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Azathioprine for prevention of clinical recurrence in Crohn's disease patients with severe endoscopic recurrence: an IG-IBD randomized double-blind trial

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Abstract. – OBJECTIVE: The recurrence of Crohn's Disease after ileo-colonic resection is a crucial issue. Severe endoscopic lesions increase the risk of developing early symptoms. Prevention and treatment of post-operative Endoscopic Recurrence (ER) have been studied with conflicting results. We compare efficacy of azathioprine (AZA) *vs*. high-dose 5-aminosalicylic acid (5-ASA) in preventing clinical recurrence and treating severe post-operative ER.

PATIENTS AND METHODS: We performed a 1-year multicenter randomized double-blind double-dummy trial. Primary end-points were endoscopic improvement and therapeutic failure (clinical recurrence or drug discontinuation due to lack of efficacy or adverse events) 12 months after randomization. We also performed a post-trial analysis on symptomatic and endoscopic outcomes 10 years after the beginning of the trial, with a median follow-up of 60 months.

RESULTS: Therapeutic failure occurred in 8 patients (17.4%) within 12 months from randomization, with no significant difference between patients treated with 5-ASA (20.8%, 5 patients) and those with AZA (13.6%, 3 patients). Therapeutic failure was due to clinical recurrence in the 5-ASA group and to adverse events in the AZA group. Endoscopic improvement at 12 months was observed in 8 patients, 2 (11.8%) in the 5-ASA group and 6 (30%) in the AZA group. No serious adverse event was recorded.

At the post-trial analysis (median follow-up 60 months), 47.8% (22/46) of patients experienced clinical recurrence: 54.2% (13/24) in the 5-ASA group and 40.9% (9/22) in the AZA group, p=0.546. Patients treated with AZA had lower risk of drug escalation. Clinical recurrence was associated with smoking (*p*=0.031) and previous surgery (*p*=0.003).

CONCLUSIONS: Our trial indicates that there was no difference in terms of treatment failure between 5-ASA and AZA in patients with severe post-operative ER. The main limit of AZA is its less favorable safety profile.

Key Words:
Crohn's Disease, Post-Surgical Endoscopic Recurrence, Prevention, Clinical Trial, Azathioprine, Mesalamine, Italian Group (IG).

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Introduction

Crohn's disease (CD) is a chronic relapsing, progressive inflammatory bowel disease (IBD) which requires surgery in more than 70% of patients[1]. The recurrence of CD after curative ileo-colonic resection is one of the most important issues in the management of IBD and frequently leads to repeated surgical procedures. Endoscopy is the most sensitive method to detect post-surgical endoscopic recurrence (ER). Many endoscopic studies have shown that Crohn's lesions develop in the neoterminal ileum or in the ileo-colonic anastomosis within the first year after surgery[2-4]. In 2014, we published data from a multicenter Italian study that showed a cumulative ER rate of 62% 6 months after resective surgery: 13.5% of patients had a Rutgeerts' score of i1, 10.0% i2, 13.5% i3, and 24.8% i4[5]. In this published study, we evaluated the entire cohort of the current registered trial (252 consecutive CD patients treated with curative bowel resection) analyzing data of all patients who underwent colonoscopy 6 months after surgery (170 out of 252) regardless of their future enrolment in the trial. Patients with no or mild lesions (Rutgeerts' score i0 and i1) have a more favorable post-operative clinical course. In contrast, patients with severe endoscopic lesions (Rutgeerts' score ³ i2) have a higher risk of developing early symptoms and complications[2]. In light of the high risk of early severe ER at 6 months, adequate timing of aggressive medical treatment is needed. Over the last two decades, prevention and treatment of post-operative ER using available medical treatment have been studied with conflicting results[6-14]. Only one double-blind double-dummy multicenter study compared the use of azathioprine (AZA) and high dose 5-aminosalicylic acid (5-ASA) for prevention of post-surgical clinical recurrence in high-risk patients who have already developed severe ER[15]. In this population of patients, no significant difference between AZA and 5-ASA could be demonstrated.

We report the data from our 1-year multicenter randomized double-blind double-dummy trial, assessing the role of AZA *vs.* high dose 5-ASA in treating early (at 6 months) severe post-surgical ER (Rutgeerts' score ≥ i2) and preventing symptomatic recurrence.

Patients and Methods

Study Design

A 1-year multicenter randomized double-blind double-dummy trial was conducted at 11 Italian referral centers for IBD from April 2005 to June 2010 [Internal Medicine, Villa Sofia-Cervello Hospital, Palermo; Department of Gastroenterology, IRCCS, Casa Sollievo della Sofferenza Hospital, San Giovanni Rotondo (FG); Department of Gastroenterology, Federico II University, Naples; Gastroenterology unit, San Camillo Forlanini, Rome; Department of Gastroenterology, San Filippo Neri Hospital, Rome; Department of Internal Medicine, Policlinico Sant'Orsola Malpighi, Bologna; Department of Gastroenterology, Policlinico Umberto I Hospital, Rome; Department of Gastroenterology, Tor Vergata University, Rome; Department of Gastroenterology, Palermo University, Palermo; Department of Gastroenterology, Messina University, Messina; Department of Gastroenterology, Padua University, Padua].

CD patients aged 18-75 years, who had been treated with a first or second curative resection of the terminal ileum and part of the right colon, were eligible for screening. Exclusion criteria included the following: conservative surgery (strictureplasty), surgery for Crohn's colitis without ileitis, presence of other unresected lesions, active perianal CD, previous bowel resection comprising more than one meter, sclerosing cholangitis, previous pancreatitis, kidney failure, viral hepatitis B or C.

At the screening visit (2 weeks after surgery), all patients started 2.4 gr daily of 5-ASA[6,16]. Endoscopic examination was performed 6 months after surgical resection and the severity of ER was evaluated according to the Rutgeerts' scoring system. Patients presenting severe ER, with Rutgeerts' score ≥ i2 (>5 aphthous lesions with normal mucosa between the lesions or diffuse aphthous ileitis with diffusely inflamed mucosa or diffuse inflammation with larger ulcers, nodules and/or narrowing), were recruited into the study.

Patients were randomized in a 1:1 ratio to receive AZA (2.0-2.5 mg/kg/day) or high dose 5-ASA [4 gr/die/day, Pentacol®, SOFAR Spa, Trezzano Rosa (MI), Italy]. Central randomization was performed *via* computer-generated randomization lists with medication distributed to each center accordingly.

To maintain investigator and patient blinding, patients were randomized to "active" AZA and "placebo" high dose 5-ASA or "placebo" AZA and "active" high dose 5-ASA.

All patients were followed-up at 15, 30 and 90 days, and then, every 3 months until 12 months

after randomization. Symptomatic clinical recurrence and adverse events were recorded at each visit.

After 12 months of treatment, endoscopic and symptomatic recurrence were evaluated in both groups of patients.

A further analysis, not included in the original trial design, was performed 10 years after randomization.

The study was performed in accordance with the amended Declaration of Helsinki and the ICH Harmonized Tripartite Guideline for Good Clinical Practice. The study was approved by the local Institutional Review Board (IRB) and registered with the number of EUDRACT 2006-001315-30. Written informed consent was obtained from all patients following regulatory authority.

Both AZA and 5-ASA were supplied by SOFAR Spa, Trezzano Rosa (MI) Italy.

Outcomes

Primary endpoints were endoscopic improvement and therapeutic failure (clinical recurrence or drug discontinuation due to lack of efficacy or adverse events) 12 months after randomization.

In addition, we performed a long-term post-trial analyses of clinical and endoscopic outcomes 10 years after the first randomization.

Endoscopic improvement was defined as a Rutgeerts' score reduction of at least 2 points from baseline. We also analyzed the data considering a reduction of at least 1 point in order to compare our results with those of Reinisch et al[15].

Clinical recurrence was defined as reappearance of symptoms with an increase of the Crohn's disease activity index (CDAI) score above 200 points. Although clinical recurrence is usually defined as a CDAI score $\geq$ 150, we considered a higher cut-off because patients with ileo-cecal resection can present an increase of daily bowel movements, especially soon after surgery.

Outcomes were calculated using an intention-to-treat analysis, for which patients who discontinued the study prior to reaching the end point were considered to be non-responders.

Safety

Safety assessment included adverse events (AEs) monitoring and measurement of laboratory parameters. AEs were recorded as "serious" according to regulatory guidance or if one of the following applied: required prolonged hospitalization, resulted in death or life-threatening, caused significant or permanent disability, judged as significant medical events by the investigator.

Statistical Analysis

The sample size necessary to achieve an 80% power to detect a reduction of clinical recurrence of 25% in favor of AZA *vs.* 5-ASA (two-sided test $\alpha = 0.05$, $\beta = 0.80$) was 116 patients (58 patients per treatment arm).

Continuous variables were reported as medians with interquartile ranges [IQR], and categorical variables as frequency and percentage. Mann-Whitney U-test and χ^2 tests (or Fisher's exact test, where needed) were used for comparison of continuous and categorical variables, respectively.

Descriptive time to event analysis was conducted to assess therapeutic failure using the Kaplan-Meier method. The log-rank test was used to compare time to failure between patients treated with AZA and 5-ASA. The following variables were assessed using univariable analysis in order to identify predictive factors of the outcome: sex, age at diagnosis, smoking habit, disease duration, history of surgery, site of disease, history of immunosuppressants, history of fistulas and extraintestinal manifestations.

Variables associated with the dependent variable on univariable analysis (probability threshold: $p \leq 0.10$) were included in the Cox regression model, then selected using a backward elimination approach. Results were considered statistically significant when $p \leq 0.05$. Proportional hazard assumptions were tested using Schoenfeld residuals tests and were not violated.

The safety population was defined as all randomized patients who received at least one dose of study medication and provided at least one follow-up safety evaluation.

All statistical analyses were performed using R version 3.4.2 (R Foundation for Statistical Computing, Vienna, Austria)[17].

Results

Trial Results

From April 2005 to June 2010, 252 consecutive CD patients who had been treated by a first or second curative resection of the terminal ileum and part of the right colon were screened for the study. According to inclusion/exclusion criteria,

211 patients were eligible: 24 patients were lost at follow-up, 82 did not undergo colonoscopy at 6 months, 105 underwent colonoscopy 6 months after surgery (Figure 1).

According to inclusion/exclusion criteria, 46 patients were randomized (characteristics of screened patients are shown in Table I): 65% males, overall median age at diagnosis was 28.0 years in the 5-ASA group and 30.0 years in the AZA group (p=0.668); median age at surgery was 34.5 years in the 5-ASA group and 38.0 years in the AZA group (p=0.878).

At the final analysis, data on post-surgical ER after 12 months of treatment were collected on 37 out of 46 patients: 1 patient did not undergo colonoscopy due to early AEs, 3 refused colonoscopy, 5 patients did not undergo colonoscopy due to study withdrawal (therapeutic failure within 12 months). We analyzed the data of all patients and for missing data we analyzed the data at the last observation. The difference between the two groups in endoscopic improvement at 12 months did not reach statistical significance based on our definition, i.e., a decrease

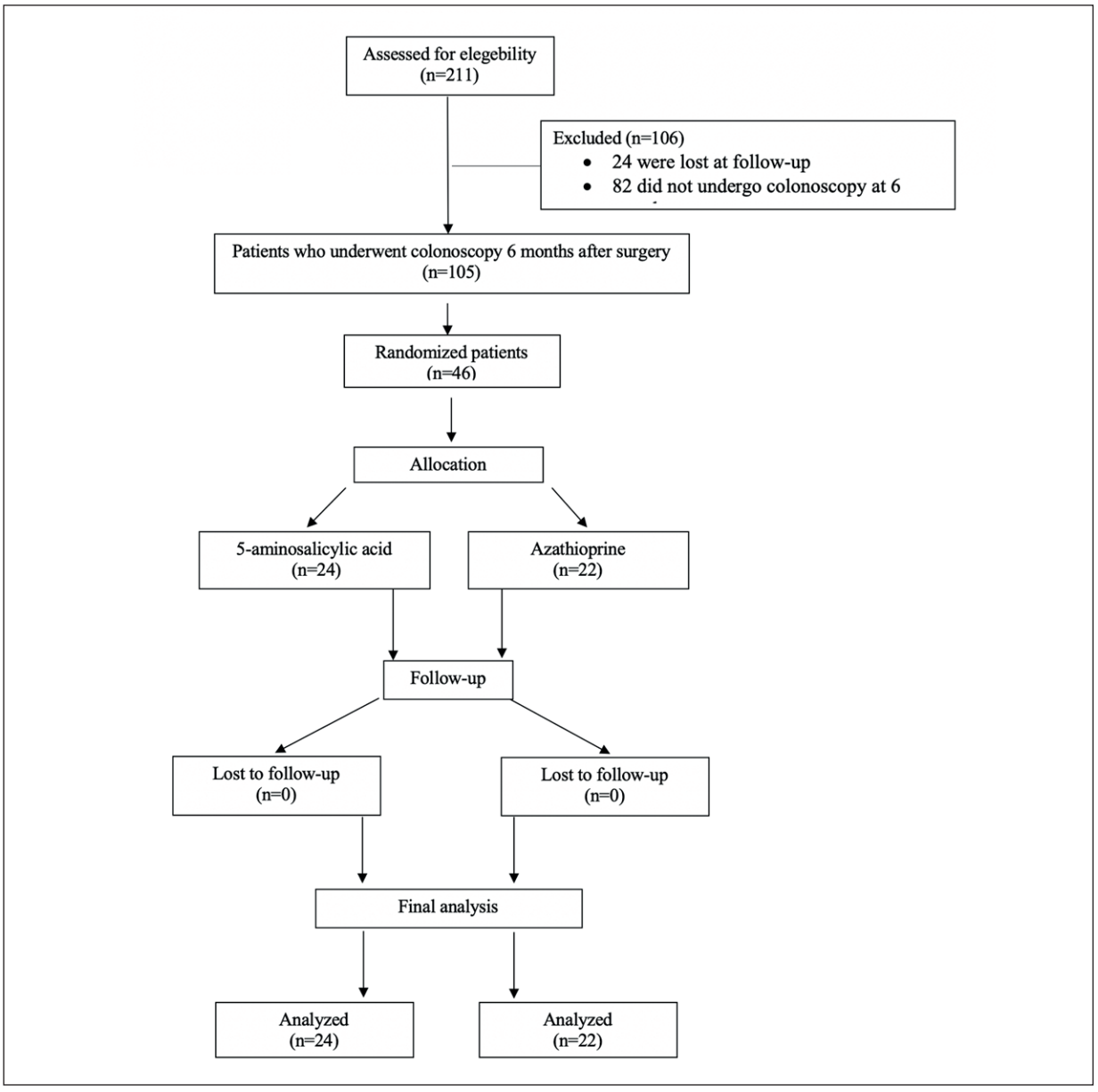

Figure 1. Flowchart of the study.

Table I. Baseline characteristics (intention-to-treat population).

	5-ASA	AZA	*p*-value
N	24	22	
Male gender (%)	16 (66.7)	14 (63.6)	1.000
Age at surgery (median [IQR])	34.5 [27.8, 51.3]	38.0 [29.3, 44.8]	0.878
Age at diagnosis (median [IQR])	28.0 [22.8, 41.8]	30.0 [26.0, 38.0]	0.668
Smokers (%)			0.248
Never	9 (37.5)	11 (50.0)	
Current	10 (41.7)	10 (45.5)	
Ex	5 (20.8)	1 (4.5)	
Family history (%)	0 (0.0)	1 (4.5)	0.965
Behavior of Crohn's disease			0.179
Stricturing	17 (70.8)	20 (90.9)	
Fistulizing	7 (29.2)	2 (9.1)	
Comorbidities			
Cardiovascular	3 (12.5)	1 (4.5)	0.665
Previous bowel resection (%)	5 (20.8)	3 (13.6)	0.800
Indication to last surgery			0.257
Stricturing disease	20 (83.3)	20 (90.9)	
Fistulizing disease	4 (16.7)	1 (4.5)	
Abscess	0 (0.0)	1 (4.5)	
Extra-intestinal manifestations (%)			0.413
None	20 (83.3)	20 (90.9)	
Peripheral arthropathy	3 (12.5)	1 (4.5)	
Cutaneous	0 (0.0)	1 (4.5)	
Axial arthropathy	1 (4.2)	0 (0.0)	
Rutgeerts' score at randomization, mean ± sd	2.71 ± 0.62	2.91 ± 0.61	0.276
Rutgeerts' score at randomization			0.618
i2	9 (37.5)	5 (22.7)	
i3	13 (54.2)	14 (63.7)	
i4	2 (8.3)	3 (13.6)	

$\geq$ 2 points in the Rutgeerts' score (2 patients in the 5-ASA group and 6 patients in the AZA group, 8.7% and 27.3% respectively, p=0.135). When we considered an improvement of at least one point of the Rutgeerts' score, as in Reinisch et al[15], the difference was statistically significant (Table II): 2 patients in the 5-ASA group versus 8 patients in the AZA group (8.3% *vs.* 36.4%, p=0.035).

Therapeutic failure occurred in 8 patients (17.4%) within 12 months from randomization without significant differences between 5-ASA and AZA (20.8% [5 patients] *vs.* 13.6% [3 patients] respectively, p=0.702). Therapeutic failure was due to clinical recurrence in the 5-ASA group (5 cases, while none in the AZA group, p=0.050) and to adverse events in the AZA group (3 cases, while none in the 5-ASA group, p=0.101), as shown in Table III.

No serious AEs were recorded during the study period: 1 patient discontinued treatment due to fever, 1 due to asymptomatic hyperamy-

Table II. Changes in Rutgeerts' endoscopic scores from baseline to the end of the trial (ITT).

	5-ASA	AZA	Overall	*p*-value
N24	22	46		
Rutgeerts' score decrease $\geq$ 2 points	2 (8.3%)	6 (27.3%)	8 (17.4%)	0.135
Rutgeerts' score decrease $\geq$ 1 point	2 (8.3%)	8 (36.4%)	10 (21.7%)	***0.035**
Ruutgeers' score at the end of the trial				0.195
i0	1 (4.2%)	5 (22.7%)	6 (13.0%)	
i1	1 (4.2%)	1 (4.5%)	2 (4.3%)	
i2	6 (25.0%)	4 (18.2%)	10 (21.7%)	
i3	10 (41.7%)	4 (18.2%)	14 (30.5%)	
i4	6 (25.0%)	8 (36.4%)	14 (30.5%)	

Table III. Therapeutic failure during the 12 month trial period due to clinical relapse or study discontinuation following drug-related adverse events.

	5-ASA	AZA	Overall	*p*-value
N	24	22	46	
Therapeutic failure	5 (20.8%)	3 (13.6%)	8 (17.4%)	0.702
Clinical recurrence	5 (20.8%)	0 (0.0%)	5 (10.9%)	**0.050**
Discontinuation due to adverse events	0 (0.0%)	3 (13.6%)	3 (6.5%)	0.101

lasemia (5-fold the normal range), and 1 due to mild pancreatitis; all these patients were in the AZA group.

Post-Trial Results

At the post-trial analysis, 47.8% (22/46) of patients experienced clinical recurrence with no significant difference between the 5-ASA group (54.2%, 13/24) and the AZA group (40.9%, 9/22), p=0.546 (Figure 2). The median follow-up was 60.0 months (IQR 25.0-103.5): 52.0 (IQR 20.5- 87.8) in the 5-ASA group and 82.5 (IQR 48.5-107.8) in the AZA group (p=0.90). Patients treated with 5-ASA during the 12 month study period, underwent the following therapies in the post-trial phase: 2 patients maintained 5-ASA; 3 were treated with AZA after 5-ASA failure; 8 with biologics; 7 with biologics after AZA failure; no data on medical treatment after the trial period were available in 4 patients.

Patients treated with AZA during the 12 month study period, underwent the following therapies in the post-trial phase: 12 patients maintained AZA; 7 were treated with biologics; 2 with 5-ASA while in clinical remission; no data on medical treatment after the trial period were available in 1 patient.

At the end of follow-up, 6 patients underwent surgery, 3 from each group. All 6 patients had been unsuccessfully treated with biologics.

At multiple Cox regression analysis (Table IV), smoking and previous surgery at randomization were significantly associated with clinical recurrence (p=0.031 and p=0.003, respectively).

Discussion

Endoscopic recurrence in CD is predictive of clinical recurrence after ileocolic resection. Rutgeerts et al[2] showed that the clinical course

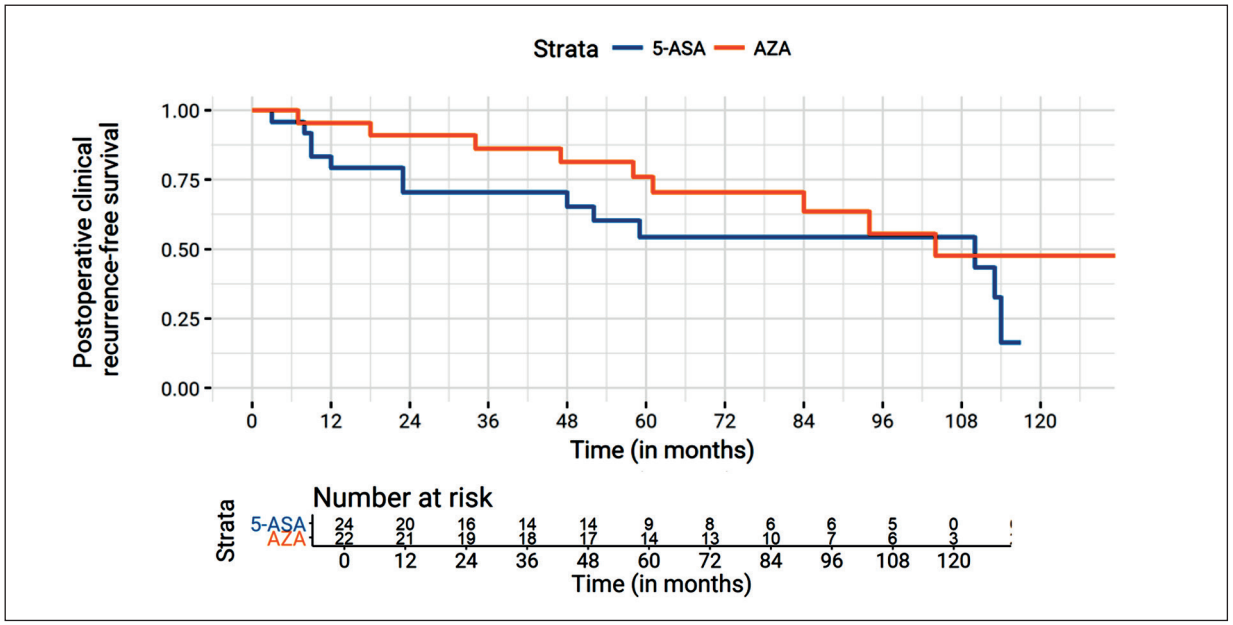

Figure 2. Kaplan-Meier plot of postoperative clinical recurrence-free survival by treatment at randomization.

Table IV. Cox PH regression model estimates for the risk of clinical recurrence.

Variable	Univariable analysis			Multiple regression model		
	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Rutgeerts' score at baseline	2.16	[1.07, 4.35]	0.032	1.44	[0.67, 3.12]	0.350
Smokers	4.74	[1.70, 13.17]	0.003	3.82	[1.23, 11.89]	0.021
Former smokers	1.07	[0.12, 9.42]	0.949	1.07	[0.12, 9.70]	0.952
Previous surgery	3.49	[1.19, 10.28]	0.023	4.39	[1.43, 13.43]	0.010
Drug (AZA vs. 5-ASA)	0.58	[0.25, 1.37]	0.213	0.67	[0.28, 1.62]	0.372

of CD following surgery was predicted by the severity of endoscopic lesions during the first year after resection. Patients with ER higher than i1 in the neoterminal ileum had an increased risk of early symptoms and complications. In 2014 we showed[5], in a large CD cohort, that a great proportion of ER is already present 6 months after curative resection and that most of these are very severe, with a Rutgeerts' score ≥ i3.

Once severe ER has been documented, it is mandatory to treat patients to avoid clinical and surgical recurrence. Many studies showed the efficacy of 5-ASA or AZA *vs.* placebo to prevent clinical recurrence after surgically induced remission[18,19]. Only one previous randomized controlled trial (RCT) compared the efficacy of 5-ASA *vs.* AZA for clinical recurrence prevention in CD patients with severe post-surgical ER[15].

In our multicenter randomized double-blind double-dummy trial, we analyzed the efficacy of high dose 5-ASA and AZA in patients with early severe post-surgical ER (Rutgeerts' score ≥ i2). In this high-risk population, 17.4% of patients experienced therapeutic failure (clinical recurrence or drug discontinuation due to adverse events) within 12 months from randomization, with no significant difference between the 5-ASA and the AZA groups (20.8% and 13.6%, respectively, p=0.702). Reinisch et al[15] reported therapeutic failure in 10.8% of patients treated with 5-ASA and in 22% treated with AZA (p=0.190). These results are consistent with ours: in both studies therapeutic failure was due to clinical recurrence in all patients treated with 5-ASA while it was related to AEs in those treated with AZA. In both studies, 5-ASA is less effective than AZA in preventing clinical recurrence: p-values are 0.050 and 0.031, respectively in our trial and Reinisch's study[15]. The main limit of AZA treatment is likely to be its less favorable safety profile.

Our investigation did not show significant differences between 5-ASA and AZA concerning endoscopic improvement (Rutgeerts' score reduction of at least 2 points). Reinisch et al[15] reported that AZA treatment was more effective than 5-ASA in inducing endoscopic improvement. They defined endoscopic improvement as a decrease ≥1 point compared to baseline, while in our study we considered a reduction of at least 2 points. When we analyzed our data using the same definition as Reinisch et al[15], we found that AZA was more effective than 5-ASA with marginal significance, probably due to our smaller sample size.

In the last 10 years, the use of biological drugs, especially anti-TNFs, has increased in the prevention and treatment of post-surgical recurrence[20]. ECCO guidelines recommended prophylactic treatment with thiopurines or anti-TNFs after ileocolonic intestinal resection in patients with at least one risk factor for post-surgical recurrence. Limited data are available regarding the management of severe post-surgical ER. Recently, the POCER study[21] showed that recommending treatment step-up (from no treatment to AZA or anti-TNF) based on early severe ER was the best option for clinical recurrence prevention. The results from this study strengthen the central role of immunomodulators in the treatment of patients with severe ER before the appearance of clinical recurrence.

In our research, a dose escalation was not contemplated. After the end of the trial period, we followed-up the enrolled population for up to ten years. Therapeutic strategies were based on clinical evaluation, without a predefined protocol. After ten years, 48% of patients experienced clinical recurrence, without differences between the two groups. These results were clearly affected by the therapeutic choices made after the end of the one-year trial period. It must be emphasized that in the 5-ASA group a higher proportion of pa-

tients underwent treatment escalation compared to those in the AZA group. Based on these findings, we could speculate that early use of AZA in severe post-surgical ER can affect long-term clinical outcomes. We propose that AZA should be preferred to 5-ASA in the presence of severe post-surgical ER and that in these cases treatment should start early after surgery, as performed in the POCER trial[21].

Furthermore, our post-trial analysis showed that smoking and previous surgery at randomization were significantly associated with clinical recurrence.

We acknowledge that our study has some limitations. First, the trial did not reach the designated sample size, due to slow patient enrolment. This was partly a consequence of patients' refusal to undergo colonoscopy 6 months after surgery. Other limitations lie in the post-trial follow-up: therapeutic choices were based on clinical evaluation, without a predefined protocol, and data on length of treatment were not available.

Despite these limitations, we believe that the final results suggest that AZA, if tolerated, continues to maintain an effective "therapeutic niche" in CD patients with severe post-surgical ER.

Conclusions

Our trial indicates that there was no difference in terms of treatment failure between 5-ASA and AZA in patients with severe post-surgical ER and that the main limit of AZA treatment is likely to be its less favorable safety profile. To our knowledge, this is the first study reporting long term clinical data in these patients, showing a lower risk of drug escalation in those treated with AZA. In addition, smoking and previous surgery at randomization resulted to be risk factors for clinical recurrence regardless of treatment. Considering the results of the current study and post-trial findings, AZA, if tolerated, could represent an effective and affordable alternative to first-line biologics in patients with severe post-surgical ER.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Authorship Statement

M. Cottone, A Orlando: study concept; F. Mocciaro acquisition of data; A. Orlando, F. Mocciaro, M. Ventimiglia, S. Renna: analysis and interpretation of data; A. Rispo, ML. Scribano, A. Testa, a. Aratari, F, Bossa, E. Angelucci, S. Onali, M. Cappello, m. Giunta, D. Scimeca, F. Macaluso, F. Castiglione, C. Papi, V. Annese, L. Biancone, A. Kohn, R. Di Mitri, M. Cottone: critical revision of the manuscript. All authors have approved the final version of the article.

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