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ORIGINAL ARTICLE

Safety of Azathioprine Therapy Adjusted to Thiopurine Methyltransferase Activity in the Treatment of Infantile Atopic Dermatitis. Report on 7 Cases

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KEYWORDS

Atopic dermatitis;
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Abstract

Background: In a small number of cases of childhood atopic dermatitis, topical therapy is ineffective, necessitating prolonged use of systemic immunosuppressants. Over the last few years, a better understanding of the metabolic pathways involved in azathioprine breakdown has enabled us to use this drug more safely. In this study, we evaluated the toxicity of azathioprine treatment adjusted to thiopurine methyltransferase activity in children with severe atopic dermatitis.

Material and methods: We performed a retrospective study of the side effects of azathioprine therapy adjusted to thiopurine methyltransferase activity in children aged under 14 years with atopic dermatitis who were treated in the dermatology department of Hospital Universitario Insular de Gran Canaria in Gran Canaria, Spain. Side effects were evaluated by analysis of leukocyte count and transaminase levels at baseline, after 1 month of treatment, and every 3 months thereafter.

Results: During the last 4 years, 7 children (mean age, 10 years) with severe atopic dermatitis received azathioprine in our department. Mean duration of treatment was 12 months (range, 1 to 38 months). Only 2 patients presented mild transient leukopenia that did not require treatment to be suspended.

Discussion: Our experience shows that, when adjusted to thiopurine methyltransferase activity, azathioprine is a safe drug for the treatment of children with severe atopic dermatitis. However, clinical trials should be performed to compare the risk-benefit ratios of the different immunosuppressants used to treat these patients.

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PALABRAS CLAVE

Dermatitis atópica;
Azatioprina;
Tiopurina
metiltransferasa

Seguridad de azatioprina según los niveles de tiopurina metiltransferasa en el tratamiento de la dermatitis atópica infantil. Experiencia en 7 casos

Resumen

Introducción: Existe un pequeño número de casos de dermatitis atópica (DA) infantil donde la terapia tópica es insuficiente para el control de la enfermedad y es necesario el uso prolongado de agentes inmunosupresores sistémicos. En los últimos años el mejor conocimiento de las vías metabólicas implicadas en la catabolización de la azatioprina (AZT) parece ofrecernos un uso más seguro de este fármaco. Hemos evaluado la toxicidad de la AZT según los niveles de tiopurina metiltransferasa (TPMT) en niños con DA grave.

Material y métodos: Estudio retrospectivo de los efectos secundarios de la AZT ajustada a los niveles de TPMT en menores de 14 años con DA que han sido tratados en el Servicio de Dermatología del Hospital Universitario Insular de Gran Canaria. La evaluación de los efectos secundarios se realizó mediante controles analíticos con recuento leucocitario y de transaminasemia en la visita basal, al mes y cada tres meses durante el tratamiento.

Resultados: En los últimos 4 años, 7 niños (media de 10 años) con DA grave han recibido AZT en nuestro Servicio. La duración media del tratamiento fue de 12 meses (rango 1-38); sólo dos pacientes presentaron una leucopenia leve transitoria que no requirió la suspensión del tratamiento.

Discusión: Según nuestra experiencia la AZT, ajustada a los niveles de TPMT, se muestra como un fármaco seguro en el tratamiento de niños con DA grave, aunque son precisos ensayos clínicos que comparen la relación riesgo/beneficio entre los inmunosupresores empleados en estos pacientes.

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Introduction

Atopic dermatitis is a chronic inflammatory disease of the skin that is managed by regular hydration and treatment of acute exacerbations based mainly on corticosteroids or topical calcineurin inhibitors.¹ However, in a small number of cases, topical treatment is insufficient to control the disease and systemic treatment must be applied. Although frequently used in clinical practice, systemic corticosteroids have not been sufficiently evaluated, and long-term therapy is limited by adverse effects; therefore, other immunosuppressants must be used to avoid prolonged or repeated use.

In the last 10 years, azathioprine (AZT), a synthetic purine analog with an anti-inflammatory and immunosuppressive effect, has become an obvious choice for treatment of severe atopic dermatitis in adults²; however, administration in children has received less attention.³ AZT is safer thanks to a better understanding of a key enzyme in its catabolism, namely, thiopurine methyltransferase (TPMT), which is affected by a genetic polymorphism.⁴ Knowledge of the degree of activity of this enzyme in individual patients seems to make it safer to use this drug, whose administration is limited by the risk of myelosuppression.

We present 7 cases of severe atopic dermatitis in children for whom AZT was adjusted to levels of TPMT.

Material and Methods

We performed a retrospective study of 7 children with atopic dermatitis who received AZT over a period of 4

months at the Department of Dermatology at Hospital Insular de Gran Canaria in Gran Canaria, Spain. The mean duration of treatment was 12 months (range, 1-38 mo) (Table 1).

The mean age of the children at the start of treatment was 10 years, (range, 7-14 y) (Table 2). All the patients had long-standing atopic dermatitis that had not responded to topical treatment or short systemic corticosteroid regimens in acute exacerbations. In 1 case, ciclosporin was also ineffective (Table 2).

Before administering AZT, we calculated TPMT levels in the peripheral blood of all patients but one (Case 3, Table 1), whose treatment started more than 3 years previously, before there was a protocol for calculating the activity of this enzyme. Measurements of enzyme activity were made using high-performance liquid chromatography, and the dose of AZT was adjusted to the activity of TPMT (Tables 1 and 3).

Clinical response was evaluated at the end of the study, depending on the need for concomitant treatment to control the disease. Thus, response was classified as complete clearance (patients requiring hydration only), good (<30 g of moderately potent topical corticosteroids monthly), moderate (>30 g/mo), and no response.

Toxicity was evaluated using regular laboratory workups (complete blood count and biochemistry) at baseline, 1 month, and every 3 months during treatment.

Results

None of the patients studied showed a deficit in TPMT activity that would contraindicate the use of the drug

Table 1 Regimens, Duration of Treatment, Clinical Response, and Side Effects During Treatment With Azathioprine

	TPMT, U/mL	Recommended Dose of AZT, mg/kg	Initial Dose	Maximum Dose	Duration of Treatment, mo	Current Situation	Improvement First Observed, mo	Clinical Response	Side Effects
Case 1	6.9	0.5	0.5	0.5	7.5	In treatment	1.5	Clearance	
Case 2	17.5	1.5	1	2	1	In treatment	1	Good	
Case 3	-	-	1.20	2	38	In treatment	1	Good	
Case 4	23.3	2.5	1	1	4	Discontinuation due to concomitant condition ^a	2	Moderate	
Case 5	16.8	1.5	1.25	1.25	15	3 mo without treatment	1	Clearance	Mild leukopenia (5th mo)
Case 6	14.4	1.5	1.5	3	6	No lesions	1	Good	Mild leukopenia (3rd mo)
Case 7	15.3	1.5	0.71	0.71	7	No treatment ^b	2.5	Moderate	

Abbreviations: AZT, azathioprine; TPMT, thiopurine methyltransferase.

^aPatient diagnosed with inflammatory bowel disease not related to administration of AZT.

^bPoor adherence to medical follow-up.

(Table 1). Dose was established according to TPMT levels, although the initial dose administered was generally lower than the recommended dose for those levels, due to the lack of experience with this agent in children (Table 1).

Clinical response began to be observed in all patients between 1 and 2.5 months after starting treatment. During this period, all the patients required concomitant topical medication, and only 2 isolated cases had to be treated with systemic corticosteroids to resolve acute exacerbations. None of the patients required systemic corticosteroids 2 months after the start of treatment.

During treatment, 2 patients received a higher than recommended dose of AZT (Cases 2 and 6, Table 1), due to poor understanding of the prescription; medication was suspended in 1 case, due to diarrhea associated with inflammatory bowel disease (Case 4, Table 1).

As for clinical response, the lesions cleared completely in 2 patients (Figure 1A and B, Case 1), 3 patients had a good response (Figure 2A and B, Case 6), and 2 had a moderate response. In one of the cases with a moderate response, treatment was suspended due to poor adherence to medical follow-up (Case 7, Table 1).

None of the patients experienced adverse events requiring suspension of treatment, and only 2 had mild transitory leukopenia that did not necessitate dose reduction (Cases 5 and 6, Table 1). One of these patients had received a dose of AZT that was higher than recommended according to the TPMT levels (Case 6, Table 1).

At present, 4 patients are receiving AZT (Table 1).

Discussion

Administration of immunosuppressants in children is limited by toxicity. Although these agents are widely used in severe infantile atopic dermatitis,¹ there is no protocol for administration, due to the lack of controlled studies comparing different therapeutic options.

Several immunosuppressants have been used in the management of severe infantile atopic dermatitis, although only ciclosporin has proven effective in controlled studies.^{5,6} Nevertheless, long-term adverse effects, such as renal toxicity, restrict its use.

Other approaches to infantile atopic dermatitis reported in case series are AZT,^{3,7} mycophenolate mofetil,⁸ phototherapy,⁹⁻¹¹ intravenous immunoglobulin,^{12,13} and omalizumab.¹⁴

AZT is a 6-mercaptopurine derivative that was first synthesized in 1956. Despite a similar therapeutic effect to that of its parenteral precursor, its oral bioavailability is much superior.¹⁵ Once inside the body, this drug can follow 3 metabolic pathways (Figure 3): an anabolic pathway, by which it is converted to an active metabolite, and 2 catabolic pathways that degrade it to inactive metabolites. The enzymes involved in the catabolic pathways are xanthine oxidase, whose activity can be reduced using drugs such as allopurinol, and TPMT, whose activity is affected by a genetic polymorphism. The activity of this last enzyme in red blood cells correlates well with its systemic activity. Measurement in white patients has made it possible to identify 3 large groups: 89% with high expression of TPMT,

Table 2 Demographic Characteristics and Previous Treatment

Case	Sex/Age	Onset of Atopic Dermatitis	Other Treatment
1	Male 7 y	During breastfeeding	Topical corticosteroids. Topical tacrolimus and pimecrolimus. Oral corticosteroids
2	Female 7 y	4 y	Topical corticosteroids. Oral corticosteroids
3	Male 9 y	2 y	Topical corticosteroids. Tacrolimus. Oral corticosteroids. Ciclosporin
4	Female 10 y	5 y	Topical corticosteroids. Oral corticosteroids
5	Male 10 y	During breastfeeding	Topical corticosteroids. Tacrolimus
6	Female 12 y	During breastfeeding	Topical corticosteroids. Topical tacrolimus and pimecrolimus. Oral corticosteroids
7	Male 14	4 y	Topical corticosteroids. Tacrolimus and pimecrolimus

Table 3 Recommended Dose of Azathioprine According to Thiopurine Methyltransferase Activity

TPMT Activity	Recommended Dose of Azathioprine
<5.1 U/mL	Do not administer
5.1-13.7 U/mL	<0.5 mg/kg/d
13.8-18.0 U/mL	<1.5 mg/kg/d
18.1-26.0 U/mL	<2.5 mg/kg/d
26.1-40 U/mL	<3.0 mg/kg/d

Abbreviation: TPMT, thiopurine methyltransferase.

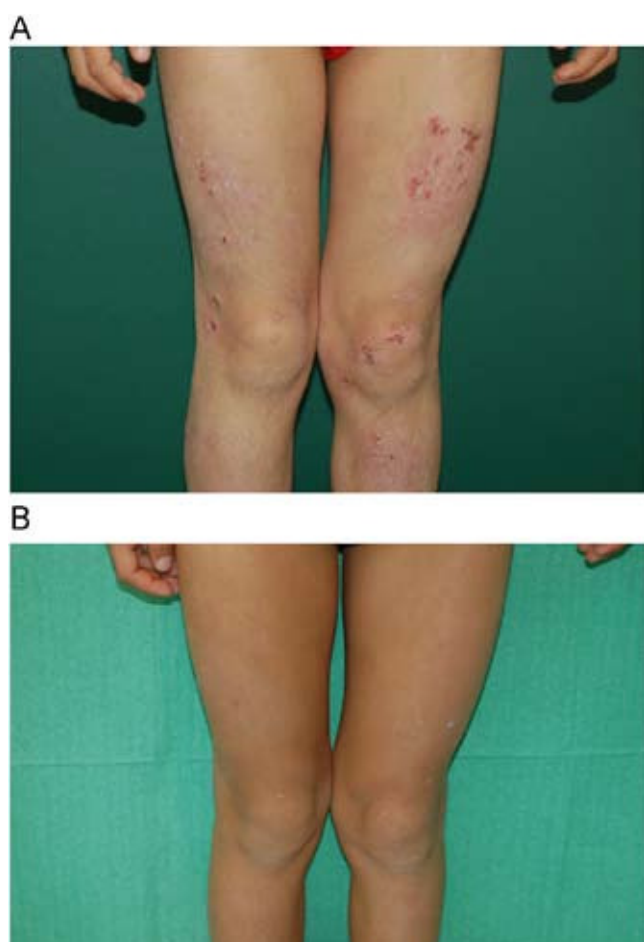


Figure 1 A, Case 1 before start of treatment. B, Case 1 after 7 months of treatment.



Figure 2 A, Case 6 before start of treatment. B, Case 6 after 6 months of treatment.

11% with intermediate expression, and 1 of every 200 or 300 patients with deficient enzymatic activity.¹⁶

The adverse effects of AZT arise mainly from long-term liver toxicity and myelosuppression, the latter related to TPMT levels, which necessitate monitoring of patients throughout treatment. Other adverse effects are shown in Table 4, the most common being gastrointestinal (eg, nausea, vomiting, diarrhea).¹⁶

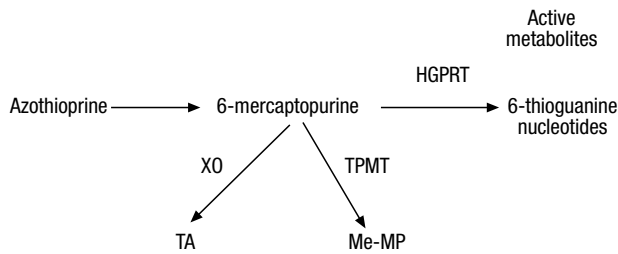


Figure 3 Metabolism of azathioprine. HGPRT indicates hypoxanthine guanine phosphoribosyltransferase; Me-MP, 6-methylmercaptopurine; TA, thiouric acid; TPMT, thiopurine methyltransferase; XO, xanthine oxidase.

Table 4 Side Effects of Azathioprine

Cancer
Squamous cell carcinoma
Lymphoma
Myelosuppression (correlated with low TPMT activity)
Neutropenia
Agranulocytosis and pancytopenia
Infections
HPV, HSV, scabies
Opportunistic infections are uncommon with AZT in dermatologic conditions
Teratogenicity
Hypersensitivity syndrome
Gastrointestinal effects
Liver toxicity
Elevated transaminase levels
Severe hepatocellular toxicity (rare)

Abbreviations: AZT, azathioprine; HPV, human papillomavirus; HSV, herpes simplex virus; TPMT, thiopurine methyltransferase.

In order to avoid toxicity, administration of AZT traditionally consisted of low initial doses combined with close laboratory monitoring and gradual increases until a therapeutic dose was reached. Many authors have recommended a regimen of 1-3 mg/kg/d with a maximum of 100 mg/d,¹⁷ whereas others have proposed a maximum dose of 2.5 mg/kg/d.¹⁶ Today, prior measurement of TPMT levels is used to determine the recommended dose of AZT and identify those patients with a high risk of toxicity in whom it should not be used; it also makes it possible to avoid administering subtherapeutic doses in patients with high enzyme activity.⁴ In patients with low TPMT levels, active metabolites accumulate and there is an increased risk of myelosuppression. In such cases, AZT should be limited. For patients with high TPMT levels, on the other hand, treatment may be insufficient at habitual doses, due to increased catabolism of the drug (Table 3). Therefore, measurement of TPMT levels enables us to optimize the therapeutic effect of AZT and minimize the risk of toxicity.

Few studies have retrospectively evaluated the toxicity and efficacy of AZT in children with severe atopic dermatitis.

Murphy and Atherton³ performed a retrospective study of 48 children who had received AZT and for whom TPMT levels had been calculated to exclude patients with a high risk of myelosuppression. Treatment only had to be suspended in 2 patients (1 hypersensitivity reaction and 1 case of herpetic eczema); 15 patients experienced transitory lymphopenia that did not necessitate discontinuation of medication. Hon et al⁷ evaluated the response in 17 children with atopic dermatitis who had received AZT and for whom TPMT levels were not calculated. In order to avoid toxicity, weekly laboratory workups were performed until the therapeutic dose was reached; no side effects requiring discontinuation of treatment were observed.

Our clinical experience confirms the safety of this treatment, as do the few studies in the literature on AZT in children.^{3,7,18} None of our patients had side effects requiring treatment to be discontinued, suggesting that previous calculation of TPMT levels makes it possible to avoid the drug in patients with low enzyme activity and, therefore, a greater risk of myelosuppression.

Although not the object of our study, measurement of efficacy (with its inherent limitations) was consistent with the literature.^{3,7,18} All our patients experienced some degree of clinical response, which began to develop after 1 month of continuous treatment. Therefore, some patients required concomitant short-term regimens of systemic corticosteroids at initiation of treatment, as was the case in the study by Murphy and Atherton.³

As our patients were children and there is little experience with AZT in this age group, we generally administered a lower initial dose than recommended according to TPMT levels (Table 1). In 2 children (Cases 4 and 7, Table 1), the therapeutic effect took longer to appear, although no causal relationship could be established. The phenomenon of subtherapeutic doses in patients with high TPMT activity has been studied by several authors.^{3,4,19}

Discontinuation was based on the clinical response according to the need for concomitant treatment to control dermatitis; thus, patients who only required hydration for control of symptoms were classed as completely cleared and their medication was withdrawn. In Case 5, with more than 1 year of treatment and more than 1 month of clearance, treatment was discontinued after a tapered regimen. However, in Case 1, whose lesions—first seen at the last checkup—cleared completely in less than 1 month, the dose was reduced to alternate days before withdrawing it completely.

There are no recommendations on the duration of treatment, as there is little published information on the use of this drug in infantile atopic dermatitis. Based on the possible persistence of therapeutic benefit once the drug is withdrawn,¹⁹ Murphy and Atherton³ decided to maintain treatment for approximately 2 years in those patients who showed a good response, before gradually withdrawing the drug. In our cases, duration of treatment did not follow a protocol. The decision to withdraw medication was based on complete clearance of lesions lasting more than 1 month (Case 5), a side effect or medical condition contraindicating continuation (Case 4), and poor adherence to medical follow-up that did not allow appropriate laboratory follow-up (Case 7).

A review of the literature showed that studies on the use of AZT in children are scarce, although some do suggest that this treatment can be very effective in adults.^{2,20} Compared with other available options and as a means of avoiding corticosteroids in severe infantile atopic dermatitis, AZT has a greater range of safety and management than ciclosporin, although its therapeutic effect can take longer.

Our experience with AZT adjusted to TPMT levels in children with severe atopic dermatitis is very positive in terms of safety and efficacy, although more powerful studies are required to confirm these results and establish suitable monitoring protocols in the management of this drug in children.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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