Effect of azathioprine or mesalazine therapy on incidence of re-hospitalization in sub-occlusive ileocecal Crohn's disease patients

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Background: Although the cost of Crohn's disease (CD) treatment differs considerably, hospitalization and surgery costs account for most of the total treatment cost. Decreasing hospitalization and surgery rates are pivotal issues in reducing health-care costs.

Material/Methods: We evaluated the effect of azathioprine (AZA) compared with mesalazine on incidence of re-hospitalizations due to all causes and for CD-related surgeries. In this controlled, randomized study, 72 subjects with sub-occlusive ileocecal CD were randomized for AZA (2–3 mg/kg per day) or mesalazine (3.2 g per day) therapy during a 3-year period. The primary end point was the re-hospitalization proportion due to all causes, as well as for surgical procedures during this period evaluated between the groups.

Results: On an intention-to-treat basis, the proportion of patients re-hospitalized within 36 months due to all causes was lower in patients treated with AZA compared to those on mesalazine (0.39 *vs.* 0.83, respectively; p=0.035). The AZA group had also significantly lower proportions of re-hospitalization for surgical intervention (0.25 *vs.* 0.56, respectively; p=0.011). The number of admissions (0.70 *vs.* 1.41, p=0.001) and the length of re-hospitalization (3.8 *vs.* 7.7 days; p=0.002) were both lower in AZA patients.

Conclusions: Patients with sub-occlusive ileocecal CD treated with AZA had lower re-hospitalization rates due to all causes and for surgical management of CD compared to those treated with mesalazine during a 3-year period. The long-term use of AZA in ileocecal CD patients recovering from a sub-occlusion episode can save healthcare costs.

Key words: inflammatory bowel disease • Crohn's disease • hospitalization • surgery • azathioprine • mesalazine

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Background

Crohn's disease (CD) is a chronic relapsing disorder of unknown cause that affects the digestive tract [1]. The disease has an insidious and persistent course that can have a more complex presentation with strictures or perforations due to the effect of the long duration of inflammatory reactions in the gut wall [2].

It is important to use objective parameters for assessing treatment effectiveness, since CD has a complex and long evolution. Therefore, the hospitalization rate is an indicator of the course of the disease and its severity, and allows a direct correlation with treatment costs [3].

Hospitalizations, including those with surgical procedures, account for 56% to 63% of the cost of CD treatment [4–7]. Some studies have estimated that the cost of hospitalized patients is up to 6 times the cost of a patient in an outpatient setting. Naturally, the idea arises that reducing the length and also the number of hospitalizations would minimize the costs of treating this disease. Effective medical treatment may reduce CD-related hospitalizations nearly 60% when it reaches its ultimate goal of keeping the patient in remission as an outpatient [8].

Mesalazine (MSZ) was the first drug used extensively in preventing CD recurrence, but its use is controversial. In initial studies, MSZ reduced the rate of disease recurrence [9], but in a meta-analysis Hanauer and Stomberg identified that MSZ use has questionable efficacy [10]. Azathioprine (AZA) is an immunomodulating drug widely used in the treatment of inflammatory bowel diseases. In a controlled study, AZA maintained 42% of patients in remission after 15 months, compared with 7% with placebo [11].

The primary aim of this study was to evaluate the effects of AZA compared to MSZ on the rate of re-hospitalizations, both for all causes and surgical procedures. It is hypothesized that subsequent therapy with AZA in CD patients recovering from a first episode of intestinal occlusion who went into remission without surgery might result in decreased re-hospitalization rate, as well as need for CD-related surgeries.

Material and Methods

Patient selection

This population sample was obtained in the Inflammatory Bowel Diseases Center at the University Hospital of Federal University of Juiz de Fora (UFJF) during the period from December 2003 to November 2007. In total, 72 patients were consecutively enrolled as soon as their first episode of intestinal semi-occlusion was responsive to clinical treatment proposed in the first 72 hours of admission and the oral intake was resumed. For inclusion in the study, the CD extent had to be restricted to the distal ileum and/or right colon.

CD diagnosis was based on clinical, radiologic, endoscopic, and histopathological criteria previously established during patient follow-up in the Inflammatory Bowel Diseases Center at the University Hospital of UFJF. The extent of the disease was defined by ileocolonoscopy and small bowel follow-up through examination within 12 months prior to study enrollment or immediately following the resolution of the sub-occlusive condition.

At entry, the patients were described as presenting intestinal sub-occlusion if they presented: new onset of classical signs and symptoms suggestive of mechanical obstruction such as abdominal pain experienced as colicky visceral pain, vomiting, bloating, and constipation; abdominal auscultation with peristalsis rumbling or metallic noises; plain, erect, and supine abdominal radiography showing the distinctive features of small bowel dilatation and the presence of fluid-air levels; or tomographic signs consistent with intestinal obstruction and absence of an abdominal abscess.

Patients presented with the following criteria were excluded: under 18 or over 65 years of age; presented intestinal obstruction refractory to medical treatment in the first 72 hours; needed urgent surgery for CD-related complications, multiple intestinal stenosis, internal fistulas, systemic infections, evidence of intra-abdominal abscess, previous intolerance of or contraindications to the use of AZA or MSZ, or use of corticosteroids within 4 weeks prior to study entry; history of steroid-dependent disease; and previous use of anti-TNFα therapy, thalidomide, or immunosuppressants. Patients were also excluded if they had previous or current history of malignancies, surgeries in the abdomen and/or pelvis, severe infections in the last 3 months, alcohol use (daily alcohol consumption above 40 g), drug addiction, or disabling chronic organ failure. Pregnant women, nursing mothers, and women who wanted to become pregnant during the study were not selected. Women with childbearing potential were subjected to pregnancy tests and instructed to use contraception during the study.

This study was conducted according to the principles of the Declaration of Helsinki. It was previously approved by the Ethics in Research Committee of the University Hospital at UFJF, and an informed consent was obtained and approved by the patients before their inclusion in the study. The results were monitored by supervisors not directly involved with the study, and serious adverse effects were reported to the study coordinator (Chebli, JM).

Treatment

Upon admission, all 72 patients received supportive care with fluid replacement, no oral intake, nasogastric tube, and

IV hydrocortisone 100 mg every 8 hours for a period of 72 hours. Treatment-resistant cases were referred for surgery and were excluded from the study. Patients who responded to medical treatment, met the inclusion criteria, and agreed to participate in the study were randomly assigned to 1 of 2 groups: AZA or MSZ.

Patients who responded to initial therapy were instructed to take the randomized drug and to eat a low-fiber diet and were converted to oral corticosteroid therapy prednisone 40 mg at 8 AM for 10 days. The dose was then tapered by 5 mg per week until its complete discontinuation by about the 8th week.

AZA was provided in 50-mg tablets, using the dose of 2–3 mg/kg and administred. AZA was administered with the following dosage: patients weighing less than 55 kg received 2 tablets/day (100 mg/day), those weighing between 56 kg and 74 kg took 3 tablets/day (150 mg/day), and those weighing more than 74 kg received 4 tablets/day (200 mg/day). MSZ in 400 mg tablets, in a pH-dependent release form, was administered at a dose of 3.2 g/day orally, divided into 3 doses (1.6 g at breakfast, 0.8 g at lunch and 0.8 g at dinner). AZA or MSZ were started when oral intake was resumed and were maintained for 36 months or until withdrawal of the patient from the study group.

During the study, concomitant use of the following drugs was not allowed: systemic steroids (except for the clinical treatment of intestinal obstruction), antibiotics (for periods longer than 14 days), non-steroid anti-inflammatory drugs (for a cumulative period not exceeding 7 days), anti-TNFα therapy, thalidomide, or any immunosuppressive drug.

Study design and follow-up

This was a prospective, randomized, controlled, investigator-blind study in which patients and the study coordinator were aware of the drug being used. The 2 blind principal investigators (SOUZA, GS; VIDIGAL, FM) assessed the incidence of re-hospitalization until the end of the study.

Patients were instructed to write down daily information about their bowel movements, abdominal pain or distention, timing of drug dosing (AZA or MSZ), concomitant use of medications, and any experienced adverse effects. Follow-up visits for revision occurred every month during the first 6 months and every 2 or 3 months until the 36th month. Patients were reassessed whenever they presented with a complaint, complication, or need for re-hospitalization. Abdominal radiographs were performed when there was a suspicion of intestinal obstruction during periodic clinical evaluation or in an emergency situation. Intestinal semi-occlusion was defined in the same manner as described in the study inclusion criteria.

Patients were withdrawn from the study when any of the following conditions occurred: drug-related adverse effects that compromised the maintenance of treatment (pancreatitis, hepatitis, severe vomiting, severe infections, persistent leukopenia, thrombocytopenia, malignancy, or aminotransferase greater than 3 times the normal levels), the patient missed 2 follow-up visits for a period exceeding 14 days, study medication was discontinued for more than 2 months, use of medication not allowed in the study, loss to follow-up, incapacitating disease, or patient request.

Indications for re-hospitalization and surgical procedures were defined by the attending physicians, subdivided into all-cause hospitalizations and surgical hospitalizations. Individuals who stopped using the medication due to adverse effects or were withdrawn from the study group for any other reason continued to be followed and received the same care as patients still in the study.

Endpoints analyzed

The incidence of re-hospitalization for all causes and for surgery was analyzed after 12, 24, and 36 months of treatment with AZA or MSZ. These analyses were based on the evaluation of patients who received at least 1 dose of study medication (intent-to-treat population [ITT]) or per-protocol population [PP]). Subjects withdrawn from the study for any reason were kept in the ITT analysis, but were excluded from the PP analysis.

Sample size calculation and randomization

Based on a maximum hospitalization rate at 3 years of 70% on MSZ, 32 patients per treatment group is enough to detect a difference of ≥35% for the AZA treatment group with 90% power and a 5% significance level (2-sided), based on a 2-group χ^2 test [12]. The number of patients in each group was increased to 36 to compensate for an anticipated dropout rate of 10%. This calculation is based on an ITT population.

The medication used by each patient (AZA or MSZ) was randomly determined by the biostatistics group at UFJF using a computer program able to randomly assign numbers to patients. Subjects were randomized to each group of 4 to ensure an equal number of patients in each group until the completion of the selection. The number generated by the program was assigned to the patient and sent confidentially to the pharmacy that dispensed the medications according to the reference number.

Statistical analysis

The statistical analysis was performed using SPSS 14.0 (SPSS, Chicago, IL, USA). Continuous variables are expressed as median

Table 1. Demographic, clinical and laboratory characteristics of patients with Crohn's disease treated with azathioprine or mesalazine.

Group	Azathioprine (n=36)	Mesalazine (n=36)	P-Value
Age (years)[#]	36±12.5	38±12.5	0.48
Duration of the disease (years)[#]	5.8±2.9	5.9±2.7	0.91
Gender			
Male	18	17	0.81
Female	18	19	
Race			
Caucasian	29	29	1.00
Non-White	7	7	
CRP*			
Normal (<6 ng/l)	13	16	0.75
Altered (>6 ng/l)	19	20	
ESR*			
Normal (<10 mm/h)	23	24	0.64
Altered (>10 mm/h)	9	12	
Platelets*			
Normal (<300,000 mm^3)	17	19	0.97
Altered (>300,000 mm^3)	15	17	

[#] Data presented as a mean ± SD; * Four patients in the AZA group did not have this data registered; CRP – C-reactive protein; ESR – erythrocyte sedimentation rate.

and range or as mean ±SD, according to their normal distribution. The proportion of hospitalizations due to all causes and for CD-related surgeries, as well as total inpatient admission number, length of hospitalization, and time interval to first hospitalization on the 2 treatment arms were compared using the χ^2 test or t-test, as appropriate.

Survival free of all-cause re-hospitalization was compared between groups by life-table analysis according to the Kaplan-Meier method. The difference in curves was tested using a log rank test. For comparison, the level of statistical significance was set at $P<0.05$ and all reported P-values are 2-tailed.

Results

The 72 patients entered the study after meeting previously established inclusion criteria. Of these, 35 patients were males and 37 patients were females. Fifty-eight patients were classified as white/Caucasian and 14 as non-white.

The MSZ and AZA groups were similar in terms of laboratory results, demographics and disease characteristics (Table 1). Four patients (11%) in the AZA group and 2 (5.5%) in the MSZ group were withdrawn from the study during follow-up due to severe adverse events (3 on AZA and 1 on MSZ) or were lost to follow-up (1 in each group) (p>0.05).

Overall, 52 (72%) of 72 patients were re-hospitalized. The proportion of re-hospitalization during 36 months in the AZA group was significantly lower compared with those of the MSZ group (61% *vs.* 83.3%, respectively; P=0.03). The number needed to treat for preventing 1 re-hospitalization favored the AZA group (NNT: 4.5). The proportion of re-hospitalization for surgery was more than 2-fold higher for patients receiving MSZ compared with AZA (56% *vs.* 25%, P=0.01). Similarly, the re-hospitalization proportion per patient (P=0.001) and the length of hospitalization expressed in days were significantly lower in the AZA group (P=0.002). The time to first re-hospitalization was significantly higher in patients treated with AZA compared to MSZ (27 *vs.* 18 months, P=0.001) (Table 2). Re-hospitalization-free survival for patients on AZA was significantly higher than that for MSZ, notably after the first year of treatment (Figure 1).

Table 3 presents the causes of re-hospitalization throughout the study. The most common cause of re-hospitalization in both groups was recurrent intestinal obstruction.

Discussion

This clinical trial clearly demonstrates the superiority of AZA compared to MSZ in reducing the rate of all-cause re-hospitalization (61% *vs.* 83%, respectively; P=0.03). Interestingly,

Table 2. Hospitalizations over 36 months in patients with sub-occlusive Crohn's disease receiving azathioprine or mesalazine.

	Azathioprine	Mesalazine	P-Value
Hospitalization proportion (n/%)**	22 (61)	30 (83.3)	0.03
Hospitalization proportion with surgery (n/%)*	8 (25)	19 (56)	0.01
Re-hospitalization per patient*,#	0.7±0.7	1.41±0.9	0.001
Number of hospitalization days*,#	3.8±4.7	7.7±5.2	0.002
Time to first re-hospitalization (months)*,#	27±10.4	18±10.7	0.001

** 36 patients evaluated in each group (ITT population); * 32 patients evaluated in the AZA group and 34 in the MSZ group; patients with severe side effects or lost to follow-up were not analyzed (PP population); # mean ±SD.
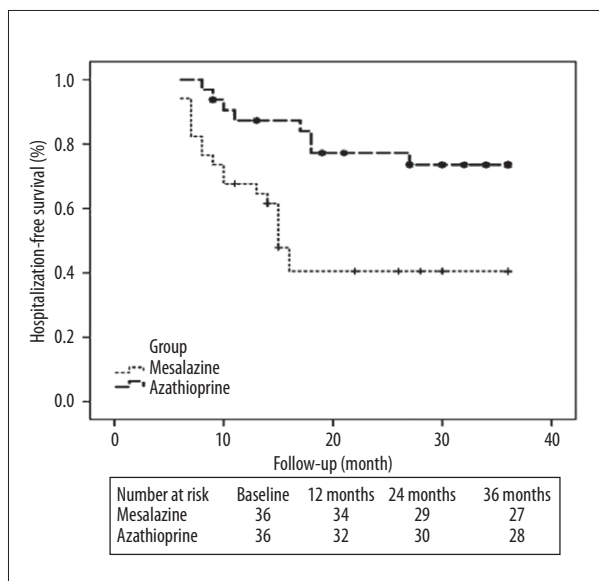

Figure 1. Survival without all-cause re-hospitalization in patients with sub-occlusive Crohn's disease during therapy with AZA or MSZ at 12, 24 and 36 months. AZA patients showed significantly higher hospitalization-free survival at 24 and 36 months (Log Rank at 12 months: 0.53; at 24 months: <0.000; at 36 months: 0.001).

Table 3. Description of all-cause re-hospitalizations in groups with Crohn's disease.

Description	Azathioprine (n=36) n (%)	Mesalazine (n=36) n (%)
Intestinal obstruction	14 (38.9)	27 (75.0)
Intestinal infection	2 (5.6)	–
Abdominal pain	2 (5.6)	1 (1.7)
Acute pancreatitis	1 (1.7)	–
Abdominal abscess	–	1 (1.7)
Surgery for bowel resection	8 (22.2)	19 (52.0)
Pneumonia	1 (1.7)	–

* Some patients had more than one hospitalization throughout the study.

treatment of 4.5 patients with AZA was able to prevent 1 re-hospitalization compared to treatment with MSZ. Additionally, AZA also halved the rate of re-hospitalization with surgery compared to MSZ (25% *vs.* 56%, p=0.01).

It is well known that the economic burden of CD is high mainly due to hospitalization and surgical procedures [13,14]. It is therefore reasonable to speculate that once AZA therapy was able to reduce these events in sub-occlusive CD, it may be associated with substantial costs offsets. In addition, it is likely that the indirect costs related with lost productivity consequent to hospitalizations also will be further reduced with AZA treatment compared with MSZ management, leading to an overall reduction in cost.

The results favoring the use of AZA could be questioned on the grounds that the medication could cause more adverse effects and, hence, higher morbidity. However, this was not observed in the current study. Although in the AZA group 3 patients (*vs.* 1 on MSZ) were excluded due to adverse effects, all patients recovered after drug withdrawal. Overall, treatment with AZA had lower morbidity than with MSZ. The length of re-hospitalization and the hospitalization proportion per patient in the MSZ group was twice that of the AZA group. In support of this, Punati et al. [14] found that the number of hospitalization days and the number of hospitalizations per patient is lower when AZA is initiated early in the course of CD treatment. Cohen et al. [15] evaluated 175 hospitalizations (143 patients) over a period of 12 months and recorded a mean hospital stay of 8.7 days, with 9.6 days for surgical admissions and 7.5 days for the hospital clinics. In our study, the mean hospital stay was 3.8 days and 7.7 days in AZA and MSZ groups, respectively. Of note, there was a significant reduction in the number of days in hospital among patients who used AZA compared to the MSZ group. Therefore, the current study suggests

a favorable effect of AZA in reducing morbidity of sub-occlusive CD. Importantly, a significant factor in improving the results of CD treatment is the optimal outpatient control of patients, which is associated with the best use of therapeutic options [16]. In this context, the present favorable results of AZA should be considered, taking into account that patients were closely monitored in a Referral Center for Inflammatory Bowel Disease, which in itself can contribute significantly to a better therapeutic outcome.

The main indicator of morbidity in this study was re-hospitalization. The temporal analysis of the phenomenon throughout 36 months is interesting. Initially, both groups began the study matched for re-hospitalization rates. But in the medium- and long-term, the difference clearly turns in favor of AZA. Thus, observing the survival curve for the variable re-hospitalization, one can see that in the first year there was no significant difference from a statistical point of view (Figure 1). However, the phenomenon is dynamic over time, and it is possible that at the end of 12 months there was a trend toward significance. This derives from the evaluation of the survival curves and statistical analysis at the end of 24 months, in which the impression left by the drawings of the curves was confirmed. It is well known that the maximum effectiveness of AZA occurs from the fourth month of use onwards [17,18]. In addition, effective sustained immunomodulation appears to be important in controlling intestinal inflammation in CD [15]. Taken together, these data might explain the finding that AZA was more effective after 12 months of use.

Importantly, in the current study, AZA therapy notably reduced the proportion of re-hospitalizations for CD-related surgical interventions compared to MSZ. Recent studies have demonstrated that thiopurines may decrease the need for surgery. Indeed, AZA therapy was associated with a decreased risk of first surgery among patients with non-stricturing, non-penetrating CD [19]. In addition, after a first surgical resection for CD, long-term treatment with thiopurines appears to cut the risk of subsequent intestinal surgery by nearly 60% [20,21]. Nonetheless, to our knowledge this is the first study to demonstrate that AZA therapy can reduce surgical hospitalizations of sub-occlusive ileocecal CD patients.

One drawback of our trial is the lack of assessment of the proportion of endoscopic mucosal healing in the AZA group. Nonetheless, it should be acknowledged that successful AZA therapy is accompanied by mucosal healing and disappearance of the inflammatory infiltrate in more than 50% of CD patients with active ileocolitis [22]. Arguably, the initiation of AZA treatment might lead to more effective mucosal immunomodulation and enhanced control of ongoing inflammation, thus allowing inflammatory lesions to heal before the establishment of irreversible fibrotic wall thickening in a certain proportion of individuals. Future research will establish the degree to which mucosal healing may improve long-term outcomes and reduce complications and hospitalizations in sub-occlusive CD patients.

Although the methodology was appropriate for the purpose of the study and allowed a comparison between AZA and MSZ, an important limitation of the study lies on the characteristics of the study population. The study included patients with a specific medical condition – ileocecal sub-occlusive CD – who responded to initial clinical treatment. As such, the data presented is valuable for patients whose characteristics resemble those of the studied groups and cannot be extrapolated to other populations of patients with CD. Furthermore, a recent study supports the use of laparoscopy ileocolic resection in appropriately selected CD patients for reduction of short-term complications and hospital length of stay when compared with open resection [23]. Ileocolic resection might be a good alternative to long-term medical therapy, particularly in patients with limited ileocecal CD. Thus, multidisciplinary research addressing issues such as medical treatment *versus* surgery in sub-occlusive ileocecal CD is necessary to aid in decision-making in these clinical settings.

Conclusions

In conclusion, for patients with ileocecal CD who had their first episode of intestinal sub-occlusion relented without surgery, subsequent treatment with AZA significantly reduced the proportion of all-cause re-hospitalization and hospitalizations for surgical procedures when compared with MSZ treatment. The long-term use of AZA in ileocecal CD patients recovering from a sub-occlusion episode can reduce healthcare costs.

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