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Original Article

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Adalimumab vs Azathioprine in the Prevention of Postoperative Crohn's Disease Recurrence. A GETECCU Randomised Trial

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Abstract

Background and Aims: Postoperative recurrence of Crohn's disease [POR-CD] is almost certain if no prophylaxis is administered. Evidence for optimal treatment is lacking. Our aim was to compare the efficacy of adalimumab [ADA] and azathioprine [AZA] in this setting.

Methods: We performed a phase 3, 52-week, multicentre, randomised, superiority study [APPRECIA], in which patients with ileocolonic resection were randomised either to ADA 160-80-40 mg subcutaneously [SC] or AZA 2.5 mg/kg/day, both associated with metronidazole.The primary endpoint was endoscopic recurrence at 1 year [Rutgeerts i2b, i3, i4], as evaluated by a blinded central reader.
Results: We recruited 91 patients [median age 35.0 years, disease duration 6.0 years, 23.8% smokers, 7.1% previous resections]. The study drugs were administered to 84 patients. Treatment was discontinued owing to adverse events in 11 patients [13.1%]. Discontinuation was significantly less frequent in the ADA [4.4%] than in the AZA group [23.2%] (dif.: 18.6% [95% CI 4.1–33.2], $p = 0.011$). According to the intention-to-treat analysis, therapy failed in 23/39 patients in the AZA group [59%] and 19/45 patients in the ADA group [42.2%] [$p = 0.12$]. In the per-protocol analysis [61 patients with centrally evaluable images], recurrence was recorded in 8/24 [33.3%] patients in the AZA and 11/37 [29.7%] in the ADA group [$p = 0.76$]. No statistically significant differences between the groups were found for recurrence in magnetic resonance images, biological markers of activity, surgical procedures, or hospital admissions.
Conclusions: ADA has not demonstrated a better efficacy than AZA [both associated with metronidazole] for prophylaxis of POR-CD in an unselected population, although tolerance to ADA is significantly better. ClinicalTrials.gov NCT01564823.

Key Words: Crohn's disease; azathioprine; adalimumab.

1. Introduction

Surgery continues to play a significant role in the management of Crohn's disease [CD], despite the growing use of immunosuppressive and biologic therapies.[1–3] However, up to 70% of patients develop postoperative endoscopic lesions proximal to the ileocolonic anastomosis, which can progress to clinical recurrence and often require repeated surgeries.[4,5]

The appropriate therapy for prevention of postoperative recurrence [POR] remains the subject of debate.[1,6–8] Thiopurines are more effective than placebo for preventing both clinical and endoscopic POR in CD, but they are associated with a high rate of adverse events often leading to drug withdrawal. Consequently, their efficiency in the prevention of severe recurrence is not absolute.[9]

Findings on routine use of thiopurines for prophylaxis of POR are heterogeneous and not universally convincing. Stratification by risk of recurrence emerges as a key challenge in postoperative management, and the initial evidence for prophylaxis with anti–tumour necrosis factor alpha [anti-TNFa] agents in more aggressive forms of the disease is limited though promising.[10] Initial data suggested that infliximab [IFX] was clearly superior to placebo at preventing endoscopic [9.1% vs 84.6%], clinical, and histological postoperative recurrence of CD, seemingly providing a rationale for aggressive postoperative prophylactic therapy with biologics.[11] However, subsequent data do not seem to confirm these very interesting initial results, at least regarding clinical recurrence.[12] Adalimumab [ADA] also seems to be very effective in this setting, although the supporting evidence derives from limited studies[13] or from its use as part of a therapeutic strategy.[14]

Anti-TNFα drugs have undoubtedly changed many treatment paradigms in the management of CD, but their possible superiority over thiopurines in the prevention of POR has not been directly tested. In this study, we report the results of a randomised controlled trial to compare early postoperative use of ADA with azathioprine [AZA] in the prevention of POR in CD.

2. Materials and Methods

2.1. Study overview

The APPRECIA Study was a phase 3, 52-week, multicentre, randomised, evaluator-blind, superiority trial sponsored by GETECCU [Spanish Working Group on Crohn's Disease and Ulcerative Colitis]. The trial was approved by the Institutional Review Board of the coordinating centre [Hospital La Fe, Valencia, Spain; EudractCT number: 2011-000885-36; ClinicalTrials.gov number: NCT01564823] and confirmed by the local ethics committees. The study period ranged from January 2012 to January 2015.

2.2. Patient selection criteria

Patients aged 18–70 years with a confirmed diagnosis of CD according to established criteria,[15] and who were candidates for clinically indicated and elective ileocolonic or ileocaecal resection, were approached to obtain their informed consent before surgery. Patients with previous intolerance to AZA and/or ADA or failure of either drug in the prevention of POR were excluded. All patients had thiopurine methyltransferase [TPMT] levels > 5 U/ml. The remaining exclusion criteria were postsurgical stoma, resection for short indolent stenosis [< 10 cm], anastomosis that was inaccessible to standard endoscopy, local macroscopic disease after resection, and the usual contraindications to anti-TNFα therapy. Patients with extraintestinal manifestations and/or perianal disease, who were likely to require anti-TNFα therapy during the study period, were also excluded.

2.3. Randomisation procedures and interventions

Central randomisation was based on a pregenerated block randomisation list stratified by centre. Patients were assigned [1:1] to receive AZA 2.5 mg/kg/day or ADA 160 mg subcutaneously [SC], then 80 mg SC at Week 2, or 40 mg SC, at Week 4 and every 2 weeks thereafter. Treatment started within the first 2 weeks after resection, and metronidazole 250 mg three times a day [tid] by mouth [PO] was added for the first 3 months. Measurements of ADA levels and 6-tioguanin nucleotides were not available in Spain at the time of the study, and thus were not measured or used in adjusting doses. Allocation was concealed by means of a computer-generated randomisation schedule without stratification or block allocation. Neither patients nor investigators were blinded to the administered treatment. Adherence to therapy was assessed by direct questioning and by counting of returned medication.

2.4. Primary study outcome

The primary outcome was evidence of recurrence of CD in the colonoscopy performed at Week 52. The bowel was prepared with polyethylene glycol to reduce the risk of aphthous ulcers. A video recording of the last 15 cm of the neo-terminal ileum was evaluated by an endoscopist blinded to treatment allocation and experienced in application of the Rutgeerts score [VP]. Incomplete ileoscopy was scored as treatment failure. The Rutgeerts score was calculated[16] with modifications reported elsewhere,[17] as follows: i0, no lesions; i1, ≤ 5 aphthous lesions; i2a, lesions confined to anastomosis; i2b, > 5 aphthous ulcers or larger areas of skip lesions; i3, diffuse aphthous ileitis with diffusely inflamed mucosa; and i4, any combination of large ulcers, nodules, and/or narrowing. Grades i2b, i3, and i4 were considered indicative of endoscopic recurrence.

2.5. Secondary endpoints

The secondary endpoints included the percentages of clinical remission (Crohn's Disease Activity Index [CDAI] ≤ 200] after 24 and 52 weeks of therapy, as well as changes in activity markers such as faecal calprotectin [BÜHLMANN fCAL® ELISA], serum C-reactive protein, and erythrocyte sedimentation rate at Weeks 24 and 52. Adverse events, hospitalisations, and surgical requirements were evaluated until Week 52.

A relevant secondary endpoint was the efficacy of AZA or ADA in the prevention of recurrence at Week 52 by magnetic resonance enterography [MRE], which was evaluated centrally by an experienced blinded reader [JR]; the MRE scores MR2 and MR3 of Sailer *et al*. were considered recurrence.[18]

2.6. Statistical methods

We defined the following populations: 1] the intention-to-treat [ITT] population, which included all consenting patients who were randomised and received at least one dose of the study medications; and 2] the per-protocol [PP] population, which included all patients who received at least one dose of the study medications and in whom the primary endpoint was assessed at the end of study or at premature withdrawal. Patients lost to follow-up were considered nonresponders, following the nonresponder imputation [NRI] approach.

The main analysis was by ITT. Categorical variables were expressed as percentages and the corresponding 95% confidence intervals [CI]. The chi-square test was used to evaluate any possible differences between the treatment groups, when applicable, and the Fisher exact test was used in the remaining cases. Continuous data were tested for normality using the ShapiroWilk test. Quantitative variables were expressed as the number of valid cases, mean, standard deviation, 95% confidence interval of the mean, median, and interquartile range, as corresponding according to the normality of the distribution. Differences between the treatment groups were analysed using the *t* test; non-normally distributed variables were compared using the Wilcoxon rank sum test.

Possible variations over time among the patients allocated to each group were assessed using the McNemar test for correlated proportions in the case of categorical variables, and the paired samples *t* test [or Wilcoxon signed rank test for lack of symmetry] in the case of quantitative variables. Statistical testing was performed with $\alpha = 0.05$ [two-tailed].

Ours was a superiority trial. The difference in the proportion of endoscopic recurrence between treatment groups was estimated at 35% [10% for ADA + metronidazole and 45% for AZA + metronidazole], considering a type I error of 5%, a two-tailed contrast with Yates' continuity correction, 90% power [1—type II error], and an allocation ratio of 1:1. Therefore, 38 patients per treatment group would be needed. Withdrawals were estimated at 10%. The minimal sample was estimated at 84 evaluable patients.

Statisticians were not involved in patient care and were blinded to the study groups.

3. Results

The study population comprised 91 patients recruited from 22 centres [Figure 1]. Six patients [6.59%] were excluded during screening [four did not fulfill the selection criteria, and two developed surgical complications before treatment], leaving 85 eligible patients; 40 patients were randomised to the AZA group and 45 to the ADA group. One of the patients in the AZA group withdrew consent before the first study dose; therefore, the ITT population included 84 patients.

The groups were similar regarding baseline characteristics, including smoking status, previous resections, CD phenotype, previous perianal disease, and previous drug exposure [Table 1].

All 84 eligible patients received at least one dose of the study drug and were included in the analysis [AZA, 39 patients; ADA, 45 patients]. A total of 68 patients completed the study [AZA, 27 patients; ADA, 41 patients].

There were 12 dropouts in the AZA group [nine adverse events, two clinical deteriorations, and one loss to follow-up] and four in the ADA group [one nonrelated death, one adverse event, one loss to follow-up, and one disease worsening].

3.1. Primary endpoint: endoscopic recurrence

The primary endpoint was assessed in 61 of the 68 patients who completed the study [AZA, 24 patients; ADA, 37] [Table 2, Figure 1].

The PP analysis revealed endoscopic recurrence in 8/24 patients in the AZA group and 11/37 patients in the ADA group (33.3% [95% CI 15.6–55.3] and 29.7 [95% CI 15.9–47.0], respectively; $p = 0.76$, nonsignificant [ns]). In the ITT analysis, therapy failed [as shown by the presence of endoscopic recurrence] in 23/39 patients in the AZA group and in 19/45 patients in the ADA group (59.0% [95% CI 42.1–74.4] and 42.2% [95% CI 27.7–57.9], respectively; $p = 0.12$, ns]) [Figure 2].

3.2. Secondary clinical endpoints

The CDAI was calculated at Weeks 24 and 52, and no significant differences were observed between the treatment groups for the absolute value [$p = 0.31$ and $p = 0.93$] or the percentage with CDAI < 200 [$p = 0.56$ and $p = 0.16$, respectively].

There were four hospitalisations in the AZA group (10.3% [95% CI 2.9–24.2]) and nine in the ADA group (20% [95% CI 9.6–34.6]) [$p = 0.21$] [Table 3]. Surgery was necessary in three patients in the AZA group (7.7% [95% CI 1.6–20.9]) and in two patients in the ADA group (4.4% [95% CI 0.5–15.1]), [$p = 0.65$]; none of the procedures were related to the initial surgery. The only procedure considered related to the study medication was a transurethral resection of a bladder tumuor in the AZA group. No significant differences were found at Week 24 or Week 52 between the groups for C-reactive protein, faecal calprotectin, or erythrocyte sedimentation rate [Table 3].

Out of the 53 evaluable resonances, a postsurgical recurrence [Sailer index mr2 or mr3] occurred in 7/21 patients in the AZA group and 9/32 patients in the ADA group (33.3% [95% CI 14.6–57.0] and 28.1% [95% CI 13.8–46.8], respectively; $p = 0.69$, ns).

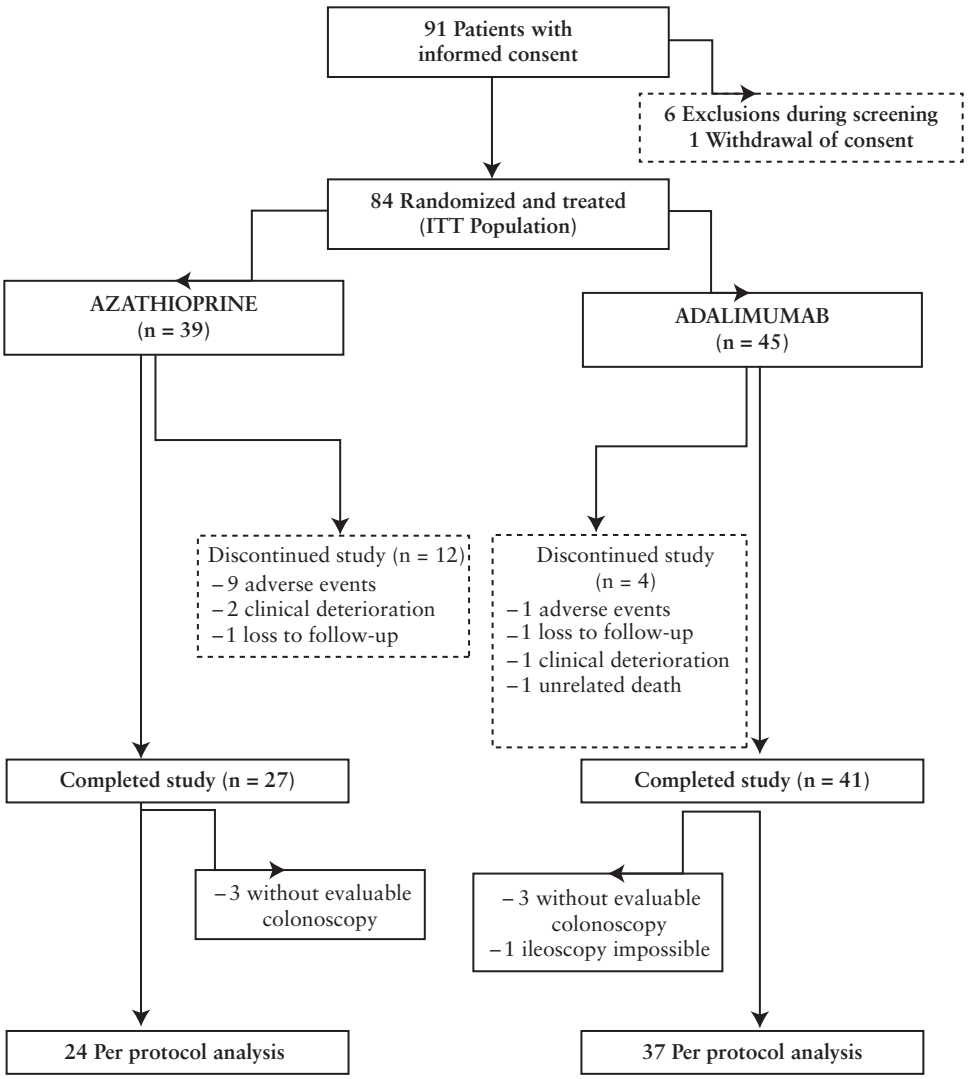

Figure 1. Flow diagram of the progress of patients through the study.

In the ITT analysis, therapy failed in 25/39 patients in the AZA group and in 22/45 patients in the ADA group (64.1% [95% CI 47.2–78.8] and 48.9% [95% CI 33.7–64.2], respectively; $p = 0.16$, ns].

3.3. Additional post hoc analyses

Analysis of data after classifying only a Rutgeerts score of 3 or 4 as treatment failures [ie, including a score of 2 as treatment success] revealed no change in the results, with no differences between the treatment arms. There were seven severe recurrences in 61 evaluable patients (11.5% [95% CI 4.7–22.2]): five in the ADA group (13.5% [95% CI 4.5–28.8]) and two in the AZA group (8.3% [95% CI 1.0–27.0]) [$p = 0.53$].

We also performed a post hoc analysis of combined endoscopic and radiological recurrence. Endoscopic recurrence and radiological recurrence [ITT analysis with NRI] were absent in 9/39 patients in the AZA group and in 18/45 patients in the ADA group (23.1% [95% CI 11.1–39.3] and 40% [95% CI 25.7–55.7], respectively; $p = 0.09$). The difference was also observed in the PP analysis, with 11/20 patients (55% [95% CI 31.5–76.9]) in the AZA group and 12/30 (40% [95% CI 22.7–59.4]) in the ADA group [$p = 0.29$].

Additionally, endoscopic recurrence rates did not differ between treatment groups when comparing patients without risk factors and patients with at least one risk factor [smoking, previous resections, penetrating phenotype] [49.3 vs 55.6%, $p = 0.72$], patients with or without previous exposure to AZA, or ADA [49.3 vs 53.3%, $p = 0.77$], or with or without previous exposure to any anti-TNF therapy [51% vs 48.6%, $p = 0.82$].

3.4. Safety and adverse events

Median exposure was 12 (interquartile range [IQR] 11.7–12.2) months for ADA and 11.9 [IQR 6.6–12.2] months for AZA. Median exposure to metronidazole showed no differences between the groups [ADA: 3, IQR 2.8–3.0 months; AZA: 3, IQR 1.7–3.5 months; $p = 0.51$].

A total of 232 adverse events were observed in 72 (85.7% [95% CI 76.4–92.4]) patients [Table 4], with no differences between the AZA group and the ADA group (89.7% [95% CI 75.8–97.1] vs 82.2% [95% CI 67.9–92.0], respectively; $p = 0.35$). Of these, 68 were considered related to the study medication, with no differences between the groups. Severe adverse events were reported in 13 patients (15.5% [95% CI 8.5–25.0]), again with no differences

between the groups. Adverse events resulting in drug discontinuation were significantly more frequent in the AZA group than in the ADA group (AZA, 23.1% [95% CI 11.1–39.3] vs ADA, 4.4% [95% CI 0.5–15.1]; $p = 0.01$).

A death by suicide was recorded in the ADA group and was not considered related to the study medication. A neoplasm [urothelial carcinoma] observed in the AZA group was classified as possibly related to the study medication and treated with endoscopic resection and intravesical chemotherapy.

Table 1. Baseline demographic and clinical characteristics of patients assigned to either treatment group [intention-to-treat population]

	Azathioprine [*n* = 39]	Adalimumab [*n* = 45]	*p*
Age—years			0.14
median	37.00	35.00	
interquartile range	31.00–47.00	30.0–40.0	
Male gender—no. [%]	23 [59]	19 [42.2]	0.12
Current smoker—no. [%]	9 [23.1]	11 [24.4]	0.91
Duration of disease—years	7.31	8.11	0.15
BMI[a]	22.38	22.52	0.66
Crohn's disease phenotype			
Localisation—no. [%]			
- L1 ileal	23 [59]	26 [57.8]	0.91
- L3 ileum + colon	16 [41]	19 [42.2]	
- L4 upper digestive tract	3 [7.7]	2 [4.4%]	0.65
Behaviour— no. [%]			
- B3	11 [28.2]	20 [44.4]	0.12
- Perianal	8 [20.5]	4 [8.9]	0.12
Previous resections— no. [%]	3 [7.7]	3 [6.7]	1
Any risk factor [smoking, B3, previous resection] — no. [%]	22 [56.4]	29 [64.4]	0.56
Centimetres of ileum resected			0.13
median	32.5	25.0	
interquartile range	15.0–45.0	15.0–32.5	
Therapies before surgery— no. [%]			
- Glucocorticoids	38 [97.4]	42 [93.3]	0.61
- Immunosuppressants [thiopurines or methotrexate]	28 [71.8]	35 [77.8]	0.52
- Anti TNFα	21 [53.8]	28 [62.2]	0.43
Postsurgical CDAI < 200— no. [%]	24/38 [63.2]	29/42 [69]	0.57

CDAI, Crohn's Disease Activity Index.

[a]The body-mass index [BMI] is the weight in kilograms divided by the square of the height in metres.

4. Discussion

Our study shows that ADA is as efficacious as AZA in the prophylaxis of POR-CD. Surgery has been described as a reset of disease course, and this window of opportunity could make a strategy based on immunosuppressants and/or anti-TNFα agents an attractive option.[12] Initial controlled data[11] point to the high efficacy of this approach, which is supported by the results of more recent meta-analyses and systematic reviews.[19,20]

We performed a head-to-head comparison of AZA, an established drug for prophylaxis of POR, with ADA, an anti-TNFα drug that is well established for the management of CD. The study was performed in the IBD units of hospitals of the Spanish National Health System, thus ensuring uniform and up-to-date standard of care.

The study population is representative of real life, and benign short indolent stenosis was the only condition excluded. We chose not to restrict inclusion to patients with presumed factors for high risk of POR. Other than smoking, which is generally considered deleterious, other factors have not unanimously been identified, even in recent multicentre studies.[21] The populations of previous studies[22,23] are limited to patients at high risk of POR. The heterogeneous criteria used to select such at-risk populations—young age, recent corticosteroid therapy, smoking, more than one surgery, and perforating disease—probably indicate the lack of sensitive and specific criteria for identification of the subset of patients requiring proactive prevention of POR, and could justify the less restrictive selection criteria adopted by our group and by others.[11–13] If new risk factors for early and/or severe recurrence emerge in the future, studies on prevention of POR will need to adapt to a new state of the art.

We calculated the Rutgeerts score with the modification that subdivides grade 2 into 2a [lesions limited to the anastomosis] and 2b [true recurring lesions].[17,23] Centralised evaluation reduced the possibility of centre bias[24] as concerns have been reported about the reproducibility of the Rutgeerts score, especially when differentiating < i2 from ≥ i2, and the potential for incorrect therapeutic decisions has been reported in > 10% of patients.[25,26] Ours is the first study in which recurrence based on MRE findings assessed centrally by an experienced blinded reader was included as an endpoint. We performed ileoscopy at 1 year because all patients were actively treated. Both groups were comparable with respect to clinical characteristics associated with a higher risk of POR.[13,14]

To date, five studies have compared anti-TNFα drugs in monotherapy with placebo or other active interventions in this setting. The first was performed by Regueiro *et al.*[11] in a nonselected population and suggested a clear efficacy for IFX. In the first comparative trial [*n* = 51] using ADA,[13] sample size was calculated according to the results of Regueiro *et al.* and included three groups, namely ADA, AZA, and mesalamine. The authors highlighted the effectiveness of ADA [6.3% endoscopic recurrence] compared with AZA [64.7%] and mesalamine

Table 2. Week 52 endoscopic findings according to the Rutgeerts score [per protocol analysis]

Patients with evaluable colonoscopy	Azathioprine *n* = 24	Adalimumab *n* = 37	Total *N* = 61	*p*
Rutgeerts index at Week 52 [Fisher exact test]				0.80
i0—no. [%]	11 [45.8%]	13 [35.1%]	24 [39.3%]	
i1 no. [%]	3 [12.5%]	6 [16.2%]	9 [14.8%]	
i2a—no. [%]	2 [8.3%]	7 [18.9%]	9 [14.8%]	
i2b—no. [%]	6 [25.0%]	6 [16.2%]	12 [19.7%]	
i3—no. [%]	1 [4.2%]	3 [8.1%]	4 [6.6%]	
i4—no. [%]	1 [4.2%]	2 [5.4%]	3 [4.9%]	
Endoscopic recurrence [chi-square]	8 [33.3%]	11 [29.7%]	19 [31.1%]	0.76

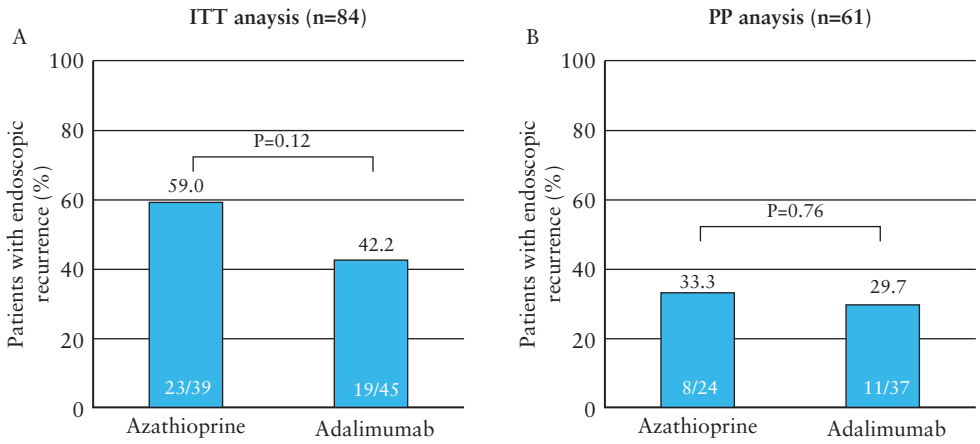

Figure 2. Primary endpoint. The percentages of patients with endoscopic recurrence in the colonoscopy at Week 52 are shown for azathioprine and adalimumab [both associated with metronidazole] in Panels A (intention-to-treat [ITT] analysis) and B (per-protocol [PP] analysis). Incomplete ileoscopy was scored as treatment failure. The Rutgeerts endoscopic grades i2b, i3, and i4 were considered indicative of endoscopic recurrence. The reported *p*-values are from two-sided tests.

Table 3. Secondary clinical endpoints

Item	Azathioprine [*n* = 39]	Adalimumab [*n* = 45]	Total[*N* = 84]	*p*
CDAI				
Week 24				0.31
median	67.0	54.0	58.0	
interquartile range	33.0–103.0	36.0–111.0	34.5–107.0	
Week 52				0.93
median	52.0	51.5	52.0	
interquartile range	34.0–89.0	28.0–109.0	30.0–96.0	
CDAI < 200				
Week 24	27 [93.1%]	42 [97.7%]	69 [95.8%]	0.56
Week 52	25 [92.6%]	38 [100.0%]	63 [96.9%]	0.16
C-reactive protein mg/L				
Week 24				0.46
median	1.0	1.0	1.0	
interquartile range	0.5–3.0	0.3–2.5	0.3–2.9	
Week 52				0.65
median	1.0	1.1	1.0	
interquartile range	0.5–2.9	0.4–3.0	0.5–2.9	
Faecal calprotectin mcg/g				
Week 24				0.37
median	74.0	46.5	56.5	
interquartile range	26.0–195.0	40.0–74.0	40.0–85.0	
Week 52				0.60
median	58.0	42.0	45.5	
interquartile range	30.0–135.9	18.0–85.0	27.5–102.0	
ESR mm/h				
Week 24				0.21
median	10.0	7.0	8.0	
interquartile range	4.0–18.0	4.0–11.0	4.0–14.0	
Week 52				0.82
median	8.0	8.0	8.0	
interquartile range	4.5–16.5	5.0–16.2	5.0–16.2	
Admissions until Week 52	4 [10.3%]	9 [20%]	13 [15.5%]	0.21
Surgery until Week 52	3 [7.7%]	2 [4.4%]	5 [6%]	0.65

Missing values are considered treatment failures [nonresponder imputation]. Normal values: C-reactive protein, < 5 mg/l; calprotectin, < 50 mcg/g; ESR, < 20 mm/h.

CDAI, Crohn's Disease Activity Index; ESR, erythrocyte sedimentation rate.

[83.3%]. In a pilot study by Armuzzi *et al.*[27] with 22 patients undergoing surgery [11 with IFX and 11 with AZA], no differences were observed between the groups. A recent network meta-analysis[19] evaluated these three studies and other available data and concluded—bearing in mind the intrinsic limitations associated with this methodology—that anti-TNF therapy is the most effective strategy for prevention of POR.

Table 4. Adverse events registered during the study

Variable	Azathioprine [*n* = 39]	Adalimumab [*n* = 45]	*p*
Adverse events possibly related to the study medication—no. [%]	18 [46.2]	20 [44.4]	0.87
Severe adverse events—no. [%]	4 [10.3]	9 [20]	0.21
Severe adverse events possibly related to the study medication—no. [%]	1 [2.6]	1 [2.2]	1
Adverse events resulting in discontinuation—no. [%]	9 [23.1] [leukopenia, 3; arthralgia, 2; urothelial carcinoma, 1; dyspepsia, 3]	2 [4.4] [dyspnoea, 1; death, 1]	0.01

Our results are consistent with the previous experience on AZA and ADA in the prevention of POR.[14,28–30] The PREVENT trial was the first large, multicentre, placebo-controlled postoperative CD study using a biologic drug. No significant differences in clinical remission were observed at Week 72 among patients treated with IFX and those treated with placebo. The percentages of clinical recurrence at 72 weeks were 12.9% for IFX and 20% for placebo, again with no significant differences. Therefore, according to this trial and in spite of its limitations [IFX used at the maintenance dose and up to 45 days after surgery], the efficacy of IFX in the prevention of clinical POR has not been demonstrated.

De Cruz *et al.*[30] recently studied CD treatment strategies after intestinal resection and found that therapy adjusted according to 6-month colonoscopy findings led to effective disease control. A subanalysis of this study showed that, in patients with a high risk of recurrence, treatment with ADA could be effective. In a study of 101 patients,[14] the same authors found endoscopic recurrence [Rutgeerts score i2–i4] in 45% of the thiopurine group and in 21% of the ADA group. The most advanced disease [Rutgeerts i3 and i4] was observed in 8% and 4% of patients taking thiopurine and ADA, respectively.

According to our results, ADA has not demonstrated a better efficacy than AZA [both associated with metronidazole] in preventing POR. Therapeutic failure was observed in 59% of patients in the AZA group and in 42.2% in the ADA group [ITT analysis; ns]. The results did not differ in the PP analysis, with 33.3% and 29.7% endoscopic recurrence in the AZA and ADA groups, respectively. Similarly, the post hoc analysis revealed no differences for severe recurrence or combined endoscopic/MRE recurrence. The high recurrence rates observed when the endoscopic and MRE analyses were combined could be due to the NRI approach. However, high rates were also observed in the PP analysis, thus raising the issue of the suitability of a combined endoscopic and cross-sectional imaging evaluation of POR, if a complete evaluation is desired.

Our population was not selected according to the presence or absence of risk factors for recurrence. This could be a weakness of our trial design, but we decided to do so believing that it would reproduce more exactly current clinical practice.

The relationship between endoscopic recurrence and several variables was also assessed. In our series, no differences were observed in the rate of endoscopic recurrence rates according to risk factors [smoking, previous resections, penetrating phenotype] or previous exposure to the study drugs or to any biologic therapy. In our opinion, it cannot be concluded that using anti-TNF had an advantage for prophylaxis of recurrence in any specific patient group or depending on the perceived higher risk of POR.

Adverse events were more frequent in the AZA group, requiring discontinuation of therapy in 23.1% of patients. This difference was significant when compared with the ADA group. Therefore, ADA is better tolerated in this setting, where 15–20% of patients receiving thiopurines were reported to be at risk of adverse events.[31]

Of note, the recurrence rates observed in the ADA group are clearly higher than those reported in other studies, which ranged between 6.3% and 21%.[13,14,32] Some of these studies limited inclusion to patients with an inflammatory phenotype; others included colonic resections or selected patients assigned to anti-TNFα therapy because of previous intolerance to AZA. Nevertheless, our results are consistent, to a certain extent, with those reported in the extensive study by De Cruz *et al.*,[30] in which patients under 'active care' showed a significant percentage of disease recurrence. Evidence obtained from databases points in the same direction.[33]

When confronting our results, it is easy to feel surprised when superiority of ADA over AZA in the peculiar setting of CD recurrence prophylaxis is not demonstrated. As prescribers, many of us have a mental image of anti-TNF drugs as being more potent than immunosuppressants. After all, they are mostly used as a rescue therapy after these latter have failed. There are a few reasons that could explain this apparently illogical result.

First, our patient population was not selected according to their recurrence risk. It is conceivable that, in a population with more predictors of severe recurrence, ADA would have been in the right ballpark to show its superiority. However this remains an assumption, because risk factors have generally been identified in retrospective series analysis. Also, Regueiro *et al.*[12] included only patients with at least one risk factor, and also failed to demonstrate a superiority of anti-TNF over thiopurines in the prevention of clinical recurrence, although endoscopic recurrence was reduced by IFX. In any case, the non-selected population was evenly distributed across both treatment groups.

Medication doses used by us were within the currently recommended range, and we do not think this could have been of relevance.

When this study was initiated, a placebo-controlled design did not seem appropriate, and we preferred instead to compare therapy with ADA and what we considered the most established and efficacious approach to prevention of POR, namely the combination of AZA and metronidazole.[22] This antibiotic was also added to the ADA group to ensure homogeneous management of both arms. In retrospect, this decision may have played a role in the absence of differences observed between the treatment groups, as the efficacy of metronidazole is clearer during the first year after surgery[34] and this could have affected disease course. However, it has been shown before in a good quality randomised trial that the addition of metronidazole does not significantly reduce the risk of endoscopic recurrence beyond the effect of AZA alone.[35]

Finally, the possibility remains that our results reflect a real equivalence of both drugs in this setting. Both have been shown to be able to heal recurrence lesions, and it is conceivable that our trial points to a real-world equivalence of anti-TNF and thiopurines in this indication.

Our study has several strengths. It is the first study where endoscopic recurrence was assessed centrally by an experienced blinded

reader, ADA was used at the induction dose, the modified Rutgeerts score was calculated excluding i2a, recurrence was defined by objective morphological criteria, and the evaluation was performed 1 year after the pharmacological intervention, as suggested in the PREVENT study.[12]

Our study is subject to a series of limitations. Power analysis was done at the time of study design, before the current data[28] were available and when the initial study by Regueiro *et al.*[11] showed impressive early results for anti-TNF in the prevention of CD recurrence [rate of endoscopic recurrence at 1 year in the IFX group 9.1%, compared with the placebo group 84.6%, $p = 0.0006$]. Sample size was calculated using the data available at the time on the efficacy of AZA and anti-TNFα drugs in this setting.[11,22] This may have resulted in an overestimation of the effect of ADA, an assumption supported by subsequent experience.[30] However, our calculation was more conservative, opting for a beta error of 5% and a power of 90% instead of the more universally adopted value of 80%. According to more recent data,[12] the study was probably underpowered and the possibility of a beta-type error is likely. The Yates correction for continuity was chosen for the same reason. We acknowledge that power calculation was probably suboptimal, being based on the available data at the start of the study but leading to an underpowered study with difficult-to-interpret results.

Another limitation is that treatment optimisation was not performed, as ADA levels and 6-tioguanin nucleotides were not available in Spain at the time of the study.

We used a dropout rate of 10%. This dropout estimation may be more adequate in clinical situations in which patients are in tight control [post-liver transplantation, Crohn's in IBD clinics…]. To our understanding, our patients would probably have more adherence at follow-up [as they had a surgery and a serious chronic pathology] than other CD patients.

In conclusion, our trial could not demonstrate the superiority of ADA over AZA [both associated with metronidazole] in the prevention of POR. ADA was better tolerated. In view of its availability, convenience, and cost, AZA should be still the drug of choice in this setting, except in the case of patients with previous or current intolerance, who should receive ADA if necessary. The efficacy of both drugs, however, is partial, and an endoscopic examination should be performed at some point to assess the presence of significant endoscopic recurrence, which can then be treated.

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Conflict of Interest

AL-S: reports grants from AbbVie, during the conduct of the study; grants and personal fees from AbbVie, MSD, Tillotts, personal fees from Ferring, Faes Farma, Shire, Hospira, Kern-Celltrion, Takeda, Pfizer, outside the submitted work. IV-M: reports personal fees from MSD, AbbVie, Shire, Ferring, Takeda, Pfizer, outside the submitted work. ED: reports grants, personal fees, and non-financial support from AbbVie, MSD, personal fees from Takeda, Hospira, Kern, Shire Pharmaceuticals, personal fees and non-financial support from Ferring, Tillots Pharma, Otsuka Pharmaceuticals, personal fees from Pfizer, Celgene, outside the submitted work. CT: reports personal fees from MSD, AbbVie, Ferring, Gebro Pharma, outside the submitted work. JG: reports personal fees from AbbVie, MSD, Shire, Ferring, Kern Pharma, Gebro Pharma, outside the submitted work. ME: reports a collaboration with Grupo Español de Trabajo en Enfermedad de Crohn y Colitis Ulcerosa [GETECCU] during the conduct of the study; other from AbbVie, MSD, Tillots-Pharma, Takeda, outside the submitted work. PM-M: reports personal fees and non-financial support from AbbVie, Ferring, Takeda, Otsuka, Shire, outside the submitted work. JPG: has served as a speaker, consultant, and advisory member for or has received research funding from MSD, AbbVie, Hospira, Kern Pharma, Takeda, Janssen, Pfizer, Ferring, Faes Farma, Shire Pharmaceuticals, Dr. Falk Pharma, Chiesi, Casen Fleet, Gebro Pharma, Otsuka Pharmaceutical, Vifor Pharma. XC: reports personal fees from AbbVie, Hospira, MSD, Shire, Allergan, outside the submitted work. JB: reports non-financial support from AbbVie, MSD, Ferring, outside the submitted work.MDM-A: reports a collaboration with AbbVie, other from Janssen, other from Takeda, other from MSD, outside the submitted work. FB: reports a collaboration with AbbVie, outside the submitted work. JR: reports grants from Genentech, personal fees from Takeda, Robarts Clinical Trials, grants from AbbVie, outside the submitted work. PN: reports grants and personal fees from MSD, grants from Otsuka, AbbVie, personal fees from Takeda, Kern, Biogen, Ferring, outside the submitted work. The other authors have nothing to disclose.

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Supplementary Data

Supplementary data are available at *ECCO-JCC* online.

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