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

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Abstract

Background

Behçet's syndrome (BS) is a multifactorial, polygenic, autoinflammatory 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 its safety. This study was conducted to determine the types and prevalence of adverse events related with azathioprine in patients with ocular BS.

Methods

We carried out a cross-sectional study of 165 patients with a confirmed diagnosis of BS who had ocular involvement. Data were collected retrospectively on disease-related characteristics and events including severity, recurrence, relapse, recovery and flare-up, as well as on azathioprine dosage and the duration of use.

Results

Of 165 enrolled patients, 103 (62.43%) were male and 62 (37.57%) were female. Adverse events of treatment with azathioprine occurred in 11 patients (6.67%). These side effects included elevation of liver enzymes 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 patients discontinued treatment, and 5 of them tapered the dose. In addition, we observed severe leukopenia in 2 patients.

Conclusion

Administration of azathioprine with due attention to the signs, symptoms, and severity of the disease, results in a reduced rate of adverse events and resolution of the ocular involvement in patients with BS.

Background

Behçet's syndrome (BS), a multifactorial, polygenic, autoinflammatory syndrome, is a rare, autoimmune type of vasculitis. It involves several organs, and is characterized by recurrent oral and genital ulcers, skin lesions, arthritis, thrombophlebitis, and uveitis (1). The underlying pathological factor 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 of the patients present eye disease as indolent anterior and posterior uveitis (2) and retinitis (3) that can lead to blindness (4).

The treatment approach depends on the individual patient, disease severity, and major organ involvement. Patients may receive corticosteroid therapy or cytotoxic drugs depending on the severity of

the disease, as controlled trials have demonstrated the efficacy of immunosuppressive therapy in the treatment of BS (5). Although management of the mucosal, dermal, and arthritic manifestations is mainly evidence-based, treatment options for ophthalmic, vascular, and neurological signs and symptoms are chosen through experience-based clinical decisions or evidence from simple observational studies (6).

Among numerous immunosuppressants, azathioprine (AZA) is a well-established medication that plays a useful role in the treatment of various autoimmune diseases, and recent studies have confirmed its efficacy in patients with BS, particularly in individuals with ocular pathology. Despite its advantages, the safety of AZA is still a topic of debate among clinicians regarding its adverse events. The most common side effects are nausea, fever, and bone marrow suppression. In addition, a few reports have noted a slightly increased risk of neoplasia in patients treated with AZA (7). Nevertheless, few studies have evaluated the advantages and disadvantages of the AZA in patients who suffer ocular manifestation of BS, as a way to assess the benefits of the drug in comparison to its adverse outcomes and effects.

In light of the information available to date, AZA administration without considering its side effects might be hazardous. The present cross-sectional study was therefore designed to investigate the frequency of clinical side effects of different dosages of AZA in patients with BS with different levels of severity of ocular involvement.

Methods

Patients:

In this retrospective study we performed a chart review of patients with a confirmed diagnosis of BS who were followed at the Behçet’s syndrome outpatient clinic, Rheumatology Research Center, Shariati Hospital, Tehran, Iran, between 2015 and 2017. Of all cases, the medical records for 165 patients who had ocular manifestations of the disease were included in this study. All patients were examined and diagnosed by a team of BS experts, and BS was diagnosed according to the International Criteria for Behcet's Disease (ICBD) criteria. All patients with the history of AZA prescription during ocular involvement in BS were eligible for inclusion in the study.

The Iranian BD dynamic activity measure (IBDDAM) questionnaire outcomes were used only for investigational purposes and had no impact on clinical decision making or treatment decisions. The patients’ IBDDAM scores were obtained in two follow-up sessions, and the overall score was calculated by adding the scores from the two sessions and dividing the sum by the interval between the two sessions (in months). The IBDDAM score evaluates 11 clinical manifestations, including oral aphthae (1 point per five ulcers), genital ulceration (1 point per ulcer), pseudofolliculitis (1 point per ten lesions), erythema nodosum (1 point per five lesions), arthritis (arthralgia 1 point, monoarthritis 2 points, polyarthritis 3 points), venous involvement (thrombophlebitis 1 point, large vessel thrombosis 2 points), intestinal manifestations (3 points for mild manifestations, 6 points for moderate to severe manifestations), central nervous system (CNS) manifestations (1 point for mild headaches, 3 points for

mild CNS involvement, 6 points for moderate to severe manifestation), epididymitis (2 points), and pathergy (1 point).

All data were collected retrospectively from the medical records.

Azathioprine dosage, duration of use, and previous history of medication use (such as immunosuppressants or corticosteroids) were recorded from the patients' medical records. The side effects of AZA were confirmed by a specific expert in the areas of ophthalmology, rheumatology, gastroenterology, dermatology, or oncology.

The patients were also monitored for side effects of AZA each month. This follow-up continued until the eye condition became stable and reached the remote phase. Thereafter the follow-up period was lengthened to 3 months, and follow-up ended when the drug was discontinued. There were no losses to follow-up.

A single ophthalmologist and rheumatologist examined the eyes in each visit. The ophthalmologist scored inflammation in each part of the eye between +1 and +4 (anterior and posterior uvea and the retina). In addition, the rheumatologist scored the amount of vasculitis. The classification published by Hosseini et al. (8) was used to establish the anatomical pattern of uveitis as anterior, intermediate, posterior, and panuveitis.

Treatment approaches were guided by the updated EULAR (The European League Against Rheumatism) recommendations for the management of Behcet's syndrome (9). The overarching principles can be summarized as follows:

► BS is a condition that typically runs a relapsing and remitting course, and the goal of treatment is to promptly suppress inflammatory exacerbations and recurrences to prevent irreversible organ damage.

► A multidisciplinary approach is necessary for optimal care.

► Treatment should be individualized according to age, gender, type and severity of organ involvement, and patient's preferences.

► Ocular, vascular, neurological, and gastrointestinal involvement may be associated with a poor prognosis.

► Disease manifestations may ameliorate over time in many patients.

In addition, EULAR highlights different types of involvement and their treatment approaches:

Eye involvement: The management of uveitis in BS requires close collaboration with ophthalmologists with the ultimate aim of inducing and maintaining remission. Any patient with BS and inflammatory eye disease affecting the posterior segment should be on a treatment regime such as AZA (IB), cyclosporine-A (IB), interferon alpha (IIA) or monoclonal anti-TNF antibodies (IIA). Systemic glucocorticoids should be

used only in combination with AZA or other systemic immunosuppressants (IIA). Patients presenting with an initial or recurrent episode of acute sight-threatening uveitis should be treated with high-dose glucocorticoids, infliximab or interferon alpha. Intravitreal glucocorticoid injection is an option in patients with unilateral exacerbation as an adjunct to systemic treatment.

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 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. Any other reasons for terminating or adjusting the drug dose were also documented. Leukopenia was considered less than 4000 WBC. In this study, leukopenia was recorded as moderate (3.0-4.0 × 10^6/ml) or severe (less than 3.0 × 10^6/ml). Altered liver enzymes in this study were defined as three times as much as the normal range for aspartate aminotransferase (AST) and alanine aminotransferase (ALT). Most of these adverse events presented after starting AZA. In addition, most of the patients during treatment took just AZA. Then, the adverse events confirmed by specialists and they told that these effects are specific to this drug.

Aims:

Primary: We aimed to investigate the frequency of clinical side effects of AZA in patients who had BS with ocular involvement. In addition, we evaluated the endpoint and the results of these side effects.

Secondary: We considered different AZA dosages and the severity of ocular involvement in order to investigate the safety of different AZA dosages.

Ethics and registration:

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

Statistical analysis:

Student’s t-test was used to compare quantitative variables between groups, and the chi-squared test was used to compare two qualitative variables in each time period. In addition, Kolmogorov-Smirnov test was used to assess normality distribution. The t-test or Wilcoxon signed-rank test was used to compare dependent variables between different times. The level of significance was set at 0.05, and all results were expressed as absolute and percent frequencies for qualitative variables, or as the mean ± SE for quantitative variables. All data were analyzed with SPSS version 23 software (SPSS Inc., Chicago, IL).

Results

A total of 165 patients with a diagnosis of ocular involvement in BS were analyzed. Their demographic characteristics, including age, age of disease onset, and concomitant medications are listed in Table 1. Mean age at the onset of BS was 31.81 ± 7.92 years and mean duration of BS was 10.64 ± 7.18 (1-35) years. Mean 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 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 at different doses ranging between 10 mg/d and 0.5 mg/kg according to the severity of their ocular disease. Cyclophosphamide (PCP) 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. Also, 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 2 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. All 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 ulcers) in 104 patients (63%, 95% CI: ± 48.4), whereas 2 patients did not have any oral or genital aphthous ulcers. Skin aphthous lesions were present in 4 patients (2.42%, 95% CI: ± 18.70), a positive pathergy test was recorded in 72 patients (43.64%, 95% CI: ± 50), pseudofolliculitis occurred in 39 patients (23.64%, 95% CI: ± 42.2), and erythema nodosum was present in 26 patients (15.76%, 95% CI: ± 32).

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), and 7 patients had deep vein thrombosis (4.24%, 95% CI: ± 20.2). One 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 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 had arthritis (10.91%, 95% CI: ± 31.3), 1 had avascular necrosis of the femoral head (0.61%, 95% CI: ± 7.8), 2 had ankylosing spondylitis (AS) (1.21%, 95% CI: ± 10.9), and 1 had arthralgia (0.61%, 95% CI: ± 7.8). Other less frequently detected manifestations were CNS 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), and multiple sclerosis (MS) in 1 patient (0.61%, 95% CI: ± 7.8). 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%, 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).

Of 8 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 MTX was discontinued 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.

All adverse events induced by azathioprine:

In 11 out of 165 patients (6.67%), AZA therapy was discontinued or tapered prematurely due to adverse events. 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 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 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 is growing for the efficacy of AZA in the treatment of ocular symptoms in BS, and AZA is currently one of the most commonly used immune modulator drugs to treat ocular BS. However, the potential risk of severe adverse events has limited the use of AZA on a large scale (10). In previous trials of AZA in patients with inflammatory bowel disease (IBD), discontinuation because of adverse events was more common in comparison to the placebo arm (11). However, studies of AZA-related adverse events in patients with ocular BS are limited. Here, we examined a well-defined population of patients with ocular BS who were treated at the BS outpatient clinic of a referral center for autoimmune diseases.

Azathioprine is widely used as the systemic drug of first choice according to most studies of ocular BS, with a recommended dosage of 2.5 mg/kg body weight (12). At our center, the typical initial dose for AZA in practice is 2-3 mg/kg/d, which is comparable to the current recommended dose of 2.5 mg/kg body weight (12). Despite their adequate initial dose, 11 out of 165 patients (6.67%) had adverse events related to AZA. The drug was discontinued in 5 patients and re-administrated in 2. All side effects resolved after decreasing the dose of the drug or discontinuing it. Of note, our findings showed a lower rate of AZA side effects, which may be due to the administration of the minimum dosage of the drug to control the patients' ocular manifestations. Meticulous follow-up in our sample of patients helped to adjust drug use and dosages in light of each patient's signs and symptoms, and to cease AZA treatment after the disease had resolved.

A previous multicenter study of 145 patients who started AZA for noninfectious ocular inflammation found that AZA was a relatively effective therapy in patients with active ocular inflammation who needed a corticosteroid-sparing agent; however, some patients will not respond to treatment or develop side effects at a rate of 0.16/person-year. One earlier study found treatment-limiting but modifiable side effects in around one-fourth of patients within 1 year (13), which is a higher rate than in the present study.

We did not observe all potential side effects of AZA in the present study. Among the adverse events noted previously in the literature are gastrointestinal upset, bone marrow suppression, elevated liver enzymes,

infection, and allergy (13). Myelosuppression is a potentially lethal complication of AZA treatment (7). Blood profiles were reviewed in all of our patients with ocular BS, and serum hemoglobin levels, leukocyte and platelet counts were monitored before and after the start of therapy. We observed severe leukopenia in only 2 patients (WBC count < 3×10^6/ml), neither of whom had clinical symptoms such as infection. The leukocyte count was corrected after AZA was temporarily discontinued in both patients, while all other patients maintained leukocyte counts within the normal range. The recently described leukopenia may be an effect of AZA; however, it may also be related to decreased disease activity or the dosage of concomitant drugs. None of our patients had thrombocytopenia during AZA therapy. Although Colombel and colleagues (14) found myelosuppression during AZA therapy in 27% of patients who had mutant alleles for the thiopurine methyltransferase (TPMT) gene, other factors were more often responsible for this side effect.

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 or 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 AZA. We suggest that the blood profile should be checked and liver enzyme levels should be tested before starting AZA, and that these laboratory values should be re-measured during the treatment period to minimize the risk of AZA-related adverse effects such as leukopenia and liver injury. Regular laboratory testing could be used for patients with primary hematological disorders or hepatic diseases, and those with an altered blood cell profile or liver enzyme function, as well as for patients who have previously used other immunosuppressive agents. However, the role of TPMT in other adverse events remains unknown, 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, 1 patient developed BCC. Nonetheless, Lewis and colleagues concluded that the benefits of AZA in patients with IBD outweigh the possible risk of lymphoma (20). At present, whether or not AZA poses a risk of neoplasia remains controversial because of differences in the doses used to treat IBD or other diseases (21).

Fever, rigors, arthralgias, and myalgias were reported in patients with heart transplants in whom AZA had been recently started (22). Our patient sample included 2 cases of high fever, chills, nausea, and arthralgia after AZA administration. According to a hypothesis proposed by Korteliz et al. (23), some concomitant drugs may interfere with AZA. Corticosteroids decrease allergy-based adverse events; however, they can also prevent leukopenia.

Limitations

Our study had of some limitations. First, we could not evaluate the effect of interactions among different concomitant medications on the development of AZA side effects, and this may have led to biases in our observations. Second, we did not have a control group to compare the outcomes between patient groups. In addition, some other adverse events and their results or AZA efficacy were not in patient's record so they limited our results.

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 patients with ocular BS, 5.4% discontinued or tapered AZA because of side effects. We observed severe leukopenia in 2 patients as determined by blood cell count. Our experience with AZA in patients with ocular BS confirms that AZA is efficient, safe, and easily accessible for the management of retinal vasculitis. Thus, we believe appropriate administration of AZA, with due attention to individual patients' signs, symptoms, and disease severity, can result in a significantly lower frequency of adverse events, as well as adequate resolution of the disease manifestations, especially ocular involvement.

Abbreviations

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

Declarations

Ethics approval and consent to participate: The Ethics Committee of Qom University of Medical Sciences approved the study protocol, and all patients provided informed consent before participating.

Consent for publication: Not applicable.

Availability of data and materials: The datasets used and analyzed in the current study are available from the corresponding author on reasonable request.

Competing interest: None declared.

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Author contributions: S.S., M.M., F.D., F.S., M.A., T.F., and H.K. conceived and planned the visits. S.S., M.M., and F.D. carried out the physical examinations. S.S. and M.M. planned and carried out the laboratory

tests. F.D., F.S., T.F., H.K., and M.A. contributed to the analysis of the results. S.S., M.M., T.F., H.K., M.A., and F.D. contributed to the interpretation of the results.

M.M. and S.M. and J.B took the lead in writing the manuscript. All authors provided critical feedback and helped shape the research, analysis and manuscript. All authors have read and approved the manuscript.

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Tables

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

Symptoms		Frequency (number and percent)
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%)

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

Patient	Initial dose (mg/kg/d)	Time to side effect (m)	Character of side 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 fold ULN)	150 (2 mg/kg/d)	Dose reduction	Cyclophosphamide
2	150 (2 mg/kg/d)	3	Increased AST/ALT (less than 3 fold ULN)	100 (1.5 mg/kg/d)	Dose reduction	Cyclophosphamide, methotrexate
3	150 (2 mg/kg/d)	1	Leukopenia	150 (2 mg/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 (2 mg/kg/d)	Discontinuation, re-administration	Cyclophosphamide, methotrexate, infliximab

8	50 (0.5 mg/kg/d)	Appeared after the first dose	High fever and chills, nausea, arthralgia	0	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	100 (1.5 mg/kg/d)	Dose reduction	-
11	250 (3 mg/kg/d)	28	Increased AST/ALT (less than 3 fold ULN)	150 (2 mg/kg/d)	Dose reduction	Cyclophosphamide, colchicine