Azathioprine for cortico-resistant noninfectious uveitis.

L'Azathiopine dans le traiment des uveites non infectieuses cortico-résistantes.

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RÉSUMÉ

Prérequis:les corticoïdes systémiques représentent le traitement de première intention dans la majorité des uvéites non infectieuses (UNI), et ce en dehors de quelques indications spécifiques comme la maladie de Behcet. Néanmoins, ce traitement peut s'avérer inefficace et le recours aux immunosuppresseurs obligatoire.

But: évaluer l'efficacité et les effets secondaires de l'azathioprine (AZA) dans le traitement des uvéites non infectieuses cortico-résistantes (UNICR).

Méthodes: cette étude prospective (2002- 2009), concernait 21 patients (âge moyen 37 ans), 37 yeux, avec UNICR, ayant reçu de l'AZA (2,5mg/kg/j), initiée par de forte dose de corticoïdes, avec un résultat final à 12 mois. Les réponses étaient considérées comme complètes, partielle ou absente pour les 3 paramètres suivants: amélioration de l'acuité visuelle (AV), amélioration de l'inflammation, épargne cortisonique. La valeur du $p < 0,05$ était considérée comme statistiquement significatif.

Résultats: les effets secondaires sont apparus chez 42,8% (9/21) des patients, parmi lesquels 5/9 patients ont dû arrêté leur traitement. Concernant l'AV, une réponse complète était notée dans 62,5% des cas, partielle dans 20,9% des cas et absente dans 16,6% des cas. Il existait une amélioration inflammatoire complète dans 70,8% des cas, partielle dans 29,1% des cas et absente dans 16,6 % des cas. Une épargne cortisonique complète était observée dans 85,7% des cas. Un succès complet des 3 paramètres était observée dans 57,1% des patient, 62,5% des yeux. La cataracte (p=0,013) et la pâleur papillaire (p=0,013) étaient associés à un pronostic visuel défavorable, une AV supérieure ou égal à 5/10 (p=0,003, RR=2,38) et un œdème papillaire (p=0,022, RR=2) à un pronostic favorable. Une AV inférieure ou égale à 1/10 (p=0,001) était associée à un échec thérapeutique sur le plan inflammatoire.

Conclusion: l'AZA est efficace dans le contrôle inflammatoire et l'épargne cortisonique dans le traitement des UNICR. Du fait de son faible coût et sa disponibilité, elle en représente un traitement de première ligne, en particulier lorsque les nouveaux traitements biologiques sont difficiles à obtenir.

Mots-clés

Azathioprine, Maladie de Behcet, Maladie de Vogt-Koyanagi-Harada, Uvéite, cortico-resistance, Effet secondaires.

SUMMARY

Background: the systemic steroids represent the first line treatment in the majority of the noninfectious uveitis, except some specific indications as the Behcet disease. Nevertheless, this treatment may be ineffective and immunosuppressive therapy is mandatory.

Purpose: to evaluate effectiveness and side effects of azathioprine (AZA) in corticosteroid resistant noninfectious uveitis (CRNIU).

Methods: This prospective study (2002- 2009), concerned 21 patients (mean age 37 years), 37 eyes, with CRNIU. Patients received oral AZA 2,5mg/kg/day, initiated in association with high dose steroids, with an end-point of 12 months. Response was defined as complete, partial response and failure, for each of the 3 following out-come measurements: improvement of BCVA, improvement of inflammation, steroids-sparing. Statistical analysis was considered significant if p value $< 0,05$.

Results: side effects occurred in 42,8% (9/21) of patients, in which 5/9 patients stopped the treatment. Regarding BCVA, complete success was observed in 62,5%, partial response in 20,9% , and failure in 16,6% of cases. Regarding inflammation, complete success was noted in 70,8%, partial response in 29,1% and failure in 16,6 % of cases. Complete response of steroid sparing was observed in 85,7% of cases without failure. Complete success of the 3 criteria was observed in 57,1% of patients / 62,5% of eyes. Cataract (p=0,013) and pallor of optic nerve head (p=0,013) were associated to poor visual prognosis, BCVA of 20/40 or more (p=0,003, RR=2,38)) and papilledema (p=0,022, RR=2) to good visual prognosis. BCVA of 20/200 or less (p=0,001) was associated to failure of AZA on inflammatory response.

Conclusion: AZA is safe and effective in corticosteroid-sparing and controlling inflammation in CRNIU. Its low cost and availability allow proposing it as a first-line option, especially when new biological treatments are difficult to obtain.

Key-words

Azathioprine ; Cortico-resistant, Uveitis, Side effects, Behcet disease, Vogt Koyanagi Harada disease.

Corticosteroids are the mainstay of therapy for most ocular noninfectious inflammatory disorders. However, in some patients, systemic steroids are insufficient to control the disease and immunomodulatory therapy (IMT) , such as azathioprine, is required.[1] Azathioprine (AZA), an inhibitor of purine synthesis, has been shown to be effective for the treatment of chronic uveitis, usually in combination with corticosteroids.[1-3] it is an old medication, well tolerated and low cost. [4] AZA has shown to prevent the developments of uveitis without severe complications in Behcet Disease (BD). [4]

The purpose of our study was to evaluate clinical outcomes of high dose of AZA therapy for corticosteroid resistant noninfectious uveitis (NIU).

METHODS

Study population

All patients who attended at department of Ophthalmology for the management of noninfectious uveitis, from 2002, were enrolled in a prospective study. To be included, patients had to have normal renal and liver function. They had to present active noninfectious posterior uveitis or panuveitis resistant to corticosteroid treatment (CST). Resistance to CST was defined by resistance to a dose of 30 mg/day of prednisolone, or persistence or aggravation of intraocular inflammation after 6 months of CST. This CST consisted of monthly intravenous pulse methyl-prednisolone (10mg/k per day during 3 days) followed by oral prednisolone (1mg /kg/day). Patients had to receive AZA as second-line agent, a single non-corticosteroid immunosuppressive therapy for ocular inflammation and a minimum of follow up of 12 months after the initiation of AZA. This study was performed with the approval of all participants and was conducted in accordance with the Declaration of Helsinki. Patients were followed beginning the time they started AZA and ending at 12 months of treatment. Patients with followed criteria was excluded from the study : age < 20-year-old ; extra-ocular active infection ; infectious uveitis ; AZA therapy for extra-ocular disease ; AZA as a first-line treatment; contre-indications to AZA ; pregnancy or breast feeding ; other second-line immunosuppressive therapy ; socio-economic conditions that not allowed a regular follow-up.

Treatment protocol and monitoring

Patient received oral AZA 2,5mg/kg/day. AZA therapy was initiated in association with CST, beginning by intravenous pulses of methylprednisolone (1 g per day over three days) followed by oral prednisone (1mg/kg/d) in all cases. Doses of prednisolone were tapered based on clinical improvement of uveitis starting two months after initiation. During AZA, acute uveitis was treated according to localization: in case of acute anterior uveitis, the patient received topic steroids, and systemic steroids in cases of acute posterior uveitis, with comeback to initial dose after one month.[5, 6] Each patient was regularly followed both by internist and ophthalmologist, monthly, who research of side effects and response to AZA. It consisted on complete ophthalmological examination including best corrected visual acuity (BCVA), slip lamp anterior segment and fundus exam (FE). Fluorescein angiography (FA) was performed in all cases. Urinalysis, chest x-ray, laboratory screening were performed regularly in all cases, to control renal and liver functions and to exclude the presence of an infectious disease. The activity of uveitis was graded from 0 to 3 based on the number of anterior chamber cells per field (0,3 cells; 1, 3–10 cells; 2, 11–30 cells; and 3,>30 cells), modified from the recommendations of Rao and Nussenblatt. [7, 8] Ocular improvement was defined as a reduction of inflammation by at least one grade. A relapse was defined as worsening of visual acuity related to inflammation, any increase in anterior chamber cell score or vitreous haze, or any new or increase of leakage of inflammatory on FA related to the initial fundus involvement, development of ocular complications or a first course of uveitis during AZA therapy.

Main outcome measures

The end-point evaluation was performed at 12 months of AZA treatment.

Response was defined as complete success, partial response and non-responder, according to clinical and FA findings and on corticosteroid-sparing, for each of the following 3 criteria: improvement of BCVA, improvement of inflammatory activity of uveitis, corticosteroids sparing. Regarding to BCVA, complete success consisted in improvement of BCVA more than one line, partial response in case of stabilization of BCVA, and failure in case of decreased of BCVA related to inflammation. Regarding to inflammation, complete success was defined as: (1) complete resolution of inflammatory activity after 2 months of initiation of AZA according to SUN Working Group criteria with no relapse over a period of at least 28 days, and (2) absence of relapse during corticosteroids tapering. Partial response was defined as : (1) complete resolution of inflammatory activity after 2 months of initiation of AZA with maintain of acalmia during 28 days minimum, and (2) complete resolution of inflammation after punctual treatment in case of acute uveitis during AZA. Failure consisted in (1) no improvement after two months of AZA, or (2) if there was no resolution of inflammation in cases of acute uveitis during AZA. Regarding to corticosteroid-sparing, (1) complete success consisted in no inflammatory relapse over a period of at least 28 days with a final dose of prednisolone at 10 mg/k/day maximum, and (2) partial response with a dose between >10 mg/day and 15 mg/day. Failure was considered if steroids could not be tapered with a dose >15mg/day of prednisolone.

The incidence of treatment-related adverse events was also analyzed.

Statistical analysis

Student's t-test was used to evaluate statistical significance in continuous variables in which there was a single measurement. In cases where quantitative parameters were compared, p-values were calculated using repeat measures analysis using ANOVA. Chi-square testing was used to calculate significance in categorical variables. A P value<0,05 was considered to be statistically significant.

RESULTS

Demographic and clinical characteristics of the study population at the time of starting AZA are summarized in Table 1. Twenty one patients (37 eyes) were included from 2002 to 2009. Their mean age was 37 years (range 24-51, median at 35 years), sex ratio was at 2,5 (15 men / 6 women). Mean duration of NIPU was 6 years-old (range 1-20 years,

median at 5 years). BD was the most frequent etiology of uveitis (15/21 patients; 71,4% of cases). Uveitis was bilateral in all cases. Mean BCVA was 20/80 (range 20/400-20/20), with 23/37 eyes (62,1%) with BCVA less 20/200, 5/37 eyes (13,5%) between 20/100-20/50 and 9/37 eyes (24,3%) 20/40. Five patients were monophtalme, with mean BCVA at 20/400, in which 4 were BD. 5/21 patients (23,8%) were in blindness. Pupillary synechia and cataract were the most frequent anterior segment complications of uveitis, noted respectively in 62,1 (23 /37 eyes) and 44,4% (16/37 eyes) of cases. Three on 37 eyes presented obtruded cataract with inaccessible fundus. In the others 34/37 eyes, involvement of optic nerve head (ONH) and macular edema (ME) were the most frequent posterior segment complications of uveitis, noted respectively in 58,8 (20/34 eyes) and 50% (17/34 eyes) of cases. Mean follow up was 19,4 months for all patients.

At the final evaluation, treatment-related adverse events occurred in 42,8% (9/21) of patients (Table 2).

Table 2 : Side effects of Azathioprine

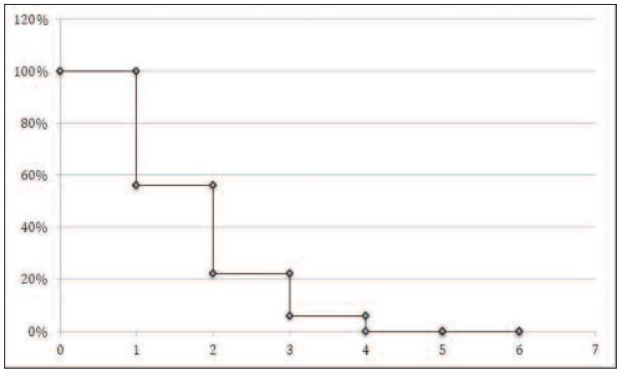
Side effects (SE)	n patients (%)	Patients(n) requiring cessation of treatment
AST increased	5 (23,8%)	3/5 (60%)
Infectious complications	3 (14,2%)	2/3 (66,6%)
Myasthenia, paresthesia, asthenia	2 (9,5%)	0
Gastrointestinal symptoms	1 (4,7%)	0
Total patients with SE (%)	9/21 (42,8%)	5/21 of all patients (23,8%) 5/9 of patients with SE(55,5%)

Tableau 1 : Demographic and clinical characteristics of the study population

patient	Age, gender	Etiology of uveitis and duration	IST before AZA	Eye	Uveitis associated anterior segment complications	Uveitis associated posterior segment complications
1	F, 42 y	VKH, 4 years	6 MP 6 CPP	1 2	Cataract. Glaucoma. PS Cataract. Glaucoma. PS	Sun set glow fundus Sun set glow fundus
2	M, 47 y	BD, 20 years				Fundus without vessels
3	M, 48 y	Idiopathic uveits, 7 years	6 MP 6 CPP	3 4	Glaucoma. SP Glaucoma. SP	Rétinal vasculitis. ME. Papillary edema. RBVO. Retinal vasculitis. ME. ERM. Papillary edema
4	M, 30 y	BD, 6 years	6 MP 1 CPP	5 6	PS PS	Retinal vasculitis. ME. Retinal vasculitis. ME.
5	F, 35 y	BD, 14 years	12 MP	7	Cataract. PS Cataract. PS	Fundus without vessels. Retinal vasculitis. ME. ERM. RBVO. Pars planitis
6	M, 37 y	BD, 2 years	12 CPP	8		Fundus without vessels. Retinal vasculitis. ME. RBVO. Pars planitis
7	F, 47 y	VKH, 9 years	6 MP 6 CPP	9 10	Cataract, PS. Cataract, PS.	Retinal vasculitis.PE Retinal vasculitis.
8	M, 28 y	BD, 10 years	6 MP	11	PS PS	
9	M, 24 y	BD, 2 years	8 MP	12	PS PS	Retinal vasculitis, ME, PE, ERM Retinal vasculitis, ME, PE, ERM
10	M, 40 y	BD, 5 years	7 CPP	13	PS, cataract PS, cataract	ME, PE, ERM ME, PE, ERM
11	M, 34 ans		6 MP	14	Cataract. PS	ME, PE, ERM
12	M, 35 years	BD, 3 years	3 CPP	15		ME, PE, ERM
13	M, 31 years	BD, 1O years BD, 5 years	6 MP	16	PS PS	Retinal vasculitits. BRVO. Retinal vasculitits. BRVO Retinal vasculitits. BRVO
14	M, 32 years	BD, 1 year	8 MP	17		Retinal vasculitits. ERM
15	F, 32 y	Sclerosis, 6 years	8 CPP	18	pseudophakic Cataract	Retinal vasculitits. ERM Retinal vasculitits. ME. PE.
16	M, 30 years		12 MP	19	Cataract. Glaucoma. PS	Retinal vasculitits. ME. PE.
17	M, 34 years	BD, 5 years	12 CPP	20	Cataract	Retinal vasculitis. Pars planitis
18	M, 42 years	BD, 6 years BD, 1 year	6 MP 3 CPP	21 22		Retinal vasculitis. Pars planitis ME
19	F, 31 y				Cataract. SP	BRVO, ERM
20	M, 38 y	Psoriasis, 5 years BD, 1 year	6 MP	23		Retinal vasculitits. ME. PE. ERM. BRVO Retinal vasculitits. ME. PE. ERM. BRVO
21	F, 51 y	Idiopathic uveitis, 4 years	6 MP	24	Cataract. SP Cataract. SP	Normal ocular echography Retinal vasculitits. ME Retinal vasculitits. ME. PE
			10 MP	25		Normal ocular echography Normal ocular echography
			12 MP	26		
			12 CPP	27		
			7 MP	28		
			7 CPP	29		
			6 MP	30		
			6 CPP	31		
				32		
			6 MP	33		
			6 MP	34		
			6 CPP	35		
				36		
			6 MP			

The major adverse event was AST increase, noted in 23,8% (5/21) of patients. Five patients (5/21, 23,8%) stopped the treatment, in which 3/5 for elevation of hepatic enzymes and 2/5 for severe infectious complications. Infectious were urinary in one case and tuberculosis associated with cytomegalovirus uveitis in the other one. Two patients discontinued treatment because of lack of efficacy. Fourteen patients (24 eyes) remained for the final evaluation. In regard to BCVA, we observed a complete success in 62,5% (15/24 eyes) and partial response in 20,9% (5/24 eyes) of cases. Failure was noted in 16,6% (4/24 eyes) of cases. In regard to inflammation, a complete success was noted in 70,8% (17/24 eyes) of cases, a partial response in 29,1% (7/24 eyes) and a failure in 16,6 % (4/24 eyes) (figure 1).

Figure 1 : Kaplan-Meier curve for the number of eyes with active uveitis with azathioprine treatment.



Y : proportion of eyes with uveitis
X : months of azathioprine treatment

Complete response of steroids sparing was observed in 85,7% (12/14 patients) and a partial response in 14,3% (2/14 patients). There was not failure in steroid sparing. A complete success of the 3 criteria was observed in 57,1% of patients (8/14 patients), or 62,5% of eyes (15/24 eyes). Cataract (p=0,013) and pallor of optic nerve head (p=0,013) were associated to poor visual prognosis. BCVA of 20/200 or less (p=0,001) was associated to failure of AZA on inflammatory response. BCVA of 20/40 or more (p=0,003, RR=2,38)) and papilledema (p=0,022, RR=2) double the chance of increase visual result after AZA (Table 3).

DISCUSSION

These data suggest that AZA was efficient for corticosteroid resistant non-infectious uveitis, with a complete success observed in 57,1% of patients (8/14 patients), or 62,5% of eyes (15/24 eyes). In regard to inflammatory response, AZA was efficient with 70,8% and 29,1% of cases gaining complete or partial response respectively, and failure in only 1/6 patients. Moreover, AZA is successful in achieving corticosteroid-sparing objectives of tapering of prednisone to 10mg or less while sustaining complete control of inflammation.

The comparison of the results of AZA in the uveitis in previously published studies is difficult because of the variability of the epidemiological data bases, the study designs, the treatment protocols and the parameters of measurement outcome. [9- 19] Only 2 series are prospective, as our study. [4, 9] Some studies reported the results in only one inflammatory disease, such as BD for Yazici and Hamuryudan, Vogt-Koyanagui-Harada for Kim, serpiginous choroiditis for Vianna and sympathetic ophtamitis for Moore. [4, 10-13] Results of BCVA were not reported in all series. [7, 14] Galor and al compared

Table 3 : Results

factor	Complete success of BCVA		Complete success of inflammation	
	p	RR	p	RR
Age of the patient 35 y	0,137	NS	0,302	NS
Age of the patient 40 y	0,300	NS	1	NS
Gender	1	NS	0,604	NS
Uveitis etiology	0,580	NS	0,604	NS
Duration of disease 2 years	0,472	NS	1	NS
Duration of disease 5 years	0,627	NS	0,145	NS
IST other than CST	1	NS	1	NS
BCVA 20/200	0,678	NS	0,001	0,39
BCVA 20/40	0,190	NS	0,003	2,38
PS	0,657	NS	0,226	NS
Seclusion of the pupil	0,352	NS	0,061	limite
Glaucoma	0,614	NS	1	NS
Cataract	0,013	0,42	0,141	NS
Papilledema	0,022	2	0,692	NS
Palor of ONH	0,013	0,33	0,357	NS
ME	1	NS	0,410	NS
Retinal vasculitis	1	NS	0,188	NS
BRVO	0,376	NS	0,09	limite
ERM	0,647	NS	1	NS

BCVA : best corrected visual acuity ; BRVO : branch retinal vein occlusion ; CST : corticosteroid therapy ; ERM : epiretinal membrane ; F : female ; IST : immunosuppressive therapy ; M : male ; ME : macular edema ; ONH : optic nerve head ; NS : non significant ; PE : papilledema ; PS : posterior synechiae ; SP : seclusion of the pupil ; y : years-old.

AZA to others immunosuppressive therapies. [15] But, despite this heterogeneity, all previous reports have noted efficiency of AZA in noninfectious uveitis. Pasadhika noted, in a multicentric retrospective series of 145 patients with noninfectious inflammatory diseases treated by AZA, at the 6 months of AZA, a control of inflammation in 69,3% of cases in intermediate uveitis, 44,2% of cases in posterior uveitis and in 23,7% of cases of anterior uveitis. [14] In a comparative prospective study concerning 73 patients with BD, completed by the study of Hamuryudan, Yazici observed that there was a significantly higher cumulative rate of absence of eye disease in the azathioprine groups (91 percent) than in the placebo groups (28 percent) (log-rank $\chi 2 = 9.8$, $P<0.001$). [4, 13]

Our statistical analyses demonstrated that there is a positive correlation between the result of AZA on the inflammation and the vision of departure superior or equal to 20/40, as noted by Yazici and Hamuryudan. [4, 13]

One of the difficulties is to determine the duration of treatment, or when to modify it in case of resistance. According to the authors, period to estimate result of the AZA treatment varied from 6 to 24 month. Pasadhika proposed a period of 6 to 12 months of AZA to estimate the result of the treatment. [9]

In regard to corticosteroids-sparing, we noted a complete success and a partial success in 85,7% and 14,3% of our patient respectively, without any failure. These results were confirmed by most of authors. [4, 8-10, 14, 15]

Another interesting finding was that side effects varied from 47,3% to 24% of cases in different series. [4, 9-15] AST increased and infectious complications are the most common reasons for discontinuation observed among the 7 patients for whom AZA was stopped due to side-effects in our study. At long-term, AZA is considered as a carcinogen drug, but its effects are not well established and its benefits are superior to its side effects. [18-22] Nevertheless, a short-term monitoring, including liver function tests and full blood count, and a long-term follow-up are mandatory in patients treated by AZA.

In another hand, we noted in our series a good medication adherence to AZA. No patient discontinued their medication and any patient was lost to follow up, we don't found any patient defaulting between the beginning end the end of the study. This could be explained by the twice-daily oral administration of AZA, comparing with intravenous administration which was necessary in hospital care units. Another advantage of AZA is the low cost compared to others alternative drugs. [15]

The major strength of our study are the prospective design, the same regular outcome measurements for all patient, and we don't have any patient loose during the study. Limitations were first the small number of patients included, because of severe treatment success estimates criteria. Multicentric studies based on the same criteria would give more significantly results.

CONCLUSION

AZA was found to be safe and effective in corticosteroid-sparing and controlling inflammation in corticosteroid resistant non-infectious uveitis. AZA should be considered as a first-line option for well-known severe uveitis, such as BD or VKH syndrom, under a short-term monthly monitoring and a long-term follow-up.

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