10.5005/jp-journals-10018-1035
ORIGINAL ARTICLE

Azathioprine Toxicity in Inflammatory Bowel Disease

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ABSTRACT

Background/aim: The aim of this study was to evaluate patients with inflammatory bowel disease (IBD) treated with azathioprine (AZA) and followed-up in our clinic to adverse effects.

Materials and methods: We analyzed patients with IBD who were treated with AZA between April 1998 and April 2008 for adverse events.

Results: Four hundred and seventeen patients that included 211 (50.6%) females (age, 38.63 ± 13.32 years) were evaluated. Two hundred and forty-two patients (58%) had ulcerative colitis, 159 (38.1%) patients had Crohn's disease and 16 (3.8%) patients had undetermined colitis. Mean follow-up period was 42.5 ± 46 months (range, 6-288 months). One hundred and eighty-nine (45.3%) patients used AZA (66% in Crohn's disease group, 32% in ulcerative colitis group). Mean AZA treatment period was 33.8 ± 32 months (range, 6-160 months). Discontinuing rate was 19.6% (37 cases). Causes of discontinuing AZA were as follows: Adverse events in 15 patients (bone marrow suppression in three, pancreatitis in two, hepatotoxicity in two, related malignancy in three and other events in five patients), inefficacy in 12 patients, postoperation in five patients and other causes in five patients. Major toxicity was seen in seven of 189 patients (3.7%).

Conclusion: Half of IBD patients were using AZA and major toxicity and malignancy development rates during AZA treatment were low. AZA is a safe immunosuppressive agent in IBD patients.

Abbreviations: AZA: Azathioprine; MP: 6-Mercaptopurine; IBD: Inflammatory bowel disease; UC: Ulcerative colitis; CD: Crohn's disease; ID: Indetermine colitis; NHL: Non-Hodgkin lymphoma.

Keywords: Azathioprine, Adverse events, Inflammatory bowel disease.

How to cite this article: Uyanikoglu A, Akyuz F, Ermis F, Pinarbasi B, Demir K, Ozdil S, Besisik F, Kaymakoglu S, Boztas G, Mungan Z. Azathioprine Toxicity in Inflammatory Bowel Disease. Euroasian J Hepato-Gastroenterol 2012;2(2):59-62.

Source of support: Nil

Conflict of interest: None

INTRODUCTION

Azathioprine (AZA), 6-mercaptopurine (6-MP), methotrexate, ciclosporin and tacrolimus all have their respective roles in treatment of inflammatory bowel disease (IBD). These immunomodulators are potent and effective medications; however, they potentially have serious toxicity. To maximize benefit and minimize risk, clinicians must understand the mechanism of action, appropriate indications, range of toxicity and proper dosing of these medications.[1] Another problem in clinics lies in the fact comparative efficacy and safety of infliximab and AZA alone or in combination for Crohn's disease.[2]

The thiopurine drugs, AZA, 6-MP and thioguanine, are widely used to treat malignancies, rheumatic diseases, dermatologic conditions IBD and solid organ transplant rejection.[3] Thiopurines remain central to IBD treatment, although future studies are required to substantiate a more personalized therapeutic approaches.[4] Serious drug toxicity leads to cessation of therapy in 9 to 25% of patients, and there is failure to achieve efficacy in approximately 15% of cases.[5] AZA and 6-MP are useful therapies in IBD. Despite their efficacy, their use is limited owing to treatment intolerance or toxicity in 10 to 15% of patients.[6]

These events may be divided into dose-independent idiosyncratic reactions and dose-related, pharmacologically explainable toxicity. Dose-independent reactions include skin rash, fever, diarrhea and pancreatitis. Most frequently observed dose-dependent adverse events are nausea, malaise and myelotoxicity. Furthermore, dose-dependent and dose-independent hepatotoxicity may occur.[7] Also, there is insufficient experience of AZA treatment in patients with past malignancy history.

There is limited information about the optimal use of thiopurinic immunomodulators in IBD and the dosage, efficacy and toxicity of these drugs has not been clearly established.[8] The aim of this study was to know the type, frequency and time course for the occurrence.

MATERIALS AND METHODS

We analyzed IBD patients who were treated by AZA between April 1998 and April 2008 for adverse events retrospectively. The diagnoses of patients were established by clinical and histologic confirmation. Demographic and clinical properties were also recorded. All IBD patients followed for at least 6 months were included in this retrospective study.

Data were obtained from the database of patients with IBD who started treatment with AZA and follow-up. Toxicities were defined, analyzed and their relationship with clinical and demographic variables were evaluated with multivariate analysis.

RESULTS

A total of 417 patients were included in the study. Out of them, 211 (50.6%) were females and 206 males (49.4%).

The mean age of the patients was 38.63 ±13.32 years, (range 16-78 years). Two hundred and forty patients (58%) had ulcerative colitis (UC), 159 (38.1%) patients had Crohn's disease (CD) and 16 (3.8%) patients had indetermine colitis (ID) (Fig. 1). One hundred and eighty-nine patients (45.3%) used AZA (66% in CD group, 32% in UC group). Mean AZA treatment period was 33.8 ± 32 months (range, 6-160 months). Discontinuation rate was 19.6% (37 cases). Causes of discontinuing for AZA were as follows: Adverse events in 15 patients, inefficacy in 12 patients, postoperation in five patients and others in five patients (patient intolerance, pregnancy, etc.) (Fig. 2).

Adverse events were; bone marrow suppression in three patients, pancreatitis in two patients, hepatotoxicity in two patients, related malignancy in three patients and other events in five patients (gastrointestinal intolerance, skin eruptions, flu like symptoms, etc.) (Fig. 3). Major toxicity (neutrophenia, hepatotoxicity, pancreatitis) was seen in seven of 189 patients (3.7%). AZA was discontinued in three patients (1.58%) due to related malignancies. Non-Hodgkin lymphoma (NHL) was observed at 18th month in one patient with UC and AZA was discontinued. While a patient with breast cancer discontinued AZA by self-decision and another patient with breast cancer continued AZA without subsequent problems.

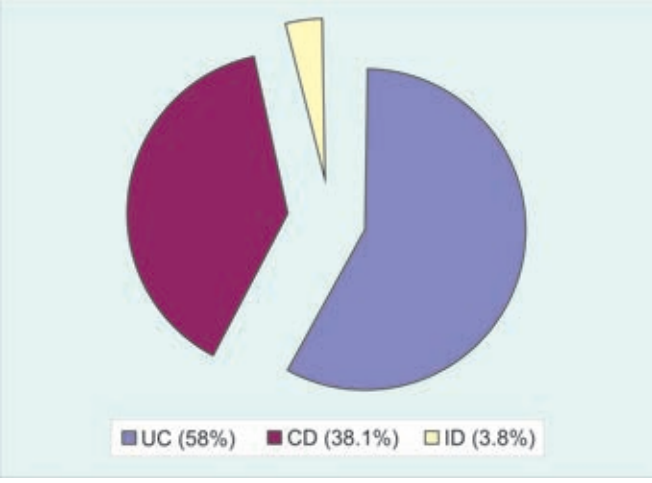

Fig. 1: Patients with ulcerative colitis (UC), Crohn's disease (CD) and unidentified colitis (IC) enrolled in this study

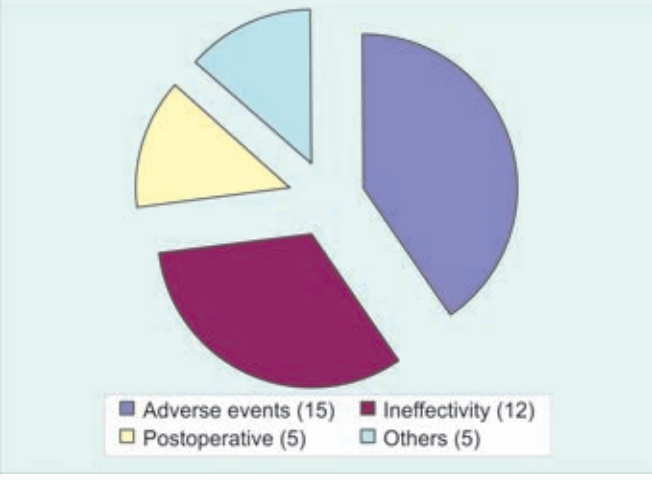

Fig. 2: Causes underlying disruption of AZA therapy

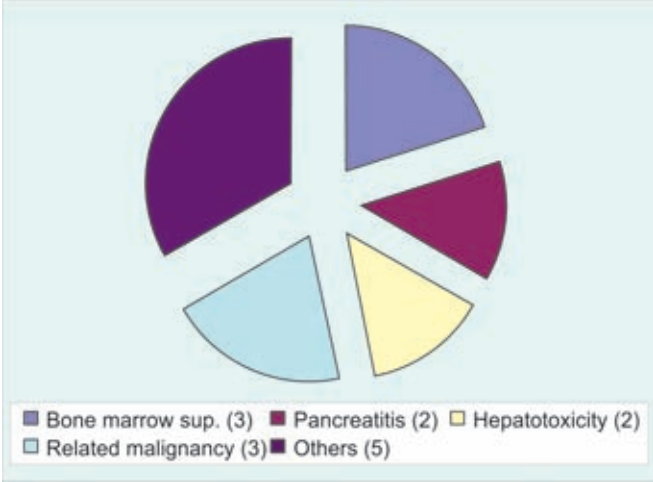

Fig. 3: Adverse events during therapy with AZA

DISCUSSION

Thiopurine drugs are useful therapies in IBD. Despite their efficacy, their use is limited owing to treatment intolerance or toxicity in 10 to 15% of patients.[6] In clinical trials, up to 15% of patients discontinued 6-MP or its prodrug AZA prematurely due to adverse events.[7] Discontinuing rate was 19.6% (37 cases) in our patients group.

Thiopurine drugs are capable of causing life-threatening toxicity, most often myelosuppression. The incidence rate of the drug-induced myelotoxicity is 3%. The incidence rate of severe myelotoxicity is less than 1% per patient and year of treatment.[3,9,10] Major toxicity (neutrophenia, hepatotoxicity, pancreatitis) was seen in seven of 189 patients (3.7%). Myelosuppression was seen in three patients (1.58%) in our series.

Bastida et al evaluated 150 courses of treatment in 126 patients. Treatment was given to induce clinical remission in 118 courses and 62% of the patients reached this outcome, which was maintained for a mean of 52 months. Factors significantly associated with withdrawal due to adverse events were starting with full doses of thiopurinic drugs and cotreatment with infliximab.[8] In other study, 92 consecutive patients were treated with AZA. Seventy of them (55 CD, 14 UC and 1 UD) were suitable for analysis. They observed 23 adverse reactions in 21 patients. Adverse events were as follows: Hematological (11.4%), digestive

intolerance (11.4%), infection (7.1%), and pancreatitis (2.8%). The prevalence was increased among UC patients (57.8 *vs* 21.8%) ($p = 0.02$)[7]. Mean AZA treatment period was 33.8 ± 32 months in our 189 patients. Discontiniuing rate was 19.6 (37 cases). One hundred and fifty-two patients continued AZA treatment. Adverse events were seen in 15 patients (7.93%). Adverse events were as follows; bone marrow suppression in three, pancreatitis in two, hepatotoxicity in two, related malignancy in three and other events in five patients.

Among AZA/MP-treated patients (690 patient-years of follow-up) the incidence of abnormal liver tests and hepatotoxicity were 7.1 and 2.6% per patient-year respectively. These drugs were withdrawn due to hepatotoxicity (liver tests > 5 N and lack of decrease despite 50% dose reduction) in 3.6% of the patients and liver tests normalized at all.[9-11] Severe hepatotoxicity was seen in only two of our patients. Eleven of 224 patients with CD experienced acute pancreatitis (4.9%).[12] Pancreatitis was seen in only two patients (1.05%) in our series.

Therapy with thiopurinic immunomodulators (AZA) represents the first option in the management of steroid-dependent ulcerative colitis. Its efficacy (70%) and its acceptable safety support this view. AZA was withdrawn in seven cases (20.6%) of 34; in four of them (with liver toxicity) treatment with MP was indicated.[13] Thirty-two percent of 242 patients with UC in our series were treated with AZA because of steroid dependency.

Immunomodulators are important agents for the treatment of CD and UC, and prescribing clinicians should be comfortable recognizing both their value and their limitations.[1] AZA was discontinued in three of 189 patients (1.58%) related malignancy in our series. We think that the contribution of AZA to the development of NHL in one patient is uncertain because NHL was discovered at 18th month of the treatment and there were multiple mutations in genetic analysis. Also ongoing AZA treatment without subsequent complication in a patient with breast cancer history suggested that there is no relationship between AZA treatment and *de novo* malignancies. This postulation is supported by the literature indicating similar lymphoma frequency in patients treated with AZA and normal population.

CONCLUSION

Half of IBD patients were treated with AZA (62% in CD and 32% in UC) and major toxicity and malignancy development rates during AZA treatment were low. AZA is a safe immunosuppressive agent for the treatment of IBD patients.

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