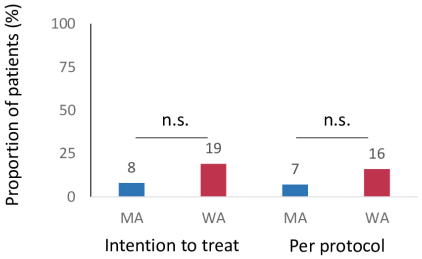
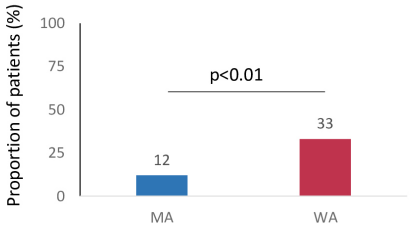
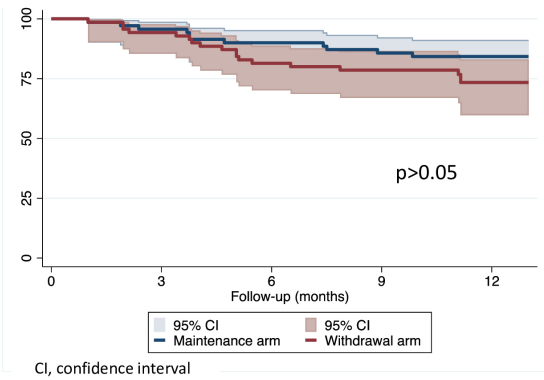



Figure 3.d. Faecal calprotectin >250 µg/g at the end of follow-up (per protocol análisis).




n.s.: p>0.05; MA, maintenance arm; WA, withdrawal arm.

Figure 4. Survival curve of clinical remission at the end of follow-up.




CI, confidence interval

the time of anti-TNF withdrawal to make recommendations for clinical practice.

**Aims:** Primary: to compare the rates of clinical remission at 1 year in patients who discontinue anti-TNF treatment vs. those who continue treatment. Secondary objectives: to know the effect of anti-TNF withdrawal on relapse-free time, mucosal healing and safety; and to identify predictive factors for relapse.

**Methods:** Prospective, quadruple-blind, multicentre, randomised, controlled trial. Patients with ulcerative colitis (UC) or Crohn's disease (CD) in clinical remission for > 6 months were randomised to maintain anti-TNF treatment [maintenance arm (MA)] or to withdraw it [withdrawal arm (WA)]. Patients who were on infliximab (IFX) received IFX 5 mg/kg or an intravenous placebo every 8 weeks, while patients on adalimumab (ADA) received subcutaneous ADA 40 mg or placebo every other week. Patients were followed-up until month 12 or up to the time of clinical relapse, whichever came first. Inclusion and exclusion criteria, trial scheme and definitions are summarized in figures 1a, 1b and 1c. Results were analysed by intention-to-treat (ITT) and by per-protocol (PP). Local investigators were blinded to faecal calprotectin (FC) and IFX and ADA trough levels. On-site monitoring was performed to assess data quality.

**Results:** 159 patients were screened, from whom 140 were randomised and comprised the ITT cohort: 70 allocated to the MA and 70 to the WA. Fifteen patients dropped out before the end of follow-up (12 months or relapse), leaving 63 patients in the MA and 62 patients in the WA for the PP analysis. The characteristics of patients in the MA and WA were similar (figure 2). The proportions of patients who maintained clinical remission -59/70 (84%), 95% confidence interval (CI)=74-92% in the MA vs. 53/70 (76%), 95%CI=64-85% in the WA- and who remained without significant endoscopic lesions at the end of follow-up were similar between groups (figures 3a, 3b, 3c). Only the proportion of patients with FC >250 mg/g was higher in the WA at the end of follow-up (figure 3d). Maintenance of clinical remission was no different between groups (figure 4). 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 between groups (4% in MA vs. 7% in WA).

**Conclusion:** Anti-TNF withdrawal in selected IBD patients in clinical, endoscopic, and radiologic remission could be feasible without an increase in the risk of clinical relapse. Long-term follow-up of these patients is warranted.