Original Article 10.30477/CJM.2022.328340.1032

Azathioprine Side Effects in Patients with Ocular Manifestations of Behçet's Syndrome

Maryam Masoumi[1*], Seyed Mohammad Hashem Montazeri[2], Fereydoun Davatchi[3,4], Farhad Shahram[3], Massoomeh Akhlaghi[3], Seyedeh Tahereh Faezi[3], Hoda Kavosi[3], Soraya Shadmanfar[3], Majid Alikhani[3], Soroush Moradi[5], Javad Balasi[6], Mohammad Mahdi Lamei Ramandi[6], Alireza Gandomi-Mohammadabadi[6]

1. Clinical Research and Development Center, Shahid Beheshti Hospital, Qom University of Medical Sciences, Qom, Iran.
2. Student Research Committee, Qom University of Medical Sciences, Qom, Iran
3. Behcet's Disease Unit, Rheumatology Research Center, Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran.
4. Behcet's Disease Chair, National Elite Foundation, Tehran, Iran.
5. Tehran University of Medical Sciences, Tehran, Iran.
6. Student Research Committee, School of Medicine, Iran University of Medical Sciences, Tehran, Iran.

ABSTRACT

Introduction: Behçet's syndrome (BS) is a systemic vasculitis characterized by skin involvement, uveitis, and arthritis. Azathioprine is an effective therapy among other immunosuppressive drugs for this disease but there is no clear data about all aspects of its side effects in BS patients with ocular manifestations. we want to determine the prevalence and types of adverse effects related with azathioprine in ocular BS patients. **Methods**: the study is cross-sectional with 165 confirmed diagnosis of BS patients who had ocular involvement. Data were collected retrospectively with medical records of the BS clinic. **Results**: Of 165 enrolled patients, Adverse events of treatment with azathioprine occurred in 11 patients (6.67%). side effects included: elevated of liver enzymes in four patients (2.43%), hypersensitive reaction in 2 patients (1.21%), leukopenia in 2 patients (1.21%), nausea in 1 patient (0.61%), skin tumor in 1 patient (0.61%), and t pancreatitis and hepatitis in one patient (0.61). **Conclusion**: azathioprine reduced the rate of adverse effects and resolution of the ocular manifestations in patients with BS and has few side effects so, it is good choice to treat patients with BS.

Keywords: Azathioprine, Behçet's syndrome, Uveitis, side effects

Recived Date: 09 February 2022
Revised Date: 13 March 2022
Accept Date: 30 March 2022
Published Date: 17 August 2022
Editor: SAA. Safavi-Naini (Conflict of interest: None)
Reviewers: SN. Salehi (Conflict of interest: None), N. Bineshfar (Conflict of Intrests: None)

*Correspondence to: Maryam Masoumi; Clinical Research of Development Center, Shahid Beheshti Hospital, Qom University of Medical Sciences, Qom, Iran.
Email address: M.masoumiy@gmail.com, Mmasoomi@muq.ac.ir
ORCID: 0000-0003-2635-2656

Cite as : Maryam Masoumi, Seyed Mohammad Hashem Montazeri, Fereydoun Davatchi, Farhad Shahram, Massoomeh Akhlaghi, Seyedeh Tahereh Faezi, et al. Azathioprine Side Effects in Patients with Ocular Manifestations of Behçet's Syndrome. Canon Journal of Medicine.2022 June; 3(2):3-8

INTRODUCTION

Behçet's syndrome (BS) is a systemic vasculitis with various manifestations. In addition to the recurrent characteristic skin involvement such as mouth and genital ulcers, this inflammatory disease can also affect other organs such as the eyes ,cardiac and the digestive system.(1, 2) Eye involvement in this disease is in the form of uveitis(3) and retinitis(4), which is seen in about half of patients(5). Pan-uveitis (anterior and posterior uveitis) is due to irreversible changes in the optic disc and retina and can cause permanent blindness in patients along with other ocular manifestations. (3)

Although drug treatment for Behcet's syndrome major complications varies from person to person depending on the severity of the disease, the type of manifestations, and the organ involvement, conventional immunosuppressant drugs and biological compounds are generally used(6). The treatment of cutaneous and articular manifestations is largely evidence-based but clinical experience and evidence from simple observational studies are involved in the choice of treatment for ocular and neuropulmonary manifestations. (7)

Azathioprine (AZA) is a known immunosuppressant that is involved in the treatment of many autoimmune and rheumatic diseases, including Behcet's syndrome with ocular involvement.(8) Common side effects include fever, myelosuppression, and nausea. In addition, several reports have been published to slightly increase the risk of lymphoma in patients treated with AZA. (9, 10).

Nevertheless, few studies have been performed on the advantages and disadvantages of AZA in the treatment of ocular's visual manifestations. This study tries to evaluate the side effects of azathioprine more accurately so that a better decision can be made about whether or not to use it in the treatment of patients.

The present cross-sectional study was designed to evaluate the safety of using this drug by evaluating the frequency of clinical side effects of AZA among BS patients with ocular manifestations.

MATERIAL AND METHODS

Study design

In this study, a diagram of patients with confirmed BS diagno-

sis who were followed up in Behcet Syndrome Clinic, Rheumatology Research Center, Shariati Hospital, Tehran, Iran, between 2015 and 2017, was performed. The medical records of 165 patients with ocular manifestations were retrospectively included in this study. According to International Standards for Behcet's Disease (ICBD), they definitely had the syndrome. Inclusion criteria included history of AZA administration during ocular involvement in BS.

Azathioprine dose, duration of drug use, previous history of drug use (such as immunosuppressants, etc.) were recorded. Patients were monitored for AZA side effects every month until the ocular status of the disease stabilized, after which the follow-up period was increased to three months and the follow-up was terminated with discontinuation of the drug. There was no harm in follow-up and the drug was discontinued at the time of side effects.

An ophthalmologist examined the eyes at each visit. The ophthalmologist diagnosed inflammation in the anterior, posterior, or retina.

The rheumatologist also assessed the extent of vasculitis. The classification of Douglas A Jabs et al. (10) was used to determine the pattern of uveitis. The anterior uveitis affects the iris and the ciliary body, and the posterior uveitis causes retinal and choroidal damage (11).

Eye involvement

Management of Behjat patients' uveitis requires teamwork with ophthalmologists. These patients should be on a medication regimen with AZA (IB), cyclosporine-A (IB), or biological therapies. Patients presenting with an early period or recurrent acute visual-threatening uveitis should be treated with high-dose corticosteroids, infliximab, or interferon alfa. Vitamin glucocorticoid injection is also a good treatment option in advanced cases Isolated anterior uveitis.

Systemic immunosuppressants can be considered for those with poor prognostic factors such as young age, male gender, and early disease onset.

Adverse events

A detailed medical record was recorded for each patient treated with AZA, describing side effects including nausea, vomiting, fever, infection, decreased blood counts, liver toxicity, and malignancies. The reason for each dose or change was also recorded. Leukopenia was considered moderate (3.0-4.0 × 106 / ml) or severe (less than 3.0 × 106 / ml). Abnormal liver enzymes were considered three times the normal range of aspartate aminotransferase (AST) and alanine aminotransferase (ALT). Note that most patients consumed only AZA during treatment and the side effects created for registration and study were first confirmed by a specialist for each patient.

Aims

Evaluation of the frequency of AZA complications in patients with BS with ocular presentation.

Ethical issues

The Medical Ethics Committee of Qom University of Medical Sciences and the medical ethics officials of the clinic approved and supervised all stages of the study according to the Helsinki ethics criteria.

Statistical analysis

Data were entered into statistical software SPSS 23(SPSS Inc, Chicago, IL) and analyzed using descriptive statistics. Qualitative data were expressed as frequencies(percentages), and quantitative data were described with statistics such as the mean and the standard deviation. Finally, the results were presented with the aid of descriptive graphs and tables.

RESULTS

A total of 165 patients with ocular involvement in BS were analyzed. Their demographic characteristics, are listed in Table 1.

Mean age at the onset of BS was 31.81 ± 7.92 years and Mean age at the onset of ocular involvement was 32.32 ± 7.96 (7-55) years. mean duration disease was 10.64 ± 7.18 (1-35) years. mean initial dose of AZA was 150 mg once daily, which corresponded to 2 mg (or slightly higher) per kilogram body weight. During the treatment period, the highest dose of AZA was 250 mg/day, which corresponded to 3 mg/kg/d. The mean duration of treatment with AZA was 76.13 months.

In our study, all 165 patients received prednisolone between 10 mg/d and 0.5 mg/kg. Cyclophosphamide (CP) was used in 101 patients at a dose of 1 g per month, and colchicine was used in 56 patients at a daily dose of 0.5-2 mg. In addition, methotrexate (MTX) was used in 50 patients at a dose of 15-25 mg per week. Cyclosporine (CsA) was used in 30 patients at a daily dose of 3-5 mg/kg. Infliximab was used in 12 patients at a daily dose of 3-5 mg/kg, and rituximab was used in two patients at a dose of 1 g on days 0 and 15.

Clinical manifestations in patients with Behçet's syndrome

Of the 165 patients with ocular involvement in BS, 103 (62.43%) were male and 62 (37.57%) were female. The male/female ratio was 1.66. Recurrent oral aphthous ulceration was the initial manifestation of the disease in 163 patients (98.80%), accompanied by genital ulceration (bipolar aphthous ulcers) in 104 patients (63%), whereas 2 patients did not have any oral or genital aphthous ulcers. Skin aphthous lesions were present in 4 patients (2.42%), a positive pathergy test was recorded in 72 patients (43.64%), pseudofolliculitis occurred in 39 patients (23.64%), and erythema nodosum was present in 26 patients (15.76%).

Table 1. Characteristics of patients with ocular BS at initiation of azathioprine therapy

Parameters		Value
Age (years)		42.30 ± 10.49 (range 21-68)
Age at the onset of BS (years)		31.81 ± 7.92
Age at the onset of ocular involvement (years)		32.32 ± 7.96 (range 7-55)
Gender (male/female)		103/62
Duration of disease (years)		10.64 ± 7.18 (range 1-35)
Concomitant drugs	Prednisolone	165 (100%)
	Cyclophosphamide	101 (61.2%)
	Colchicine	56 (33.9%)
	Methotrexate	50 (30.3%)
	Cyclosporine	30 (18.2%)
	Infliximab	12 (7.3%)
	Rituximab	2 (1.2%)

Table 2. Clinical manifestations of BS

Symptom		Frequency No. (%)
Mucocutaneous involvement	Oral aphthous ulcers	163 (98.80%)
	Genital aphthous ulcers	104 (63.00%)
	Skin aphthous ulcers	4 (2.420%)
	Positive pathergy test	72 (43.64%)
	Pseudofolliculitis	39 (23.64%)
	Erythema nodosum	26 (15.76%)
Vascular involvement	Superficial thrombosis	5 (3.00%)
	Deep vein thrombosis	7 (4.24%)
	Superior vena cava syndrome	1 (0.61%)
	Sagittal sinus thrombosis	1 (0.61%)
	Aneurism of carotid artery	1 (0.61%)
	Aortic aneurysm	1 (0.61%)
Musculoskeletal involvement	Arthritis	18 (10.91%)
	Arthralgia	1 (0.61%)
	Ankylosing spondylitis	2 (1.21%)
	Avascular necrosis of femoral head	1 (0.61%)
Epididymo-orchitis		6 (3.64%)
CNS involvement		6 (3.64%)
Renal involvement (glomerulonephritis)		1 (0.61%)
Concomitant disease	Crohn disease	1 (0.61%)
	Multiple sclerosis	1 (0.61%)
Posterior uveitis		163 (98.80%)
Anterior uveitis		102 (61.82%)
Retinal vasculitis		157 (95.15%)

Vascular involvement was present in 14 patients (8.49%). Superficial thrombosis was observed in five patients (3.0%), and seven patients had deep vein thrombosis (4.24%). One patient had superior vena cava syndrome (0.61%), one patient had sagittal sinus thrombosis (0.61%), 1 patient had aneurism of the carotid artery (0.61%), and one patient had an aortic aneurysm (0.61%).

Musculoskeletal involvement was seen in 22 patients (13.34%): 18 patients had arthritis (10.91%), one patient had avascular necrosis of the femoral head (0.61%), 2 patients had ankylosing spondylitis (AS) (1.21%), and one patient had arthralgia (0.61%). Other less frequently detected manifestations were CNS involvement in 6 patients (3.64%), epididymo-orchitis in 6 patients (3.64%), renal involvement characterized by glomerulonephritis in 1 patient (0.61%), Crohn disease in one patient (0.61%), and multiple sclerosis (MS) in one patient (0.61%). Table 2 summarizes the frequencies of clinical manifestations in our series.

Ocular manifestations in patients with Behçet's syndrome

Ophthalmic manifestations in patients with BS are noted in Table 2. Of the 165 patients with ocular BS, 163 had posterior uveitis (98.80%), 102 had anterior uveitis (61.82%), and 157 had retinal vasculitis (95.15%).

Of eight patients who had posterior uveitis without retinal vasculitis, 6 had only posterior uveitis, and 2 patients had both posterior and anterior uveitis. In 3 patients, AZA was prescribed after treatment with MTX failed because of resistance. In 1 patient, AST and ALT elevation (three times as much as the normal value) was caused by MTX toxicity so that AZA was administered. In 3 patients with incomplete response to MTX, AZA was added to MTX. Two of these 3 patients also received colchicine together with AZA and MTX. The added dose of AZA is higher in resistant patient (250mg/day) than in patient with incomplete response (150mg/day).

All adverse events induced by azathioprine

In 11 patients (6.67%), AZA therapy was discontinued or tapered due to adverse events. To diagnose specific adverse events of AZA, MTX and cyclophosphamide discontinued for a period of 1 month and found that these 11 patients still had adverse events, so we attributed all adverse events to AZA. The adverse events leading to AZA discontinuation are shown in Table 3. One patient developed basal cell carcinoma (BCC) after 5 years of AZA use. Two patients were hospitalized because of high fever(Body temperature above 38.5°) and chills, nausea, arthralgia, and increased serum level of liver enzymes, which resolved after drug discontinuation. In 1 patient, adverse events after the start of AZA treatment led to hospitalization due to concomitant pancreatitis and hepatitis. Another 2 patients treated with a dose of 150 mg/d (2 mg/kg/d) had severe leukopenia, which resolved after temporary drug discontinuation.

The dosage of AZA was reduced in 4 patients due to elevated values of liver function tests (LFT). In 4 patients treated with a dose of 150-250 mg/d (2-3 mg/kg), LFT values increased more than or less than three times as much as the upper limit of normal (ULN), so their dosage was reduced to 50-150 mg/d (0.5-1.5 mg/kg), after which liver enzymes values returned to normal (Table 3).

In 1 patient LFT increased more than 3-fold the ULN after treatment for 6 months with 200 mg/d AZA. The dosage was changed to 150 mg/d, after which the patient recovered. One patient who used 150 mg/d AZA had increased LFT less than 3-fold the ULN after 3 months. The dosage was reduced to 100 mg/d and the patient recovered. In another patient treated with 250 mg/d AZA for 28 months, LFT increased less than 3-fold ULN. The dosage was change to 150 mg/d, and again, the patient recovered. In 1 patient treated with 200 mg/d for 3 months, LFT increased more than 3-fold the ULN and the patient reported nausea. Therefore the dose was reduced to 100 mg/d, and the patient recovered (Table 3).

Hepatitis and pancreatitis (LFT > 3-fold the ULN, alkaline phosphatase (ALP) > 3-fold the ULN, and increased amylase up to 302) were side effects seen in 1 patient after treatment with 150 mg/d for 3 months. The patient recovered after AZA was discontinued.

In 1 patient treated with 100 mg/d AZA, nausea and vomiting appeared after 3 years; these side effects resolved after the drug was discontinued (Table 3).

Transient severe leukopenia was recorded in 2 patients

Table 3. Side effects leading to drug discontinuation or dose change in 11 patients with ocular BS

Case	Initial dose (mg/kg/d)	Time to side effect (m)	Character of side effect	Final dose	Plan	Concomitant drugs (except prednisolone)
1	200 (2.5 mg/kg/d)	6	Increased AST/ALT (more than 3 fold ULN)	(mg/kg/d)	Dose reduction	Cyclophosphamide
2	150 (2 mg/kg/d)	3	Increased AST/ALT (less than 3 fold ULN)	150 (2 mg/kg/d)	Dose reduction	Cyclophosphamide, methotrexate
3	150 (2 mg/kg/d)	1	Leukopenia	100 (1.5 mg/kg/d)	Discontinuation, re-administration	Cyclophosphamide
4	150 (2 mg/kg/d)	3	Pancreatitis and hepatitis	150 (2 mg/kg/d)	Discontinuation	Cyclophosphamide, methotrexate, colchicine
5	150 (2 mg/kg/d)	1 week	High fever and chills, nausea, arthralgia	0	Discontinuation	Cyclophosphamide
6	150 (2 mg/kg/d)	60	Basal cell carcinoma	0	Discontinuation	Cyclophosphamide
7	150 (2 mg/kg/d)	3	Leukopenia	0	Discontinuation, re-administration	Cyclophosphamide, methotrexate, infliximab
8	50 (0.5 mg/kg/d)	Appeared after the first dose	High fever and chills, nausea, arthralgia	150 (2 mg/kg/d)	Discontinuation	-
9	100 (2 mg/kg/d)	36	GI discomfort (nausea and vomiting)	0	Discontinuation	-
10	200 (2.5 mg/kg/d)	3	Increased AST/ALT (more than 3 fold ULN) and nausea	0	Dose reduction	-
11	250	28	Increased AST/ALT (less than 3 fold ULN)	100 (1.5 mg/kg/d)	Dose reduction	Cyclophosphamide, colchicine

who received 150 mg/d (2 mg/kg) AZA, one in the first month of treatment (WBC count 2300) and one after 3 months (WBC count 1900). They both recovered after 1 month without any change in treatment (Table 3).

In 2 patients AZA was discontinued because of allergy. In 1 patients who was prescribed 150 mg/d (2 mg/kg/d), fever, arthralgia and skin involvement (redness) appeared after 1 week, along with increased LFT (more than 2-fold the ULN). This patient recovered after the drug was discontinued. In the other patient, the initial dose of 50 mg/d (0.5 mg/kg/d) was associated with allergic reactions (skin redness) and the drug was discontinued.

In 1 patient who received 150 mg/d (2 mg/kg/d) AZA for 5 years, the patient stopped the drug due to recovery from ocular disease for 1 year. However, this patient later developed BCC (Table 3).

DISCUSSION

Evidence of the effectiveness of AZA in the treatment of ocular manifestations in BS is increasing and its use is common. However, its side effects have overshadowed the decision to use it extensively (10). In previous AZA trials, discontinuation due to side effects was significant compared with the placebo group.

Azathioprine is used as the first choice according to most studies in ocular BS, with a dosage of 2.5 mg/kg body weight (11). At this study, the usual starting dose for AZA in practice is 2-3 mg / kg / d. Despite an adequate initial dose, 11 patients (6.67%) had AZA-related side effects. The drug was discontinued in 5 patients whose side effects resolved after reducing or discontinuing the drug. The findings of this study showed fewer side effects than AZA. This may be due to a minimal dose.

Although some studies find that treating ocular Behcet with a combination of immunosuppressants and steroids, contrary to our results, is complicated, but they are consistent with us in the low side effects of azathioprine (compared to other drugs) and its effectiveness.(12)

A demographic study close to our study in which AZA was used for non-infectious ocular inflammation showed that AZA was a good treatment. However, no response to treatment and complications were reported at a rate of 0.16 per person per year. A previous study reported limiting but modifiable side effects in a quarter of patients (13), a much lower number in our study.

the adverse events demonstrated before are gastrointestinal upset, myelosuppression, Liver enzyme level defect, infection, and allergy (13). Blood profiles were reviewed in all patients, and Blood cell count indices monitored before and after the therapy. severe leukopenia in 2 patients (WBC count < 3 × 106/ml) was observed, the numbers of WBC was corrected after AZA was discontinued in 2 patients.

We don't have patient with thrombocytopenia but Colombel and colleagues (14) found myelosuppression during AZA therapy in 27% of patients who had mutation for the thiopurine methyl-transferase (TPMT) gene.

It was not possible for us to test for TPMT activity, which inactivates thiopurines such as AZA, before starting treatment with AZA(15). However, periodic laboratory tests can be used for patients with blood or liver disorders. However, the role of

TPMT in other side effects is unknown a (16).

The role of thiopurines in the development of lymphoma in patients with rheumatoid arthritis, IBD and solid organ transplantation has been proposed and confirmed in previous studies (17, 18)However, Lewis et al. Argue that the benefits of AZA outweigh the potential risk of malignancy(19). In the present study, 1 patient developed BCC. The role of this drug in neoplasms is debated due to differences in therapeutic doses of IBD or other diseases (20)

Fever, arthralgias, and myalgias were reported in heart transplanted patients and rheumatoid arthritisTreated with AZA (21-23). 2 cases of our patients have high fever, nausea, and arthralgia after AZA administration. According to a hypothesis proposed by Korteliz et al. (4), some drugs may interfere with AZA for example, Corticosteroids decrease allergic adverse effects.

Failure to evaluate the effect of interaction between different drugs on the development of AZA side effects and possible bias in observations. Designing more detailed and comparative studies between different and large groups of patients taking azathioprine can be helpful.

CONCLUSION

The data from our study show that AZA is acceptable in most patients. The side effects of this drug often improve with discontinuation. All AZA side effects occurred in only 11 of 165 patients (6.67%). These side effects included increased AST / ALT, pancreatitis, hepatitis, fever and chills, leukopenia, arthralgia, and gastrointestinal upset (nausea and vomiting). Basal cell carcinoma. Our experience suggests that AZA is safe for patients with BS with ocular clinical presentation and for efficient management of retinal vasculitis, and that appropriate administration of AZA can significantly reduce complications in patients.

ETHICAL CONSIDERATION

All stages of the study were reviewed and approved by the Ethics Committee of Qom University of Medical Sciences based on the Helsinki protocol. In addition, all patients participating in the study were given informed consent and permission to access medical records in writing

CONFLICT OF INTRESETS

There are no conflicts of interest in terms of the present manuscript.

AVAILABILITY OF DATA AND MATERIALS

The datasets used and analyzed in the current study are available from the corresponding author on reasonable request.

ABBREVATIONS

BS= Behçet's syndrome, AZA=Azathioprine, ICBD= International Criteria for Behcet's Disease, EULAR=The European League against Rheumatism, , MTX=methotrexate, CsA=cyclosporine, BCC=basal cell carcinoma, LFT=liver function tests, AST=aspartate aminotransferase, ALT=alanine aminotransferase, ULN=upper limit of normal, IBD=Inflammatory bowel disease

REFRENCES

1. Hatemi G, Seyahi E, Fresko I, Talarico R, Hamuryudan V. One year in review 2020: Behçet's syndrome. Clin Exp Rheumatol. 2020;38 Suppl 127(5):3-10.
2. Soraya S, Maryam M, Fereydoun D, Massoomeh A, Hoda K, Javad B, et al. Cardiac Manifestations in Iranian Patients with Behçet's Disease. The Journal of Tehran University Heart Center. 2021;16(3).
3. Kitaichi N, Miyazaki A, Iwata D, Ohno S, Stanford M, Chams H. Ocular features of Behcet's disease: An international collaborative study. The British journal of ophthalmology. 2007;91:1579-82.
4. Korelitz BI. Steroids may prevent leukopenia, hastening response to IV azathioprine in treatment of Crohn's disease. Gastroenterology. 2000;118(6):1281.
5. Benezra D, Nussenblatt R. Ocular manifestations of Behçet's disease. Journal of Oral Pathology & Medicine. 1978;7(6):431-5.
6. Alibaz-Oner F, Direskeneli H. Advances in the Treatment of Behcet's Disease. Curr Rheumatol Rep. 2021;23(6):47-.
7. Kinlen LJ. Incidence of cancer in rheumatoid arthritis and other disorders after immunosuppressive treatment. Am J Med. 1985;78(1a):44-9.
8. Hatemi G, Christensen R, Bang D, Bodaghi B, Celik AF, Fortune F, et al. 2018 update of the EULAR recommendations for the management of Behçet's syndrome. Annals of the Rheumatic Diseases. 2018;77(6):808-18.
9. Connell WR, Kamm MA, Ritchie JK, Lennard-Jones JE. Bone marrow toxicity caused by azathioprine in inflammatory bowel disease: 27 years of experience. Gut. 1993;34(8):1081-5.
10. Dean L. Azathioprine Therapy and TPMT and NUDT15 Genotype. In: Pratt VM, Scott SA, Pirmohamed M, Esquivel B, Kane MS, Kattman BL, et al., editors. Medical Genetics Summaries. Bethesda (MD): National Center for Biotechnology Information (US); 2012.
11. Saadoun D, Wechsler B, Terrada C, Hajage D, Le Thi Huong D, Resche-Rigon M, et al. Azathioprine in severe uveitis of Behçet's disease. Arthritis care & research. 2010;62(12):1733-8.
12. Zhao M, Wang H, Jiao X, Wei WB. [Clinical observation of 85 patients with Behçet's uveitis treated with immunosuppressive agents combined with steroids]. Zhonghua Yan Ke Za Zhi. 2013;49(3):202-6.
13. Pasadhika S, Kempen JH, Newcomb CW, Liesegang TL, Pujari SS, Rosenbaum JT, et al. Azathioprine for ocular inflammatory diseases. American journal of ophthalmology. 2009;148(4):500-9.e2.
14. Colombel JF, Ferrari N, Debuysere H, Marteau P, Gendre JP, Bonaz B, et al. Genotypic analysis of thiopurine S-methyltransferase in patients with Crohn's disease and severe myelosuppression during azathioprine therapy. Gastroenterology. 2000;118(6):1025-30.
15. de Jong DJ, Goullet M, Naber TH. Side effects of azathioprine in patients with Crohn's disease. European journal of gastroenterology & hepatology. 2004;16(2):207-12.
16. Smith JL, Wilkinson AH, Hunsicker LG, Tobacman J, Kapelanski DP, Johnson M, et al. Increased frequency of posttransplant lymphomas in patients treated with cyclosporin, azathioprine, and prednisone. Transplantation proceedings. 1989;21(1 Pt 3):3199-200.
17. Asten P, Barrett J, Symmons D. Risk of developing certain malignancies is related to duration of immunosuppressive drug exposure in patients with rheumatic diseases. J Rheumatol. 1999;26(8):1705-14.
18. Hricik DE, Mayes JT, Schulak JA. Independent effects of cyclosporine and prednisone on posttransplant hypercholesterolemia. Am J Kidney Dis. 1991;18(3):353-8.
19. Lewis JD, Schwartz JS, Lichtenstein GR. Azathioprine for maintenance of remission in Crohn's disease: benefits outweigh the risk of lymphoma. Gastroenterology. 2000;118(6):1018-24.
20. O'Connor A, Qasim A, O'Moráin CA. The long-term risk of continuous immunosuppression using thioguanides in inflammatory bowel disease. Ther Adv Chronic Dis. 2010;1(1):7-16.
21. Saway PA, Heck LW, Bonner JR, Kirklin JK. Azathioprine hypersensitivity. Case report and review of the literature. Am J Med. 1988;84(5):960-4.
22. KNOWLES SR, GUTPTA AK, SHEAR NH, SAUDER D. Azathioprine hypersensitivity-like reations–a case report and a review of the literature. Clinical and Experimental Dermatology. 1995;20(4):353-6.
23. Jeurissen ME, Boerbooms AM, van de Putte LB, Kruijsen MW. Azathioprine induced fever, chills, rash, and hepatotoxicity in rheumatoid arthritis. Ann Rheum Dis. 1990;49(1):25-7.

Author Contribution: SS, MM, FD, FS, MA, TF, and HK conceived and planned the visits. SS, MM, and FD. carried out the physical examinations. SS and MM planned and carried out the laboratory tests. FD, FS, TF, HK, MA , SmhM. contributed to the analysis of the results. SS, MM, SmhM ,TF, HK, MA, and FD contributed to the interpretation of the results.
MM , SmhM ,SM, JB took the lead in writing the manuscript.MM and SmhM

edited all manuscript. All authors provided critical feedback and helped shape the research, analysis and manuscript. All authors have read and approved the manuscript.

Funding statement: This research has received no funding support.

Acknowledgements: Thank K. Shashok (Author aide in the Eastern Mediterranean) for improving the use of English in the manuscript.Preprint was previously allowed to be published in a journal, which will be resubmitted for publication due to their reluctance and after modification, updating and extensive changes. Preprint link: https://doi.org/10.21203/rs.3.rs-133649/v1