British Journal of Dermatology 2004; **151:** 1123–1132. DOI: 10.1111/j.1365-2133.2004.06323.x

Guidelines

Guidelines for prescribing azathioprine in dermatology

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Accepted for publication 14 May 2004

Summary Azathioprine has been available as an immunosuppressive agent for over 40 years, and current routine usage in dermatology is not restricted to licensed indications. Advances in understanding the metabolic fate of azathioprine have led to significant changes in prescribing practice and toxicity monitoring by U.K. dermatologists. The current state of knowledge concerning the use of azathioprine in dermatology is summarized, with identification of strength of evidence. Clinical indications and contraindications for azathioprine usage in dermatology are identified. Evidence-based recommendations are made for routine safety monitoring of patients treated with azathioprine, including pretreatment assessment of red blood cell thiopurine methyltransferase activity.

Disclaimer

These guidelines have been prepared for dermatologists on behalf of the British Association of Dermatologists and reflect the best data available at the time the report was prepared. Caution should be exercised in interpreting the data; the results of future studies may require alteration of the conclusions or recommendations in this report. It may be necessary to depart from the guidelines in the interests of specific patients and in special circumstances. Just as adherence to guidelines may not constitute defence against a claim of negligence, so deviation from them should not necessarily be deemed negligent.

Introduction

Azathioprine is an immune-modulating drug that was originally developed for the control of graft rejection in transplant surgery. Since it became available in the early 1960s, azathioprine has also been prescribed for a range of autoimmune and immune-mediated dermatological conditions. Licensed indications include dermatomyositis, systemic lupus erythematosus and pemphigus vulgaris. It is used for these conditions either alone or, more commonly, in combination with corticosteroids. Therapeutic effect is typically delayed for weeks or even 2–3 months, and includes a steroid-sparing effect that reduces long-term toxicity of corticosteroids. Azathioprine is also used quite frequently as monotherapy in nonlicensed indications including atopic eczema.

Adverse drug reactions with azathioprine occur in 15–28% of patients[1–3] and include myelosuppression, nausea and vomiting, rash, pancreatitis and hypersensitivity. Polymorphism in the thiopurine methyltransferase (TPMT) gene predicts haematological adverse drug reactions in 5–10% of patients treated with thiopurine drugs.[1] The remaining adverse drug reactions are unexplained, and may be mediated by immune mechanisms or by other variables affecting the metabolic fate of the drug. It is therefore essential to continue monitoring blood counts throughout treatment with azathioprine.[4]

Methods

The aim of the search strategy was to identify recent and past publications relating to the clinical pharmacology of azathioprine that were relevant to its current usage within dermatology. The evidence gathered

These guidelines were commissioned by the British Association of Dermatologists Therapy, Guidelines and Audit Subcommittee. Members of the committee are A.D.Ormerod (Chairman), A.S.Highet, D.Mehta, R.H.Meyrick Thomas, C.H.Smith, J.C.Sterling and A.Anstey. Conflicts of interest: No additional funding was received by the authors of these guidelines to support this work. None of the authors has a conflict of interest to declare.
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includes some derived from disciplines other than dermatology, such as gastroenterology, where azathioprine usage is high and experience with TPMT-guided prescribing is established.

Types of studies

Randomized, double-blind, placebo-controlled trials; well-designed controlled trials without randomization; well-designed cohort or case–control analytical studies; evidence from multiple time series with or without intervention; opinions of respected authorities based on clinical experience, descriptive studies or reports of expert committees.

Search strategy for identification of studies

A computer-assisted search of the online bibliographic databases Medline, PubMed and Embase was carried out to identify potentially relevant papers published between 1966 and 2003. Other databases searched included the Royal College of Physicians Guidelines database, CINAHL, the Cochrane library, DARE, AMED and HMIC. The following search terms were used: azathioprine; 6-mercaptopurine; dermatology; adverse drug reactions; clinical monitoring; TPMT; thiopurine methyltransferase. Citations were limited to those in English, French, Spanish, Italian and German. Manual searches of the reference lists from the relevant papers were performed in order to identify additional studies that may have been missed by the computer-assisted strategy. These guidelines include evidence derived from the key papers identified by the search strategy.

Risks and benefits of azathioprine therapy in dermatology

Particular emphasis has been placed on assessing the risks and benefits of azathioprine therapy for patients with dermatological disease. These guidelines attempt to establish an explicit link between evidence and recommendations for clinical usage. This is sometimes difficult, as decisions in clinical medicine occur in the context of single patients and do not always relate to the context from which a guideline recommendation has been made. Finally, these guidelines have been subjected to expert review by nondermatologists (acknowledged) with recognized expertise in the prescribing of azathioprine. In line with other British Association of Dermatologists (BAD) guidelines it is the intention for these guidelines to be reviewed and updated in 5 years.

Pharmacology

Azathioprine is a prodrug with no inherent immunosuppressive activity. Azathioprine is an imidazole derivative of 6-mercaptopurine (6-MP) and is therefore classed as a purine analogue. It was developed in an attempt to produce a drug with the same immunosuppressive activity as 6-MP but with significantly slower metabolism. Following oral administration, azathioprine is rapidly and almost completely absorbed from the gut. No azathioprine crosses the blood–brain barrier, but there is otherwise an even distribution of the drug throughout the body. The plasma half-life is just 3 h owing to rapid nonenzymatic conversion to 6-MP, the active compound, and imidazole derivatives. 6-MP has a long half-life and is metabolized by three competing pathways (Fig. 1). Active 6-thioguanine nucleotide metabolites are generated by the action of hypoxanthine guanine phosphoribosyl transferase (HPRT). Xanthine oxidase, which is inhibited by allopurinol, metabolizes 6-MP to inactive 6-thiouric acid. The third of the competing pathways involves methylation of 6-MP to 6-methyl mercaptopurine, an inactive compound, which is catalysed by TPMT.

Azathioprine mode of action

6-MP readily crosses cell membranes, and is converted by the enzyme HPRT into a number of active purine thionucleotide metabolites. The exact mode of action of azathioprine at a cellular level remains unclear, but thionucleotide metabolites of 6-MP are believed to compete with their endogenous counterparts in many biochemical pathways. Nucleotides have a number of important roles in all cells: they are precursors of DNA and RNA, they are essential carriers of energy (e.g. adenosine triphosphate and guanosine triphosphate), and they function as cellular second messengers. These nucleotide-dependent processes endow azathioprine with both immunosuppressive and cytotoxic properties. There is also evidence that imidazole derivatives and the thiopurine intermediates have independent immunosuppressive properties.[5]

The significance of thiopurine methyltransferase in the clinical pharmacology of azathioprine

There is marked interpatient variability in the generation of immunosuppressant metabolites, resulting from

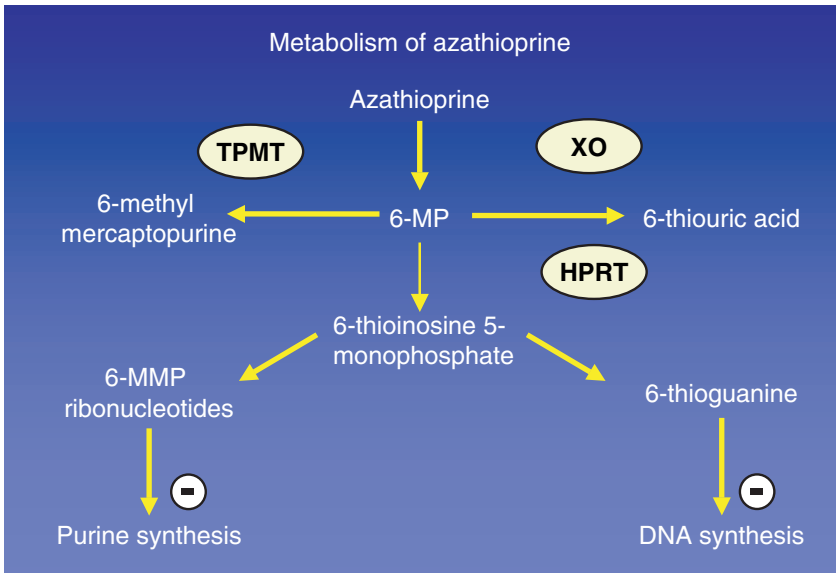

Figure 1. Metabolism of azathioprine. The first metabolite is 6-mercaptopurine (6-MP). This may be metabolized in three ways: (i) methylation to inactive 6-methyl mercaptopurine (6-MMP) catalysed by thiopurine methyl transferase (TPMT); (ii) oxidation to inactive 6-thiouric acid catalysed by xanthine oxidase (XO); and (iii) hypoxanthine guanine phosphoribosyl transferase (HPRT) catalyses the conversion of 6-MP to 6-thioinosine 5-monophosphate which is further converted to 6-thioguanine. 6-Thioguanine has an inhibitory effect on DNA synthesis.

a common genetic polymorphism in TPMT, one of three competing pathways for 6-MP metabolism (Fig. 1). Eleven per cent of the population has low TPMT activity and is vulnerable to myelosuppression with azathioprine treatment.[6] Furthermore, one in 300 individuals has undetectable TPMT activity,[6] and is susceptible to rapid-onset, prolonged, life-threatening pancytopenia if treated with conventional doses of azathioprine.[7] A recent large clinical study on patients being treated with azathioprine showed the rate of undetectable TPMT activity to be higher, at one in 200 patients;[4] however, the cases in this series were not randomly selected and there may have been some bias towards a higher rate of 'problem cases'. Inhibition of xanthine oxidase, the third enzyme in this system (Fig. 1), produces the same effect on azathioprine metabolism as deficiency in TPMT: decreased metabolism of 6-MP to inactive metabolites, and increased generation of immunosuppressant 6-thioguanine nucleotides. This explains the potentially serious drug interaction between azathioprine and allopurinol.[8,9]

Azathioprine indications in dermatology

Indications are listed in Table 1. Azathioprine is a popular drug with dermatologists, as it is perceived as an immunosuppresive drug in which the potential benefits outweigh the potential risks. The main area of use in dermatology is in the treatment of autoimmune dermatoses, in particular bullous pemphigoid[10–12] (Grade B; level IV; see Appendix 1), and pemphigus vulgaris[13,14] (Grade B; level II-iii) where azathioprine is used as a steroid-sparing agent. Accumulating evidence also suggests a role for azathioprine as a single agent in the treatment of severe, recalcitrant atopic dermatitis[15–17] (Grade A; level I). Double-blind, placebo-controlled trials have shown azathioprine to be of benefit in chronic actinic dermatitis[18] (Grade A; level I) and Behçet's disease[19] (Grade A; level I). It may also be effective as monotherapy in the treatment of severe, recalcitrant psoriasis[20] (Grade C; level IV). Azathioprine is sometimes used in the treatment of other rare dermatological conditions including Wegener's granulomatosis,[21] pyoderma gangrenosum,[22] pityriasis rubra pilaris,[23] lupus erythematosus[24] and lichen planus,[25] but evidence to support its usage in these conditions is anecdotal[26] (Grade C; level IV).

Table 1 Licensed and unlicensed indications for azathioprine in the treatment of dermatological disorders

Licensed indications	Unlicensed indications
Systemic lupus erythematosus	Atopic dermatitis
Dermatomyositis	Psoriasis
Pemphigus vulgaris	Bullous pemphigoid
	Chronic actinic dermatitis
	Pyoderma gangrenosum
	Pityriasis rubra pilaris
	Wegener's granulomatosis
	Cutaneous vasculitis

Azathioprine contraindications

Azathioprine is contraindicated in patients with known hypersensitivity to the drug[27–29] (Grade A; level III). Evidence of teratogenicity with azathioprine in humans

is equivocal,[30] but adequate contraceptive precautions are advised when either partner is taking azathioprine. Azathioprine is also contraindicated in pregnancy (except where benefit may outweigh risk such as in allograft recipients)[30–32] (Grade A; level II-ii). 6-MP has been identified in colostrum and in the breast milk of women receiving azathioprine treatment. Women on azathioprine should therefore be advised to bottle feed their babies. It is strongly recommended that azathioprine should not be used in patients whose TPMT status is unknown[4,15] (Grade A; level II-ii). Very low or absent TPMT activity is a contraindication to the usage of azathioprine because of the high risk of life-threatening pancytopenia[24] (Grade A; level II-ii). Concurrent treatment with allopurinol results in an important drug interaction which may cause significant myelosuppression, and should therefore be avoided[8,9] (Grade A; level III).

There are concerns that azathioprine treatment increases the risk of developing a malignancy. Accumulating evidence suggests that this risk is smaller than was originally feared.[33,34] Nevertheless, patients should be advised of this risk, and it is recommended that azathioprine treatment should not usually be initiated or continued in patients with known malignancy (Grade A; level III).

Contradictions to azathioprine:

- It is strongly recommended that azathioprine should not be used in patients whose TPMT status is unknown
- Known hypersensitivity to azathioprine (or 6-MP)
- Azathioprine is contraindicated in patients who may be pregnant or hope to become pregnant in the near future (except where benefit may outweigh risk)
- Women taking azathioprine should not breast feed their babies
- Very low or absent TPMT activity
- Concurrent allopurinol treatment
- Concurrent malignant disease where azathioprine treatment may increase the risk of disease progression
- Renal or hepatic insufficiency (relative contraindication)

Pretreatment thiopurine methyltransferase assessment

Azathioprine prescribing practice among U.K. dermatologists has changed in recent years, with increased demand for pretreatment assessment of TPMT activity.[4] This is explained by greater awareness of the significance of interpatient variability in TPMT activity that coincided with availability of a National Health Service laboratory service for TPMT assay (Guy's Hospital, Purine Research Laboratory). The justification for pretreatment TPMT measurement is the presumed improvements in safety and efficacy that follow from knowing its activity. In acute lymphoblastic leukaemia (ALL) treated with 6-MP, lower TPMT activity tended to be associated with a better outcome,[35] although ALL patients with lower TPMT activity appeared to be at greater risk of developing second malignancies.[35] Although there are currently no published prospective studies for dermatological conditions which demonstrate improved prognosis, TPMT screening prior to azathioprine treatment is considered by some clinicians to be essential (Grade A; level II-ii).[4,10]

Knowledge of TPMT prevents those with very low or undetectable TPMT from receiving azathioprine, and may prevent fatal myelosuppression. This is the most important aspect of measuring TPMT. Prior TPMT assessment also identifies those with intermediate activity who would be predicted to suffer toxicity on standard doses of azathioprine but who might tolerate and respond to tailored doses of azathioprine. Other components of the azathioprine metabolic pathways may rarely be deficient or exert an immunosuppressive effect, including deficiency in purine-5′-nucleotidase and xanthine oxidase, and lethal immunosuppressive effects mediated by imidazole derivatives.[5] Dermatologists should therefore be aware that knowledge of TPMT status does not preclude the necessity for monitoring for azathioprine toxicity by regular blood tests. Genotype tests for the commonest mutations in the TPMT gene are of interest to clinicians, but do not provide the functional result which measurement of the enzyme activity provides.[36] Furthermore, the TPMT genotyping tests are not yet available in the U.K. as a routine laboratory test. Thus, dermatologists are advised to continue to use the TPMT enzymatic assay.

- Pretreatment TPMT measurement should be performed in all patients prescribed azathioprine for treatment of dermatological conditions

Azathioprine dosage

The recommended dosage of azathioprine for dermatological indications is 1–3 mg kg^{-1} daily, adjusted within these limits according to response. If no improvement occurs in the patient's condition within

3 months, consideration should be given to withdrawing azathioprine. Care should be taken when prescribing azathioprine in the elderly: it is recommended that the dosage used is at the lower end of the range. There are currently no data to support prescribing azathioprine in doses outside the above range. However, modified dosage regimens based on TPMT activity have been published for both adults[16,37] and children[38] (Grade C; level III), and are the logical progression of this pharmacogenetic assessment.

Azathioprine should not be used in patients with very low/absent TPMT activity (deficient), as the danger of severe and prolonged myelosuppression is significant[20,39] (Grade A; level II-ii). Patients with inflammatory bowel disease and low TPMT activity have been shown to be at increased risk of azathioprine toxicity.[39] Thus, for patients with low TPMT activity, alternative systemic therapies should be considered (Grade A; level II-ii). If a trial of azathioprine is deemed appropriate in this situation, a low-dosage regimen should be used (0·5–1 mg kg^{-1} daily) and extra care taken with haematological surveillance (Grade B; level III).

In patients with high TPMT activity (see Appendix 2 for laboratory ranges), the azathioprine dose should be at the higher end of the range of 1–3 mg kg^{-1} daily. It is probably safe to treat these patients from the outset with dosages of azathioprine towards the top end of this dosage range provided the usual measures are taken to monitor for myelosuppression. However, azathioprine intolerance unrelated to TPMT activity is not uncommon, and a lower initial dose of azathioprine is advocated by some authors for the first month of therapy, even in patients with high TPMT activity.[10] In patients with inflammatory bowel disease, high TPMT activity predicts treatment failure with azathioprine.[3] Thus, in dermatology patients with high TPMT activity, azathioprine dosage should be at the top of the recommended dose range of 1–3 mg kg^{-1} daily. In patients who fail to respond to 3 months of this dosage regimen, and in whom no adverse effects occur, dosage above the 1–3 mg kg^{-1} daily range might be considered for a trial period (Grade C; level III). However, if this approach is adopted, care should be taken in monitoring for myelosuppression and possible hepatotoxicity.

- If no therapeutic response is observed within 3 months of starting azathioprine, treatment should usually be withdrawn
- In patients with very low/absent TPMT activity (deficient), azathioprine is contraindicated
- In patients with low TPMT activity, azathioprine should either not be prescribed or, if used, the dose should be low (0·5–1 mg kg^{-1} daily) with careful monitoring for myelosuppression
- In patients with normal or high TPMT activity, azathioprine dosage should commence at the top of the 1–3 mg kg^{-1} daily dosage range. In patients who fail to respond, and in whom no adverse effects occur, dosage above the 1–3 mg kg^{-1} daily range might be considered for a trial period

Monitoring for azathioprine-induced toxicity

The data sheet for azathioprine recommends weekly monitoring of full blood count (FBC) for the first 8 weeks of treatment. However, the *British National Formulary* states that the 'evidence of the practical value (of weekly FBC for 8 weeks) is unsatisfactory', and recommends weekly FBCs for the first 4 weeks, followed by reduced frequency of monitoring to a minimum of once every 3 months. Routine monitoring for azathioprine toxicity should also include liver function tests (LFTs) as hepatoxicity is a recognized complication of azathioprine therapy.[10,11,40,41] Thus, it is advised that dermatologists carry out weekly blood tests (FBCs and LFTs) until maintenance dose is achieved, followed by regular monitoring reducing to a minimum of once every 3 months for the duration of therapy[42] (Grade A; level I).

For higher dosages and for patients with hepatic or renal impairment, initial blood count monitoring more frequently than once weekly is advised. Return to weekly FBCs and LFTs should also follow an increase in dosage in azathioprine in patients already established on this treatment. It is also advised that patients on azathioprine be instructed to report immediately any evidence of infection, unexpected bruising or bleeding or jaundice. In patients with low TPMT activity (3–8 nmol h^{-1} mL^{-1} red blood cells), monitoring for FBC and LFTs should be more frequent than outlined above due to the increased risk of toxicity. Acute pancreatitis is a rare but well-recognized side-effect of azathioprine treatment.[43] In azathioprine-treated patients with acute abdominal pain and/or severe vomiting, acute pancreatitis should be considered and serum amylase measured.

Monitoring for azathioprine toxicity should include:

- Weekly monitoring of FBC and LFTs for the first 4 weeks of therapy, or until the maintenance dose is achieved; reducing to a minimum of once every 3 months for the duration of therapy

- More frequent monitoring of FBC and LFTs is advised in patients with hepatic or renal impairment, in the elderly and in those treated with high doses of azathioprine
- Increase in dosage of azathioprine should be accompanied by return to weekly FBC and LFTs for 4 weeks, reducing to a minimum of once monthly or every 2 months for the duration of therapy

Azathioprine-induced susceptibility to infection

In transplant recipients, the immunosuppressive activity of azathioprine in combination with corticosteroids can lead to an increased susceptibility to viral, bacterial and fungal infections which manifest in the skin and in other body organs (azathioprine data sheet). In dermatology, azathioprine is most commonly prescribed for management of immunobullous disorders, where combination with systemic steroids is the norm. Evidence of infection in such patients is inconsistent, and in the absence of reliable information on this topic dermatologists should assume an increased rate of infection as for transplant recipients. Infection in elderly patients with bullous pemphigoid treated with azathioprine and prednisolone has been identified as a significant cause for mortality, particularly when compared with rates of such fatal infections in patients treated with prednisolone alone.[44]

The use of azathioprine monotherapy does not appear to give rise to a marked increase in susceptibility to such infections (azathioprine data sheet). However, the immunosuppressive activity of azathioprine could result in an atypical and potentially deleterious response to live vaccines. Thus, administration of live vaccines to patients receiving azathioprine is contraindicated on theoretical grounds. A diminished response to killed vaccines may occur, and has been observed with hepatitis B vaccine in patients treated with a combination of azathioprine and corticosteroids. In view of the potential severity of primary varicella zoster in the immunosuppressed, patients who have not previously had chickenpox should be identified at the outset of azathioprine prescribing and advised to seek immediate attention if they subsequently come into contact with someone who has chickenpox or shingles.[45]

- Azathioprine in combination with prednisolone is associated with an increased risk of infection, which may be fatal in the elderly. Dermatologists are advised to use the minimum necessary doses of immunosuppressive therapies to control immunobullous diseases in the elderly[10] (Grade A; level II-ii)
- Live vaccines are contraindicated for patients receiving azathioprine (Grade A; level III)
- Killed vaccines may elicit a diminished immune response in patients receiving azathioprine (Grade B; level II-ii)

Azathioprine-related malignancy

The inhibitory effect of azathioprine on the immune surveillance system could, on theoretical grounds, lead to an increased rate of malignancy with long-term therapy. The increased incidence of neoplasms in azathioprine-taking immunosuppressed renal transplant recipients[46] cannot easily be compared with patients receiving azathioprine for other diseases due to the strong antigenic stimulation by the graft and the taking of two or more immunosuppressive drugs.[47] Importantly, there was no increase in the rate of malignancies in a large number of azathioprine-treated, nontransplant patients compared with placebo-treated controls.[48] Long-term treatment with azathioprine for inflammatory bowel disease was not associated with a significant increase in malignancy compared with matched controls.[34] However, long-term treatment with azathioprine for rheumatoid arthritis showed an increased rate of lymphoma which was estimated at one case of lymphoma per 1000 patient years of azathioprine treatment.[33] The evidence concerning mutagenicity in relation to azathioprine is unclear, and there is also no clear evidence that azathioprine *per se* is oncogenic in humans. However, the significantly increased rate of skin malignancies in transplant recipients compared with the general population is undisputed, and may in part be due to the immunosuppressive effects of azathioprine. Despite this, reports of skin malignancy in patients receiving long-term azathioprine monotherapy are rare, suggesting that the risk, if it exists, is probably small.

- Dermatologists should make patients aware of the possible increased risk of malignancy related to long-term azathioprine therapy (Grade B; level IV)
- Skin photoprotection should be advised when relevant (Grade B; level IV)

Azathioprine-induced hypersensitivity reactions

Idiosyncratic hypersensitivity reactions with azathioprine are recognized, but are rare.[49] Manifestations include nausea, diarrhoea and vomiting, malaise, dizziness, fever, rigors, rashes (urticarial, maculopapular and vasculitic) and even circulatory collapse. The drug should be discontinued immediately and circulatory support initiated if necessary. The aetiology of the reaction is unknown. Rechallenge should be avoided, as the reaction is generally more severe and occasionally life-threatening.

Management of azathioprine-induced complications

Clinical manifestations of chronic azathioprine overdosage are those of bone marrow suppression: unexplained infection, ulceration of the throat, bruising and bleeding. The most obvious aspect of management of this complication is to take the necessary measures to prevent it happening in the first place. This should include measurement of TPMT status, in combination with monitoring of the FBC as described above. Isolated lymphopenia is not uncommon with azathioprine therapy and may be due to lymphocytotoxicity induced by azathioprine-derived imidazole derivatives.[5] Dose reduction is recommended if the lymphocyte count falls below $0{\cdot}5 \times 10^{9}\ L^{-1}$.

If bone marrow suppression occurs, the earliest feature is leucopenia followed by reduction in platelet count. Early changes in these parameters with a downward trend but absolute levels within normal ranges should alert the clinician to the need for continued vigilance in haematological assessment and should raise the option of reduced dosage or withdrawal of treatment. More significant myelosuppression with blood indices below the normal ranges should be managed by immediate withdrawal of azathioprine. Regular monitoring of the FBC will indicate whether the blood count suppression is significant. Platelet count below $50 \times 10^{-9}\ L^{-1}$ and neutrophil count below $1{\cdot}0 \times 10^{9}\ L^{-1}$ should be managed jointly with a haematologist.

Azathioprine-induced hepatotoxicity should be diagnosed early (by carrying out frequent monitoring of LFTs as recommended in these guidelines) and managed by dosage reduction or withdrawal of azathioprine. Gastrointestinal upset is common with azathioprine treatment and may occasionally require dosage reduction or withdrawal of treatment. Practical suggestions on how to manage gastrointestinal upset include splitting the dose of azathioprine, starting at a lower dose and then increasing to the required dose, and taking azathioprine with, or shortly after food.

Patient information and informed consent

Because of the potential for serious adverse effects associated with azathioprine, patients should be carefully counselled before starting treatment. Patients who are unable to comply with close monitoring are unsuitable for treatment with this drug. It is recommended that the following points are discussed, an azathioprine patient information sheet is provided, and written documentation of this made in the case notes.

1. Azathioprine has a slow onset of action and benefit may not be apparent until 2–3 months after starting treatment. The importance of regular blood tests, which are particularly frequent at the start of treatment, should be reinforced. The drug should be taken once or twice daily, with or after food.
2. The prescribing physician should explain whether use of azathioprine is for a licensed indication or not.
3. Patients should be advised to seek urgent medical attention if they develop signs and symptoms of bone marrow impairment or liver impairment, such as unexplained bruising, sore throat, high fever or jaundice. It is important to explain that symptoms of azathioprine hypersensitivity may initially be mistaken for 'flu'.
4. Patients taking azathioprine who have not had chickenpox should seek immediate attention if they come into contact with someone who has chickenpox or shingles for consideration of zoster immune globulin. Patients taking azathioprine should not be given live vaccines, and due to the risk of orofaecal transmission, other members of their household should be given inactive (rather than live) polio vaccine.
5. There may be a small increase in the risk of malignancy with long-term treatment with azathioprine. The drug should be continued only when benefits outweigh the risks.
6. Patients should be warned that the following treatments may interact with azathioprine:

Allopurinol inhibits the enzyme xanthine oxidase and prolongs the action of azathioprine with potential for increased toxicity. Concomitant administration should be avoided.

Sulfasalazine inhibits TPMT activity and may potentiate azathioprine toxicity.

Warfarin. The anticoagulant effect may be impaired by azathioprine.

Myelosuppressive drugs such as penicillamine and co-trimoxazole should be avoided due to the possibility of inducing serious haematological toxicity.

Angiotensin-converting enzyme inhibitors have been reported to induce severe leucopenia in patients taking azathioprine.

Live vaccines are contraindicated on theoretical grounds in patients taking azathioprine.

7 Pregnancy should be avoided during treatment with azathioprine, and women taking this drug must ensure that they use adequate contraceptive precautions.

8 Patients should be warned that sudden onset of abdominal pain, with or without severe vomiting, may be due to pancreatitis related to the azathioprine treatment. Patients should seek urgent medical attention. Serum amylase should be checked urgently in this situation.

- Before azathioprine is prescribed, the clinician should provide the patient with an azathioprine patient information sheet, and discuss the anticipated benefits and possible side-effects

Conclusions

Better understanding of azathioprine therapeutics has resulted from its continued use for more than 40 years. Insight into the genetic basis of drug metabolism has resulted in changes in routine usage of azathioprine aimed at improving drug efficacy and safety. Measurement of TPMT activity before prescribing azathioprine combined with alterations in the routine prescribing of azathioprine is the best example to date of the evolving field of pharmacogenetics.[50,51] This is due to the unusual occurrence of a single allelic variant (i.e. that encoding low/absent TPMT activity) resulting in a significant clinical effect. Thus, the case for pre-azathioprine screening is clear-cut and is increasingly endorsed by clinician demand for this service. There is now the need to reassess azathioprine usage in the face of the change in the way it is prescribed in clinical practice, by further epidemiological research on adverse and beneficial drug effects.[52]

Audit of azathioprine prescribing

This paper includes highlighted recommendations for good practice in relation to the prescribing of azathioprine. Any one of these could be used to establish agreed local standards of care against which audit could be performed. For example, 'indications for usage of azathioprine' might be one area, taking into account the licensed indications for azathioprine and the conditions for which there is good evidence to support its use from randomized controlled trials. There is now a broad consensus among U.K. dermatologists that pretreatment TPMT measurement is necessary for improved safety and more effective dosage selection for patients treated with azathioprine. Thus, audit on usage of TPMT screening could follow the development of agreed local standards of care concerning this investigation. Routine monitoring of azathioprine toxicity is another area where recommendations are made, and locally agreed standards could precede an audit to assess compliance with that standard. Perhaps the most novel audit project concerns what we tell our patients. The recommendations for patient information in this document exceed what most dermatologists currently do. A patient information sheet has also been developed by the BAD (available on the patient section of the BAD website: http://www.bad.org.uk/patient) to be used in combination with detailed patient-focused discussion of the merits and hazards of this drug.

Acknowledgments

The authors wish to acknowledge the following contributors: Dr Alex Holme, Dr Simon Meggit, Dr Jeremy Sanderson, Dr Tony Marinaki, Dr Catherine Davies and Dr Jonathan Berg. Mrs Joanna Dundon is acknowledged for assistance with the search strategy.

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Appendix 1. *Levels of evidence on which the guideline is based*

The consultation process and background details for the British Association of Dermatologists (BAD) guidelines have been published previously.[53,54] The patient information sheet to accompany this guideline is available on the BAD website: http://www.bad.org/patient

Level	Type of evidence
I	Evidence obtained from at least one properly designed, randomized controlled trial
II-i	Evidence obtained from well-designed controlled trials without randomization
II-ii	Evidence obtained from well-designed cohort or case–control analytical studies, preferably from more than one centre or research group
II-iii	Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence
III	Opinions of respected authorities based on clinical experience, descriptive studies or reports of expert committees
IV	Evidence inadequate due to problems of methodology (e.g. sample size, or length of follow-up, or conflicts of interest)
Grade of recommendation	
A	There is good evidence to support the use of the procedure
B	There is fair evidence to support the use of the procedure
C	There is poor evidence to support the use of the procedure
D	There is fair evidence to support the rejection of the use of the procedure
E	There is good evidence to support the rejection of the use of the procedure

Appendix 2. *Measurement of erythrocyte thiopurine methyltransferase (TPMT) activity*

- TPMT activity should be checked before starting therapy, as azathioprine may induce TPMT enzyme activity
- In cases of doubt, clinicians should discuss the result with the testing laboratory. Genotyping may be helpful in selected cases
- Whole blood is required for analysis (4 mL in ethylenediamine tetraacetic acid)
- Turnaround time for results varies according to laboratory and demand, but is usually within 2 weeks
- The blood sample should be appropriately packaged and labelled and sent by first-class post at room temperature
- Patients who have recently received blood products can have misleading TPMT results
- The following two U.K. National Health Service laboratories provide TPMT testing. Costs of tests are available on demand from each laboratory:

The Purine Research Laboratory, 5th Floor, Thomas Guy House, Guy's Hospital, London SE1 9RT, U.K.

Department of Clinical Biochemistry, City Hospital, Dudley Road, Birmingham B18 7QH, U.K.

The details of TPMT testing by the two laboratories are as follows

	Guy's Hospital	Birmingham City Hospital
Method	Tandem mass spectrometry	High-performance liquid chromatography
Units	pmol h^{-1} mg^{-1} haemoglobin	nmol h^{-1} g^{-1} haemoglobin
	Very low/absent < 10	Deficient < 5
	Low 10– < 25	Low 6–24
	Normal 25–50	Normal 25–55
	High > 50	High > 55

The methodology for TPMT testing used by the laboratory at Guy's Hospital measures the formation of 6-methyl mercaptopurine from the substrates 6-mercaptopurine and *S*-adenosylmethionine. The 6-methyl mercaptopurine product is quantified by tandem mass spectrometry relative to a deuterated 6-methyl mercaptopurine internal standard.

The methodology for TPMT testing at Birmingham City Hospital uses 6-thioguanine as substrate and measures the product 6-methyl-thioguanine by high-performance liquid chromatography with fluorescence detection.