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Review article

Azathioprine in dermatology

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Introduction

Azathioprine (AZA) is a cytotoxic antimetabolite which inhibits purine synthesis. It is an essential metabolic pathway in the replication and proliferation of leukocytes and lymphocytes. It was developed from its parent drug 6-mercaptopurine (6-MP) in 1959, and found its initial use in organ transplant recipients to prevent graft rejection[1]. Due to its favourable therapeutic index, it has since been widely utilised as a corticosteroid-sparing agent. Dermatologists have successfully used azathioprine for over 40 years to treat various diseases. Despite the introduction of newer targeted immunosuppressives like JAK-STAT inhibitors and biologics; high costs, restrictions on off-label use, and limited long-term experience with these newer drugs have prevented a complete shift away from classical immunosuppressive agents, which have stood the test of time. Azathioprine continues to be an important part of current treatment guidelines on pemphigus, bullous pemphigoid, systemic lupus erythematosus and is also used widely in developing countries for alopecia areata and atopic dermatitis.

Pharmacology

Pharmacokinetics

Azathioprine reaches its peak plasma concentration after 2 hours of oral intake with around 88% bioavailability[2]. It can cross the placenta but doesn't cross the blood-brain barrier. It gets almost completely metabolised to its active metabolite 6-thioguanine (6-TG). When azathioprine is given in conventional dosing protocol, this metabolite accumulates in tissues and provides peak clinical immunosuppression at 2-3 months. Therefore, azathioprine is used as maintenance agent along with faster acting drugs like corticosteroids. As azathioprine is completely metabolised, a negligible amount is excreted in its original form.

Metabolism

After administration, azathioprine is rapidly converted into 6-mercaptopurine, mainly in the erythrocytes. It is further metabolised by the one of the three competing pathways (Figure 1). It is converted to its active form, 6-thioguanine (6-TG) metabolite by the enzyme hypoxanthine-guanine phosphoribosyl transferase (HGPRT). However, it is degraded into inactive metabolites by thiopurine methyl transferase (TPMT) and xanthine oxidase (XO). Reduced activity of either of the degradative pathways will result in more active metabolite and hence leads to toxicity.

TPMT polymorphism

TPMT activity can be reduced in certain patients with genetic polymorphism. Currently, both functional activity testing and enzyme allele sequencing are available. By the functional assays that measure the activity, three groups of patients can be identified: those with high activity; intermediate activity; and low activity. Dose modification is required in patients with reduced activity to prevent myelosuppression. Data from the western countries show that the prevalence of heterozygous polymorphism is approximately 10% and of homozygous polymorphism is approximately 0.03%[3]. In studies from Southeast Asia, the incidence of heterozygous polymorphism ranged from 1.2 to 10%; homozygous polymorphism was seen in only 1 of 1566 (0.06%) patients in a study by Davavala *et al*[4].

Xanthine oxidase

Drugs that inhibit xanthine oxidase pathway like allopurinol and febuxostat when co-administered with azathioprine lead to production of more active metabolite leading to excessive immunosuppression and myelosuppression. Hence, the dose of azathioprine should be reduced by 75% in these patients.

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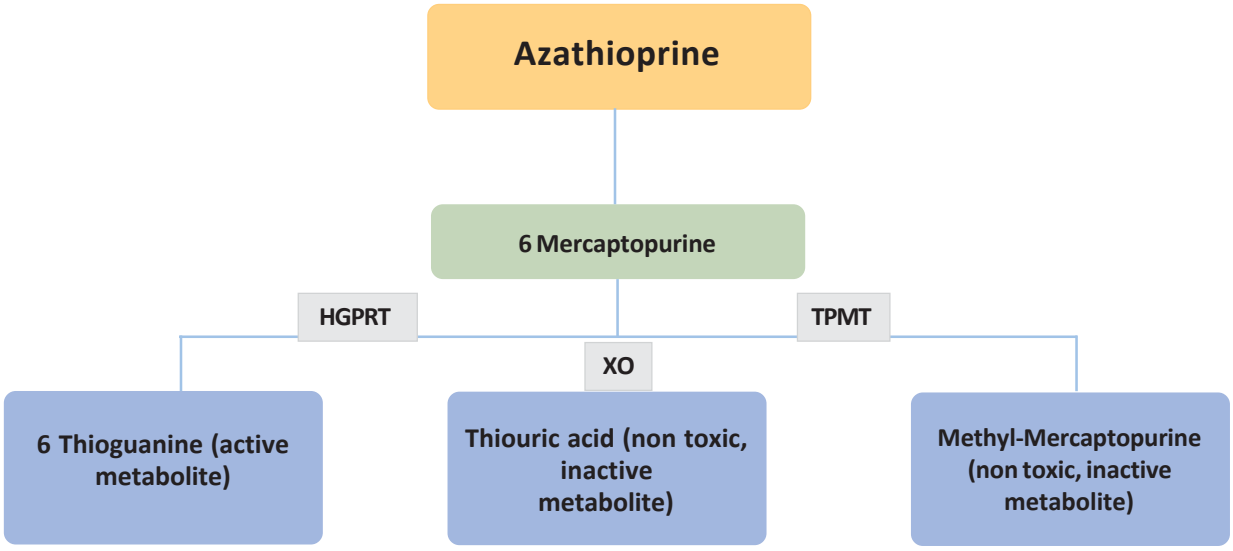

Figure 1. *Azathioprine metabolic pathway.*

Nudix hydrolase 15 (NUDT15)

NUDT 15 is also an important enzyme responsible for converting azathioprine into inactive metabolites. Individuals with reduced or absent activity of this enzyme are prone to severe myelosuppression. Many studies have found that reduced activity of NUDT is more common than that of TPMT in Asian population. Hence, most of European guidelines and American guidelines for screening patients having a high risk of azathioprine-induced myelosuppression might not be applicable to Asian population. As screening for these genetic mutations is costly and not available everywhere, most clinicians rely on routine clinical and laboratory monitoring of blood counts and liver function tests in patients receiving azathioprine.

Mechanism of action

The active metabolite 6-TG is a purine analogue which is similar in structure to both adenine and guanine. Thus, it gets incorporated into the DNA and RNA instead of purine nucleotides, inhibiting DNA replication and cell division, and may even triggering apoptosis. In addition, it inhibits de novo and salvage pathway synthesis of purine nucleotides via feedback mechanism. Azathioprine affects T cell, B cell and antigen presenting cells. Azathioprine reduces both T-cell mediated function as well as B-cell-mediated antibody production. It has thus antiproliferative, immunosuppressive and anti-inflammatory effects.

Dosage

The usual adult dose of azathioprine is 1-3mg/kg/day, which can be given in a once or twice daily oral dose. The dose is adjusted according to response, side effects and TPMT level (Table 1). It can be taken along with food to reduce gastric upset.

Table 1. TPMT levels and recommended dosages of azathioprine

TPMT level and genotype	Dosage of azathioprine
High TPMT >15.1-26.4U/ml or homozygous wild type	Upto 2-2.5mg/kg daily
Medium TPMT 6.3-15 U/ml or heterozygous wild type	Upto 1.0 mg/kg daily
Low TPMT <6.3U/ml or homozygous mutant type	Do not give azathioprine

Azathioprine administered as a weekly pulse dose of 300 mg (6 tablets of 50 mg each) has also been tried[5]. It has proven effective in the management of contact dermatitis due to parthenium (IB), chronic plaque psoriasis (IIB), and alopecia areata (IB). The

adverse effect profile was found to be nearly identical to that of daily azathioprine. Therefore, the weekly azathioprine pulse seems to be a safe and effective alternative to the daily regimen[5].

Pretreatment workup

Baseline clinical evaluation should include discussing the risk-benefit profile and adverse effects with the patient. The patient should be counselled regarding the need for clinical monitoring, periodic blood tests, and contraception. A detailed drug history including current use of allopurinol or febuxostat should be taken.

Azathioprine is a category D drug in pregnancy. A multicentre study of 189 pregnancies exposed to it compared with 230 unexposed pregnancies also found no difference in the malformation rate between the groups. Conversely, they found an association with lower birth weight, gestational age, and prematurity[7]. Motherisk conducted a meta-analysis to evaluate the fetal safety of thiopurines used for treating Inflammatory bowel disease (IBD) during pregnancy, involving 494 IBD patients exposed to thiopurines and 2,782 IBD controls[8]. The authors concluded that the observed associations between thiopurines and prematurity and congenital malformations were likely due to the confounding influence of disease activity[8].

Laboratory investigations like complete blood count, liver function test, kidney function tests with electrolytes, viral markers, urine analysis and chest X-ray are to be done pretreatment. Baseline and annual tuberculosis screening should be done using Mantoux test or interferon gamma release assay. Laboratory tests like complete blood count, liver function tests are repeated fortnightly for the first 2 months and then every 2-3 months. TPMT levels can be done if it is available.

Application in dermatology

Azathioprine has received FDA approval for organ transplant recipients and severe rheumatoid arthritis. Although it has not received FDA approval for any dermatological diseases, it is very commonly used in dermatologic practice, ranging from dermatitis to autoimmune bullous diseases.

Some common indications where azathioprine is routinly used in dermatologic practice are:

Atopic dermatitis

Mild atopic dermatitis is usually well controlled with topical immunosuppressive agents and moisturisers. But in patients with moderate to severe disease not responding to topical drugs, azathioprine is an effective drug alone or in combination with short course of oral corticosteroids. It is a less expensive alternative to cyclosporine in patients with atopic dermatitis.

Two systematic reviews and meta-analysis which compared the effectiveness and safety of systemic treatments in atopic dermatitis showed azathioprine superior to placebo with a moderate effect. However, it had a higher cumulative incidence rate of adverse effects compared to placebo, including myelosuppression and hepato-toxicity (50%-74% for azathioprine and 11%-24% for placebo), as is expected with an immunosuppressive agent[9,10].

Contact dermatitis

Occupational contact dermatitis, like parthenium dermatitis, are common in Southeast Asian countries. With daily dosing of 1-3mg/kg/day, azathioprine has shown significant clinical improvement by achieving >60% reduction in clinical severity of parthenium dermatitis in around 86% of patients over 12 months. Weekly pulse dosing regimen (300mg/week) by Verma et al. also demonstrated similar efficacy with 58.3% achieving >75% improvement and 41.7% showing 60% clearance[5]. Weekly pulse regimen reduced cost by around 60% without compromising on safety[5]. Our research has shown that azathioprine is equally effective as 2mg daily betamethasone in parthenium dermatitis, and it has lower adverse effects and relapses[11]. Since most of the affected individuals belong to lower socio-economic strata, azathioprine is a relatively safe and affordable long-term maintenance agent in such patients.

Chronic actinic dermatitis

Azathioprine is commonly used in patients with chronic actinic dermatitis (CAD) not controlled with topical medications and photoprotection. Although some consider it the first choice for long-term immunosuppression in CAD, mycophenolate mofetil is gaining popularity due to its better adverse effect profile. In a recent study, it achieved EASI in 40% of patients in 11.2 weeks[12].

Immuno-bullous disorders

Azathioprine is a commonly used drug in the management of autoimmune diseases including pemphigus and bullous pemphigoid. As early as 1978, controlled trials comparing azathioprine plus

prednisolone to prednisolone alone indicated that azathioprine has a steroid-sparing effect[13]. The therapeutic effects of azathioprine begin from one week to seven months. It stops the disease progression and promotes re-epithelialization as early as eight weeks after starting treatment in bullous pemphigoid[12].

A systematic review of 11 studies in pemphigus vulgaris and pemphigus foliaceus concluded that although the quality of included studies was not high, there was evidence to support a steroid-sparing effect of azathioprine which appeared greater than that of both cyclophosphamide or mycophenolate mofetil[14].

Vitiligo

Azathioprine is often used as a systemic agent for achieving stability and repigmentation in progressive vitiligo. Although it is less efficacious and slower in halting progression than oral mini pulse, it has a better safety profile[15]. Due to its better adverse effect profile, it can be used in patients with contraindication to corticosteroids or as a steroid-sparing agent in patients requiring recurrent oral mini pulse therapy. Efficacy of azathioprine increases significantly when combined with NB-UVB or PUVASOL. With concurrent phototherapy, azathioprine is equally effective to oral mini pulse with phototherapy and is better than either of the therapies used alone. A randomised controlled trial has demonstrated that a combination of low dose azathioprine (0.6-0.75 mg/kg) with PUVA leads to faster onset of re-pigmentation (5 vs 8 sessions) and overall better re-pigmentation rate (58.4% vs. 24.8%) over 4 months in comparison with PUVA alone[15].

Thus, current evidence suggests that azathioprine has low efficacy as monotherapy in vitiligo, but has a steroid-sparing effect and good efficacy when combined with phototherapy.

Lichen planus

Most patients with lichen planus (LP) require topical immunosuppressive agents but in severe forms like eruptive and erosive lichen planus systemic agents are warranted. In such cases, azathioprine is an important adjuvant with steroid-sparing effects.

In our prospective study of nine patients with erosive oral and generalised LP, complete resolution in 77.8% of cases at doses of 2 mg/kg/day over 3-7 months, with improvement evident within 4-6 weeks[16]. Similarly, in a comparative trial evaluating azathioprine, dapsone, and narrowband UVB (in 90 patients with generalised LP, azathioprine achieved complete response (>90% lesion clearance) in 57.1% and partial response (50-90%) in 35.7% patients[17]. In addition to these studies, our clinical experience has demonstrated that azathioprine is effective and affordable in the management of lichen planus.

Other uses

Azathioprine has been used to treat Behçet syndrome, pityriasis rubra pilaris, erythema multiforme, vasculitis, cutaneous lupus, Reiter syndrome, graft-versus-host disease, prurigo nodularis and acne fulminans.

Adverse effects

Azathioprine is an affordable and effective drug with relatively safe adverse effect profile but if consumed without recommended monitoring, it can lead to adverse effects.

Gastrointestinal (GI) adverse effects

Adverse effects related to GI system are most common with azathioprine which include nausea, vomiting and diarrhoea. Most of these appear within the first few days of treatment and are mostly self-limiting. In some cases, reducing dose, splitting dose, and taking azathioprine with meals help to alleviate these symptoms. Pancreatitis is also very rarely reported with azathioprine.

Hepatic adverse effects

Mild transient elevation of liver enzymes is sometimes seen with azathioprine, which can self-resolve or might require dose reduction of azathioprine. Life-threatening hepatic damage can rarely occur with long-term administration of azathioprine. Hence, regular monitoring of liver enzymes, especially AST and ALT, is recommended.

Haematological adverse effects

Myelosuppression, though rare, is one the most life-threatening complications of azathioprine occurring due to genetic susceptibility (TPMT or NUDT 15 mutation) or drug interaction (allopurinol or febuxostat). In genetically susceptible individuals, myelosuppression can occur even at low doses and can be fatal. Therefore, genetic or enzymatic testing is recommended, but it is either unavailable and is expensive, especially in developing nations. Hence, it is important to recognise that despite tests being normal, patients can still develop myelosuppression, hence a regular monitoring of counts is recommended. After baseline screening, complete blood

count monitoring is recommended every 2 weeks for the first 2 months and then every 2-3 months during therapy.

Infections

Patients on azathioprine are at slightly higher risk of acquiring infections than normal population. The risk is higher among patients receiving higher doses, receiving multiple immunosuppressive agents, having leukopenia with azathioprine, elderly individuals with associated comorbidities.

Risk of developing tuberculosis is around 6-7 times higher in comparison to non-immunosuppressed patients. This risk further increases when combined with other immunosuppressives, especially TNF-α inhibitors. Therefore, patients must be screened for active or latent tuberculosis before starting azathioprine.

Other adverse effects

Azathioprine can also cause hypersensitivity reactions, alopecia, reactivation of infection from live vaccination, cutaneous and hematological malignancies, though these adverse effects are rare and are mostly reported in case reports.

Conclusion

Azathioprine is a highly effective and safe immunosuppressive agent in treating immunobullous disorders, allergic dermatitis, contact dermatitis, lichen planus, vitiligo and other immune mediated diseases. Given the high cost and limited evidence of newer immunosuppressants, azathioprine still remains a key therapeutic agent in these conditions.

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