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Research Article

Effects of Azatioprine in Patients with Diagnosis of Intestinal Inflammatory Disease: A Systematic Review

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Abstract

Objectives: Evaluate through a systematic review of the medical literature the incidence of patients who developed infectious or non-infectious side effects after the use of azathioprine for the treatment of Inflammatory Bowel Disease.

Method: Were analyzed studies from the MEDLINE (National Library of Medicine) database published over the last twenty-five years (until May 2017) which have both diagnostic criteria' and 'therapeutic approach' chapters, written in English, and has the following combination of keywords: Inflammatory Bowel Disease, azathioprine, treatment, side effects. The pieces of evidence found in those studies were judged by two independent reviewers.

Results: Five studies that fulfilled the afore mentioned criteria were included in this review. AZA was superior to placebo in controlling maintenance of remission of IBD, as well as effective in relapse control in patients who undergone ileocecal resection. The side effects, however, were significant. These include gastrointestinal intolerance, acute pancreatitis, jaundice, hepatotoxicity, and myelosuppression.

Conclusion: Despite the various side effects related to the use of AZA, treatment should not be discontinued except in the occurrence of severe side effects. Lymphopenia was described as one of the most common hematological manifestations but was not always accompanied by infectious reactions.

Continuous laboratory monitoring may contribute to avoid adverse effects from lymphocyte declines. Lastly, it was observed that AZA has been shown to be a safe therapy for the maintenance of inflammatory remission in patients with IBD and can be used for a long period of time.

Keywords: Inflammatory Bowel Disease; Azathioprine; Treatment; Side Effects

Introduction

Inflammatory Bowel Diseases (IBD) comprise Ulcerative Colitis (UC) and Crohn's Disease (CD), both of which have a chronic presentation, can cause frequent relapses and require prolonged medical attention, negatively impacting the quality of life of their sufferers [1].

UC was first described in London, in 1859, by the pathologist Samuel Wilks after the autopsy of a patient who had bloody

diarrhea. Almost a century later, in 1931, Sir Arthur Hurst, with the help of rectosigmoidoscopy, performed a detailed description of the endoscopic characteristics of the disease [2].

Crohn's Disease, although named after the fundamental contribution of Burrill B. Crohn and his collaborators in the mid-1930s, already found reports from Ancient Greece and Alexandria [1].

In both cases, there was relative difficulty in differentiating patients affected by what is now called IBD from those affected by infectious-parasitic enterocolitis [2].

The treatment of IBD seeks not only to keep the patient in clinical remission, but also to induce endoscopic and histological remission of the disease, in order to avoid its possible complications [1].

With regard to UC, the choice of treatment involves the staging of the disease, when analyzing the extent of the inflammatory process, through colonoscopic examination associated with the histopathological results. In addition, clinical and laboratory variables should be observed, and one of the main classifications used for this purpose is that of Truelove and Witts, which takes into account the number of bowel movements, the presence of fresh blood in the stool, body temperature, heart rate, hemoglobin and erythrocyte sedimentation rate (ESR) [1].

In CD, similarly, when deciding on therapeutic improvement, it is mandatory to observe the location and extent of the disease, its phenotype (inflammatory, stenosing or penetrating), the existence of intestinal manifestations and the patient's degree of psychosocial impairment [2].

The pharmacological arsenal for the treatment of IBD is vast, and the main drugs used are aminosalicylates, corticosteroids, antibiotics, immunosuppressants and biologics. In Brazil, there is biological therapy directed against tumor necrosis factor-alpha, represented by Infleximab and Adalimumab, in addition to specific anti-integrin therapy, Vedolizumab [2].

One of the most used drugs to maintain remission in patients with IBD is Azathioprine (AZA). It is a drug developed about fifty years ago, whose effectiveness has been proven in several clinical trials and meta-analyses [4].

AZA is an imidazolyl derivative of 6-mercaptopurine and acts as an immunosuppressant antimetabolite, with an oral bioavailability of 47.4% and rectal bioavailability of 1.3 to 5.3%. It undergoes hepatic metabolism with oxidation and methylation reactions, crossing the placental barrier and being excreted in breast milk [4].

Despite the many benefits, AZA can cause a wide range of side effects that can range from the most varied gastrointestinal intolerance to more serious effects, such as pancreatitis, liver failure and myelosuppression – PLOS 2/17, a crucial component of myelosuppression, may represent a risk factor for the appearance of opportunistic infections, especially for patients with other chronic diseases [1].

The recommended dose of AZA is 2 to 3 mg/kg for patients with Crohn's Disease and 1.5 to 2.5 mg/kg for patients with UC, and its administration is recommended along with food in order to avoid adverse effects such as nausea. or vomit [2].

Its use during pregnancy generates controversy in the literature. The FDA classifies it as class D, that is, it indicates positive evidence of risk to the fetus. Several authors, however, consider its use safe during pregnancy, advising against its interruption in women who are using it and already in remission [2].

Thus, the objective of this systematic review was to verify the main side effects of the use of AZA in the treatment of IBD.

Methods

Search strategy

The most relevant studies originally published in English in the last twenty-five years (until May 2017) were analyzed, using the MEDLINE (National Library of Medicine) databases as reference. In order to select the studies with the greatest scientific evidence, we considered only clinical trials. The search strategy used the key term: "inflammatory bowel disease" AND "azathioprine" AND "side effects".

The inclusion and exclusion criteria were applied freely and independently by two experienced reviewers who studied the subject, who judged the selected studies based on the points raised in each exposed item (table 1).

Inclusion criteria	
Outline	Studies published in the last twelve years Studies carried out in humans
Patients	Patients using Azathioprine to treat IBD
Information	Study with diagnostic criteria and therapeutic approach Information on the clinical evolution of patients
Language	Only in English
Exclusion Criteria	
Outline	Unclear or poorly described study Design with no diagnostic data Design with no therapeutic approach correlated with the use of medications
Information	Information that is unclear, poorly described or inadequate
Publication form	Only in summary
Main clinical and epidemiological outcomes	
Side effects	

Table 1: Inclusion and exclusion criteria and main results.

Results

122 studies were identified involving the keywords described above. To meet the established objective and criteria, the following terms were included, in the following order: "12years" and "humans", obtaining a total of 52 studies. However, only 5 were part of the scope of this review, meeting the pre-selected inclusion and exclusion criteria. The summary of the main results of the studies is described in table.

Study	Patients	Treatment	Side Effects
Keyko Ohno., *et al.* (2004)	Patients older than 18 years with active UC. A total of 244 patients were included in the analysis.	Oral AZA or 6MP therapy with minimum treatment durations of one month for remission induction or three months for remission maintenance.	Bone marrow suppression, mild gastrointestinal intolerance, acute pancreatitis, jaundice, hair loss and skin rash have been reported as adverse reactions to AZA. The OR of the use of AZA to induce disease remission, compared to placebo, was 1.45 (95% CI: 0.68 to 3.08), demonstrating that there was no statistical significance in the association. However, for maintenance of remission, AZA proved to be a protective factor, with an OR of 2.26 (95% CI: 1.27 to 4.01). The number needed to treat (NNT) was 6.
Fernando Gomollón., *et al*. (2008)	Six randomized controlled trials (286 patients) of at least 12 months duration comparing AZA (or mercaptopurine) versus placebo or mesalazine for UC.	Use of Azathioprine in the treatment of inflammatory bowel disease, particularly in maintaining remission in patients.	Most adverse events occur early in treatment and after the first few weeks, tolerance to the drug is generally very good. The main risks of AZA misuse are myelotoxicity, hepatotoxicity and perhaps the development of malignancies, particularly lymphomas. The Remission Rate is 67%, with an OR of 2.16.

P. SEKSIK., *et al*. (2009)	A total of 230 patients were included in a prospective cohort. Episodes of benign infections were collected and the incidence of benign infections was compared between the group of patients treated with AZA and patients without AZA.	The (AZA+) group consisted of 169 patients with IBD who were taking Azathioprine. The (AZA –) group consisted of 61 patients who received primarily mesalazine (77%).	This study suggests that the incidence of herpes outbreaks (OR 1.0 to 2.6 vs. 0.2 to 0.8 per year, p = 0.04) and the worsening of viral warts (17.2% (AZA+) vs. 3.3% (AZA), P = 0.004) are increased in patients with Inflammatory Bowel Disease receiving AZA. The study, however, found no statistical difference in the incidence of upper airway infections between the analyzed groups (2.2 to 2.3 vs. 2.1 to 2.1, P = 0.77).
Pascal Frei., *et al*. (2013)		AZA and 6-MP as treatment in patients undergoing ileocecal resection.	The major dose-dependent side effect of thiopurines is drug-induced myelosuppression which is seen in 2%-5% of Caucasian patients. Asian (or at least Japanese) patients have a higher risk of myelotoxicity. Infectious complications are mostly dose-dependent, but idiosyncratic side effects are also observed. Infectious complications during thiopurine therapy can occur even in the absence of a leukopenia.
MariusVögelin., *et al*. (2016)	Records of patients on thiopurines were examined for lymphopenia (defined as <1,500 lymphocytes/µl) during treatment with this medication.	We retrospectively examined the medical records of 1070 patients with inflammatory bowel disease. We identified 100 subjects who developed a total of 161 episodes of lymphopenia during thiopurine treatment between 2002 and 2014. The occurrence of opportunistic infections was documented. A control group consisted of patients with inflammatory bowel disease who received thiopurines but did not develop lymphopenia. All data were obtained from electronically archived medical reports from the Inflammatory Bowel Disease clinic of the Clinic of the Division of Gastroenterology and Hepatology of the University Hospital of Zurich, Switzerland.	Of a total of 161 episodes of lymphopenia, 23% were severe (<500C/µl). In this subgroup, thiopurine dosage was modified in 64% (dose reduction: 32%, medication discontinued: 32%). We identified 9 cases (5.5%) of opportunistic infections, of which only two occurred during severe lymphopenia. An opportunistic infection (4.5%) was identified in the control group. No association was found between opportunistic infections and severity of lymphopenia. All patients who experienced opportunistic infections were receiving additional immunosuppressive medications.

Table 2

Discussion

Our results confirm the premise that the use of Azathioprine in Inflammatory Bowel Disease proved to be effective in the maintenance treatment of the remission of inflammatory activity and also showed benefits in patients submitted to ileocecal resection, in order to avoid recurrence of the disease. It was demonstrated that the use of AZA should not be suspended during the treatment of IBD, although its side effects constitute an important bias to be evaluated before starting the treatment.

A pioneering meta-analysis performed by KeykoOhno., *et al*. involving 81 studies between 1966 and 2003 from the Medline, Cochrane and Japana Central Revuo Medicine database initially demonstrated that AZA was not effective in ensuring inflammatory remission in patients with active disease, OR from 1.45 (95% CI: 0.68 to 3.08). However, for maintenance of remission, AZA proved to be a protective factor, with an OR of 2.26 (95% CI: 1.27 to 4.01). The number needed to treat (NTT) was [6].

With regard to side effects, bone marrow suppression, mild gastrointestinal intolerance, acute pancreatitis, jaundice, alopecia, and skin rashes have been observed. Comparison of the side effects of AZA versus placebo found an OR of 2.11 (95% CI: 0.92 to 4.84), indicating a tendency for drug therapy to be worse than placebo, but not showing statistical significance in the result.

Fernando Gomollón., *et al*. (2008) sought to analyze the long-term effectiveness of AZA in patients with CD, through the study of six clinical trials and a meta-analysis published in the Annals of Internal Medicine in 2008, finding a remission rate of 67%, with an OR of 2.16 (95% CI 1.35 – 3.47) , when compared with placebo, plus an NNT of 7 patients for relapse prevention.

He concludes that most adverse events occur early in treatment and that after the first few weeks, tolerance to the drug is generally very good. The main risks of AZA misuse are myelotoxicity, hepatotoxicity and perhaps the development of malignancies, particularly lymphomas. The author was able to demonstrate that treatment with AZA alone (without association with biological therapy) is adequate to maintain remission in patients with CD, and should be continued in the absence of important side effects (degree of recommendation A; level of evidence: I) Still regarding the adverse effects of AZA treatment in patients diagnosed with IBD, P. Seksik., *et al*. carried out a prospective cohort with 230 patients, 169 using AZA and 61 using Mesalazine, who were observed for the development of upper airway infections (URIs), herpetic eruptions and genital warts of viral origin.

The study concluded that there is no statistical difference between patient groups with regard to ARIs (2.2 to 2.3 vs. 2.1 to 2.1, p = 0.77).

Differences were observed only with regard to herpetic eruptions (OR 1.0 to 2.6 vs. 0.2 to 0.8 per year, p = 0.04) and worsening of viral warts (17.2% AZA+ vs. 3.3% AZA-, p = 0.004) in the which increases have been observed in IBD patients receiving AZA. A bias observed in this study is that the author did not consider the degree of inflammatory activity of the disease in both groups, and when observing the clinical indications for treatment with AZA and Mesalazine, there is no doubt that the second is prescribed for patients with a more limited degree of activity.

Seksik also observed that of a total of 161 episodes of lymphopenia, 23% were severe (<500C/µl). In this subgroup, thiopurine dosing was modified by 64% (dose reduction: 32%, medication discontinued: 32%). Nine cases (5.5%) of opportunistic infections were identified, of which only two occurred during severe lymphopenia. Only one opportunistic infection (4.5%) was described in the control group. No association was found between opportunistic infections and severity of lymphopenia.

Vögelin., *et al*. performed a large retrospective study between 2002 and 2014, with 1,070 patients with a previous diagnosis of IBD, who received treatment with AZA, 6-mercaptopurine or 6-thioguanine, identifying that 161 of these patients developed episodes of lymphopenia. In this subgroup, 23% developed severe lymphopenia, according to the inclusion criteria established by the author (lymphocyte count < 500 c/ul). Given this laboratory situation, the thiopurine dosage was modified by 64% (dose reduction: 32%, medication discontinued: 32%). Nine cases (5.5%) of opportunistic infections were identified, of which only two occurred during severe lymphopenia. An opportunistic infection (4.5%) was identified in the control group.

At the end of the study, the author concluded that opportunistic infections were not more frequent in patients with severe cases

of lymphopenia. Considering one interpretation, the possibility that thiopurine-induced lymphopenia does not cause immune impairment as relevant as lymphopenia induced by other types of immunosuppressive diseases, such as HIV for example.

All data were obtained from electronically archived medical reports from the Inflammatory Bowel Disease Outpatient Clinic of the Division of Gastroenterology and Hepatology at the University Hospital of Zurich, Switzerland.

Finally, there is the study published by Pascal Frei., *et al*. in the World Journal of Gastroenterology in 2013, in which conclusions similar to those exposed above were observed, regarding the lack of evidence of the use of thiopurines to induce remission in IBD, highlighting its importance in maintaining the remission of the inflammatory activity of the disease.

He also analyzes the use of thiopurines in the postoperative period of colectomy in patients with CD, highlighting two randomized clinical trials that indicate that AZA and 6-MP are superior to placebo for the prevention of relapses. In one of these studies, 81 patients who underwent ileocecal resection were followed, and 19 of them discontinued the treatment. Of the remainder, endoscopic recurrence was observed in 43.7% of patients receiving AZA and in 69% of patients receiving placebo ($p = 0.48$), which demonstrates a significant reduction in recurrence in the two groups studied, although the absolute values of recurrence are still expressive.

The treatment of fistulas with these drugs was also shown to be superior to placebo (54% to 21%) in meta-analyses of studies that included patients with perianal, enterocutaneous, enteroenteric and rectovaginal fistulas. He highlighted that although complete closure of these fistulas may not be seen in all patients, medication has an important effect on fistula-related symptoms such as inflammation, discomfort, and draining discharge.

Conclusion

AZA proved to be effective in maintaining the remission of inflammatory activity in patients with IBD, although its side effects constitute an important bias to be evaluated before starting treatment. These effects constitute a heterogeneous spectrum of manifestations ranging from bone marrow suppression, mild gastrointestinal intolerance, acute pancreatitis, jaundice, alopecia, and skin rashes. It was demonstrated that, although AZA can induce severe lymphopenia, this did not mean a higher rate of diseases related to immunosuppression.

Benefit was also observed in the use of AZA in patients submitted to ileocecal resection, in order to avoid relapses of the disease, in addition to its use in patients who developed some type of fistula due to the activity of the disease. An important bias found in several analyzed studies was the fact that patients with different degrees of inflammatory activity of the disease were compared, which represents an additional factor to be considered in the appearance of side effects from the use of AZA.

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