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Original article

Azathioprine use in patients with Inflammatory Bowel Disease. Adherence to treatment and adverse events. A single center experience

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SUMMARY

Background: Azathioprine is frequently used in achieving and maintaining remission in patients with inflammatory bowel disease. Aim: We performed a prospective study on patients with inflammatory bowel disease receiving azathioprine who were followed up at our hospital, in order to record their adherence to treatment and the frequency of adverse events. Methods: Fifty seven patients (23 males, 34 females, mean age 40.3 years) were included in our analysis. Thirty patients had Crohn's disease and 27 patients were diagnosed with ulcerative colitis. All patients were followed up at our outpatient's clinic with complete blood counts, liver enzymes and pancreatic enzyme levels monitored at weeks 1, 2, 4, 8 and 12 after initiation of azathioprine administration, with subsequent testing every 12 weeks for the duration of azathioprine treatment. Meanwhile, all patients, after 1 year of azathioprine administration, fulfilled a specialized questionnaire in order to determine their adherence to treatment. Results: The most common adverse event was a rise in amylase levels occurring in 3 of our patients (5.3%). Leukopenia requiring dose reduction (leukocyte count < 3.5 x 10^9) was seen in 2 patients (3.5%), while severe leukopenia (leukocyte count < 2.5 x 10^9) was seen in only 1 patient (1.7%). In this patient leukocyte count returned to normal after azathioprine discontinuation. Hepatotoxicity was less common occurring in 1.7% of our study population (1 patient only). Nonadherence rate was 24.5% of the patients included. The only factor associated with a better adherence was a more complicated course of the disease (p=.02). Conclusions: Azathioprine use in patients with inflammatory bowel disease appears to be safe, with adverse events being reversible and occurring in a minority of those treated. An important proportion of patients with IBD admit to forgetting some doses of the prescribed medication in the setting of a specialized unit of a referral centre.

Key Words: Azathioprine, inflammatory bowel disease, adverse events, patients' adherence to treatment

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INTRODUCTION

Inflammatory bowel disease (IBD), which encompasses Crohn's disease and ulcerative colitis, is characterized by chronic, intermittent, and unpredictable inflammation of the gastrointestinal tract resulting in symptoms such as recurrent diarrhea, abdominal pain, fatigue, arthritis and perianal disease.[1] Depending on presenting symptoms, severity of illness and individual patient's disease course, treatment can involve multiple medications with varying regimens, infusions, dietary changes, and surgery. Among these medications, azathioprione has gained a prominent place as an immunosuppressive maintenance therapy for both Crohn's disease and ulcerative colitis.[2]

Azathioprine (AZA) use may produce undesirable side effects, mainly myelotoxicity and hepatotoxicity.[3] However, the frequency of these adverse events is not well recorded, especially in Greek patients. Furthermore, non adherence to treatment is a pervasive and significant behavioural health issue in patients with chronic illnesses.

The adherence rate of Greek patients receiving azathioprine is also not known.

Given the above mentioned uncertainties, we performed a prospective study in order to record the rate of adverse events occurring in a cohort of IBD patients receiving azathioprine and also to assess the adherence to the prescribed treatment, as well as to identify factors associated with higher treatment compliance.

METHODS

All patients on azathioprine treatment, who were followed up at the specialized IBD outpatient clinic of our Unit, from January 2006 till January 2008, were considered for entry in our study. Inclusion criteria were: (a) diagnosis of Crohn's disease or ulcerative colitis, (b) 16 - 80 years of age, (c) prescribed azatinoprine use. Exclusion criteria were: (a) refusal to participate, (b) history of colectomy for ulcerative colitis, (c) disease duration less than 1 year.

All patients receiving azathioprine were followed up at our IBD outpatient's clinic with complete blood counts, liver enzymes and pancreatic enzyme levels monitored at weeks 1, 2, 4, 8 and 12 after initiation of azathioprine administration, with subsequent testing every 12 weeks for the duration of azathioprine treatment.

Patients who consented to participate were asked to answer an anonymous structured questionnaire, after one year of azathioprine administration, in order to assess adherence to treatment. Nonadherence patients were those admitting to forgetting ≥1 dose of the prescribed medication during the week.

This study was approved by the hospital Institutional Review Board. All recruitment and data collection was conducted by the principal investigator or one of the subinvestigators.

Statistical analysis

Results are expressed as mean values ± SD or frequencies; x^2 test for qualitative variables and Student *t*-test for quantitative variables were used to compare adherent and nonadherent patients. Possible factors associated with nonadherence were calculated using multivariate logistic regression analysis. All statistical analysis were performed using the SPSS 12.0 for Windows package (SPSS Inc., Chicago IL).

RESULTS

Fifty seven patients (23 males, 34 females, mean age 40.3 years) were included in our analysis. Thirty patients had Crohn's disease and 27 patients were diagnosed with ulcerative colitis. Patient characteristics, as well as information regarding disease location are presented in table 1.

The median follow up period was 13.2 months (range 12 – 24 months). During this follow up period, the most common adverse event was a rise in amylase levels (2-3 times the upper normal limits) occurring in 3 of our patients (5.3%). Leukopenia requiring dose reduction (leukocyte count < 3.5 x 10^9) was seen in 2 patients (3.5%), while severe leukopenia (leukocyte count < 2.5 x 10^9) was seen in only 1 patient (1.7%). In this patient leukocyte count returned to normal after azathioprine discontinuation. Hepatotoxicity (rise of aminotransferase levels twice from the

Table 1. Clinical characteristics of the patients
All data expressed as frequencies, or mean ± SD. CD location and behavior as defined by the Vienna classification[20].

Age (yrs)	40.3±13.5	36.3±12	44.8±13.8
Gender (M/F)	29/28	15/15	14/13
Time from diagnosis (mos)	111.6±65.3	108.8±62.3	114.9±68.9
CD location			
Ileum/colon/ileocolon/upper GI (%)		29/29/37/5	
CD behavior			
Inflammatory/stricturing/fistulizing (%)		33/33/44	
UC location			
Distal/extensive (%)			53/47
Previous hospitalization for IBD attack (%)	47	59	33
Steroid dependence (%)	22	27	16
Steroid refractoriness (%)	9	3.5	16.2
Infliximab treatment (%)	9	16	0
Intestinal resection (%)	29		

upper normal limits) was less common, occurring in 1.7% of our study population (1 patient only).

As regards the structured questionnaire (table 2), 14 patients (24.5%) admitted to forgetting ≥1 dose of the prescribed medication during the week, but only 1 of them (7.1%) did so intentionally. The median number of these "drug oversights" was 2 days per week (interquartile range, 1–2). The main reasons given by patients for a noncompliant behavior were weekend period (16.4%), working days (9.8%), and not being at home (9.8%). Only a minority of cases admitted inconvenience or difficult drug administration, excessive medication, or drug-related side effects.

Using multivariate analysis, the only factor associated with a better adherence was a more complicated course of the disease, defined as steroid dependency, steroid refractoriness, need for infliximab treatment, hospitalization, or surgery (p=0.02) (table 3).

DISCUSSION

Most patients with Crohn's disease or ulcerative colitis require long term maintenance therapy, in order to keep their disease in remission. Azathioprine has gained a prominent place as an immunosuppressive maintenance therapy for IBD and is used in many centres throughout the world[2]. However, its therapeutic role has been under discussion because of toxicity.

Adverse effects may occur in 15 to 30% of patients and those most commonly seen are hepatotoxicity and myelotoxicity.[4] Hepatotoxicity is believed to be a rare adverse event and hepatitis is considered to be an idiosyncratic reaction to azathioprine. Nodular regenerative hyperplasia (NRH), veno-occlusive disease, peliosis hepatis, fibrosis and sinusoidal dilatation are regarded as signs of dose-dependent hepatotoxicity. Myelotoxicity is usually seen as leukopenia or thrombocytopenia due to myelodepression[5]. According to our results these adverse events were seen in a minority of those treated and were not severe in most of the cases. In the only patient with severe leukopenia, it is of note that this was reversible when the drug was discontinued.

During the complex metabolisation process of AZA, multiple metabolites are generated. Azathioprine undergoes a rapid nonenzymatic conversion in the liver yielding 6-mercaptopurine (6-MP).[6] Following intracellular uptake, 6-MP is metabolised by three enzymes (xanthine oxidase, thiopurine methyltransferase (TPMT) and hypoxanthine phosphoribosyl transferase). Xanthine oxidase and TPMT catalyse the reaction of 6-MP to 6-thiouric acid (6-TU) and 6-methylmercaptopurine (6-MMP), respectively. The hypoxanthine phosphoribosyl transferase enzyme system is responsible for the formation of 6-thioinosinemonophosphate (6-TIMP) which may ultimately be transformed into the pharmacologically active 6-thioguaninenucleotides (6-TGN): 6-thioguanine-monophosphate (6-TGMP), 6-thioguanine-diphosphate (6-TGDP) and 6-thioguanine-triphosphate (6-TGTP). The pharmacologically active metabolites are the 6-thioguaninenucleotides (6-TGN), which are believed to induce apoptosis of activated T lymphocytes, hence leading to suppression of the overactive immune defence mechanisms. The proposed range of 6-TGN is 235

Table 2 Medication-taking behavior questionnaire

1. Which oral medications are you currently taking for IBD? (List with available drug trade name given.)
2. Which rectal medications are you currently taking for IBD? (List with available drug trade names given.)
3. In a 1-week period, do you forget any doses of your azathioprine medication? If the answer is affirmative
   a. How many days (in a 1-week period) does it happen?
   b. When you "forget" to take the medication, is it usually intentional or unintentional?
   c. The main reason for you to skip 1 dose is (you can have >1 answer):
      • coincidence of medication with working time
      • weekends (change in the daily routine)
      • going out (work, social events …)
      • medication-related side effects
      • difficulty in taking the medication (large pills, rectal administration, bad taste)
      • I think it is not necessary to take all or "so much" medication
      • other…
   d. Which medication do you tend to "forget"?

Table 3 Factors favoring compliance

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Gender	.27
Age	.31
Time from diagnosis	.17
IBD (CD/UC)	.78
Education (none or basic/high school–college/university)	.78
Job situation	
Student	.33
Unemployed	.07
Disease-related disability	.08
Working	.13
Retired	1.00
Steroid dependence	.31
Steroid refractoriness	.53
Previous hospitalization for IBD attacks	.49
Intestinal resection	.17
Infliximab treatment	.14
Aggressive disease*	.02

**Aggressive disease* is defined as steroid dependency, steroid refractoriness, intestinal resection, infliximab treatment, or previous hospitalization for IBD attacks.

to 450 picomoles/8 x 108 per red blood cell (RBC). High 6-TGN levels (>450 picomoles/ 8 x 108 RBC) have been associated with an increased risk of developing a myelodepression and high levels of the methylated product of 6-MP (6-methylmercaptopurine (6-MMP)) with hepatotoxicity.

As regards adherence to azathioprine therapy, according to our knowledge, this is the first study to address this issue in Greek patients. Adherence may be defined as the extent to which patient's behavior (in terms of taking medication, following a diet, modifying habits, or attending clinics) coincides with medical or health advice.[7] IBD has to be considered a high-risk situation for non-adherence to medical treatment because it is a chronic condition, affecting mainly young people. Moreover, given the recurrent nature of IBD, remission periods may be prolonged, making it difficult for patients to comply with drug treatments when they feel well.[8] The long-term goals of improving adherence are to reduce the frequency of disease relapse, the incidence of long-term complications (i.e., colon cancer), and the overall health costs.[9]

There is no gold standard method to measure adherence, but interview and questionnaire methods are most commonly used because they are easy to obtain and inexpensive.[10] Using such a questionnaire we found a non-adherence rate of 24.5%, which should be considered significant and should be addressed by physicians treating patients with IBD. In our analysis patients with a short duration of disease were excluded to reduce a possible bias because of a hypothetical lower awareness of chronic illness. Patients who have had a colectomy for UC were also excluded, because they become theoretically free of disease, whereas those who had it for CD remain at risk for disease recurrence.

Our results are in accordance with those reported in the literature.[11-15] Studies including a large number of patients have shown that patient's compliance was higher for immunomodulators than for aminosalicylates. In a recent study performed in a small series of pediatric IBD patients, self-reported rates of "complete adherence" of 70% and 43%, for immunomodulators and aminosalicylates, respectively were seen.[16] In an observational study, Bloomfeld and Onken[17] reported the initial azathioprine/6-mercaptopurine metabolite levels of 9187 patients with digestive diseases. In this large series, only 3% of patients had undetectable levels of metabolites, suggesting noncompliance to treatment; however, 46% of patients were underdosed, resulting from an inadequate prescribed regimen by the doctor or an inadequate patient compliance.

Major predictors associated with poor adherence include presence of psychological problems or cognitive impairment, treatment of asymptomatic diseases, inadequate follow-up or discharge planning, drug-related side effects, patient's lack of belief in the benefit of treatment or lack of insight into the illness, poor physician–patient relationship, presence of barriers to care or medications, missed appointments, complexity of treatment, and medication cost[18]. Some of these factors have also been reported to be quite specific for IBD patients, specifically those related to physician–patient relationship, depression, disease inactivity, and short disease duration[19]. In our series, we found that only a "complex" pattern of disease was associated with a better adherence. Disease activity was not evaluated as a predictive factor of adherence because there were only a few patients with active IBD.

In summary, our study illustrates the potential toxicity of AZA and stresses the need for continuous close monitoring of patients taking thiopurines in general. Routinely performed laboratory controls, including full white blood counts and liver function tests, seem mandatory. As regards, non-adherence to azathioprine therapy this seems to be common. Non-adherence may contribute to a worse disease course, decreased quality of life, and higher economic cost of disease. In addition to general major predictors of poorer adherence, a less complex IBD course is more often associated with worse medication-taking behavior. We believe that, the impact of adherence /nonadherence on disease outcomes should continue to be a focus of research in order to better understand the impact of this disease management behaviour on patient well being.

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