Efficacy and safety of long-term thiopurine maintenance treatment for ulcerative colitis in Turkey: A single-center experience

Funda Özgenç[1], Miray Karakoyun[2], Çiğdem Ecevit[3], Hamiyet Hekimci[4], Ezgi Kıran Taşçı[1], Gülin Erdemir[3]

[1]Department of Pediatric Gastroenterology, Hepatology and Nutrition, Ege University School of Medicine, İzmir, Turkey
[2]Department of Pediatric Gastroenterology, Hepatology and Nutrition, Tepecik Training and Research Hospital, İzmir, Turkey
[3]Department of Pediatric Gastroenterology, Hepatology and Nutrition, Dr. Behçet Uz Children Hospital, İzmir, Turkey
[4]Department of Pediatric Hematology, Ege University School of Medicine, İzmir, Turkey

Cite this article as: Özgenç F, Karakoyun M, Ecevit Ç, Hekimci H, Kıran Taşçı E, Erdemir G. Efficacy and safety of long-term thiopurine maintenance treatment for ulcerative colitis in Turkey: A single-center experience. Turk J Gastroenterol 2018; 29: 650-4.

ABSTRACT

Background/Aims: Thiopurines are widely used in the treatment of inflammatory bowel disease, but data are limited. Or aim was to determine the outcome of thiopurine application in children diagnosed with ulcerative colitis (UC).

Materials and Methods: Forty-eight patients with UC, diagnosed at our center between 2005 and 2016 and applied azathiopurine (AZA), were included in the study. Data were collected retrospectively. The diagnosis of UC was based on the conventional clinical, radiological, histological, and endoscopic assessment. All patients with UC at this intercept were analyzed at the 4- and 6-week and 3-month intervals after remission to determine patient characteristics, thiopurine properties, and its efficacy and toxicity. Determination of remission, relapse, and steroid refractoriness/dependency were guided according to the European Crohn's and Colitis Organisation consensus.

Results: Azathiopurine was started at the median 1 month (0-12 months), and it was applied thereafter for maintenance (n=43). Response to remission induction was obtained in 40 (93.7%) patients. The median duration of the AZA treatment was 24 months (5-63). In 34 (85%) of the 40 children, it was well tolerated until the last visit. During the follow-up, adverse events occurred in 6 patients. These are leucopenia, neutropenia, vomiting, diarrhea, and skin rush.

Conclusion: Thiopurine is an appropriate treatment option for remission in patients with UC. For a long-term follow-up, it is very important to identify patients with UC who have clinical remission with side effects and with thiopurine application.

Keywords: Ulcerative colitis, azathiopurine, effectiveness, adverse events

INTRODUCTION

Ulcerative colitis (UC) is an immune-mediated inflammatory reaction of the intestinal mucosa, characterized by relapse and remission. Immune modulation with thiopurines (TP) is a widely used mode of treatment for inflammatory bowel disease (IBD). Although they are considered the drug of choice for steroid refractory or resistant patients, thiopurines have also shown efficacy in the induction and maintenance of remission in adult populations (1,2). Recent reports support the potency of thiopurines in the management of IBD (3,4). Once the remission is established, maintenance is elicited in two-thirds of patients at 1 year with thiopurines (5). Hyams et al. (6) has recently reported that TP alone establish remission up to 1 year in half of the children with UC. A large cohort of pediatric patients has documented efficacy in up to 50% of patients at 1 year, and a more recent report documented that long-term use of TP is well tolerated and relatively safe (6).

The knowledge about the effectiveness, failure, and toxicity of long-term treatment with TP is limited. Adverse drug reactions are divided into two categories: idiosyncratic and dose dependent. An adverse reaction probably falls in the first category if it occurs a few weeks after the treatment commences in an immunologically mediated and unpredictable manner. Reactions include fatigue, dizziness, vomiting, diarrhea, fever, myalgia, arthralgia, rash, and hypotension (7), and they can also rarely include renal insufficiency, pneumonia (8-10), and pancreatitis, an increase of liver enzymes, hepatitis, cholestatic jaundice, or hepatic veno-occlusive disease (11). Even though

ORCID IDs of the authors: F.Ö. 0000-0002-7394-1392; M.K. 0000-0002-6533-6256; Ç.E. 0000-0002-3980-8686; H.H. 0000-0001-8347-1817; E.K.T. 0000-0001-5842-0292; G.E. 0000-0002-9726-8219.

Corresponding Author: **Miray Karakoyun; miraykarakoyun@hotmail.com**
Received: **July 12, 2017** Accepted: **March 30, 2018**

DOI: **10.5152/tjg.2018.17151**

TP is widely used among children and adolescents, there are no data concerning its long-term use over the course of 1 year within the pediatric population. Therefore, in the current study, we aimed to evaluate the efficacy, tolerability, adverse reactions, and safety of a long-term TP use in a cohort of children with UC.

MATERIALS AND METHODS

Data were collected retrospectively from the records of patients diagnosed with UC at our center between 2005 and 2016. The diagnosis of UC was based on radiological, conventional clinical, histological, and endoscopic evaluation. Only patients with moderate and severe ulcerative colitis were included in the study. All UC patients at this intercept were analyzed at the 4-week, 6-week, and 3-month intervals after the occurrence of remission to determine patient characteristics, thiopurine properties, and its efficacy and toxicity. The determination of remission, relapse, and steroid refractoriness/dependency was guided by the European Crohn's and Colitis Organisation consensus. The pediatric UC activity index had not been used until 2009 in our unit; therefore, scoring was excluded from the evaluation due to missing cases.

Thiopurine was prescribed by a pediatric gastroenterologist after the parents' consent was obtained, according to the local protocol. Azathioprine (AZA) (Immuran, GlaxoSmithKline, Middlesex, UK) was started at a dose of 2-2.5 mg/kg/d at the time of diagnosis or as the maintenance therapy during evaluation for a dose reduction of steroids at 4, 8, or 12 weeks. An active infection, bone marrow suppression, and pre-existing liver disease were accepted as contraindications for TP use.

Forty-eight UC cases were evaluated, and sequential numbers were calculated for those who continued to use AZA at 3, 12, 24, 36, 48, and 60 months. Clinical remission was defined by a decrease in UC symptoms, including a reduction in stool frequency, reduced rectal blood loss, and weight gain. The AZA treatment was withdrawn due to the unresponsiveness and/or development of adverse events (AEs).

The occurrence of new symptoms or signs, the deterioration of pre-existing conditions, and any laboratory abnormalities occurring after the initiation of AZA were considered to be AEs. A complete blood count and renal and liver function tests were recorded at follow-up visits, and symptoms associated with laboratory/imaging reports were registered. Hepatotoxicity, gastrointestinal complaints, myelotoxicity, pancreatitis, fever, malaise, arthralgia, and a variety of other conditions were classified as AEs. Hepatotoxicity was defined as the acceleration of liver enzymes twice or more than the upper normal limit. Nausea and vomiting were accepted as adverse gastrointestinal events. Leukocyte counts lower than 3,500/mm^3, thrombocyte levels under 150,000/mm^3, and/or hemoglobin levels below the age reference limit were defined as myelotoxicity. Clinical pancreatitis was defined based on the classical clinical symptoms associated with elevated acute phase reactants and amylase, and/or lipase levels over two times greater than the upper normal limit. A peripheral or mucosal temperature over 38.5°C and 39°C, respectively, was accepted as fever. An abdominal ultrasound was performed on patients who had miscellaneous complaints during the TP follow-up, and parenchymal changes in the liver and spleen were recorded. The study was prepared in accordance with the Helsinki Declaration.

Statistical analysis

The data are presented descriptively. The Student's t-test and one-way analysis of variance were used where appropriate. A Kaplan-Meier analysis was used to designate TP continuation, and the influence of co-treatments was researched by a Cox-regression analysis. All the statistical analyses were performed using the MedCalcx Software (Ostend, Belgium, https: medcalc.org, 2013) version 12.7.7.

RESULTS

Forty-eight patients with UC who received AZA were included in the study. The mean age was 12.4±3.5 years, and the group included 33 females (68.7%) and 15 males (31.25%). The patient characteristics are shown in Table 1. The follow-up periods of the patients were a minimum of 1 year, a maximum of 10 years, and a median of 6 years. Azathioprine was started at a median of 1 month (0-12 months) and prescribed as part of remission induction in 5 cases (10.4%, 2 left-sided, 3 pancolitis), while it was started after for maintenance (n=43). The response to remission induction was obtained in 40 (93.7%) patients, and calcineurin inhibitors were started in 5 cases. During the follow-up, infliximab was initiated in 8 cases, and only 1 patient underwent colectomy because of recurrent relapses in the follow-up. The relapse rate of patients on AZA appeared in 14 (29.1%) cases at a median time of 13 months (5-26) (Table 1).

The mean duration of AZA treatment was 24 months (5-63). In 34 (85%) of the 40 children, AZA was well tolerated until the last visit. After the first year, 68.5% of the

patients did not have to use steroids or another rescue therapy, along with 58.3% of patients who received AZA for maintenance therapy after the second year. Due to adverse effects, 6 patients could not tolerate treatment.

Table 1. Baseline patient characteristics (n=48)

Sex (male/female)	15/33
Mean age (years)	12.4 (±3.5)
IBD in family (n, %)	5 (10.4)
Symptom (n, %)	
Abdominal pain	4 (8.33)
Diarrhea	4 (8.33)
Bloody defecation	23 (47.9)
All	11 (22.9)
Unknown	6 (12.5)
Location (n, %)	
Left colon	5 (10.4)
Pancolitis	35 (72.9)
Unknown	6 (12.5)
Terminal ileum	2 (4.1)
Remission induction treatment (n, %)	
Systemic steroid+5-ASA	43 (89.6)
Systemic steroid+thiopurine+ASA	5 (10.4)
Response to induction treatment (n, %)	
Full response	33 (68.8)
Partial response	7 (14.6)
No response	8 (16.6)
Rescue therapy (n, %)	
Infliximab	8 (16.6)
Calcineurin inhibitors	5 (10.4)
Relapse rate (n, %)	14 (29.1)

IBD: inflammatory bowel disease; ASA: 5-aminosalicylic acid

Table 2 summarizes the characteristics of 6 patients. Dose reduction (1 mg/kg/d) resulted in the normalization of neutropenia in 2 cases, and AZA was switched to AZA/MP in 2 remaining cases who had gastrointestinal complaints. Mercaptopurine was well tolerated in Case 3, but neutropenia and gastrointestinal disturbance were sustained on MP in Case 4. Concomitant aminosalicylate (n: 24) or biologic agent application (n: 4) was not related to AZA discontinuation (p=0.5).

Laboratory findings at the baseline and last visit are shown in Table 3. No significant difference was observed under AZA treatment. The mean duration of AZA treatment was 24 months (5-63).

DISCUSSION

In the treatment of UC, thiopurines are widely used; however, control data are limited (6,12). Clinical supervision and patient follow-up are necessary to determine the AEs that occur during thiopurine therapy. Regular monitoring of laboratory indices, such as peripheral blood count and pancreatic and liver function tests, can thus be utilized (13,14). Normal follow-ups on laboratory indicators can also be monitored. There is no consensus on monitoring thiopurine activity and the toxicity determinants of the active thiopurine metabolite, and their use is not fully suggested or accepted, depending largely on the local practitioners' and clinicians' choices (15). Thiopurine metabolite monitoring is not available at our center, so laboratory purine markers are absent in the current analyses.

Controlled trials have shown that thiopurine is effective in steroid tapering and maintaining remission in patients with UC (11). Many meta-analyzes have also shown the efficacy of thiopurine for the induction and maintenance of remission in patients with UC (3, 16). Hyams et al. reported 103 patients at a 2-year follow-up after thiopurine initiation, with 51 (50%) having CS-free (corticosteroid-free) inactive disease and 13 (13%) having CS-free

Table 2. Characteristics of patients with side effects due to AZA treatment

Patient	Sex	Age	Diagnosis	AZA Duration (months)	Reason for AZA Discontinuation
1	F	14	UC	30	Leukopenia
2	M	16	UC	10	Neutropenia
3	M	14	UC	7	Vomiting, diarrhea
4	F	3	UC	37	Neutropenia, vomiting, diarrhea
5	F	8	UC	1	Skin rush
6	F	13	UC	15	Vomiting

AZA: azathioprine; M: male; F: female; UC: ulcerative colitis

Table 3. Laboratory test results and their comparison at baseline and follow-up

Parameter	Baseline	Last Visit	p
Hemoglobin (mmol/L)	10.1±1.8	11.7±2.04	0.97
WBC (x10^9/L)	10.4±4.6	7.7±3.4	0.61
PLT (x10^9/L)	355000±133000	468000±158000	0.12
ALT (U/L)	18.9±17.8	15.9±8.4	0.91
AST (U/L)	23.4±14.5	20.3±6.3	0.05
GGT (U/L)	39±122.8	28.6±41.3	0.00
Total bilirubin (mg/dL)	0.49±0.39	0.53±0.29	0.70
Albumin (gr/dL)	3.67±0.69	3.58±0.65	0.96
Sedimentation (mm/hour)	27.6±21.6	26.8±18.2	0.76
CRP (mg/L)	0.8±2.76	0.5±2.1	0.8

WBC: white blood cells; PLT: platelet; ALT: alanine amino transferase; AST: aspartate amino transferase; GGT: gama glutamyl transferase; CRP: C-reactive protein

inactive disease without rescue therapy. Forty-six of these patients were evaluated at 5 years, and 7% of them showed CS-free mild disease without rescue therapy (6).

In the Lev-Tzion's study, at 4 months, 35 (64%) of the 59 evaluable patients were in clinical remission, at 12 months, and 3153% of the 59 patients were clinical remission (12). In our study, the clinical remission rate without a steroid therapy was 68.5% at 12 months and 58.3% at 2 years.

It is potentially helpful to use thiopurine to prevent the AEs of steroids in patients with UC taking steroids for a long time. According to the study by Hyams et al., after the first year, 49% of patients did not need to use steroids, while after the second year, 50% of patients did not need to use steroids (6). According to our study, these rates were 68.5% and 58.3%, respectively. The AEs of thiopurine may lead to treatment cessation. In the study by Satoshi et al., 28.8% of patients were observed to experience AEs, and the treatment was discontinued in 6 patients. These AEs included EBV (Epstein Barr Virus) in 1 patient, vomiting in 1 patient, pancreatitis in 1 patient, leukopenia in 1 patient, and liver disfunction in 2 patients (17).

Chaparro et al. (18) reported findings from a comprehensive and prospective cohort study in Spain, where 67% of 1,026 patients discontinued thiopurine therapy due to AEs, such as nausea, arthralgia, alopecia, abdominal pain, liver and pancreatic toxicity, leucopenia, myelotoxicity, and infection. Thiopurine methyltransferase or thiopurine S-methyltransferase (TPMT) should be measured before the thiopurine therapy is initiated, because severe pancytopenia has been reported in patients with TPMT deficiency (18). It is important to note that the TPMT levels do not predict the majority of myelotoxicity cases, and ongoing hematologic surveillance is very important (19). Reports indicate that 50% to 75% of thiopurine-induced leukopenia cases occur in patients with normal TPMT levels (20, 21). However, we could not measure the TMTP level in our hospital. In our study, an AE was observed in 6 (15%) patients. There were no deaths or malignancies in the patient population during the study period. The AEs in our study included nausea in 2 patients, vomiting, diarrhea, and neutropenia in 2 patients, leukopenia in 1 patient, and skin rash in 1 patient. For these AEs, the medicine doses in 2 patients were decreased, while the AEs of 2 patients resolved spontaneously. In addition, because the AEs continued in 2 patients, the treatment was changed to mercaptopurine.

The present study has several limitations, being conducted on a single-center patient population and having a retrospective design. As a result, long-term observational data show that thiopurine therapy in patients with UC is beneficial in maintaining remission. The patients with UC can be sustained in remission by thiopurine for a long-term surveillance. The security border of thiopurine treatment is related to therapeutic effect, toxicity, and intolerance. A regular follow-up is obligatory to ensure this effect.

Ethics Committee Approval: Ethics committee approval was received for this study from the Local Ethics Committee.

Informed consent: Written informed consent was obtained from the patients' parents who participated in the present study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - F.O., C.E.; Design - F.O., M.K.; Supervision - F.O., G.E., M.K., E.K.T.; Materials - M.K., E.K.T.; Data Collection and/or Processing - M.K., H.H.; Analysis and/or Interpretation - M.K., F.O., H.H., G.E.; Literature Search - F.O., M.K., E.K.T., C.E.; Writing Manuscript - M.K., F.O.; Critical Reviews - F.O., M.K.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

REFERENCES

1. Lee K, Kim Y, Seo G, Kim T, Yang S. Use of Thiopurines in Inflammatory Bowel Disease: A Consensus Statement by the Korean Asso-

ciation for the Study of Intestinal Diseases (KASID). Intest Res 2015; 13: 193-207. [CrossRef]
2. Prefontaine E, Sutherland LR, Macdonald JK, Cepoiu M. Azathioprine or 6-mercaptopurine for maintenance of remission in Crohn's disease. Cochrane Database Syst Rev 2009; 21: CD000067. [CrossRef]
3. Timmer A, McDonald JW, Tsoulis DJ, Macdonald JK. Azathioprine and 6-mercaptopurine for maintenance of remission in ulcerative colitis. Cochrane Database Syst Rev 2012; 12: CD000478. [CrossRef]
4. Takatsu N, Matsui T, Murakami Y, et al. Adverse reactions to azathioprine cannot be predicted by thiopurine S-methyltransferase genotype in Japanese patients with inflammatory bowel disease. J Gastroenterol Hepatol 2009; 24: 1258-64. [CrossRef]
5. Ardizzone S, Maconi G, Russo A, Imbesi V, Colombo E, Bianchi PG. Randomised controlled trial of azathioprine and 5-aminosalicylic acid for treatment of steroid dependent ulcerative colitis. Gut 2006; 55: 47-53. [CrossRef]
6. Hyams JS, Lerer T, Mack D, et al. Outcome following thiopurine use in children with ulcerative colitis: a prospective multicenter registry study. Pediatric Inflammatory Bowel Disease Collaborative Research Group Registry. Am J Gastroenterol 2011; 106: 981-7. [CrossRef]
7. Andrade RJ, Agúndez JA, Lucena MI, Martínez C, Cueto R, García-Martín E. Pharmacogenomics in drug induced liver injury. Curr Drug Metab 2009; 10: 956-70. [CrossRef]
8. Bodelier AG, Masclee AA, Bakker JA, Hameeteman WH, Pierik MJ. Azathioprine induced pneumonitis in a patient with ulcerative colitis. J Crohns Colitis 2009; 3: 309-12. [CrossRef]
9. Ananthakrishnan AN, Attila T, Otterson MF, et al. Severe pulmonary toxicity after azathioprine/6-mercaptopurine initiation for the treatment of inflammatory bowel disease. J Clin Gastroenterol 2007; 41: 682-8. [CrossRef]
10. Nagy F, Molnar T, Makula E, et al. A case of interstitial pneumonitis in a patient with ulcerative colitis treated with azathioprine. World J Gastroenterol 2007; 13: 316-9. [CrossRef]
11. Ledder OD, Lemberg DA, Ooi CY, Day AS. Are thiopurines always contraindicated after thiopurine-induced pancreatitis in inflammatory bowel disease? J Pediatr Gastroenterol Nutr 2013; 57: 583-6. [CrossRef]
12. Lev-Tzion R, Renbaum P, Beeri R, et al. Rac1 Polymorphisms and Thiopurine Efficacy in Children With Inflammatory Bowel Disease. J Pediatr Gastroenterol Nutr 2015; 61: 404-7. [CrossRef]
13. Anastasia Konidari, Wael El Matary. Use of thiopurines in inflammatory bowel disease: Safety issues. World J Gastrointest Pharmacol Ther 2014 May 6; 5: 63-76. [CrossRef]
14. Dewit O, Starkel P, Roblin X. Thiopurine metabolism monitoring: implications in inflammatory bowel diseases. Eur J Clin Invest 2010; 40: 1037-47. [CrossRef]
15. Travis SP, Stange EF, Lémann M, et al. European evidence-based Consensus on the management of ulcerative colitis: Current management. J Crohns Colitis 2008; 2: 24-62. [CrossRef]
16. Khan KJ, Dubinsky MC, Ford AC, Ullman TA, Talley NJ, Moayyedi P. Efficacy of immunosuppressive therapy for inflam¬matory bowel disease: a systematic review and meta-analysis. Am J Gastroenterol 2011; 106: 630-42. [CrossRef]
17. Satoshi Y, Takuya Y, Minoru M, et al. Efficacy and Safety of Long-Term Thiopurine Maintenance Treatment in Japanese Patients With Ulcerative Colitis Intest Res 2015; 13: 250-8.
18. Chaparro M, Ordás I, Cabré E, et al. Safety of thiopurine therapy in inflammatory bowel disease: long-term follow-up study of 3931 patients. Inflamm Bowel Dis 2013; 19: 1404-10. [CrossRef]
19. Gearry R, Barclay M, Burt M, et al. Thiopurine S-methyltransferase (TPMT) genotype does not predict adverse drug reactions to thiopurine drugs in patients with inflammatory bowel disease. Aliment Pharmacol Ther 2003; 18: 395-400. [CrossRef]
20. Colombel J, Ferrari N, Debuysere H, et al. Genotypic analysis of thiopurine S-methyltransferase in patients with Crohn's disease and severe myelosuppression during azathioprine therapy. Gastroenterology 2000; 118: 1025-30. [CrossRef]
21. Ansari A, Hassan C, Duley J, et al. Thiopurine methyltransferase activity and the use of azathioprine in inflammatory bowel disease. Aliment Pharmacol Ther 2002; 16: 1743-50. [CrossRef]