World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/esps/
wjg@wjgnet.com
doi:10.3748/wjg.v19.i7.1040

World J Gastroenterol 2013 February 21; 19(7): 1040-1048
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

REVIEW

Use of thiopurines in inflammatory bowel disease

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Received: June 5, 2012 Revised: July 16, 2012
Accepted: August 14, 2012
Published online: February 21, 2013

Abstract

The use of thiopurines as immunosuppression for the treatment of refractory or chronic active inflammatory bowel disease is established for both Crohn's disease and ulcerative colitis. Nevertheless, many questions remain concerning the optimal treatment regimens of azathioprine, 6-mercaptopurine and thioguanine. We will briefly summarize dose recommendations, indications for thiopurine therapy and side effects which are relevant in clinical practice. We discuss some currently debated topics, including the combination of azathioprine and allopurinol, switching of thiopurine therapy in case of side effects, the use of azathioprine in pregnancy, the infection risk using thiopurines and the evidence when to stop thiopurines. Excellent reviews have been published on the thiopurine metabolic pathway which will not be discussed here in detail.

Key words: Thiopurines; Inflammatory bowel disease; Crohn's disease; Ulcerative colitis; Immunosuppression; Infection

Frei P, Biedermann L, Nielsen OH, Rogler G. Use of thiopurines in inflammatory bowel disease. *World J Gastroenterol* 2013; 19(7): 1040-1048 Available from: URL: http://www.wjgnet.com/1007-9327/full/v19/i7/1040.htm DOI: http://dx.doi.org/10.3748/wjg.v19.i7.1040

DOSING AND MONITORING OF THIOPURINES

Thiopurines used for inflammatory bowel disease (IBD) treatment are azathioprine (AZA), 6-mercaptopurine (6-MP) and occasionally also 6-thioguanine (6-TG). The most commonly used thiopurine is AZA. The hepatic enzyme glutathione-S-transferase rapidly cleaves the prodrug AZA to 6-MP[1], which is then metabolized in both liver and gut by several enzymes: (1) thiopurine-s-methyltransferase (TPMT) catalysing 6-MP to 6-methyl-MP (6-MMP); (2) xanthine oxidase catalyzing 6-MP to thiourea; and (3) hypoxanthine-guanine-phosphoribosyltransferase converting 6-MP to 6-thioguanine nucleotides (6-TGN). 6-TG is the final effector-metabolite[2] which slowly accumulates in cells, and this metabolite is probably responsible for the delayed onset of action after 10-12 wk[3].

Dose recommendations for AZA and 6-MP vary slightly between Western guidelines, with a daily dose of 2-3 mg/kg AZA and 1-1.5 mg/kg 6-MP recommended by the AGA[4], and a daily dose of 1.5-2.5 mg/kg AZA and 0.75-1.5 mg/kg 6-MP recommended by the European Crohn's and Colitis Organisation (ECCO)[5]. However, these recommendations do not necessarily hold true for other ethnicities. Several Japanese studies showed that Japanese IBD patients might reach sufficient 6-TGN values with substantially lower AZA and 6-MP dosages in adults[6,7], children and adolescents[8]. If 6-TG is exceptionally used, it should be started at a much lower dosage of approximately 20 mg per day and should not exceed

25 mg daily[9]. However, it has to be strengthened that there are limited indications for use of 6-TG in IBD. 6-TG can be used in IBD patients who need a thiopurine for maintenance therapy but who are intolerant (or resistant) to 5-aminosalicylic acid (5-ASA) [in ulcerative colitis (UC)], AZA, 6-MP and methotrexate [in Crohn's disease (CD)], and who do not have an option for surgery[9]. Biological therapy could be considered as an alternative to 6-TG in this setting. The ECCO guidelines[5] concluded in 2006 that thioguanine cannot currently be recommended for maintenance of CD due to a high frequency of liver abnormalities (mainly nodular regenerative hyperplasia). According to the current literature, this might, however, be explained by the use of too high dosages of 6-TG resulting in 6-TGN levels exceeding 1000 pmol/8 × 10^8 erythrocytes which is much more than the target levels of 250-500 pmol/8 × 10^8 erythrocytes usually recommended when using AZA or 6-MP[10-12]. Thus, if 6-TG is used as therapy for selected IBD patients, the 6-TGN levels should be controlled regularly combined with close monitoring of liver values[13], hematology and especially liver biopsy after one, three and then every three years[9]. However, the histopathological diagnosis of nodular regenerative hyperplasia is difficult with a very poor inter-observer agreement, even among experts[14]. Alternatively, non-invasive monitoring such as magnetic resonance imaging may be considered[15].

The dose recommendations as mentioned above are based on "Western" or "Caucasian" guidelines/evidence and are linked to the assumption that the TPMT pathway is "normal". A diminished TPMT activity due to mutations of the *TPMT* gene leads to toxic levels of 6-TGN, which is a risk factor for drug-induced myelosuppression[16]. TPMT mutations are not uncommon in Caucasian populations (mutation prevalence approximately 10%), but rarer in *e.g.*, Chinese patients (5%) or even very rare in Japanese patients (1%)[17], which questions the usefulness of routine TPMT monitoring in these patients. The role of pharmacogenetics has recently been addressed in an excellent review by Chouchana *et al*[18] and is shortly summarized below.

To achieve an optimal therapy, it seems crucial to find the correct concentration of intracellular 6-TGN (serum levels are of no value). Concentrations that are too high lead to myelosuppression, whereas concentrations that are too low result in a lack of efficacy in IBD[16,19]. TGN-levels can be measured irrespective of the time of intake of thiopurines. The commonly recommended 6-TGN concentration is 235-500 pmol/8 × 10^8 erythrocytes. In a meta-analysis[20], patients with 6-TGN levels above the threshold value of 235 were more likely to be in remission than those below the threshold value (62% *vs* 36%, $P < 0.001$). The usefulness of therapeutic drug monitoring has recently been supported in a Dutch study[21]. However, the minimum effective dose is unknown. No dose-response study has ever been carried out, but at least one study showed that an increase in AZA dosage (2.02-2.72 mg/kg daily) can induce response in some patients[22]. Since there is only a very weak correlation between thiopurine dosage and 6-TGN levels[20] and some ethnic variability[6,7], the authors believe that 6-TGN levels should be regularly measured. Measuring the 6-TGN levels alleviates uncertainties when AZA therapy is combined with 5-ASA in UC[23]. In a recent and well-performed prospective study, the addition of 2 g of 5-ASA increased the total amount of 6-TGN by 50%, and methylmercaptopurine ribonucleotide levels were reduced after adding 4 g of 5-ASA[24]. Further studies are needed to show whether 6-TGN measurements might be useful to improve thiopurine therapy.

TPMT MONITORING

Beside the above mentioned measurement of thiopurine metabolites, TPMT genotyping (analysis of single nucleotide polymorphisms which influence the TPMT activity) and phenotyping (measuring the TMPT activity) can be applied before therapy with AZA or 6-MP is initiated. A recent study concluded that genotyping should be favoured for pre-treatment TPMT function since it is the more reliable test[25]. This evaluation may help to identify slow metabolizers which are at risk of toxicity[4]. Nevertheless, a recently meta-analysis stated that there is not yet enough evidence to advocate for routine TPMT testing[26]. The United States Food and Drug Administration (FDA), but not the ECCO, recommends TPMT monitoring before the initiation of thiopurine therapy. In 2011, the first guideline for a thiopurine starting dose according to TPMT phenotype/genotype was developed[27]. A reduction to 30%-70% of the full dose is recommended in patients with an intermediate activity (heterozygote). In patients with low/absent activity (homozygous mutant or compound heterozygote), an alternative drug should be considered or AZA starting dose must be reduced by a 10-fold, administered thrice weekly, and under close monitoring. For patients with intermediate and low/absent TPMT activity, a therapeutic drug monitoring is recommended four weeks after treatment initiation. Patients with a very high activity might benefit from an increase in AZA dosage up to 3.0 mg/kg per day[18]. Nevertheless, it is important to note that TPMT testing does not predict the long-term risk of myelosuppression or idiosyncratic adverse events such as fever, arthralgias, hepatitis or pancreatitis[28]. Regular hematologic monitoring remains necessary[26], initially at least every second week until the patient has been on a stable dose for a month; in the later course at least every third month[29,30], including a complete blood count including a differential count, especially to check the lymphocyte level but also platelets as well as amylase, and liver enzyme levels[4,30,31].

INDICATIONS FOR AZATHIOPRINE OR 6-MERCAPTOPURINE

No evidence for induction of remission in active IBD

There is not enough evidence to recommend thiopurines

for inducing remission in active IBD[32] based on five randomized controlled trials (RCTs) in active CD[33-37] and on two RCTs in active UC[38,39].

Prevention of relapse in quiescent IBD

In quiescent CD, AZA and 6-MP are effective at preventing a relapse based on two RCTs comparing AZA with placebo[33,37], and three RCTs comparing continued AZA *vs* withdrawal in patients who had been successfully maintained on AZA[40-42]. These studies showed a significantly higher relapse rate in the placebo groups as compared with the active treatment[32]. Additionally, a RCT evaluating glucocorticoid-dependent CD patients suggested that AZA was better than placebo at reducing the need for glucocorticoids[43].

In quiescent UC, AZA and 6-MP are effective at preventing a relapse based on three RCTs comparing AZA with placebo[38,39,44]. Overall, 60% of patients can be kept in remission if AZA is continued for 9-12 mo[32]. Similarly, another RCT which evaluated AZA withdrawal in 79 patients, who had been maintained on this drug for a minimum of 6 mo, showed a significant reduction on the relapse rate on AZA *vs* placebo after one year (36% *vs* 59%)[45] .

Post-operative treatment of CD with thiopurines

Two RCTs in postoperative CD suggest that AZA or 6-MP is superior to placebo at preventing recurrence after surgery[46,47]. Furthermore, thiopurines administered postoperatively significantly reduced the clinical recurrence rates in population-based cohorts[48,49]. Thus, thiopurines might be a useful strategy, although anti-tumour necrosis factors (anti-TNFs) might be more efficient in preventing CD relapses postoperatively[50,51], especially among high risk patients (smokers, perforating disease or $\geqslant$ second operation)[50].

Treatment of fistulising CD with thiopurines

A meta-analysis in fistulizing CD demonstrates a significantly higher response rate to AZA and 6-MP as compared to placebo (54% *vs* 21%)[52]. The analyzed studies included patients with perianal, enterocutaneous, enteroenteric and rectovaginal fistulas. However, only in a minority of patients, AZA and 6-MP will lead to a complete fistula closure, but symptoms such as inflammation, discharge and discomfort are often substantially reduced. Since response of fistulas to these drugs will need several months, immunosuppression will be reasonable only as second-line treatment if fistulas don't necessitate immediate surgery. Antibiotics are commonly used as first-line treatment and need to be started in parallel[53].

An overview of indications for thiopurines in IBD is given in Table 1.

ADVERSE EVENTS

AZA and 6-MP have similar side effects leading to discontinuation of therapy in 39% of patients in a large Dutch cohort[54], however, rates of intolerance are usually far lower. Most adverse events occur within the first 3 mo[55]. More than 50% of AZA intolerant patients tolerate 6-MP long-term[56]. Common side effects can be divided into dose-dependent and idiosyncratic side effects.

The major dose-dependent side effect of thiopurines is drug-induced myelosuppression which is observed in 2%-5% of Caucasian patients[57,58]. It can occur at any time with 25% of cases appearing beyond the first year[55]. Asian (or at least Japanese patients[6,7]) have a higher risk of myelotoxicity. It has been speculated that viral infections might contribute to myelosuppression, however, clear evidence is missing. Determining TPMT activity before starting thiopurines might avoid early myelosuppression, but regular haematological monitoring remains necessary in every patient.

Infectious complications are mostly dose-dependent, but sometimes idiosyncratic side effects. Infectious complications during thiopurine therapy can occur even in the absence of a dose-dependent leukopenia[4,59,60], especially when using a combination of thiopurines with corticosteroids which may induce a dose-dependent lymphocyte depletion. We recommend avoiding a lymphopenia of $< 600/\mu L$ based on data from a rheumatological study[31]. Doing this, severe immunodeficiency is likely to be avoided[31] Hepatotoxicity can manifest as early drug-induced hepatitis, nodular regenerative hyperplasia after years of therapy, sinusoidal dilatation or fibrosis[61]. It is important to note that IBD *per se* is a risk factor for nodular regenerative hyperplasia[62]. Hepatotoxicity induced by thiopurines seems more often dose dependent than idiosyncratic. In many patients, elevated transaminases respond to dose reduction. In a prospective monocentric cohort, 21 of 123 patients showed a transient or constant elevation of alanine aminotransferase levels[63]. If liver enzymes are repeatedly elevated, thiopurines need to be discontinued.

The most frequent idiosyncratic side effects are nausea, vomiting, and malaise in up to 15% of all patients[64]. Some advocate to slowly increase the dosage when thiopurine therapy is started, or to take it before nighttime. However, the best way to start thiopurine therapy still has to be determined[4]. Other common side effects are headache, fatigue, anorexia, weight loss, stomatitis, alopecia, arthralgia, muscular weakness and rash, which may occur in more than 10% of patients. If these side effects are reported, it should be determined whether they disappear after dose reduction[4,59,60,65,66]. In case of arthralgias/myalgias upon AZA, a switch to 6-MP can be explored[55].

Pancreatitis is an important idiosyncratic side effect and occurs in up to 4% of the patients[4,60], especially during the first weeks of treatment[67]. A minor and asymptomatic increase in serum amylase ("pancreatic hyperenzymemia") is frequently observed, but only poorly understood and not discussed in current guidelines. Some authors prefer to reduce dosing, or stop treatment

Table 1 Indications for thiopurines in inflammatory bowel disease

	Indication	No indication
Crohn's disease	Maintaining remission in moderate (to severe) CD (any site of disease especially for extensive disease) Maintaining remission in CD with early relapse (< 3 mo after the last flare) or frequent flares (more than two per year) Fistulizing CD (in combination with antibiotics, if no early start of anti-TNF or surgery necessary) Postoperative prevention of CD recurrence (unless high-risk situation such as repeated surgery or current smoker) In combination with anti-TNFs in case of severe CD (rapid step-up or top-down)	Induction of remission (as a sole therapy in active disease)
Ulcerative colitis (treated with 5-ASA at optimal dose unless intolerant)	Maintaining remission in steroid-dependent UC Maintaining remission in UC with early relapse requiring steroids Maintaining remission in UC with frequent flares requiring steroids Maintaining remission in UC after induction of remission by ciclosporin, tacrolimus, or *i.v.* steroids Acute or chronic refractory pouchitis	Induction of remission (as a sole therapy in active disease)

CD: Crohn's disease; UC: Ulcerative colitis; TNF: Tumour necrosis factor; 5-ASA: 5-aminosalicylic acid.

in case of lack of biochemical response[68]. Thiopurines must be discontinued if amylase increase is associated with typical pain symptoms (*i.e.*, toxic pancreatitis). After AZA-induced pancreatitis, a switch to 6-MP is not recommended since these patients are less likely to tolerate 6-MP[64]; However, evidence against the use of 6-MP in AZA-induced pancreatitis is weak. As earlier outlined, 6-TG is a debated alternative to AZA and 6-MP in case of intolerance[9], which is, however, not recommended by some authors[69,70].

WHEN AND HOW TO CHANGE THIOPURINE THERAPY IN CASE OF SIDE EFFECTS?

In the case of idiosyncratic side effects, it might be reasonable to change from AZA to 6-MP, as discussed above. Furthermore, in so-called preferential 6-MMP metabolizers which achieve only low 6-TGN levels due to high 6-MMP levels with associated hepatotoxicity, adding low-dose allopurinol as a XO inhibitor to dose-decreased AZA (25%-33% of intended dose[71], might switch the AZA metabolism to 6-TGN instead of 6MMP. Close monitoring of 6-TGN metabolites and hematology is in such cases necessary (weekly during the first month, then every other week for the next month)[69]. This strategy often allows to reach therapeutic levels of 6-TGN and clinical remission, but may also to reduce or even alleviate nausea as one of the major early side effects in more than 80% of patients[72]. Interestingly it seems possible to achieve higher 6-TGN and lower 6-MMP levels in preferential 6-MMP metabolizers by simply splitting the daily thiopurine dose[73] or by switching to 6-MP.

MALIGNANT COMPLICATIONS

Treatment with AZA/6-MP is associated with a potential risk of developing lymphoma[74], including hepatosplenic T-cell lymphoma (HSTCL)[75]. Although the relative risk of lymphoma is increased four to five-fold[74,76], the absolute risk still remains rather small, and currently available data show that the benefits of thiopurines used in IBD greatly outweigh its risks[77]. The same holds true for non-melanoma skin cancer[78-80], which in a large cohort of 108.518 IBD patients collected from 1997 to 2009 was shown to occur significantly more often in IBD patients on thiopurines especially among those with CD than controls[79], correlating with the length of receiving thiopurines. Of 32 cases of nonmelanoma skin cancer in a large cohort[80], only 5 cancers occurred in immunomodulator-naïve patients, but 9 and 18 cancers occurred in patients who had previously taken or were currently on thiopurine therapy. Based on these studies, a dermatologic exam should be considered before and regularly during immunomodulator therapy; especially in elderly patients. It should in this context be mentioned that skin protection is rather crucial.

WHEN SHOULD THIOPURINE MONOTHERAPY BE STOPPED?

When to stop a successful immunosuppression is one of the most difficult decisions in IBD therapy. Five studies focussing on this question were recently reviewed by Clarke and Regueiro[81]. According to a randomized, controlled study from 2005, even CD patients who were in remission on AZA for at least 3.5 year profited from prolonged AZA therapy (relapse risk 8% *vs* 21% on placebo)[40]. Similar results have been gained from other studies[82]. Five years after stopping AZA, 3/4 of patients suffer from relapse. Nevertheless, a treatment stop seems justified since almost all patients re-treated with thiopurines were able to regain remission (23 of 24 patients; many with a combined short course of glucocorticoids)[83]. Independent predictors for a flare are a C-reactive protein-level of > 20 mg/L, a haemoglobin-level < 12 mg/dL, and an absolute neutrophil count of > 4×10^9/L at baseline. Since more than half of the patients with risk factors experienced a clinical flare-up within 24 mo (compared to only 15% of patients without negative predictors), a continuous course of thiopurine therapy is recommended for these patients.

In UC, several studies have shown that a prolonged AZA therapy helps to reduce the risk of relapse. Six months is certainly the minimum length of immunosuppression (with at least 3 mo disease-free interval off glu-

cocorticoids)[84,85], but other studies showed that 18 mo is significantly better than 6 mo[81].

In clinical practice, decision on the length of immunosuppressive therapy means weighing benefits of immunosuppression on IBD and risk of malignancies and other complications. The risk factors should be analysed before immunosuppression is stopped. Best candidates for stopping immunosuppression will probably be IBD patients in deep, prolonged remission with a short duration of time between diagnosis and immunomodulator treatment[81]. Nonetheless, prospective RCTs are needed for the development of evidence-based tapering schemes regarding AZA and 6-MP treatment, both in CD as well as in UC.

IMMUNOMODULATORS AND BIOLOGIC THERAPY

Many experts in the field currently advocate a "top down" approach with early combination therapy for moderate to severe CD based on evidence from three infliximab and azathioprine studies in CD[86-88], including the famous SONIC trial[86]. Nevertheless caution is advised as the number needed to treat for the combination therapy is 8, meaning that only one out of 8 patients will definitely benefit from the combination. For the combination of AZA and adalimumab, there are only retrospective and hardly convincing data[89]. Future trials need to determine whether it is crucial to start with anti-TNFs and thiopurines at the same time, or whether a sequential addition of thiopurines to anti-TNFs will have the same effect in the patients experiencing a benefit from this combination.

Furthermore, there are not enough available data on how long the concomitant use of immunomodulators should be maintained in patients receiving infliximab. There are no studies which documented a sustained efficacy of concomitant use of immunomodulators beyond 6-12 mo[90,91]. If therapy should be reduced, then AZA and not infliximab may be stopped. In the recently published prospective STORI (Stop Infliximab in Patients With Crohn's Disease) study on infliximab stop in patients in remission under combined immunosuppression, nearly half of all patients suffered from relapse within 1 year when infliximab was stopped despite continuing azathioprine[92]. In contrary, the risk of relapse after stopping AZA seems lower than after stopping infliximab. Thus, in a single referral center observational study on CD patients who stopped AZA after being in remission under combined AZA and infliximab for at least 6 mo, 15% of patients relapsed after 1 year[93].

THIOPURINES IN PREGNANCY AND LACTATION

Even though thiopurines belong to FDA pregnancy category D, the risk seems minimal. Two studies[94,95] did not find any evidence for an increased risk of pregnancy-related complications. Probably, the only major side effect of thiopurines is the risk of preterm birth[95-97], which, however, might be simply a disease effect. Furthermore, thiopurine levels in breast milk of mothers treated with AZA seem harmless[98] and without any long-term effects in these babies. Thus, it can be concluded that thiopurines can be administered safely to women with IBD, prior to and at the time at conception, as well as during pregnancy and lactation. Indeed, in a recent survey among gastroenterologists showed that more than 90% would recommend continuous thiopurine treatment[99].

CONCLUSION

Indications for use of thiopurines in IBD and ways to monitor therapy have been well established. In clinical practice, the possibility of 6-TGN measurement to monitor therapy seems underused. It is likely that broader use of TGN monitoring, and a combination of thiopurines with low dose allopurinol in case of inefficiency or side effects allows to (achieve or) maintain clinical remission in more patients. For the thiopurine/allopurinol combination, but also for 6-TG therapy, prospective trials to document the benefit (and risk) are urgently needed. Furthermore, more trials are needed to elucidate whether an early "top down" approach for combination of thiopurines with anti-TNF will bring a long-term benefit for patients as compared to a step-up approach in case of a non-response to thiopurines. Criteria when a successful thiopurine therapy for maintenance of remission can be stopped also need to be elucidated in future prospective trials. Risk communication with patients, but also referring physicians, about benefit, side effects and the above mentioned uncertainties remain challenging. Benefits are the quality of life gained by medically maintained remission; the avoidance of surgery (in CD and UC) and avoidance of colorectal cancer through efficient anti-inflammatory therapy. Risks are, however, (opportunistic) infections, lymphomas such as HSTCL and side-effects such as pancreatitis.

Accordingly, thiopurine therapy remains a hot topic in IBD.

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