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Original article

Mucosal healing for predicting clinical outcome in patients with ulcerative colitis using thiopurines in monotherapy

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ABSTRACT

Background: Mucosal healing (MH) has emerged as a desirable treatment goal for patients with ulcerative colitis (UC). Currently little is known about the efficacy of using thiopurine immunosuppressants in monotherapy to achieve and maintain long-term MH in UC. This study analyzes the efficacy and the clinical impact of MH in patients with UC responded to thiopurine immunosuppressants in the long term.
Methods: An open, observational, cohort study in 20 patients with UC had been in clinical remission in monotherapy with thiopurine immunosuppressants for at least 1 year. MH was assessed by endoscopy. The patients according to the Mayo Endoscopic Score (0 vs 1 and 2), were followed until the end of the study or patient relapse. (according to Truelove and Witts criteria).
Results: Mean treatment time was 5.4 years. Twelve (60%) patients presented a Mayo Endoscopic Score of 0. A total of 18 patients were followed up for a median of 27.1 months. After endoscopy, 4 patients (22.2%) presented relapse, with a mean time of 27.5 months for a score ≥1 (95% CI; 18.2–36.8) versus 54.3 months for a score = 0 (95% CI 47.2–61.3) ($p = 0.032$).
Conclusions: This study shows the efficacy of thiopurine immunosuppressants in achieving mucosal healing in patients who respond to thiopurine immunosuppressants in the long term. We also observe the presence of endoscopy activity is not a rare event in this group of patients and is a predictor of early relapse.

1. Introduction

The main treatment goal until a few years ago in inflammatory bowel disease (IBD) was to accomplish the induction and maintenance of clinical remission or an improvement in symptoms [1,2]. Until recently, mucosal healing (MH) endpoints had not been included in clinical studies [3]. However, the United States Food and Drug Administration (FDA) currently recommends that disease remission be deemed the main endpoint of clinical trials in ulcerative colitis (UC), defined as macroscopic disappearance of blood in stool and endoscopic definition of MH [4]. Although the notion of MH in UC as this sort of predictor has an intuitive appeal (maintenance of longer-term remission and fewer complications) data, in fact, remains limited [1,3,5–8]. More data is needed before any definitive statements can be made on the value of MH in UC.

Most of the data available shows the efficacy of thiopurine immunosuppressants (AZA and MP) in achieving clinical remission [9–11] but there are very few studies on the efficacy of these drugs in terms of MH [12,13]. None of these studies assesses the long-term efficacy of thiopurine immunosuppressants in monotherapy for achieving and maintaining MH in UC.

This study only enrolled patients with UC, in monotherapy with thiopurines and long-term clinical remission, who were included in a surveillance program for dysplasia. The first aim was analyzing the efficacy of thiopurines for healing the mucosa, assessed by endoscopy, and the second goal was finding the clinical impact of completely restoring the colonic mucosa in this subset of patients.

2. Materials and methods

We conducted an open, observational, cohort study in clinical practice at a single center in Madrid. The recruitment phase was continuously open between January 2004 and July 2008. Postcolonoscopy follow-up started in January 2004 and ended in May 2009. Patient follow-up started with the performance of colonoscopy in a surveillance program for dysplasia and was maintained either until the study ended or the patient relapsed. Diagnosis of UC was based on standard clinical, radiologic, endoscopic, and histologic criteria [14]. At the date of

Abbreviations: 5-ASA, 5-aminosalicylic acid; AZA, azathioprine; CD, Crohn's disease; ECCO, European Crohn's and Colitis Organization; ESR, erythrocyte sedimentation rate; FDA, Food and Drug Administration; IBD, inflammatory bowel disease; MCV, mean corpuscular volume; MH, mucosal healing; MP, mercaptopurine; SD, standard deviation; TNFα, tumor necrosis factor α; TPMT, thiopurine methyltransferase; UC, ulcerative colitis.

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colonoscopy, inclusion criteria included being between the ages of 18–75. Patients with UC were treated in monotherapy with AZA or MP, and have achieved long-term clinical remission for at least 1 year (following Truelove and Witt's criteria [15] (see Appendix A)), and normal biochemical parameters (platelet count and C-reactive protein).

Exclusion criteria included concomitant use of other drugs (either oral or rectal) with efficacy in the treatment of UC (5 ASA, salazopirin, corticoids, ciclosporin and antiTNFα) or use of nonsteroidal anti-inflammatories, antibiotics for more than 10 days, spasmolytics and antidiarrheics during the year preceding performance of the colonoscopy; and any patient who, at any medical visit to our center in the year preceding performance of the colonoscopy had presented clinical symptoms defined as an increase in the number of bowel movements, hematochezia, rectorrhagia or abdominal pain, or alterations in blood tests unrelated with the use of thiopurine immunosuppressants, which included inflammatory parameters, full blood count, renal and liver function parameters, albumin and electrolytes.

The indication for a complete colonoscopy to cecum was a surveillance program for early detection of colon neoplasm in UC. All endoscopies were performed by the same endoscopist. The grade of endoscopic activity was determined according to the Mayo score or Disease Activity Index (DAI) [16] as follows: 0, normal or inactive; 1, mild (erythema, decreased vascular pattern, mild friability); 2, moderate (marked erythema, absent vascular pattern, friability, erosions); and 3, severe (spontaneous bleeding, ulceration). Patients were classified on the basis of the maximum Mayo score recorded in any area of the colon. MH was defined as a value of 0 in Mayo score. In all remaining Mayo scores (1, 2 and 3), MH was deemed not to have been achieved.

Data collected included demographic characteristics (age, sex, smoking and family history) and medical charts (disease extension and duration, clinical symptoms and analysis, reason for use of AZA and MP).

In all patients, the final target dose was: AZA, 2.5 mg/kg/day; and MP, 1.5 mg/kg/day. The immunosuppressant dose was then adjusted at each visit based on each patient's clinical and analytical results and dose-adjustment and clinical and analytical monitoring rules corresponding to the medication [17].

2.1. Patient follow-up

After the colonoscopy, we examined patients every three months. At the end of each visit, the clinical activity of the disease was graded in accordance with Truelove and Witt's criteria [15] as: absent (remission); mild; moderate; or severe. Patient follow-up was maintained either until the end of the study or patient relapse. When a relapse occurred, we recorded its severity and the time relapsed since the performance of the endoscopy.

The Hospital's Ethics Committee approved the study and all subjects signed an Informed Consent Form.

2.2. Statistical analysis

Qualitative variables are shown with their frequency distribution. For quantitative variables, median, range and standard deviation (SD) were calculated; variables that failed to follow a normal distribution are expressed as median and interquartile range (IQR). Cumulative incidence of relapse was calculated using Kaplan–Meier survival analysis, and time relapsed until the appearance of a flare up was compared between the two groups using the log-rank test. All data was processed and analyzed using the Statistical Package for the Social Sciences (SPSS) version 15.0 for Windows (SPSS Inc., Chicago, IL, USA).

3. Results

A total of 143 patients with UC were included in our surveillance program for dysplasia, only 20 patients (16 men and 4 women, mean age 43.1 years, range [18–63 years]) met the inclusion criteria. These patients were in monotherapy with thiopurines for mesalazine intolerance (5 patients), patient's choice (9 patients) or decision of the physician as a strategy to improve compliance (6 patients).

The baseline characteristics of these patients are shown in Tables 1 and 2. Mean duration of disease from UC diagnosis to colonoscopy was 11.3 years, range [4–21 years]. Only one patient (5%) had left-sided colitis. Most patients were corticodependent (n = 15; 75%) and the most widely used immunosuppressant treatment was AZA (n = 14; 70%). Mean duration of treatment with thiopurine immunosuppressants was 5.4 years, range [1.1–9.7].

3.1. Classification of patients according to Mayo endoscopic score

Tables 1 and 2 show the characteristics of patients according to a Mayo endoscopic score of 0 or higher (≥1). None of the variables included in Table 1 showed statistically significant differences between

Table 1
The baseline characteristics of patients.

	All patients	Mayo endoscopic score = 0 12 (60%)	Mayo endoscopic score ≥ 1 8 (40%)
Sex			
Men	16(80%)	9 (75%)	7 (87.5%)
Women	4 (20%)	3 (25%)	1(12.5%)
Tobacco			
Smokers	4 (20%)	4 (33%)	–
Non-smokers	10 (50%)	5 (42%)	5(62.5%)
Ex-smokers	6 (30%)	3 (25%)	3(37.5%)
Extension			
Pancolitis	6 (30%)	3 (25%)	3(37.5%)
Extensive	13 (65%)	8 (67%)	5 (62.5%)
Left-sided	1 (5%)	1 (8%)	–
Corticoids			
Corticorefractory	15 (75%)	2 (17%)	3(37.5%)
Corticodependent	5 (25%)	10 (83%)	5 (62.5%)
Treatment			
AZA	14 (70%)	7 (58%)	7 (87.5%)
MP	6 (30%)	5 (42%)	1 (12,5%)
Current mean age in years	43	44.2	41.5
Mean (SD; min–max range)	(11;18–63)	(9.1;33.1–63.2)	(13.5;18–60.6)
Time from initiation of AZA/MP to colonoscopy in years.	5.4	5.7	5.1
Mean (SD; min–max range)	(2.4; 1.1–9.7)	(2.1; 2.6–9.7)	(2.9; 1.1–9)
Time from diagnosis to colonoscopy in years.	11.3	11.7	10.7
Mean (SD; min–max range)	(5.5;3.9–21)	(5.8; 5.5–21)	(5.3;3.9–19.4)

Numbers are N (%).