Side Effects of Azathioprine in Patients with Ocular Behçet's disease

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Abstract

Background:

Behçet's disease is an autoimmune, rare, multi-system vasculitis characterized by recurrent oral and genital ulcers, uveitis, skin lesions, and arthritis. Azathioprine has been well established as an effective therapy among other immunosuppressive drugs; however, concerns remain about the safety of azathioprine. This study is conducted to determine various types and prevalence of adverse effects of azathioprine in patients with ocular Behçet's.

Methods:

We carried out a cross-sectional study on 165 patients with confirmed diagnosis of Behçet's who suffered from ocular involvement. Data concerning the different episodes of the disease, including severity, recurrence, relapse, recovery and flare up of Behçet's disease, were collected retrospectively, as well as the azathioprine dosage and duration of consumption.

Results:

Of 165 enrolled patients, 103 patients (62.43%) were male and 62 patients (37.57%) were female. Adverse events of treatment with azathioprine occurred in 11 patients (6.67%). Side effects occurred in 11 patients (6.67%) taking azathioprine. These side effects included elevation of liver enzyme in 4 patients (2.43%), hypersensitivity 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 concomitant pancreatitis and hepatitis in 1 patient (0.61%). Six of these cases discontinued and five of them tapered the dose. In addition, we observed severe leukopenia in two patients.

Conclusion:

Administration of azathioprine, with due attention to the signs, symptoms, and severity of the disease, results in a reduced rate of adverse effects, and resolving of the ocular involvement in Behçet's disease patients.

Background:

Behçet's disease (BD) is an autoimmune, rare, vasculitis, which invades several organs, and is characterized by recurrent oral and genital ulcers, skin lesions, arthritis, thrombophlebitis, and uveitis [1]. The underlying pathology is vasculitis due to viral or immunologic causes. Ocular involvement, especially panuveitis (anterior and posterior uveitis), is a result of irreversible, progressive, ischemic changes in the

retina and optic disc [2]. Approximately half the patients present eye disease as an indolent anterior and posterior uveitis [2] and retinitis [3] that can lead to blindness [4].

The treatment approach depends on the individual patient, the severity of the disease, and major organ involvement. Patients will receive corticosteroid therapy or cytotoxic drugs, depending on the severity of the disease, as controlled trials demonstrated the efficacy of immunosuppressive therapy in the treatment of BD [5]. Although instructions regarding the mucosal, dermal, and arthritic manifestations are mainly evidence-based, decisions on the treatment of ophthalmic, vascular, and neurological signs and symptoms are made by experience-based clinical decisions or evidence from simple observational studies.

Among numerous immunosuppressants, azathioprine (AZA) is well-established medications that play a useful role in the treatment of the various autoimmune diseases, and recent studies have confirmed its efficacy in patients with BD, particularly in individuals suffering ocular pathology. Despite its advantages, the safety of AZA is still a topic of debate among clinicians regarding its adverse effects. The most common side effects are nausea, fever, and bone marrow suppression. Besides, few studies in the literature have revealed a slightly increased risk of neoplasia in patients treated with AZA [7]. Nevertheless, there are few studies to evaluate the advantages and disadvantages of the AZA prescription in patients who suffer ocular manifestation of the BD, to assess the benefits of the drug, in comparison to its adverse outcomes and effects.

With due attention to the facts mentioned earlier, the AZA administration with ignoring its side effects might be hazardous. On this basis, in the present study, we aimed to run a cross-sectional study, to investigate the frequency of clinical side effects of AZA in Behçet's patients with ocular involvement, considering different consumption dosages and severity of the ocular involvement.

Methods:

Ethics and registration:

The study protocol has been registered with Tehran University of Medical Sciences' Ethics Committee. Every step was implemented under the supervision of Tehran University of Medical Sciences' Research Committee.

Patients:

We performed a chart review of patients with a confirmed diagnosis of BD, visiting the outpatient clinic of Behçet's disease, Rheumatology Research Center, Shariati Hospital, Tehran, Iran, between 2015 and 2017. Of these cases, 165 patients who had ocular manifestations of the disease, enrolled in the current study. All patients were examined and diagnosed by a team of BD experts. All patients with the history of AZA prescription during ocular involvement in BD were eligible for the study. Data were collected retrospectively from the medical records. Data concerning the different episodes of the disease, including

severity, recurrence, relapse, recovery and flare-up of BD, were collected, as well as the Azathioprine consumption dosage, duration of the prescription, previous history of medication consumption (such as immunosuppressives or corticosteroids), and adverse effects after the AZA using.

Further, all patients were followed up during their treatment with AZA, and the follow up was ended after drug discontinuation.

Adverse effects:

A record was maintained for every patient treated with AZA, detailing side effects of the drug, such as fever, nausea, vomiting, infection, leukopenia, thrombocytopenia, anemia, fever, hepatotoxicity, and skin cancers. Besides, any other reasons for terminating or adjusting the dose of the drug were documented. Leukopenia is considered less than 4000 WBC. In this study, Leukopenia is considered as moderate (3.0–4.0 * 106/ml) or severe (less than 3.0 * 106/ml). Altered liver enzymes in this study are defined as more than two levels higher from normal ranges for Aspartate aminotransferase (AST) and alanine aminotransferase (ALT).

Statistical analysis:

The student T-test used for comparing quantitative variables between groups and, the chi-square test was used for comparing two qualitative variables in each time and Mann Whitney U test for comparing dependent variables between different times. The level of significance was set at 0.05, and all results were expressed by frequency (percent) for qualitative variables and mean ± SE for quantitative variables. All data were analyzed using SPSS version 23. Software (SPSS Inc., Chicago, IL).

Results:

Patients:

Altogether 165 patients were analyzed due to the diagnosis of ocular Behçet's. Patients' demographic characteristics, including age, age of disease onset, and concomitant administered medications are listed in Table 1. Age at the onset of BD was 31.81 ± 7.92 years and the duration of BD was 10.64 ± 7.18 (1–35) years. Age at the onset of ocular involvement was 32.32 ± 7.96 (7–55) years. The mean initial dose of AZA was 150 mg once daily, which corresponds to 2 mg (or a little superior) per kilogram body weight. During the treatment period, the highest dose of AZA was 250 mg/day, which corresponds to 3 mg/kg/d. The mean duration of treatment with AZA was 76.13 months.

In our study, all 165 patients got prednisolone in a different dose between 10 mg/d to 0.5 mg/kg according to the severity of the ocular disease.

Cyclophosphamide (PCP) was used in 101 patients in a dose of 1 g per month, and Colchicine was used in 56 patients in a daily dose of 0.5-2 mg. Also, methotrexate (MTX) was used in 50 patients in a dose of 15–25 mg per week, cyclosporine (CsA) was used in 30 patients in a daily dose of 3–5 mg/kg, infliximab

was used in 12 patients in a daily dose of 3–5 mg/kg and rituximab was used in 2 patients in a dose of 1 g in days of 0 and 15.

Clinical manifestations of Behçet's patients:

Of the 165 ocular Behçet's patients, 103 (62.43%) patients were male, and 62 (37.57%) patients were female. The male/female ratio was 1.66. All of the patients had mucocutaneous lesions. Recurrent oral aphthous ulceration was the initial manifestation of the disease in 163 patients (98.80%, 95% CI: ± 13.4) accompanied by genital ulceration (Bipolar aphthous) in 104 patients (63%, 95% CI: ± 48.4); while two patients did not show any oral or genital aphthous. Skin aphthous in 4 patients (2.42%, 95% CI: ± 18.70), positive pathergy test in 72 patients (43.64%, 95% CI: ± 50), pseudofolliculitis in 39 patients (23.64%, 95% CI: ± 42.2) and erythema nodosum in 26 patients (15.76%, 95% CI: ± 32) were present.

Vascular involvement was present in 14 patients (8.49%, 95% CI: ± 9.1). Superficial thrombosis was observed in 5 patients (3.0%, 95% CI: ± 15.40). 7 patients had deep vein thrombosis (4.24%, 95% CI: ± 20.2). 1 patient had superior vena cava syndrome (0.61%, 95% CI: ± 7.8), 1 patient had sagittal sinus thrombosis (0.61%, 95% CI: ± 7.8), 1 patient had superior vena cava syndrome (0.61%, 95% CI: ± 7.8), 1 patient had aneurism of the carotid artery (0.61%, 95% CI: ± 7.8) and 1 patient had an aortic aneurysm (0.61%, 95% CI: ± 7.8).

Musculoskeletal involvement was seen in 22 patients (13.34%, 95% CI: ± 12.7). 18 patients had arthritis (10.91%, 95% CI: ± 31.3), 1 patient had avascular necrosis of femoral head (0.61%, 95% CI: ± 7.8), Ankylosing spondylitis (AS) in 2 patients (1.21%, 95% CI: ± 10.9) and arthralgia in 1 patient (0.61%, 95% CI: ± 7.8). Other manifestations, less frequently detected, were Central Nervous System involvement in 6 patients (3.64%, 95% CI: ± 18.7), epididymo- orchitis in 6 patients (3.64%, 95% CI: ± 18.7), renal involvement characterized by glomerulonephritis in 1 patient (0.61%, 95% CI: ± 7.8), Crohn disease in 1 patient (0.61%, 95% CI: ± 7.8), Multiple sclerosis (MS) in 1 patient (0.61%, 95% CI: ± 7.8). Table 2 describes the frequencies of clinical manifestations in our series.

Ocular manifestations of Behçet's patients:

The detailed BD manifestations in patients are summarized in Table 2, as well as ophthalmic manifestations. Of the 165 patients with ocular Behçet's, 163 had posterior uveitis (98.80%, 95% CI: ± 13.4), 102 had anterior uveitis (61.82%, 95% CI: ± 48.80) and 157 had retinal vasculitis (95.15%, 95% CI: ± 25.0) (Table 2).

Of eight patients suffering posterior uveitis without retinal vasculitis, six patients had only posterior uveitis, and two patients had both posterior uveitis and anterior uveitis. In three patients, AZA prescribed due to resistance to MTX after MTX was discontinued. In a patient, AZA administered due to Increased AST/ALT (more than two levels from normal value), followed by the toxicity of MTX. In three patients with incomplete response to MTX, AZA was added to MTX. Two of these three patients also got Colchicine with AZA + MTX).

All adverse effects induced by azathioprine:

In 11 out of 165 patients (6.67%), AZA therapy was discontinued or tapered prematurely due to adverse effects. The adverse effects leading to AZA discontinuation are shown in Table 3. One patient developed basal cell carcinoma (BCC) five years after initiation of the drug. Two patients were hospitalized because of high fever and chills, nausea, arthralgia, and increased serum level of liver enzymes which resolved after drug discontinuation. In one patient, adverse effects after the onset of AZA led to hospitalization due to concomitant pancreatitis and hepatitis. Another two patients with 150 mg/d (2 mg/kg/d) dosage of AZA had severe leukopenia, which resolved after the temporary drug discontinuation.

The dosage of AZA was reduced in 4 patients due to increased values of liver function tests (LFT). In four patients we prescribed with 150–250 mg/d (2–3 mg/kg) that make increase the level of LFT (more or less than 2-times upper limit standard) so we change the dosage to 150 – 50 mg/d (0.5–1.5 mg/kg) that they recovered, and the liver enzymes became normal as below. (Table 3)

In one patient after 200 mg/d for six months had increased in LFT more than 2-time ULN that change to 150 mg/d was recovered. In one patient after 150 mg/d for three months had increased in LFT less than 2-time ULN that change to 100 mg/d was recovered. In one patient after 250 mg/d for 28 months had increased in LFT less than 2-time ULN that change to 150 mg/d was recovered. In one patient after 200 mg/d for six months had increased in LFT more than 2-time ULN and nausea that change to 100 mg/d was recovered. One patient after 150 mg/d for three months had hepatitis and pancreatitis (LFT > 2ULN, alkaline phosphatase (ALP) > 3ULN, Increased Amylase:302 and after disconnecting of the drug was recovered. One patient had nausea and vomiting after 100 mg/d for three years, which resolved after stopping the AZA. (Table 3). Two patient got transient severe leukopenia which one of them after 150 mg/d (2 mg/kg) had transient Leukopenia (WBC:2300) in the first month and the other with 150 mg/d (2 mg/kg) first 3 month (WBC:1900) that they recovered after 1 month of complication of the drug without changing in treatment. (Table 3)

In two patients due to allergy to AZA, the drug was discontinued. In one of these patients after 150 mg/d (2 mg/kg/d) administration for one week, the patient had fever and arthralgia and skin lesion (redness) and increased LFT more than 2-time UNL, hence, the drug disconnected and the patient was recovered. In the other patient after only using one dose of 50 mg/d (0.5 mg/kg/d), allergic reactions occurred in the form of redness in the skin and the drug was disconnected. Furthermore, in one patient after 150 mg/d (2 mg/kg/d) administration for five years, the patient stopped the drug due to the recovery of ocular disease for a year, however, later on, he was affected with Basal cell carcinoma. (Table 3)

Discussion:

The evidence for the efficacy of the AZA is growing in the treatment of ocular symptoms in BD; therefore, AZA is one of the most common immune modulator drugs in the treatment of Ocular Behçet's today. The potential risk of severe adverse effects has limited the use of AZA on a large scale [8]. In previous trials on inflammatory bowel disease (IBD) patients, AZA discontinuing is more common in comparison with

placebo because of adverse effects [9]. However, there are limited studies on adverse events of AZA in patients with Ocular Behçet's.

Here, we examined a well-defined population of ocular Behçet's patients, treated in the outpatient clinic of BD of a referral center for autoimmune diseases.

Azathioprine is widely used as the systemic drug of the first choice in most of the literature in ocular Behçet's with the advised dosage of 2.5 mg/kg body weight [10]. In our center, the typical initial dose for AZA in practice would be 2–3 mg/kg/d, which is a relatively comparable dose with the current advised dose for AZA of 2.5 mg/kg body weight [11]. Despite the adequate initial dose, 11 out of 165 patients (6.67%) were shown adverse effects due to AZA. The AZA was discontinued in 5 patients and re-administrated in 2 ones. All side effects were resolved after decreasing the dose of the drug or its discontinuation. However, our findings showed a lower rate of AZA side effects in enrolled patients that might be due to the administration of the minimum dosage of the drug to control the patients' ocular manifestations. Besides, patients were followed up meticulously in our study that helped to adjust drug dosage and consumption by patients considering the patients' signs and symptoms and ceasing it after resolving the disease.

A previous multi-center study in 145 patients starting AZA for non-infectious ocular inflammation found that AZA is a relatively effective therapy in patients with active ocular inflammation who need a corticosteroid-sparing agent; however, some patients will not respond to treatment or develop side effects at a rate of 0.16/person-year. Treatment-limiting side effects seen in around one-fourth of patients within one year, but usually were modifiable, which is more than our study. [12].

We did not observe all potential side effects of AZA in the present study. Previously mentioned adverse events in the literature included gastrointestinal upset, bone marrow suppression, elevated liver enzymes, infection, and allergy [12]. Myelosuppression is a potentially lethal complication in treatment with AZA [13]. A blood profile has been reviewed in all of our ocular Behçet's patients. Whereas, Serum hemoglobin levels, leukocyte, and platelet counts were monitored before and after the onset of therapy. We observed severe leukopenia in only two patients (WBC count < 3 * 106/ml) without clinical symptoms such as infections. The leukocyte count was corrected after the temporary discontinuation of AZA in both patients, while other patients exhibited average levels for leukocyte count. The recently described leukopenia might be the effect of AZA; however, it might also be related to decreased disease activity or dosage of concomitant drugs. None of our patients represented thrombocytopenia during AZA therapy. Colombel and his team [14] found that myelosuppression during azathioprine therapy seen in twenty – seven percent of patients who had mutant alleles of the thiopurine methyltransferase (TPMT) gene but more often caused by other factors.

A complex multi-step pathway is involved in the metabolism of thiopurines. The key enzyme in this pathway is TPMT, which participates in the inactivation of thiopurines. Genetic heterogeneity of the TPMT enzyme leads to low/absent enzyme activity in 0.3% of individuals and intermediate activity in 10% of individuals [15]. It was not possible for us to test patients for TPMT activity before starting

treatment with thiopurines. We suggest checking the blood profile and liver enzyme tests before starting the AZA and repeating both in a period of treatment to minimizing the adverse effects of the drug such as the risk of leukopenia and liver injury. The regular laboratory tests could be applied in patients who suffer primary hematological disorders or hepatic diseases and have an altered level of the blood cells or liver enzymes, in addition to patients who have had previously consumed other immunosuppressive agents. Moreover, the role of TPMT in other adverse effects is yet to be known, and myelosuppression is commonly caused by other factors [16].

Previous studies implicated the potential role of AZA in the induction of malignancies. The role of Thiopurines has been confirmed in the occurrence of malignant lymphoma and non-Hodgkin lymphoma in patients with rheumatoid arthritis, solid organ transplantation, and IBD [17–19]. In the present study, a case of basal cell carcinoma was observed. Lewis and his team confirmed that the benefits of AZA in IBD patients outweigh the possible risk of lymphoma [20]. Altogether, whether or not AZA poses the risk of neoplasia, remains controversial due to the doses used to treat IBD or other diseases [21].

Reports of fever, rigors, arthralgias, and myalgias are recorded in patients with cardiac transplants in whom Azathioprine has been recently initiated [22]. Here we reported two cases of high fever, chills, nausea, and arthralgia after Azathioprine administration. A hypothesis by Korteliz et al [23] described that some concomitant drugs might interfere with AZA. Corticosteroids decrease allergy-based adverse effects; however, they prevent leucopenia.

Our study was of some limitations. First, we could not evaluate the interaction of the different concomitant medications on the development of AZA side effects, which might have led to a bias in our observations. Second, we did not have a control group to compare the outcomes of the patients between groups.

Conclusion:

In conclusion, our data suggest that AZA is well-tolerated in the majority of patients, and possible adverse events are likely to be reversible after drug discontinuation or dose adjustment. In ocular Behçet's patients, 5.4% discontinued or tapered AZA because of relative side effects. We observed severe leukopenia in two patients determined by blood cell count. Our experience with AZA in ocular Behçet's patients confirms that AZA is efficient, safe, and easily accessible for the management of retinal vasculitis in BD. Thus, we believe appropriate administration of AZA, with due attention to patient's signs and symptoms, and severity of disease results in the significantly lower frequency of adverse effects, as well as the sufficient resolving of the disease manifestations, especially ocular involvement.

Abbreviations

Behçet's disease (BD), azathioprine (AZA), methotrexate (MTX), cyclophosphamide (PCP), cyclosporine (CsA), liver function tests (LFT)

Declarations

Competing Interests:

The authors declare that there are no competing interests.

Funding:

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Consent for participation and publication:

Every participant had consented verbally and also filled a written predesigned participation consent and publication release form. The process was under supervision of Tehran University of Medical Sciences' Ethics Committee.

Authors' contributions:

All the authors had equally contributed to all parts of this study, and have read and approved the final manuscript.

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Tables

Table 1. Characteristics of patients with Ocular BD at initiation of azathioprine therapy

Parameters		Value (number-percent)
Age (years)		42.30±10.49 (21-68)
Age at the onset of the onset of BD (years)		31.81 ± 7.92
Age at the onset ocular involvement (years)		32.32 ± 7.96 (7-55)
Gender (male/female)		103/62
Duration of disease (years)		10.64 ± 7.18 (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 BD

Symptoms		Frequency (number-percent)
Mucocutaneous involvement	Oral aphthous	163 (98.80%)
	Genital aphthous	104 (63.00%)
	Skin aphthous	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%)
Musculoskletal involvement	Arthritis	18 (10.91%)
	Arthralgia	1 (0.61%)
	Ankylosing spondylitis (AS)	2 (1.21%)
	Avascular necrosis of femoral head	1 (0.61%)
Epididymoorchitis		6 (3.64%)
CNS involvement		6 (3.64%)
Renal involvement (glomerulonephritis)		1 (0.61%)
Concomitant disease	Crohn disease	1 (0.61%)
	Multiple sclerosis (MS)	1 (0.61%)
Posterior uveitis		163 (98.80%)
Anterior uveitis		102 (61.82%)
Retinal vasculitis		157 (95.15%)

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

Patient	Initial dose (mg/kg/d)	Time to adverse effect (m)	Character of adverse effect	Final dose (mg/kg/d)	Plan	Concomitant drugs (except Prednisolone)
1	200 (2.5 mg/kg/d)	6	Increased AST/ALT (more than 3 levels from normal value)	150 (2 mg/kg/d)	Dose reduction	Cyclophosphamide
2	150 (2 mg/kg/d)	3	Increased AST/ALT (less than 3 levels from normal value)	100 (1.5mg/kg/d)	Dose reduction	Cyclophosphamide Methotrexate
3	150 (2 mg/kg/d)	1	Leukopenia	150 (2mg/kg/d)	Discontinuation,,re-administration	Cyclophosphamide
4	150 (2 mg/kg/d)	3	Pancreatitis and hepatitis	0	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	150 (2mg/kg/d)	Discontinuation,,re-administration	Cyclophosphamide, Methotrexate, Infliximab
8	50 (0.5mg/kg/d)	Appeared at the first dose	High fever and chills, nausea, arthralgia	0	Discontinuation	-
9	100 (2mg/kg/d)	36	GI discomfort (Nausea and vomiting)	0	Discontinuation	-
10	200 (2.5 mg/kg/d)	3	Increased AST/ALT (more than 3 levels from normal value)+Nausea	100 (1.5 mg/kg/d)	Dose reduction	-
11	250 (3 mg/kg/d)	28	Increased AST/ALT (less than 3 levels from normal value)	150 (2mg/kg/d)	Dose reduction	Cyclophosphamide, Colchicine