

Use of thiopurines in inflammatory bowel disease: Safety issues

Anastasia Konidari, Wael El Matary

Anastasia Konidari, Department of Paediatric Gastroenterology, Alder Hey Children's NHS Foundation Trust, Liverpool L12 2AP, United Kingdom

Wael El Matary, Section of Paediatric Gastroenterology, Department of Paediatrics, Faculty of Medicine, University of Manitoba, Manitoba R3A 1S1, Canada

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Correspondence to: Dr. Wael El Matary, MD, Associate Professor, Section of Paediatric Gastroenterology, Department of Paediatrics, Faculty of Medicine, University of Manitoba, AE 408-840 Sherbrook Street, Winnipeg, Manitoba R3A 1S1, Canada. welmatary@hsc.mb.ca

Telephone: +1-11-2047871039 Fax: +1-11-2047871450

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Abstract

Thiopurines are widely used for maintenance treatment of inflammatory bowel disease. Inter-individual variability in clinical response to thiopurines may be attributed to several factors including genetic polymorphisms, severity and chronicity of disease, comorbidities, duration of administration, compliance issues and use of concomitant medication, environmental factors and clinician and patient preferences. The purpose of this review is to summarise the current evidence on thiopurine safety and toxicity, to describe adverse drug events and emphasise the significance of drug interactions, and to discuss the relative safety of thiopurine use in adults, elderly patients, children and pregnant women. Thiopurines are safe to use and well tolerated, however dose adjustment or discontinuation of treatment must be considered in cases of non-response, poor compliance or toxicity. Drug safety, clinical response to treatment and short to long term risks and benefits must be balanced throughout treatment duration for different categories of patients. Treatment should be individu-

alised and stratified according to patient requirements. Enzymatic testing prior to treatment commencement is advised. Surveillance with regular clinic follow-up and monitoring of laboratory markers is important. Data on long term efficacy, safety of thiopurine use and interaction with other disease modifying drugs are lacking, especially in paediatric inflammatory bowel disease. High quality, collaborative clinical research is required so as to inform clinical practice in the future.

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Key words: Thiopurines; Azathioprine; Mercaptopurine; Inflammatory bowel disease; Adult; Children; Therapeutic drug monitoring

Core tip: This review summarises the safety issues around thiopurine use in adult and paediatric inflammatory bowel disease. Adverse drug effects, toxicity and malignancy risks, interactions with concomitant medications, clinical and laboratory drug surveillance and value of pharmacogenetics in therapeutic drug monitoring are discussed.

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INTRODUCTION

Thiopurines are commonly used for maintenance of clinical remission in inflammatory bowel disease (IBD)^[1,2]. They include azathioprine, mercaptopurine (MP) and thioguanine (TG). The onset of their action may vary from 4 to 16 wk^[3-5]. Thiopurine induce apoptosis of antigen specific T cells following repetitive encounters with

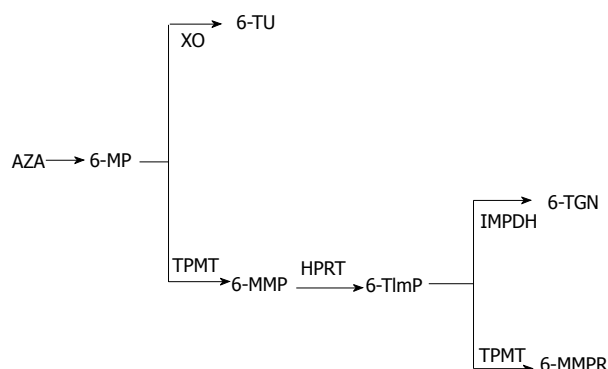


Figure 1 Metabolism of azathioprine and mercaptopurine. AZA: Azathioprine; MP: Mercaptopurine; XO: Xanthine oxidase; 6-TU: 6-thiouric acid; TPMT: Thiopurine methyltransferase; 6-MMP: 6-methylmercaptopurine; HPRT: Hypoxanthine phosphoribosyltransferase; 6-TImP: 6-thioinosino-5' monophosphate; IMPDH: Inosine monophosphate dehydrogenase; 6-MMPR: 6-methylmercaptopurine ribonucleotides; 6-TGN: 6-thioguanine nucleotides.

the antigen over a prolonged period of time^[6]. Continued medium to long term use is recommended^[7], however there is lack of evidence about optimal treatment duration so as to sustain the therapeutic efficacy in both Crohn's disease (CD) and ulcerative colitis (UC)^[8-11].

Safety issues and risk/benefit analysis must be considered prior to and during treatment with thiopurines, therefore regular follow up for detection of poor response, dose adjustment or treatment modification is necessary. Surveillance is essential for prompt identification of adverse drug events, thiopurine toxicity, interactions with concomitant medication and loss of response over time. Factors including genetic differences, age, disease duration and severity, comorbidities and the environment may influence treatment efficacy and safety^[12-14].

MECHANISM OF ACTION OF THIOPURINES

Thiopurines are structural purine analogues which, when orally administered, are absorbed across the gastrointestinal tract epithelium and carried by the portal venous system to the liver before entering systemic circulation. Trials of intravenous thiopurine infusions have been reported^[15,16]. Azathioprine is a pro-drug with good oral bioavailability and long duration of action. In the liver, azathioprine undergoes enzymatic^[17,18] and non-enzymatic reduction in the presence of glutathione and releases MP and 6-TG. There is a paucity of evidence on the use of thioguanine^[19], but its use has been associated with severe irreversible hepatotoxicity and therefore is not currently recommended outside a clinical trial setting^[20]. Small scale retrospective cohort studies by van Asseldonk *et al*^[21] and Herrlinger *et al*^[22] advocate short term efficacy of thioguanine for maintenance of remission; however the risk of hepatotoxicity outweighs potential clinical benefits. MP is converted to thioinosine monophosphate (tIMP) by hypoxanthine guanine phosphoribosyltransferase (HGPRT); tIMP is either converted to inactive inosine-triphosphate

(ITP by ITPase) or 6TImP (6 thioinosino-5' monophosphate), by thiopurine methyltransferase (TPMT), which inhibits nucleic acid synthesis. Through this cytotoxic effect on dividing cells, thiopurines inhibit clonal proliferation during the induction phase of the adaptive immune response; as a consequence, antibody and cell mediated immune responses of the effector phase are also suppressed^[23]. 6-TG is ribosylated and phosphorylated by HGPRT and irreversibly inhibits 6-thioguanine nucleotides (6-TGN) production. Various metabolites are enzymatically produced during this process: mainly active metabolites are 6-TGN, which mediate the pharmacologic effect of thiopurines, and 6-methylmercaptopurine ribonucleotides (6-MMPR) which are formed by TPMT and principally mediate thiopurine induced hepatotoxicity (Figure 1).

The immunosuppressive effect of thiopurines has been reported to be exerted by alternative mechanisms; for instance by gene expression suppression of inflammatory genes such as α4-integrin, tumour necrosis factor (TNF) ligand superfamily member 10 and TNF receptor superfamily member 7^[24]. Other proposed in vitro mechanism by Tiede *et al*^[25] is through inhibition of GTPase Rac1 activation by azathioprine metabolite 6-thioguanine triphosphate (6-Thio-GTP) in CD4⁺ human T lymphocytes^[26].

THERAPEUTIC EFFECTIVENESS OF THIOPURINES

Recent Cochrane reviews have highlighted that azathioprine is beneficial for maintenance but not induction of remission in active CD and UC^[10,27]. Thiopurines exert indirect steroid sparing effect due to their effectiveness in sustaining prolonged clinical remission^[10,28,29], especially when used in moderate to severe IBD^[30]. Reduced rates of first laparotomy in adults with CD and positive effect in the avoidance of advanced colorectal cancer have been reported^[31,32]. No clear evidence on surgery sparing benefit has been demonstrated in a population based study which investigated the effect of immunosuppressive drugs and surgery rates over time^[33]. Thiopurine use has been shown to improve quality of life in adult patients with IBD^[34,35]. Children also tolerate thiopurines and can achieve prolonged remission^[36,37].

A meta-analysis by French *et al* investigated relapse rates following withdrawal of azathioprine in CD and reported lack of strong evidence in support of continuous thiopurine treatment beyond 18 mo for maintenance of remission in CD^[38]. Fraser *et al* in a 30 years review reported sustained efficacy for five years in adult patients with CD and UC^[8]. A randomised controlled trial by Hawthorne *et al*^[39] reported that early withdrawal of azathioprine in UC patients in clinical remission for at least six months, resulted in significantly higher relapse rate, when compared to patients on minimum of two years continuous treatment. Thiopurines are therefore safe, effective medicines with a pivotal role in the treatment of

Table 1 Reported incidence of thiopurine adverse drug effects

ADE	Incidence
GI symptoms ^[155]	8%
Hepatotoxicity ^[179,180]	3%-15%
NRH ^[51]	0.6%-1.28%
Pancreatitis ^[155]	4%
Leucopenia ^[180]	2%-15%
Myelotoxicity ^[155]	4%
Lymphoma ^[155]	0.1%
Infections ^[180]	0.3%-7.4%
Intolerance ^[57,155]	17%

ADE: Adverse drug effects; GI: Gastrointestinal; NRH: Nodular regenerative hyperplasia.

IBD^[40].

THIOPURINE ADVERSE DRUG REACTIONS: IMPLICATIONS FOR SAFETY

Adverse drug reactions have historically been divided in idiosyncratic and intrinsic (dose dependent). The first type is probably immune mediated, unpredictable and can occur within few weeks of treatment commencement. Reactions include intolerance and hypersensitivity manifestations, such as malaise, dizziness, vomiting, diarrhoea, fever, myalgia, arthralgia, rash and hypotension^[41]. Rare idiosyncratic reactions include renal impairment^[42], pneumonitis^[43-45], and pancreatitis^[46].

Thiopurine-induced liver dysfunction secondary to methylated intermediate metabolites can manifest as elevated liver enzymes, hepatitis, cholestatic jaundice or hepatic veno-occlusive disease. Liver impairment following thiopurine administration has been divided into three categories: hypersensitivity, idiosyncratic cholestatic reactions, and nodular regenerative hyperplasia (NRH). Characteristic nodules of hypertrophied hepatocytes with adjacent areas of atrophied hepatocytes arise following thiopurine induced sinusoidal endothelial injury or obliterative portal venopathy^[47,48]. Dose-dependent toxicity is possible in cases of NRH^[20,49]. The cumulative incidence of NRH in IBD patients treated with thiopurines is approximately 0.6% and 1.28% at 5 and 10 years respectively^[50]; patients on higher dose of thiopurines have increased risk of NRH^[51]. NRH however can occur in thiopurine-naïve patients with IBD (reported incidence 6%) and IBD may be an independent predisposing risk factor^[51]. Pathogenesis of NRH is obscure. Reported risk factors for NRH, other than thiopurine dose in patients with IBD, are male gender, older age, stricturing disease and small bowel resection^[50,52,53]. Mild liver impairment presenting with raised liver function tests, which represents the majority of cases, may resolve with or without dose reduction^[20].

Bone marrow toxicity manifesting as myelosuppression and/or aplasia is the most severe haematological adverse drug reaction and leads to discontinuation of treatment^[54]. Haematological toxicity presenting as leucopenia

is presumed to be avoided with reduced doses^[55], however there are studies which do not support that this type of toxicity is dose related^[56,57]. Patients with UC treated with immunomodulators have demonstrated a higher incidence of infections than patients not on thiopurines^[58], due to impaired immune response. In particular, patients with inflammatory bowel disease are at increased risk of acquiring opportunistic infections (OR = 3.1; 95%CI: 1.7-5.5)^[59], for instance cytomegalovirus (CMV) infection (especially pneumonitis or enteritis), which may cause aggravation of underlying disease and failure of immunosuppressive treatment^[60]. Pneumocystis jiroveci pneumonitis is an opportunistic infection with severe morbidity. Antibiotic prophylaxis should be considered on a case by case basis, especially in patients with advanced age, increased disease severity and extensive disease^[61]. Parasitic or other fungal infections are extremely rare in IBD^[62].

Due to thiopurine induced immunosuppression, 3-5 yearly pneumococcal and annual prophylactic influenza vaccinations with trivalent inactivated vaccine are recommended^[62]. International consensus guidance recommends varicella, tuberculosis, Hepatitis B, Hepatitis C, HIV screening and prophylactic vaccination (not BCG) prior to treatment with immunomodulator^[62,63].

The incidence of adverse drug events are summarised in Table 1.

SAFETY OF THIOPURINES IN ELDERLY PATIENTS

In the elderly population, there is good evidence of functional alterations in cells from the innate and adaptive immune systems resulting in a state of dysregulated immune function and increased susceptibility to infection^[64-66]. There are data to demonstrate that mainly bacterial infections (urinary tract infections and community acquired pneumonia), and few viral infections, such as influenza, are more prevalent and severe in the elderly patients with IBD than in younger adults^[66].

Elderly patients (> 65 years of age) on immunosuppressants are at increased risk of developing malignancies^[67], when compared to younger adults and children. Past or co-existing comorbidities, such as previous cancer, predispose them to additional malignancy risk, for example lymphoma^[68].

In elderly patients therefore, the benefit of long term (over 5 years) thiopurine use may not outweigh the risks^[69]; disease chronicity and severity may of course exert a confounding effect in observed outcomes in this population. Adverse drug events such as NRH have been more frequently reported in older age^[51].

SAFETY OF THIOPURINES IN CHILDREN

Variation in disease management is common in paediatric IBD due to lack of high quality randomised controlled trials in children. The ongoing development of service networks will accelerate collaborative standardised re-

search in children with IBD for generation of high quality evidence and improvement of care^[70].

The thiopurines have been rarely implicated in lymphoproliferative disorders in childhood IBD. The relative risk is 3-4 folds increased, however the absolute risk is very low^[71].

In paediatric IBD, early life onset of disease translates into longstanding disease activity requiring life-long medication^[72]. Paediatric-onset UC has a different phenotype than adult-onset disease with more extensive (pan colitis) and more aggressive disease course. Special consideration in the decision making process about treatment in children must be given to growth, puberty and bone density accrual. A large number of children are at risk for steroid-dependency, therefore steroid sparing strategies with early use of immunomodulators such as thiopurines are recommended in high-risk patients^[73]. On the other hand, the safety profile of immunosuppressive therapy in children stipulates a more conservative approach, with early treatment intensification applied in patients with severe or refractory disease^[12]. Punati *et al.*^[30] published a prospective multicentre observational study where early thiopurine use was associated with reduced corticosteroid exposure and possibly fewer hospitalizations per patient. Similarly, Riello *et al.*^[37], in a retrospective study of 105 children treated with thiopurines, reported that the majority of patients who were in steroid-free remission by 12 mo, remained in prolonged remission.

SAFETY OF THIOPURINES DURING PREGNANCY

Use of thiopurines is not an absolute contraindication throughout pregnancy; however data on their safety profile during pregnancy is insufficient. The human placenta is believed to act as a barrier; a human placental perfusion model has been used to demonstrate the binding of the drug to placental tissue. Maternal pharmacokinetic parameters could restrict the fetal exposure to drug metabolite^[74]. Fetal 6-TGN levels correlated with maternal 6-TGN in a prospective study of 28 pregnant women on thiopurines; maternal thiopurine metabolism was affected during pregnancy. 60% of the neonates were noted to be anaemic at birth^[75]. Casanova *et al.*^[76] conducted a retrospective multicentre study with 571 pregnant women and found no increase in adverse outcomes for pregnant women and newborns following exposure to thiopurine. There is no evidence whether IBD or medical therapy [5 aminosalicylates (5-ASA), thiopurines, corticosteroids] during pregnancy increase the risk of major congenital anomalies in the off-springs; this was recently shown in a retrospective case control study of women with IBD ($n = 1703$) and women without the disease ($n = 38481$)^[77]. Akbari *et al.*^[78] identified the risk of preterm delivery in a recent meta-analysis which reviewed the effects of thiopurines on birth outcomes of female and male patients with IBD; despite this, exposure to thiopurine at the time of conception was not associated with increased risk of

congenital abnormalities. The development and immune function of children exposed to thiopurines in utero has not been affected until the age of six years^[79].

RISK OF MALIGNANCY AND THIOPURINES: IMPLICATIONS FOR SAFETY

Thiopurines can increase the incidence of malignancies by different plausible mechanisms, such as by incorporating 'rogue' thiopurine nucleotides in the DNA or by rendering DNA highly sensitive to ultraviolet radiation, thereby promoting mutagenesis^[80-82].

Four to six fold increased risk of hematologic malignancies^[83] has been observed in patients treated with azathioprine; however no causality has been established to date. Risk increases gradually over successive years of therapy and discontinuation of thiopurine therapy reduces the risk^[84]. The absolute risk of lymphoma however is low; balancing the potential risk of lymphoma against the risk of undertreatment IBD should inform decision making in the medical management of IBD^[85].

Latent or primary opportunistic EBV infection during immunosuppressive therapy may result in post-transplant like lymphoproliferative disease or haemophagocytic lymphohistiocytosis^[86,87]; the latter has also been reported following CMV infection^[88]. 5% of EBV negative peripheral T cell lymphomas reported in IBD patients are non-Hodgkin's hepatosplenic T cell lymphomas (HSTCL) with poor prognosis^[89,90]. A systematic review on medication, therapy duration and patient age in reported cases of HSTCL concluded that most patients were male, younger than 35 years old, and had received at least 2 years of combined treatment with anti-TNF agent and thiopurine^[91] or anti-TNF monotherapy^[92].

Relative increase in non-melanoma skin cancer was shown in a large retrospective cohort study of over 50000 adult patients with IBD, conducted by Long *et al.*^[93]; thiopurine treatment of a minimum of three months has been associated with increased risk of non-melanoma skin cancers compared to controls. Melanoma skin cancer may increase by 37% according to a meta-analysis investigating the risk of melanoma in a cohort of 172837 patients with IBD; however no specific increase in risk has been associated with thiopurine treatment *per se*^[94].

Since the beginning of this century, there is a controversy in the medical literature with regards to increased risk of gastrointestinal neoplasia in patients with IBD.

A meta-analysis by Eaden *et al.* in 2001 investigated the colorectal cancer risk in UC, and reported a risk of 3% (95%CI: 2.2-3.8) at 10 years, 5.9% (95%CI: 4.3-7.4) at 20 years, and 8.7% (95%CI: 6.4-10.9) at 30 years after diagnosis. A non-significant increase in the risk of colorectal cancer (CRC) by decade of disease was also reported. In 2005, a more recent meta-analysis of population based studies by Jess *et al.* however reported a 2.4 (95%CI: 2.1-2.7) fold increase in CRC risk in patients with UC^[95].

Canavan *et al.*^[96] performed a meta-analysis to ascertain the combined relative risk of gastrointestinal malignancies and reported increased relative risk in CD. The most recent meta-analysis by Lutgens *et al.*^[97] has updated CRC risk in both ulcerative and Crohn's colitis, by investigating time trends, and identifying high-risk modifiers; it has been concluded that the risk of CRC is increased in patients with IBD but not as high as previously reported and that the risk of CRC is significantly higher in patients with longer disease duration, extensive disease, and IBD diagnosis at young age^[97].

Thiopurine treatment did not decrease the risk of colorectal neoplasia in UC ($n = 315$ patients)^[98]. Beaugerie *et al.*^[99] nevertheless conducted a large prospective cohort study with 20000 patients and found that thiopurine treatment significantly lowered the multivariate adjusted hazard ratio for colorectal neoplasia (HR = 0.28, 95%CI: 0.1-0.9; $P = 0.03$). A recent meta-analysis by Gong *et al.*^[100] which addressed the same issue concluded that thiopurines exerted a chemo prophylactic effect and a tendency of reducing advanced colorectal neoplasms in IBD, however due to the heterogeneity of included studies, the authors suggested that the results should be interpreted with caution.

Young female smokers with concomitant 5-aminosalicylic acid and thiopurine exposure^[101] are at increased risk of cervical cancer; it is still unclear whether the disease itself or whether the treatment may predispose to cervical dysplasia^[102]. Evidence to date is inconclusive; no clear increase in relative risk secondary to the use of thiopurines has been shown in the majority of relevant studies, with the exception of a population based case control study by Singh *et al.*^[103], which reported increased risk for cervical dysplasia or cancer in patients on both steroids and immunomodulators. Lees *et al.*^[104] conducted a large case control study where women with IBD were not shown to have increased rates of abnormal cervical smears unless they smoked; this finding was not affected by immunosuppressant therapy or disease phenotype. Cervical cancer surveillance and HPV vaccination is currently recommended^[102].

Treatment with immunosuppressive drugs had no major impact on the increased risk of developing new or recurrent cancer in a prospective cohort of 405 IBD patients with pre-existing history of cancer^[105]. Pasternak *et al.*^[106] conducted a retrospective cohort study and reported that azathioprine treatment in IBD was associated with marginally increased risk for lymphoma and urinary tract cancer, therefore reported an overall increased risk of malignancy with azathioprine treatment (RR = 1.41; 95%CI: 1.15-1.74) interestingly though, previous use of azathioprine or increasing cumulative received doses did not increase the cancer risk. Finally, a meta-analysis of Masunaga *et al.*^[107] investigated whether long-term administration of immunosuppressants in patients with IBD increased the risk of malignancy and concluded that treatment did not increase the overall cancer risk in patients with IBD; drugs other than thiopurines, such as cyclosporine, methotrexate, tacrolimus were included in the analysis.

CLINICAL AND BIOCHEMICAL SURVEILLANCE FOR ENHANCED DRUG SAFETY: THERAPEUTIC DRUG MONITORING

Clinical surveillance and patient follow up are required for identification of adverse drug events throughout the duration of thiopurine treatment; this can be enhanced by regular monitoring of laboratory indices, such as peripheral blood counts, pancreatic and liver function tests^[108]. There is a lack of consensus on the usefulness of active thiopurine metabolite monitoring as surrogate markers of thiopurine efficacy and toxicity. Their use is not widely recommended or adopted^[109] and largely depends on local practices and individual clinician preferences.

Higgs *et al.*^[110] published a meta-analysis about the increased risk of myelosuppression in patients with intermediate TPMT activity and concluded that in spite of controversial findings between studies, "higher 6-TGN levels were generally associated with clinical remission". Gonzalez-Lama conducted a prospective multicentre cohort study which did not support determination of TPMT activity or 6-TGN concentrations for prediction of treatment outcome; no clinically useful serum metabolites threshold value was identified for dose adjustment purpose^[111]. Poor correlation between 6-TGN levels and thiopurine dose has also been reported by other studies^[4,56,112,113], however metabolites levels may contribute to earlier and safer dose tailoring, especially in patients with poor clinical response or non-compliance^[114-117].

Measurement of active thiopurine metabolite levels in addition to regular full blood count monitoring, especially over the first 1-2 mo after treatment commencement, and regularly thereafter has been proposed^[118-120]. 6-MMPR levels and liver enzymes may be used in combination as surrogate markers of hepatotoxicity; a 6-MMPR cut-off value $> 5700 \text{ pmol}/8 \times 10^8 \text{ RBC}$ has been recommended as indication of liver dysfunction^[117,121-123]. There is currently no clear consensus on optimal frequency of blood monitoring^[124].

DRUG INTERACTIONS: IMPLICATIONS FOR THIOPURINE SAFETY PROFILE

Allopurinol

Allopurinol is known to reduce thiopurine-induced hepatotoxicity^[125] and may have a synergistic therapeutic effect to patients who preferentially produce 6-MMPR, rather than 6-TGN^[126-128]. The underlying mechanism remains enigmatic. Different pathways have been proposed: (1) allopurinol inhibition of both xanthine dehydrogenase and TPMT and promotion of 6-TGN production at the expense of 6-MMPR^[129]; (2) TPMT inhibition by allopurinol's active metabolite oxypurinol^[130]; and (3) increased HGPRT activity and subsequent 6-TGN increase^[131]. Co-administration of allopurinol has been reported to al-

low thiopurine dose reduction by up to 75%^[23]; this may enhance efficacy in azathioprine refractory patients and avoid high doses with potential dose dependent adverse events; conversely combined therapy could potentially induce toxicity in azathioprine-naïve patients due to the synergistic effect of these two medicines. Combination therapy with allopurinol is therefore currently not widely used, due to the lack of adequate high grade evidence from double blinded randomised controlled trials assessing the risk-benefit ratios of dual therapy, especially in paediatrics.

5-aminosalicylates

5-ASA have been reported to increase 6-TGN and decrease the production of 6-MMPR in two prospective adult studies^[132,133]. de Boer *et al*^[134] conducted a prospective multicentre pharmacokinetic study and reported a significant dose-dependent increase in 6-TGN levels in cases of 5-ASA co-administration. It was concluded that patients refractory to standard thiopurine therapy may benefit from the co-administration of 5-ASA. A systematic review by Andrews *et al* addressed the clinical outcomes following concomitant 5ASA and thiopurines administration; it was unclear whether combination therapy improved outcomes of disease control, drug toxicity or compliance, but concurrent therapy could decrease colorectal risk at “acceptable cost”^[135]. An increased risk of myelotoxicity has been noted in children with IBD treated with combination therapy^[136]. Nguyen *et al*^[137] in a study of 71 children with IBD, reported more frequently observed lymphopenia and elevated 6-TGN concentrations, without increase in remission rate in patients on combined treatment. A favourable clinical outcome has been described by Tajiri *et al*^[56] in paediatric UC, however a high rate (40%) of myelosuppression was noted. The clinical benefit of combination treatment therefore needs to be further researched and careful weighted against toxicity risk^[132].

Anti-tumour necrosis factor alpha agents

New disease modifying drugs such as infliximab, adalimumab have been increasingly used in adult and paediatric gastroenterology. Infliximab is the first anti-TNF alpha agent ever introduced in the treatment of IBD and therefore has been more widely researched to date. It is a partially humanised monoclonal antibody against tumour necrosis factor alpha (TNF- α), a cytokine mediator of inflammation. Historically anti-TNF alpha drugs were principally introduced as rescue medical therapy in patients with treatment refractory, severe or extensive disease^[138].

A top-down versus a “bottom-up” approach to treatment is the epicentre of attention within the international community of gastroenterologists; early introduction versus rescue use of anti-TNF agents, with or without concomitant thiopurine for prompt treatment intensification and avoidance of disease complications is the dilemma in current clinical practice^[139,140].

Combination therapy with infliximab and azathioprine

has been reported more favourable than monotherapy for induction and maintenance of steroid-free remission, and for avoidance of postoperative recurrence^[140,141]. Higher serum trough concentrations of infliximab, lower anti-infliximab antibodies and better clinical outcomes may occur more frequently in patients receiving combination therapy with azathioprine^[139,142]. Colombel *et al*^[139] specifically reported that combination may be superior to azathioprine or infliximab alone, not only for induction and maintenance of steroid free remission, but also for increased mucosal healing rates in adult patients with moderate to severe CD. The described effect was sustained at one-year follow up. The beneficial effects of combination therapy on mucosal healing, steroid-free remission and sustained increase in quality of life have been reported in both UC^[143] and CD^[144]. Sokol *et al*^[145] conducted a prospective cohort study and reported favourable six month outcomes with regards to disease activity, infliximab dose and need of other anti-TNF alpha agents such as adalimumab.

On the contrary, Lichtenstein *et al*^[146] pooled data from multicentre prospective randomised controlled trials in adult patients with IBD and concluded that concomitant use of immunomodulators-principally thiopurines but also methotrexate in isolated cases with CD did not significantly increase efficacy or alter thiopurine safety; infusion reactions were about 50% less in combined therapy than in infliximab monotherapy.

Van Assche *et al*^[147] conducted an open label randomised controlled trial to evaluate the influence of anti-TNF alpha discontinuation after patients had been in remission for at least six months with combined therapy; no clear benefit of continuing combined therapy beyond six months from clinical remission was demonstrated.

Combination of anti-TNF agents with thiopurines may therefore enhance immunosuppression, however the risk of related adverse drug reactions and toxicity is also enhanced^[148]. Combination therapy may also be associated with higher relative risk of opportunistic infections in UC, but no significantly increased absolute risk of serious infections has been observed^[58,149].

Limited evidence exists on drug interactions between azathioprine and adalimumab. The latter has recently obtained approval by the European Medicines Agency and the United States Food and Drug Administration for use in adult patients with moderate-to-severe, active, refractory UC, who are intolerant to corticosteroids and thiopurines^[150]. Adalimumab is effective in inducing and maintaining remission in patients with active, moderate-to-severe, luminal or perianal CD, or patients with previous loss of response or intolerance to infliximab^[151-153]. A recent prospective case series of twelve adult patients with CD reported that 6-TGN and 6-MMPR were not influenced by concomitant administration of adalimumab during a 12 wk follow up period^[154]. The same study reported no change in TPMT, ITPase or HGPRT enzyme activity after 4 wk of combined treatment. More research is required into the efficacy and safety of combination treatment.

THIOPURINE TOXICITY: IS ALTERNATIVE THIOPURINE USE SAFE?

Chaparro *et al* has recently reported the findings of a large prospective nationwide cohort study from Spain, where 67% of 1026 patients had to discontinue thiopurine treatment due to adverse drug events such as nausea, arthralgia, alopecia, abdominal pain, liver and pancreatic toxicity, infection, leucopenia, myelotoxicity. 37% percent of them were restarted on the same thiopurine. 40% had recurrent side effects; 4% following treatment with the same thiopurine and 36% after introduction of an alternative thiopurine^[155]. Interestingly even in patients with severe complications such as hepatotoxicity, thiopurine re-introduction was tolerated in 74% of cases; abdominal pain recurred in 18% of cases, nausea and arthralgia recurrence close to 50% was noted. 85% of patients demonstrated recurrence of pancreatic toxicity, recurrence rates of infection and bone marrow failure were 80% and 65% respectively. Overall over half of the patients tolerated re-introduction of thiopurine treatment following drug induced side effects.

Ledder *et al*^[46] published a small case series of four adult patients with successful introduction of mercaptopurine following azathioprine induced pancreatitis.

A recent meta-analysis on alternative use of mercaptopurine in adult patients with IBD who suffered azathioprine-induced toxicity ($n = 455$ patients), concluded that favourable outcomes had been observed in two-thirds of patients where trial of mercaptopurine was implemented^[57]. In detail, 62% with gastrointestinal toxicity, 81% with hepatotoxicity and 36% with flu-like illness had been able to tolerate mercaptopurine. Trial of mercaptopurine is therefore advised in cases of azathioprine intolerance, except in patients with severe pancreatitis or bone marrow aplasia. Among patients who discontinued mercaptopurine for further adverse effects, 59% experienced the same adverse effect as they had with azathioprine.

Further studies are required so as to quantify the hepatotoxicity risk associated with thioguanine as an alternative therapy for IBD treatment; metabolism of this non-conventional thiopurine does not generate 6-methyl mercaptopurine^[156].

VALUE OF PHARMACOGENETICS IN THIOPURINE SAFETY MONITORING

Observed genetic polymorphisms have been reported to play pivotal role in the occurrence of adverse drug reactions for various drugs, including thiopurine^[157,158], warfarin^[159], antiepileptic^[160] and anti-retroviral drugs^[161]. Inter-individual variability in drug response reflects differences in genetic polymorphisms which, to some extent, may be responsible for variation in drug metabolism^[116,162].

TPMT is an extensively researched example of the clinical applicability of pharmacogenetics; pre-treatment testing is currently implemented; common variant alleles such as TPMT*2, TPMT*3A, TPMT*3C, TPMT*8 may

give rise to decreased enzyme production; heterozygous or homozygous TPMT deficient patients require decreased dose upon treatment commencement, or thiopurine avoidance respectively. Weinshilboum and Sladek first reported that approximately 0.3% Caucasians have complete deficiency, approximately 10% have low or intermediate activity and about 90% have high activity^[163]. Numerous studies have since verified the differences in TPMT levels and activity between different ethnic group^[164-166].

Pre-treatment determination of TPMT genotype and phenotype may be useful for prediction of thiopurine toxicity; TPMT testing is however not universally implemented by gastroenterologist^[167-169], because evidence on its predictive value for thiopurine toxicity in IBD is still unclear; Colombel *et al*^[170] has reported that the majority of adult patients with myelotoxicity had normal TPMT genotype. The controversy in the medical literature may exist because of the non-absolute concordance between genotype and phenotype (TPMT activity status)^[167,171], and the diversity in the laboratory methods (enzymatic, radiochemical, high performance liquid chromatography assays) used for quantification of TPMT activity in red blood cells^[172]. A systematic review by Booth *et al*^[173] reported that in patients with intermediate and low enzymatic activity, genotyping sensitivity to identify patients with low enzymatic activity ranged from 70.33% to 86.15% (lower-bound 95%CI: 54.52%-70.88%; upper-bound 95%CI: 78.50%-96.33%) and was therefore imprecise. Despite this finding, variant genotype and low TPMT activity were reported to be strongly associated with haematological toxicity.

Additional polymorphic genes implicated in thiopurine metabolism are under investigation for possible effect on effectiveness and safety. These are the ITPase^[174], the guanine monophosphate synthetase (GMPS mediates tIMP conversion to tGMP) and the glutathione S transferases (GST which catalyses MP production from azathioprine)^[175,176].

Smith *et al*^[177] reported that single nucleotide polymorphism (SNP) of aldehyde oxidase (AOX1) c.3404A > G may predict lack of response ($P = 0.035$, OR = 2.54, 95%CI: 1.06-6.13); when combined with TPMT activity, this information allowed stratification of a patient's chance of response to azathioprine, ranging from 86% in patients where both markers were favourable to 33% where both were unfavourable ($P < 0.0001$)^[177].

A common SNP, associated with a dramatically reduced ABCC4 function, has been identified in approximately 14%-18% of the Japanese population. In these patients, the OR of carrying the ABCC4 variant and having leucopenia following thiopurine introduction has been reported to be 3.30 (95%CI: 1.03-10.57; $P = 0.036$)^[178].

In the future, the pharmacogenetic approach may enhance pre-treatment safety and prompt dose adjustment^[179].

CONCLUSION

Safety of thiopurine treatment in IBD stipulates fine tun-

ing between therapeutic efficacy, intolerance and toxicity. This balance must be achieved on a long term basis. Combination therapy with new disease modifying drugs has further modified the safety profile of thiopurines; the importance of such interactions has yet to be confirmed in large studies across all age groups. There is a need for a standardised approach in therapeutic drug monitoring. Further research into disease pathogenesis and pharmacokinetic/pharmacodynamic pathways may identify potentially useful biomarkers for thiopurine safety monitoring. High quality, prospective and collaborative clinical research will establish a robust evidence foundation which will safely inform future clinical practice.

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