Research Article ISSN 2639-9334

Gastroenterology, Hepatology & Digestive Disorders

Effectiveness of Azathioprine in Maintaining Remission in Crohn's Disease: A Systematic Review

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Received: 20 July 2019; **Accepted:** 10 August 2019

Citation: Marcella Correa da Silva Coelho, Ana Carolina Paiva Botelho, Patrícia Britte Bruno, et al. Effectiveness of Azathioprine in Maintaining Remission in Crohn's Disease: A Systematic Review. Gastroint Hepatol Dig Dis. 2019; 2(1): 1-6.

ABSTRACT

Objective: *To use a systematized review to determine the effectiveness of azathioprine in maintaining remission in Crohn's disease.*

Method: *This study is a systematic review of the literature based on a bibliographic survey having the US National Library of Medicine (PubMed) data collection as the investigative source. The survey was delimited between January 2018 and May 2018 with the following descriptive terms: "Azathioprine" AND "Crohn's disease". The inclusion criteria were as follows: original articles, experimental models in humans, published either in English or Portuguese. All studies that did not meet the inclusion criteria and those that did not address the scope of this research were excluded. The information was selected according to its relevance and separated into themes that would allow a more didactic interpretation of the results.*

Results: *A total of forty studies were evaluated, of which 28 were excluded and 12 were made part of this review. Azathioprine has been effective in the sustained remission of the disease in most cases, especially in moderate to severe patients. A total of 378 patients were assessed.*

Conclusion: *Azathioprine has shown to be an effective therapy, indicated for the maintenance of remission in refractory (corticosteroid-dependent) and recurrent cases of moderate to severe patients. The patient and the disease should be stratified and treated individually. Treatment of Crohn's disease is complex, and in many cases patients cannot return to their normal daily activities.*

Keywords

Crohn's Disease, Therapy, Azathioprine.

Introduction

Crohn's disease (CD) has two peaks of incidence in the population; a larger one, in young adults between ages 20-30, and a smaller one, in ages 60 and above. In addition, it affects both males and females in a similar way [1].

CD is a chronic inflammatory disorder that can lead to severe impairment in all the digestive tract and often requires surgery for complications. Available data demonstrated that the percentage of patients requiring surgery during the course of the disease is still up to 75%. Because the main location is the terminal ileum, with or without the proximal colon, the most common intervention is ileocolic resection [1]. CD is also more prevalent in the white race and individuals of Jewish origin; however, it is not uncommon to see it in blacks and other dark-skinned people.

It is a disease of unknown origin, influenced by genetic, environmental, dietary and infectious factors (viruses and bacteria). It is characterized by a discontinuous transmural granulomatous inflammation, leading to intestinal fibrosis and strictures, mainly in the ileum. There is increasing evidence that it is associated with a deregulated intestine, CD4+-type immune response and T helper lymphocytes that produce high levels of pro-inflammatory

cytokines [2].

The association between smoking and the disease was established epidemiologically. When analyzed by sex and population, the prevalence of smoking in a global sample was higher than that in the general population. A multivariate analysis, however, failed to show the smoking status as a modifying effect in determining azathioprine (AZA) response. Tobacco is still associated with an increased risk of recurrence of the postoperative disease [1,3].

AZA has been used for the treatment of inflammatory bowel diseases for over thirty years. Its use in CD has been evaluated in multiple studies. To date, AZA and its active metabolite, 6-mercaptopurine (6-MP), remain the main therapy for patients with refractory or steroid-dependent CD. However, the ideal length of treatment in patients with remission of the disease due to long-term use of the medication is still debatable [4].

Thiopurines, mercaptopurine (MP) and its prodrug, and AZA are maintenance therapies in patients with moderate to severe CD. Unfortunately, approximately 40-50% of patients do not respond to or tolerate treatment. Differences in response and toxicity may reflect individual variations [5].

AZA is an inactive prodrug that is metabolized by concurrent pathways. One pathway leads to the formation of 6TGN which, in some retrospective studies, has been correlated with clinical response. In a concurrent pathway, the thiopurine methyltransferase (TPMT) enzyme catalyzes the formation of 6-methyl-mercaptopurine ribonucleotides (6MMPR) that have been correlated with hepatotoxicity. TPMT activity is genetically determined. Measurement of TPMT activity has been recommended by the Food and Drug Administration (FDA) and the American Gastroenterological Association (AGA) prior to commencing weight-based dosing; adjustments may be guided by metabolite concentrations to improve response by minimizing toxicity [5].

The objective of this article was to use a systematized review to determine the effectiveness of azathioprine in maintaining remission in Crohn's disease.

Methods

The PubMed dataset was used as the research source, by using the keywords “Azathioprine" AND "Crohn's disease”, only in humans and restricting it to randomized controlled articles. Those that did not address the scope of this research were excluded (Table 1).

Inclusion Criteria	
Design	Controlled and randomized clinical trials.
Patients	Patients with moderate to severe Crohn's disease; Patients treated exclusively with azathioprine.
Intervention	Use of azathioprine.
Language	English and Portuguese.
Exclusion Criteria	
Design	Unclear or poorly described randomization criteria; Studies where the control group was not treated with azathioprine.
Intervention	Unclear, poorly described or inadequate interventions.
Form of publication	Abstract only.
Main Clinical Outcomes	
	The efficacy of azathioprine in maintaining remission of Crohn's disease.

Table 1: Inclusion and Exclusion Criteria, and Main Outcomes.

Results

A total of forty studies were evaluated, of which 28 were excluded, 12 were analyzed and six were eligible because they dealt exclusively with the use of AZA (Table 2). The total study sample included 378 patients. Figure 1 represents the flowchart that was used to select the study articles.

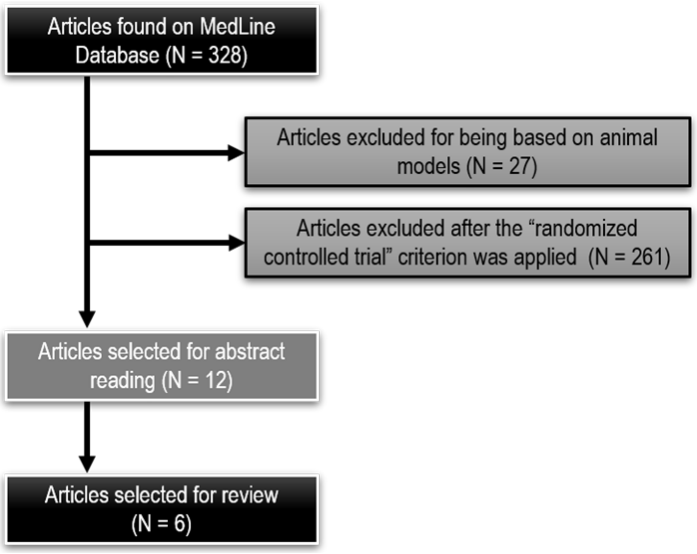

Figure 1: Study Selection Process Flowchart.

AUTHOR	INTERVENTION	OUTCOME
Wenzl et al. [9]	Randomized double-blind clinical trial. Patients in therapy for more than 4 years, remission for more than 12 months and CDAI > 150; n = 52.	Clinical relapse in patients on continuous AZA vs. placebo, for a 2-year period.
Zhang et al. [7]	Prospective study; patients with active CD were included and randomized in Group A (1 mg/kg/day) and Group B (2 mg/kg/day) AZA; n = 25 each group.	CR rate, relapse-free, at weeks 12, 24 and 48.
Dassopoulos et al. [5]	A multicenter, double-blind, randomized, controlled trial, comparing weight-based vs. individualized dosage in inducing and maintaining remission; n = 50.	Clinical and sustained remission at week 16 after initiating weight-based vs. individual AZA dose (dependent on TPMT activity).
Panés et al. [10]	Prospective double-blind study. Patients for the AZA group (n = 68) vs. placebo group (n = 63).	Sustained corticosteroid-free remission after 76 weeks.

Treton et al. [4]	Randomized clinical trial with 66 patients in remission during treatment, undergoing long-term evaluation after AZA discontinuation.	Relapses at 1, 3 and 5 years after AZA withdrawal.
Vilien et al. [6]	Randomized clinical trial; 29 patients with CDAI > 150, subjected to withdrawal of medication after more than 2 years of sustained remission.	Relapses after 1 year of follow-up, based on CDAI and potential surgical interventions.

Discussion

In general, CD treatment is aimed at controlling clinical and endoscopic remission, maintaining remission (or sustained remission), avoiding extraintestinal manifestations (mainly arthralgias and eye disorders) and surgical complications, improving the quality of life and maintaining good nutritional status. This therapy involves dietary and behavioral guidelines, the use of continued medications, and potential surgeries for complications of the disease.

Patients should be stratified prior to starting drug therapy. Thus, several factors should be considered: severity, extent of disease, predictive factors of poor prognosis (diagnostic time, for example), patient preferences, past history, age, sex (young male patients are at greater risk of hepatosplenic lymphoma from using immunosuppressants [IMS]), pregnancy duration, and cost-effectiveness.

The strategy indicated to initiate any AZA therapy needs to highlight the predictive factors of the most severe or "incapacitating" disease, which are: young patients (< 40 years at diagnosis); perianal disease; need for corticosteroids at diagnosis; extensive and deep ulcers on colonoscopy; stricturing and penetrating disease; involvement of the upper gastrointestinal tract (GIT), proximal small intestine, extensive or rectal ileum CD; no endoscopic remission after clinical remission; aggressive disease with many relapses during the year; major weight loss; presence of granulomas; obesity; smoking; high ASCA, anti-OmpC and anti-CBir1 titers; mutations in the NOD2/CARD15, ATG16L1, and MDR genes.

In a 12-month open study [6], patients with inactive CD after two years or more (median 37 months) on AZA treatment were randomized to IMS withdrawal or maintenance of treatment. The primary endpoint was relapse defined as: increased CD activity index ≥ 75 and CD activity index >150 or disease activity requiring intervention. Of 29 patients, 28 completed the observation period or relapsed. Eleven out of 13 (85%) patients on continued AZA use remained in remission, compared with seven out of 15 (47%) withdrawing from therapy (p = 0.043). When treated at a dose > 1.60 mg/kg/day, the difference was even greater, i.e., eight (89%) vs. four (33%) out of 12, respectively (p = 0.017) [6].

For Zhang et al. [7], AZA is widely used to treat Crohn's disease at a recommended dose of 2-2.5 mg/kg/day. In the study, fifty patients with active CD were included and randomized to two groups (n = 25 each). Group A (GA) received 1 mg/g/day, and Group B (GB) received 2 mg/kg/day AZA. The complete remission (CR) rate and the response rate at weeks 12, 24, and 48 were assessed using intention-to-treat (ITT) analyses and per protocol (PP). Adverse events and recurrence rate were also assessed. At week 48, the CR rate and the response rate in GB (ITC: 50.0% and 59.1%, PP: 57.9% and 68.4%) were significantly higher than in GA (ITT: 13.0% and 17.4%, PP: 16.7% and 22.2%) (p < 0.05). Nine adverse events occurred, including pancreatitis (n = 1), arthritis (n = 2) and myelosuppression (n = 6). There was no significant difference in adverse events between the two groups. However, the recurrence rate was significantly higher in GA than in GB (p = 0.042) [7].

The time to AZA action is estimated at eight to 12 weeks, with its ideal activity occurring within three to four months of continued use. Therefore, some more severely ill patients who are refractory to the use of corticosteroids and quite symptomatic begin the treatment already using IMS (a therapy known as "accelerated conventional step-up") because they do not tolerate the dwell time of the drug in the body [8].

Dassoupolus et al. [5] evaluated the efficacy and safety of the dose- vs. weight-based dosage on the induction and maintenance of remission in steroid-treated CD adults. The primary outcome was clinical remission at 16 weeks. In the weight-based group, subjects received 2.5 mg/kg/day. In the individualized dosing group, the initial AZA dose was 1.0 mg/kg/day (intermediate TPMT activity) or 2.5 mg/kg/day (normal TPMT). The result was 60% relapse in the individualized dose group and 25% when weight-based [5].

The TPMT enzyme is genetically dosed and has been shown to be important in decreasing and controlling AZA hepatotoxicity in patients with moderate to severe CD. The values are inversely proportional, that is, the greater the enzymatic activity, the lower the dose of the medication, and, consequently, the lower its side effects [5].

In the Aztec [10] study, patients were randomly assigned to groups receiving AZA (1-2.5 mg/kg) or placebo, both on corticosteroids. The primary endpoint would be the assessment of AZA in newly diagnosed patients (<8 weeks) and the percentage of patients in remission with no corticosteroids at 18 months. After 76 weeks of treatment, 30 AZA-treated patients (44.1%) and 23 placebo-treated patients (36.5%) were in sustained corticosteroid-free remission (difference of 7.6%; 95% CI: 9.2 to 24.4%, p = 0.48). Relapse rates (CD Activity Score > 175) and corticosteroid dependence were similar between the groups. However, the proportion of patients with a CDAI > 220 from week 12 was higher in the placebo group. Therefore, AZA was more effective in preventing recurrences in moderate to severe patients (11.8% vs. 30.2%; p = 0.01) when used early. Serious adverse events occurred in 14 patients using AZA (20.6%) and seven in the placebo group (11.1%) (p = 0.16), leading to discontinuation of the drug during the study [10].

Two meta-analyses concluded that AZA is effective for the maintenance of remission in CD patients. But a more recent meta-analysis (published in November 2017) identified five studies evaluating the effect of this IMS in inducing CD remission,

showing no significant effect [10].

The study described by Treton et al. [4] selected a sample of patients aged > 18 years old on continuous AZA treatment for at least 42 months; no clinical relapse during the period; no treatment with oral steroids (10 mg/day), artificial nutrition or other IMS medication; and no biological agent during the same time. Patients whose disease was limited to the perianal region and who were using the medication to prevent postoperative recurrence were excluded. The primary endpoint was the one-, three-, and five-year relapse rate analysis. Based on this, the conclusion was that after AZA withdrawal, during or at the end of the clinical trial, 32 of 66 patients had relapses. Therefore, abstinence from the drug is associated with a high risk of relapse of the disease, regardless of the length of remission on this treatment. These data suggest that if AZA is well tolerated, it should not be discontinued. A C-reactive protein concentration of 20 mg/L (risk, 58.6; 95% CI: 7.5-457; p = 0.002), a hemoglobin level below 12 g/dL (risk, 4.8; 95% CI: 1.7-13.7 ; p = 0.04), and a neutrophil count of ≥ $4x10^9$/L (risk 3.2; 95% CI: 1.6-6.3; p = 0.003) were independently associated with an increased risk of relapse [4].

In a randomized, double-blind, placebo-controlled AZA withdrawal trial with a 24-month follow-up period [9], patients had been on continuous therapy for ≥ four years with no exacerbation of the disease during the 12 months prior to inclusion, associated with a CD Activity Index < 150 at baseline. During the two-year follow-up, clinical relapse occurred in four of 26 (15%) patients on continuous AZA and in eight of 26 (31%) patients on placebo9. Stricture as a complication of CD is a significant clinical problem. Despite many recent advances in patient management, occlusive or sub-occlusive symptoms are observed and remain a clinical challenge. Although it is clear that surgical intervention is indicated for obstructive ileocecal stricture that does not respond to drug therapy, the ideal clinical approach for intestinal sub-occlusion remains controversial [11].

The conventional therapy for CD treatment was compared to conventional accelerated therapy (early use of AZA) in a French study, RAPID. The proportion of patients in corticosteroid-free and non-biological remission per quarter over time was similar in both groups. However, in the "accelerated conventional step-up" group, where IMS was prescribed immediately at diagnosis, there were fewer active perianal lesions (simple fistulas) and fewer surgical interventions [12].

According to the review of the selected studies, CD is a chronic inflammation of the GI tract which goes through periods of relapse and remission and may progress over time to complications such as stricture, fistulas or abscesses. Mild to moderate symptoms are treated with mesalamine, budesonide or systemic corticosteroids. The therapeutic benefit of this is often confronted by side effects from long-term exposure. In addition, oral or systemic corticosteroids are not effective for maintenance therapy. AZA and 6-MP are prescribed for patients in whom first-line therapies fail – in particular, those who are dependent on or do not respond to corticosteroids. Approximately 40% of patients treated with AZA remain in remission within one year [8,12].

Conclusion

According to these studies, AZA was shown to be effective in the sustained remission of CD, mainly in moderate to severe patients. Adverse effects did not differ significantly between patients taking lower or higher doses of the drug (mean ideal dose: 2.5 mg/kg/day), and weight was the main measure for this estimate. Abstinence from medication was related to higher rates of relapse, even after long periods of remission (4 years or more). Therefore, when well tolerated, it should not be discontinued. In addition, this drug was very important in the immediate initial treatment of patients with fistulas and perianal involvement, reducing the need for surgeries.

However, therapy should be individualized with patient stratification for severity, with periodic monitoring based on laboratory tests (complete blood count, liver function, pancreatic and renal function), due to the risks of intolerance and side effects.

References

1. Armuzzi A, Felice C, Papa A, et al. Prevention of postoperative recurrence with azathioprine or infliximab in patients with Crohns disease: an open-label pilot study. J Crohns Colitis. 2013; 7: 623-629.
2. Neurath MF, Wanitschke R, Peters M, et al. Randomised trial of mycophenolate mofetil versus azathioprine for treatment of chronic active Crohns disease. Gut. 1999; 44: 625-628.
3. Candy S, Wright J, Gerber M, et al. A controlled double blind study of azathioprine in the management of Crohns disease. Gut. 1995; 37: 674-678.
4. Treton X, Bouhnik Y, Mary JY, et al. Azathioprine withdrawal in patients with Crohns disease maintained on prolonged remission: a high risk of relapse. Clin Gastroenterol Hepatol. 2009; 7: 80-85.
5. Dassopoulos T, Dubinsky MC, Bentsen JL, et al. Randomised clinical trial: individualized versus weight-based dosing of azathioprine in Crohn's disease. Aliment Pharmacol Ther. 2014; 39: 163-175.
6. Vilien M, Dahlerup JF, Munck LK, et al. Randomized controlled azathioprine withdrawal after more than two years treatment in Crohns disease: increased relapse rate the following year. Aliment Pharmacol Ther. 2004; 19: 1147-1152.
7. Zhang Y, Xia JJ, Xiao P, et al. Standard-dose versus low-dose azathioprine in the treatment of Crohns disease: a prospective randomized study. J Dig Dis. 2016; 17: 747-755.
8. Colombel JF, Sandborn WJ, Reinisch W, et al. Infliximab, azathioprine, or combination therapy for Crohns disease. N Engl J Med. 2010; 362: 1383-1395.
9. Wenzl HH, Primas C, Novacek G, et al. Withdrawal of long-term maintenance treatment with azathioprine tends to increase relapse risk in patients with Crohns disease. Dig Dis Sci. 2015; 60: 1414-1423.
10. Panés J, López-Sanromán A, Bermejo F, et al. Early azathioprine therapy is no more effective than placebo for

newly diagnosed Crohns disease. Gastroenterology. 2013; 145: 766-774.

11. Vidigal FM, de Souza GS, Chebli LA, et al. Azathioprine is more effective than mesalazine at preventing recurrent bowel obstruction in patients with ileocecal Crohns disease. Med Sci Monit. 2014; 20: 2165-2170.
12. Cosnes J, Bourrier A, Laharie D, et al. Early administration of azathioprine vs conventional management of Crohns Disease: a randomized controlled trial. Gastroenterology. 2013; 145: 758-765.