Side effects from the use of azathioprine in Crohn's disease: A systematic review

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ABSTRACT

Introduction: Crohn's disease is a chronic, relapsing and inflammatory condition. Azathioprine (AZA) is an immunosuppressive drug used for maintenance of the disease remission. However, the side effects this drug causes to patients, makes it questionable, as to its safety, for health.
Purpose: To determine the type and severity of side effects caused by AZA treatment in Crohn's disease.
Materials and methods: Through systematic review of literature, 85 studies were found, 10 of which were selected. The selection criteria were: a) articles, which were primary studies, reviews or meta-analyzes, b) available in full text, c) written in English and d) finally articles, referring to humans.
Results: Studies show that AZA, is drug of choice, for treating Crohn's disease. However, side effects from its use are numerous and increasing in severity. According to the survey results, people who used this drug, developed at some point in their treatment, side effects such as hepatotoxicity, myelotoxicity, acute pancreatitis ($p<0.001$), gastrointestinal intolerance, general hardship, blood disorders, fever wave, itching and arthralgia.
Conclusions: Recommendations from these studies show that side effects immerge from almost all systems in the patient's body, but it is not proven if all of them have to do exclusively with the drug or the disease's nature. As AZA holds a prominent role in disease's treatment, the use of more thorough controls is recommended for simultaneous treatment of side effects.
Key words: Azathioprine, Crohn's disease, side effects of azathioprine, azathioprine toxicity

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INTRODUCTION

Crohn's disease (CD) is a disease of unknown cause, which creates inflammation to any point of the gastrointestinal tract wall, from the mouth all the way to the anus [1,2].

However, the areas that are primarily affected are the small and large intestine and in particular the final section of the small intestine, the ileum, and the end portion of the colon, the rectum. The exact cause of CD remains a mystery. In the past, it was believed that diet and stress were the main causes of the disease. However, it is now known that although these factors can aggravate the disease, they aren't the main reason of cause. The latest surveys show that a number of factors, such as heredity and an abnormal functioning immune system may play a role in its development [1,2].

The disease mainly affects people aged 15-40 years and is equally found in both genders [3]. It is characterized by exacerbations and remissions, some of the symptoms in the phase of exacerbation are: A. Diarrhea; B. Abdominal pain and cramps; C. Blood in feces; D. Reduced appetite and weight loss; E. Hepatitis and cholangitis; F. Iridocyclitis; G. Arthritis; H. Fatigue; I. Dermatitis; J. Fever; K. Delayed development in children [3].

The drugs commonly used are corticosteroids, sulfasalazine and immunesuppressive drugs such as azathioprine (AZA). The goal of treatment is to reduce the inflammation of the intestine and other systems and organs that are probably affected by this systemic disease. The main aim is to bring remission and a symptomatic improvement of the patient. Surgical treatment is only used for severe complications of the CD [3,4].

AZA, a medicine used for CD's treatment, is a chemical similar to that of purine. It competes with purine's metabolism and can inhibit the synthesis of DNA, RNA and proteins. It can also affect cellular metabolism and inhibit mitosis [5,6].

The mechanism of its reaction is probably due to the incorporation of thiopurine in the structure of DNA, causing chain termination and cytotoxicity [5,6].

AZA is not an active drug itself but is activated in the body. This happens in several steps. At first it is slowly and almost completely converted to 6-mercaptopourine (6-MP) by reductive cleavage of the thioether. This is mediated by glutathione and similar compounds in the intestinal wall, the liver and on red blood cells, without the aid of enzymes [7].

AZA is used to manage moderate, severe or chronic forms of the active disease and thus maintaining clinical remission. But the side effects that may result from it's treatment are numerous.

MATERIALS AND METHODS

For the construction of this study, the medical bibliography was searched using the electronic databases of PUBMED, GUT and ECCO, with the use of the following keywords: azathioprine in Crohn's disease, toxicity and side effects. In total, 85 primary studies were found. The criteria's of the articles chosen were:

- primary studies, reviews or meta-analyzes,
- available in full text,
- written in English,
- published in the period 1993-2016
- focused on humans.

Initially, a study of all the summaries of the articles was conducted in order to make a final choice. 75 articles from the searched bibliography were excluded and 10 were included, of which 9 were cohort studies and 1 was a systematic review.

RESULTS

Out of the 85 articles that appeared from the search, 28 were rejected after going through their titles and their summary, as they refer to the side effects of AZA in other diseases or to inflammatory diseases of the intestine in general and not specifically in CD. Moreover, 30 researches were excluded, after the examination of their full text, due to their lack of epidemiological and statistical data. Finally, 17 studies were not included for being descriptive reviews. Thus, the final research sample consisted of 10 articles.

During 2014, Guerra et al, published the results of a research, which took 9 years to complete at the university hospital of Spain Universitario de Fuenlabrada. In the cohort study conducted, 212 patients with CD were involved along with 57 patients with ulcerative colitis (UC) and 4 patients with indeterminate colitis, all of whom had been treated with AZA. 50% of the patients were men of an average age of 42, while the 40% of these were smokers. The indications for treatment with AZA were the following: 78% were dependent on Steroids, 10.8% were treating fistula created from CD, 4.8% for precaution after a bowel resection, 3% due to being irresponsive to steroids and 3.4% for other reasons. Treatment occurred 24 months after diagnosis of the disease and the average daily dose was 2.2mg/kg/ day. Side effects were observed in 43.6% of the patients, 91 with CD and 28 with ulcerative colitis (p=0.27). Due to having an intolerance to the drug, 58 patients discontinued the treatment with AZA. The most common side effects were: hepatotoxicity (11.7%), gastrointestinal intolerance (11.4%), myelotoxicity (7%), pyrexia (6.2%), acute pancreatitis (4.8%) and

arthralgia/ myalgia (1.5%). The patients who discontinued the treatment with AZA, were treated with mercaptopurine. The results of this research showed that treatment with AZA proved efficient against idiopathic inflammatory diseases (IID), despite the side effects, which can be treated by replacing the drug with mercaptopurine [8].

During 2014, Estrada presented the results of a cohort study that was carried out in the hospital Vitoria- Álava in Spain. This study demonstrated the frequency of side effects and their type during treatment with AZA and also how the treatment was modified in order to deal with the side effects. The research included 198 patients of whom 50.5% were women, 43.4% with ulcerative colitis (5.8% proctitis, 43% with left colitis and 51.2% with pancolitis) and 56.6% with CD (ileitis 54%, 3% in the presence of the large intestine, 43% ileocolic disease). Side effects were observed in 42 patients of whom 54.7% were required to discontinue treatment with AZA. Side effects in patients with CD were as following [9]: dyspepsia (1 patient), cholestasis (4), hypertransaminasemia (2), acute pancreatitis (2), myelotoxicity (5), infections (3), alopecia (2). The results from the research indicated that the most common side effects were myelotoxicity (4.5%), hepatic abnormalities related to structural function (8%), indigestion (3%) and acute pancreatitis (2.5%). Cases of neoplasia or death were not found. They also concluded that therapy with AZA is effective against IID, despite the side effects, which can be treated by stopping this therapy or decreasing the dosage.

Dharmasiri et al. [10] during 2014, presented results from a cohort study, which took place at the Royal Bournemouth hospital in the United States. The goal of this research was to prove whether treatment with AZA was safe enough for elderly patients. There were 25 patients involved, 7 with CD and 18 with UC. The average age of the patients was 78 and 16 of the patients were male. All the patients were monitored for at least a year and 12 of the patients had an intolerance to AZA. The reasons for discontinuing treatment with AZA after 34 days of use were of the following: hepatitis (2 patients), vomiting (5), pancreatitis (1), myelosuppression (1), joint pain (1), infection (1), general malaise (1). At the same time, 13 patients tolerated the therapy and a group of these patients withdrew because the symptoms worsened. Furthermore, 4 deaths were noted, 2 in the group of patients that took AZA as part of their treatment and 2 in the group of patients that discontinued the treatment with AZA. Thus, it was shown from this research that treatment with AZA was effective with the elderly patients. However, intolerance to AZA was observed at a much higher level with the elderly than that of younger ages (48% intolerance in 3 months). It can be dealt with by decreasing the dosage of AZA or by administrating allopurinol together with AZA. But this has to be verified with further research [10].

Connell et al. conducted a cohort study at the St. Markos Hospital in London for 27 years, from 1964 to 1992 [11]. The aim of the study was to identify the side effects that treatment with AZA had on marrow bone. In this study 739 patients were involved, the average dosage of AZA given was 2 mg/kg/ day. 37 of the patients discontinued that therapy due to intolerance to the drug. Out of these patients 5 experienced symptoms and 32 were asymptomatic. The conclusion of this study was that myelotoxicity was unusual to occur when this drug was administrated in a controlled way even though it is dangerous [11].

During 2004, De Jong, Dj. et al. [12], worked on a cohort study at the University Hospital Medical Centre Nijimegen, in Holland. The purpose of this study was to assess the rate of side effects that lead to discontinuation of the therapy with the AZA drug and to define the prognostic factors lead to its termination. The results of 50 patients with CD who took the treatment were analyzed. Due to intolerance to AZA, 15 patients discontinued the therapy. At the start of the therapy, a small but significant decrease in white blood cells was observed within 6 weeks (From 10.6 to $9.5*10^9$/l), while asymptomatic leucopenia (< 3.0 x 10^9/l) was noted in 2 patients. Moreover, 3 of the patients were hospitalized because of serious side effects. The condition was reversible as soon as the drug therapy stopped. The results of this study showed that 22% of the patients discontinued the therapy early due to the side effects it caused. These patients continued treatment with prednisolone, at low doses, which can be useful, if administrated together with AZA in order to prevent some of the side effects [12].

Weersma et al. [13], during 2004 presented the result from a cohort study that took place in the University Hospital Groningen of Amsterdam in Holland. The aim of this study was to identify the side effects of the AZA therapy in the following diseases: Systemic lupus erythematosus, after liver and kidney transplant, Wegener Granulomatosis, autoimmune hepatitis, rheumatoid arthritis, UC and CD. 1564 patients took part in this study. 11 out of 224 patients that had CD showed signs of acute pancreatitis compared to 2/129 patients with autoimmune hepatitis, 2/388 after kidney transplant, 1/254 after liver transplant. Thus, acute pancreatitis was more prevalent in patients that suffered from CD. Discontinuation of treatment with AZA was followed after occurrence of toxicity: 73/317 patients with rheumatoid arthritis, 20/94 with ulcerative colitis, 52/224 with CD, 5/73 with SLE, 6/85 with Wegener granulomatosis, 8/129 with

autoimmune hepatitis, 17/254 after liver transplantation and 22/388 following kidney transplantation. The main result of this research was that liver toxicity as a side effect of treatment with AZA occurs largely in CD compared to other diseases and discontinuation of the therapy is observed most often inflammatory bowel diseases (IBD) and rheumatoid arthritis [13].

Fraser et al. [14], during 2002 conducted a systematic review, taking data from the medical department of Auckland University in New Zealand. The purpose of this study was to show whether the long term use of AZA was associated with malignancy. The AZA was administered in 622 of 2204 patients (271 with CD and 355 with UC). The mean total duration of use of AZA was 27 months, the average time monitoring of the diagnosis of patients was 13.7 years and the mean follow-up time from the start of the treatment with azathioprine was 6.9 years. The data showed that 31 cancers were observed in 30 patients treated with AZA and 77 cancers in 70 patients not receiving. Moreover, 8 patients had lymphoma, of whom 3 were receiving AZA (p = NS). The main outcome of this study was that there was no increased risk for malignancy in patients treated with AZA, therefore, long term treatment with AZA does not associate with the development of malignancy [14].

Martinez et al. [15], during 2001, conducted a cohort study in the hospital La Fe of Valencia in Spain. The aim of the study was to determine the frequency and the type of side effects that come with the treatment with AZA in patients with IBD. They selected 70 patients, 55 with CD, 14 with ulcerative colitis and one patient with indeterminate colitis. There were 23 adverse events in 21 patients, who were blood related at a rate of 11.4%, digestive intolerance to 11.4%, inflammation in an amount of 7.1% and pancreatitis 2.8%. These side effects were observed at higher rates in patients with UC than with CD, with respective rates of 57.8% versus 21.8% (p=0.02). Specifically, the discomfort and pancreatitis occurred in the first half of the treatment of AZA and the hematological disorders were known within 3 months to 4 years from the start of treatment. The inflammation occurred within 8 months to 5 years from the start of the treatment [15].

López-Martín et al. [16], during 2011, published a cohort study with data from the Spanish hospital Universitario de La Princesa in Madrid. The aim of the study was to determine the side effects caused by thiopurines namely AZA and 6MP to IBD. The survey included 377 patients diagnosed with the disease in 2008. 47% were male and 53% female with an average age of 43 years. 348 of these patients received AZA and 44 MP. 51 patients out of 377 experienced side effects, which are the following: myelotoxicity in 18 patients (incidence 16 months), acute pancreatitis in 10 patients [appeared in 27 days from the start of treatment with a statistically significant association with Crohn's disease (p=0.03) and smoking (p=0.01)], gastrointestinal intolerance in 10 patients, 9 patients with hepatotoxicity, hypersensitivity rash in 1 patient, bilateral deafness in 1 patient and a serious weakening in 1 patient. Discontinuation of therapy was performed in 84 patients. Also, there was a significant correlation between the incidence of side effects with CD (p=0.008). Therefore, they concluded that the thiopurines cause side effects in patients, which although relatively mild, are to be taken seriously [16].

Mazor et al. [17], published a cohort study, that was carried out in the hospital of Rambam Healthcare Campus of Haifa in Israel, in order to clarify the risk factors that increase the likelihood of a person with CD to develop side effects. Therefore, according to the article, the study included 176 patients with the above disease who were treated with thiopurines (45 patients with AZA and 131 with 6-MP). The factors considered in these patients were the specific genotypes GSTM1, GSTT1 and TPMT, age, ethnicity and smoking. The results showed that 24 patients developed side effects such as pancreatitis, myelosuppression and hepatotoxicity. The main risk factors seems to be smoking and GSTM1-null genotype for causing the side effects during treatment with thiopurines [17].

DISCUSSION

It is a fact that CD, is a chronic and idiopathic disease that accompanies the patient throughout his life from the moment it appears in his body. As mentioned before, there is no cure for the disease. AZA reduces both the symptoms of the disease and the possibility of surgery. However, there are doubts regarding its safety. A lot of side effects have been witnessed in significant levels in patients, with a prominent position given to hepatotoxicity, myelotoxicity and pancreatitis. If such complications are not immediately detected, they can be fatal to the patient's life.

During pregnancy, disease activity must be minimized. Most medications used to treat CD are considered low risk during pregnancy. AZA is a pregnancy category D drug. This means that there is evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks. Active disease poses more risk to the fetus than most CD's medications, so the benefits of treatment clearly outweigh the risks. Whatever medications helped maintain

remission before pregnancy should be continued during pregnancy, except methotrexate or antibiotics. Vaginal delivery is recommended except in instances of active perianal disease or a history of fistulas. Breast-feeding should not be discouraged as most medications are considered safe [18]. According to remarkable surveys , use of AZA during pregnancy does not provoke preterm birth or teratogenicity [19,20].. Data has shown that 6-MP was undetectable in the neonatal blood [21].

AZA is well established for the maintenance of remission However, a significant proportion of patients are intolerant to AZA. It is not clear if this intolerance is a marker of poor prognosis for patients. AZA intolerance acts as a surrogate marker for patients with CD who in future have poorer symptom control. A few studies have indicated that mercaptopurine treat AZA's gastric intolerance in patients with IBD [22].

In conclusion, frequent rechecking are required during and even after therapy, so as to quickly perceive any negative changes. Further studies could be made regarding the combination of AZA with other drug for better results, as well as the relation between the dose of the drug and the side effects.

CONCLUSIONS

According to the results of the systematic review some conclusions can be generated regarding the nature of the side effects, as well as how frequently they appear. More specifically, hepatotoxicity is shown in six of the ten studies at a rate starting from 0.0022% and reaching up to 11.7%. Another equally as important side effect, myelotoxicity (as a generic term) is shown in six of the ten studies ranging from 0.01% to 7%. Then, leukopenia occurs at a rate from 0.03% to 0.8% and thrombocytopenia at 0.007%. Other blood disorders are presented at a rate of 11.7%. Furthermore, an equally important side effect is acute pancreatitis, which occurs in seven out of the ten studies with rates ranging from 2.5% to 4.9% and p-value <0.01. Also, symptoms associated with gastrointestinal intolerance occur at a rate ranging from 4% up to 11.4%. Specifically, dyspepsia corresponds to 3% of the total rate, nausea to 0.009%, diarrhea to 0.004%, vomiting from 0.009% to 10% and abdominal pain equal to 0.02%. Moreover, we observe that fever has a significant percentage that corresponds to 6.2%, arthralgia from 0.03% to 4%, while general malaise receives a rate starting from 0.01% up to 4%. In addition, generalized infection was observed without further definition, at a rate of 0.03% to 7.1%. Finally, pruritus as a symptom, corresponding to a small percentage of 0.01%.

Flowchart containing the method of reference selection:

- Total articles obtained after searching keywords (n = 85)
- Total studies that were excluded because of descriptive reviews (n = 17)
- Total studies that were rejected after reading the title and summary, and did not meet the criteria (n = 28)
- Total studies that were excluded after reading this entire article, due to lack of demographic and statistical data (n = 30)

The following table lists the characteristics of the studies included in the systematic review.

All 10 studies are then analyzed extensively so that, during the process, they can be compared to each other and to export the results.

Author/Year/Title	Type of Study	Country of conduct	Period of conduct	Participants	Identifier	Results	Confounders
Effectiveness and adverse events of azathioprine in inflammatory bowel disease: 9-year follow-up study Guerra et al, 2014	Cohort Study	Spain	June 2004 - May 2013	Hospital Universitario de Fuenlabrada 50% men 40% smokers Average age 42 years.	212 patients with Crohn's Disease (CD). 57 patients with UC (Ulcerative Colitis) 4 patients with indeterminate colitis.	Side effects were observed in 43.6% (95%CI37-50%) of patients. 91 (42.9%) with CD, 28 (49.1%) with UC (p=0.27) Hepatotoxicity: 11.7% Gastrointestinal Intolerance: 11.4% Myelotoxicity: 7% Fever: 6.2% Acute Pancreatitis: 4.8% Arthralgia/Myalgia: 1.5%	Ulcerative colitis, Mercaptopurine, Methyltransferase levels
Adverse effects of azathioprine in patients with inflammatory bowel disease (IBD) Estrada et al, 2014	Cohort Study	Spain	2014	Hospital in Vitoria-Álava, Spain 50,5% women	198 patients. 43.4% with ulcerative colitis (5.8% proctitis, 43% left colitis and 51.2% pancolitis), 56.6% with CD (54% ileitis, 43% ileocolonic disease, 3% colonic presentation)	21,2% of patients showed side effects. The most common side effects were: abnormal liver function tests (8%), myelotoxicity (4,5%), indigestion (3%), acute pancreatitis (2,5%).	Ulcerative colitis
Azathioprine in the elderly - Is it tolerated and is it safe? Dharmasiri et al, 2014	Cohort Study	United Kingdom	June 2005-October 2012	Royal Bournemouth Hospital, Department of Gastroenterology United Kingdom Average age 78 years. 16 were men. Patients were observed for at least 1 year.	25 patients were included, (7 with Crohn's disease, 18 with Ulcerative colitis)	12 patients showed intolerance to AZA. Treatment was discontinued due to the following side effects: hepatitis 8%, vomiting 10%, pancreatitis 4%, myelosupression 4%, pain in joints 4%, infection 4%, general hardship at 4%. 4 deaths were noted. 13 patients continued the treatment and clinical achieved and recession gastrointestinal.	Ulcerative colitis Methyltransferase
Bone marrow toxicity caused by azathioprine in inflammatory bowel disease: 27 years of experience. W R Connell, M A Kamm, J K Ritchie, J E Lennard-Jones 1993	Cohort Study	United States	1964-1991	St Mark's Hospital, London	739 patients took part in the study (422 with CD, 284 with UC, 33 with colitis indeterminate) Average dose: 2mg/kg/day From the 422, 218 were women and 204 were men.	16/422 showed signs of leukopenia (5 were men and 11 were women) during the first 36 months since the start of treatment with AZA. (0.03%) 3/422 showed signs of thrombocytopenia (all 3 were men) during the first 38 months since the start of treatment with AZA. (0.007%)	Ulcerative colitis
Side effects of azathioprine in patients with Crohn's disease de Jong J, Goullet M, Naber TH. 2004	Cohort Study	The Netherlands	2004	Department of Gastroenterology and Hepatology, University Medical Centre Nijmegen, The Netherlands	112 patients with Crohn's Disease. 50 of them, who were under treatment with AZA, were included in the study.	15/50 patients discontinued treatment with AZA due to side effects. A decrease in the number of white blood cells was noted in 6 weeks time (median $10.6 \pm 95\ 10^9$/l), while asymptomatic leukopenia (<3.0 10^9/l) appeared in 2 patients.	Prednisone 5-aminosalicylates

Increased incidence of azathioprine-induced pancreatitis in Crohn's disease compared with other diseases R. K. Weersma et al, 2004	Cohort Study	The Netherlands	1995-2002	Information System of the university hospital Groningen, Amsterdam 1564 patients received AZA due to: Lupus erythematosus, rheumatoid arthritis, Wegener Granulomatosis, autoimmune hepatitis, Crohn's disease, ulcerative colitis, kidney transplantation or liver transplantation.	224 patients were afflicted with Crohn's Disease. The average dose of AZA to those patients was 123 mg/day (1,75 mg/kg) Men 79 Women 145 Average Age: 39 years	11/224 patients with Crohn's Disease developed acute pancreatitis (4,9%) Other side effects: 20/24 patients developed nausea and vomiting. 6/224 developed abdominal pain. 1/224 developed diarrhea. 5/224 developed fever. 3/224 develo-ped pruritus. 5/224 developed hepatitis. 4 patients out of 224 developed myelosupression, while 8 of them arthralgia. 3 patients out of 224 developed general weakness.	Lupus erythematosus, rheumatoid arthritis, Wegener Granulomatosis, autoimmune hepatitis, Crohn's disease, ulcerative colitis, kidney transplantation or liver transplantation
Long-term risk of malignancy after treatment of inflammatory bowel disease with azathioprine A. G. Fraser et al, 2002	Systematic review	New Zealand	2002	University of Auckland, New Zealand Mean follow-up of patients: 13.5 The mean follow-up since the start of the treatment with AZA was 6.9 years. The mean total duration of therapy was 27.1 months.	626 patients took part in the study who received treatment with AZA. (271 with Crohn's Disease and 355 with Ulcerative colitis).	31 cases of cancer were noted in 30 patients who were treated with AZA and 77 cases of cancer were noted in 70 patients who were not treated with AZA. 8 patients under treatment with AZA had lymphoma. Thus proving that treatment with AZA is neither associated with increase in cancer cases (ρ=0.2), nor with the appearance of specific types of cancer: colorectal (ρ=0.8), bronchial (ρ=0.2),breast (ρ=0.5) and lymphoma (ρ=0,5).	Ulcerative colitis
Adverse effects of azathioprine in the treatment of inflammatory bowel disease Martínez et al, 2001	Cohort study	Spain	2001	Hospital La Fe, Valencia	70 patients were studied, from who 55 were afflicted with Crohn's Disease and 14 with Ulcerative colitis, while there is also a chance of indeterminate colitis.	23 types of side effects were noted in 21 patients. Hematological 11.4% Intolerance of the digestive system 11.4% Infection 7.1% Pancreatitis 2.8% 9 patients (12.8%) discontinued the treatment due to severe intolerance.	Ulcerative colitis 6-mercaptopurine

Adverse events of thiopurine immunomodulators in patients with inflammatory bowel disease. López-Martín et al, 2011	Cohort study	Spain	2008	Hospital Universitario de La Princesa Madrid 377 patients 47% men 53% women Average age: 43 Average daily dose: 2.5mg/kg/day.	377 patients under treatment with AZA (55% CD and 42% UC and 3% indeterminate colitis.)	51 patients out of 377 developed side effects. 18 patients developed myelotoxicity (4.8%) 15 patients develop-ped gastrointestinal intolerance (4%) 10 patients developed acute pancreatitis (2.7%). Secondary liver toxicity was developed in a percentage of 2.4%. From the 51 patients, 84% discontinued the treatment with AZA.	6-mercaptopurine Smoking
Risk factors for serious adverse effects of thiopurines in patients with Crohn's disease. Mazor Y et al, 2013	Cohort Study	Israel	2013	Rambam Health Care Campus, Haifa, Israel	176 patients with CD. (45 with AZA and 131 with 6MP.)	24 patients developed side effects. Most important side effects: myelosuppression, hepatotoxicity and pancreatitis.	Genotypes Age Smoking Ulcerative colitis

Conflicts of interest

The authors declare that they have no conflicts interests.

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