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REVIEW

Thiopurines in inflammatory bowel disease revisited

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Abstract

Although a great variety of new drugs have been introduced for the therapy of inflammatory bowel diseases so far, a definite cure of the disease is still out of scope. An anti-inflammatory approach to induce remission followed by maintenance therapy with immunosupressants is still the mainstay of therapy. Thiopurines comprising azathioprine and its active metabolite mercaptopurine as well as tioguanine, are widely used in the therapy of chronic active inflammatory bowel disease (IBD). Their steroid sparing potential and efficacy in remission maintenance are out of doubt. Unfortunately, untoward adverse events are frequently observed and may preclude further administration or be life threatening. This review will focus on new aspects of thiopurine therapy in IBD, its efficacy and safety.

Key words: Thiopurines; Mercaptopurine; Tioguanine; Azathioprine; Ulcerative colitis; Crohn's disease

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INTRODUCTION

The main aim in treating patients with inflammatory bowel disease (IBD) taking into account the armamentarium of available therapeutic agents is to choose the most efficient therapeutic regimen on an individual basis in order to achieve remission of disease. Two aspects have to be kept in mind to achieve this goal: first is to treat the patient with the greatest efficacy regarding disease remission and probably obtaining mucosal healing. And in second place treat with the greatest safety and minimal toxicity. One integral part of this management strategy is the use of immunosuppressants after remission induction. Most commonly used among this group are the thiopurines azathioprine (AZA) and mercaptopurine (MP). AZA and MP need to be activated by metabolism to 6-thioguanine nucleotides (6-TGN). Although these nucleotides disturb proper DNA synthesis it has not conclusively shown, that 6-TGN are the one and only molecules responsible for proper action. However, immunosuppressive function seems to be mediated in part by induction of apoptosis in lymphocytes. A correlation of therapeutic benefit and 6-TGN levels has been put into question. Although thiopurines are widely used, several safety concerns remain. Tioguanine has been proposed as an alternative to overcome such problems, as it skips the metabolic conversion to 6-methyl mercaptopurine (6-MMP) which is responsible for hepatotoxicity. This review will discuss efficacy and safety of thiopurine therapy in IBD.

PHARMACOLOGY OF THIOPURINES

Oral bioavailability is variable and inversely proportional to the oral dose (AZA 27% to 83%, MP 5% to 37%). After oral intake 88% of AZA is rapidly converted non-enzymatically to 6-MP and S-methyl-4-nitro-5-thioimidazole in erythrocytes and human cells. This process relies on sulphydryl-containing compounds such as cysteine and glutathione. Deposition and consumption of the latter is in part controlled by glutathione-S-transferase activ-

ity[1]. 6-MP as the active metabolite undergoes a complex biotransformation into active and inactive metabolites that easily transfer membranes. At first 6-MP undergoes extensive first pass catabolism by xanthine oxidase (XO) forming 6-thiouric acid which is excreted by the kidneys. Allopurinol is a well known inhibitor of XO. In addition, 6-MP is a substrate for thiopurine methyltransferase (TPMT), the rate limiting enzyme of detoxification. Methylation results in the inactive metabolite 6-MMP. The active metabolites of 6-MP are initially formed by hypoxanthine phosphoribosyltransferase (HPRT). The first active intermediate thioinosine monophosphate is then rapidly converted to the 6-TGN which are accredited to be the paramount effectors of thiopurines. Their cytotoxic and immunosuppressive effect is attributed to their incorporation into cellular nucleic acids resulting in inhibition of lymphocyte proliferation. Beside this action, 6-TGN might play an important role in the signaling cascade of apoptosis in lymphocytes by inhibiting Rac 1 activation in T-cells[2]. Competing with this intracellular activation is the thiol-methylation by TPMT. The individual capacity of this enzyme influences the relative proportion of intracellular active 6-TGN produced by a given individual and has important implications in predicting toxicity. TPMT polymorphism will be discussed elsewhere (see below). Pharmacology of thiopurines is comprehensively summarized in[3,4].

USE OF THIOPURINES IN CROHN'S DISEASE

The efficacy of thiopurines has been demonstrated in several trials both for induction and maintenance of disease free remission in Crohn's disease (CD). The first study demonstrating the efficacy of MP to induce remission was reported by Present *et al*[5]. Sixty-seven percent of the patients treated with 1.5 mg/kg MP daily responded as compared to 8% in the placebo group. The today well known delayed onset of action was additionally well described in this study with a mean time to response of 3.1 mo. The efficacy in remission maintenance was clearly shown in the landmark withdrawal trial by Candy *et al*[6]. Several other studies reported variable responses ranging from 36%-100%[7-11]. A major drawback of some of these studies was their short duration. Due to the thiopurines' time lag of action the therapeutic gain might have been underestimated. Despite these varying results updated meta analysis favour therapy over placebo with an odds ratio of 2.43 (95%CI: 1.62-3.64) regarding remission induction with AZA or MP[12,13]. In case of remission maintenance the OR for AZA is 2.32 (95%CI: 1.55-3.49) with a number needed to treat (NNT) of 6 and with MP 3.32 (95%CI: 1.40-7.87) with a NNT of 4, including 7 trials[14].

As one third of the patients become steroid dependent and 20% of the patients loose response to steroids after one year[15], an early introduction of immunomodulators seems mandatory, at least in patients who fail to taper off steroids. An elegant study by Markowitz *et al*[16] in children with new onset of CD underlines the potential of early MP administration for remission maintenance. Steroid pulse therapy in combination with MP resulted in a reduction of relapse rates from 28% to 4% after 6 mo and from 47% to 9% after 18 mo compared to steroids alone. Additionally, a significant steroid sparing effect was observed. These results suggest a short term steroid use for induction of remission and thiopurines for long term steroid-free maintenance therapy.

A recent randomised controlled trial assessed steroid free remission in active CD after 26 wk of treatment with AZA, infliximab or the combination of both[17]. While AZA was less beneficial than infliximab, the best results were obtained with combined treatment. Similar findings were reported regarding mucosal healing. The inferior performance of AZA as a single agent may be related to the defined primary aim and time point.

USE OF THIOPURINES IN ULCERATIVE COLITIS

Although thiopurines are widely used in the treatment of patients suffering from ulcerative colitis (UC) controlled data are limited[18-21]. If thiopurines have any place in the treatment of UC it is for remission maintenance or steroid-dependence. A recent meta-analysis including 6 studies reported an OR of 2.56 in favour of thiopurines (95%CI: 1.51-4.34)[22]. Moreover, a steroid sparing potential of thiopurines in UC is obvious[20,21].

In patients presenting with steroid refractory disease thiopurines play a role as they enhance the beneficial effect of the rescue therapy with cyclosporine[23]. Despite fundamental evidence, thiopurines remain a therapeutic option for UC patients failing 5-ASA monotherapy or requiring multiple steroid courses[24]. One half of the UC patients responding to a first course of corticosteroids will require immunosuppressives mainly because of steroid-dependence[25]. In accordance with the SONIC trial for CD, a similar study was conducted in UC[26]. The results and drawbacks are comparable though the difference between AZA and infliximab monotherapy vanished. Thus, combination treatment was stated to be the most effective with regard to steroid-free remission and mucosal healing at 16 wk.

OPTIMAL DURATION OF TREATMENT?

An unresolved question after successful initiation of thiopurine treatment is, how to assess the optimal duration of treatment. Bouhnik *et al*[27] reported that the beneficial effects disappear after 4 years of AZA treatment, based on a small number of patients. In a controlled study AZA withdrawal was not equivalent to continued therapy with AZA for maintenance of remission in patients with CD who had been in remission on AZA for more than 3.5 years[26,28]. In case of UC the data are sparse. A retrospective survey reported that relapse rates were higher in UC patients with a short duration of AZA administra-

tion indicating a favourable longevity of treatment[29]. In accordance with a large observational study in England AZA sustains remission in CD as well as UC for at least 5 years[30].

Thus far patients should be informed about indefinite treatment especially in complicated cases and after recurrent surgery. The decision to withdraw the drug has to be made on an individual relapse-risk assumption.

MUCOSAL HEALING

The surrogate marker mucosal healing is increasingly acknowledged as a treatment goal despite the lack of prospective data to assume disease course prediction. First insight in endoscopic healing was given by D' Haens *et al*[31] who found that the majority of AZA treated CD patients were able to achieve near to complete mucosal healing. Mantzaris *et al*[32] found that after 1 year of maintenance therapy in clinically quiescent CD, AZA was superior to budesonide in improving endoscopic healing and histological remission. In steroid dependent UC AZA was more effective than 5-ASA in achieving clinical and endoscopic remission[33]. More data can be extracted from the SONIC and UC SUCCESS trials (endoscopic healing with AZA in CD at 26 wk 16.5%, UC at 16 wk 37%) contradicting former results[17,26]. As shown in CD thiopurines are effective drugs to induce remission and mucosal healing and to maintain it in UC as well[34].

SAFETY OF THIOPURINES

Adverse events during the use of thiopurines in the treatment of patients with IBD can be categorized as non-dose dependent (allergic/idiosyncratic) side effects on one hand and dose dependent ones on the other[35-37]. In general the number needed to harm is 15.

Five percent to ten percent of the patients do not tolerate thiopurines regardless of the dose and their underlying drug metabolism. Most common reactions are flu-like illness, fever, nausea, rash, abdominal pain, pancreatitis and allergic reactions that typically occur within 2-4 wk after initiating therapy. This has not been conclusively related to TPMT polymorphisms but wildtype glutathione-S-transferase is overrepresented in those patients[38]. About half of those patients can be successfully re-challenged with MP which lacks an imidazole ring. This switch cannot generally be recommended for patients who experienced pancreatitis. Patients with an allergic reaction should be allocated to alternative immunomodulators such as methotrexate. In the following a few severe adverse events shall be enlightened in detail.

Myelotoxicity

The most common side effect in the treatment of IBD patients with thiopurines is myelosuppression, which is mostly manifested as leucopenia and occurs in 2.2% to 15% of the patients[37-39]. The majority of those events respond to dose reduction, but infectious complications increase if the white blood cell count falls below 2000/μL. Therefore special care is warranted in those patients and in patients on multiple immunosuppressants. TPMT deficiency accounts for one fourth of the leukopenia in CD treated with thiopurines whereas the rest is obscure[40]. A drop in platelets may occur in conjunction with leucopenia or as a single event. If it is not reversible after dose reduction or discontinuation of therapy patients need to be further evaluated with a special focus on hepatotoxicity.

Hepatotoxicity

The exact mechanisms of hepatotoxicity by thiopurines are not clarified[41,42]. Some of the patients develop a mild elevation in their liver function tests and most of them respond to dose reduction. Hence, a cessation of therapy is not necessary. In those patients whose liver enzymes do not normalize over time further exploration is necessary. Potentially serious hepatic side effects occur with the development of nodular regenerative hyperplasia in patients treated with tioguanine[43] as well as AZA[42-44] resulting in progressive liver damage and portal hypertension. An alternative is the use of the XO-inhibitor allopurinol in combination with 1/4 of the standard dose of a thiopurine which increases 6-MP bioavailability and reduces 6-MMP formation thereby limiting the risk of hepatotoxicity but long-term prospective studies are lacking[45-48].

Malignancy

The incidence of cancer and lymphoma in IBD and the influence of thiopurines is still a controversial topic[49-53]. 6-Thioguanine accumulates in the DNA of thiopurine treated patients and is able to interact with UVA to generate reactive oxygen species. It has recently been shown that the UVA/DNA 6-TG interaction irreversibly inhibits transcription in cultured human cells and provokes polyubiquitylation of the major subunit of RNA polymerase II. This persistent transcription-blocking DNA lesions seem to be responsible for acute skin responses to sunlight and predispose for the development of skin cancer[54]. Recently published data point to an increased risk for non-melanoma skin cancer (NMSC). The incidence rate ratio was higher among patients with IBD compared with controls (1.64, 95%CI: 1.51-1.78). Persistent thiopurine use (> 365 d) was even stronger associated with NMSC (adjusted OR 4.27, 95%CI: 3.08-5.92)[55]. There is one study that contradicts these results[56], but three others confirm the data and report an increased risk for NMSC in patients with IBD treated with thiopurines[57-59]. To summarize, up to now these patients should be protected against UV radiation and should undergo lifelong dermatologic screening.

The issue of lymphoma is open for discussion. There is an ongoing debate if the disease itself already increases the risk for the development of lymphoma. Additionally a confounding factor should be kept in mind as patients with an aggressive course of the disease do have a greater

innate risk for lymphoma and besides a higher likelihood to receive thiopurine treatment[60]. There are some studies finding no association between thiopurine treatment and lymphoma in IBD while others suggest an increased incidence[61-69]. A meta-analysis of the above mentioned data revealed a relative risk of four for all lymphomas in patients on thiopurine treatment compared with those with IBD not receiving thiopurines[70]. This increase was confirmed in a recent prospective evaluation of french IBD patients with a hazard ratio of 5.28 for ongoing thiopurine treatment[71,72]. Of interest is the potentially overt risk in patients with double immunosuppression but the data are lacking so far. The rare variant of hepatosplenic lymphomas with fatal outcome has to be acknowledged and is related to thiopurines as well as TNF blockers.

Thiopurines have been demonstrated to be risk-neutral in the context of the development of colorectal cancer in IBD patients[73]. And there are various studies available with regard to cervical cancer related to HPV 16 and 18 infection. So far there is no clear picture due to the paucity of data and the risk of cervical cancer seems to be comparable to the general population. Although there is no evidence for an increased risk of other solid tumors the lack of data always needs to be taken into consideration[61].

Taken together thiopurine treatment in patients with IBD has a potential to induce or propagate neoplasia. This relative risk increase is most significant for lymphoma and NMSC in second place but the risk-benefit ratio supports the continuation of treatment in IBD.

Use in pregnancy

Women with IBD have similar rates of fertility compared to the general population. Unfortunately they have a greater rate of adverse pregnancy outcomes which are related to disease activity. Therefore an immunosuppressive treatment of patients with severe disease course is mandatory during pregnancy. Although thiopurines are rated D (positive evidence of human fetal risk, but potential benefits may warrant its use) by the Food and Drug Administration they seem to be safe and well tolerated during pregnancy[74]. There are smaller studies that found an increased risk of congenital malformations, perinatal mortality, and preterm birth[75,76]. Opposing results are presented by Francella *et al*[77] in their analysis on 155 patients who conceived after IBD was diagnosed. There was no statistical difference regarding rates of spontaneous abortion, abortion as a result of a birth defect, major congenital malformations, neoplasia or increased infections after the intake of MP. This is now confirmed by the registered data from the CESAME study[78].

OPTIMIZING SAFETY AND EFFICACY

Due to their complex metabolism and genetic polymorphisms in metabolizing enzymes there is a wide inter- and intra-patient variation in the concentrations of active and toxic metabolites. In 9%-25% of patients serious drug toxicity leads to a cessation of therapy and therapeutic efficacy is unachievable in about 15% of patients[79].

TPMT measurement

TPMT competes with XO and HPRT for the substrate 6-MP. The TPMT gene carries genetic polymorphisms that lead to a nearly 50-fold variation in the enzyme activity between individual patients[80]. Hence, low TPMT activity leads to a greater conversion of 6-MP to 6-TGN (the predominant active metabolite) *via* the HPRT pathway. This is not only associated with greater therapeutic activity but also a higher likelihood of myelotoxicity. On the other hand high TPMT activity results in greater 6-MMP production at the expense of active metabolites.

A growing number of single nucleotide polymorphisms within the TPMT gene are identified, but the frequency among approximately 30 known alleles is very low except for the 3A/C alleles. There are population differences in the frequency of abnormal TPMT alleles especially in relation to the 3A and 3C genotypes, with more than 90% of the patients carrying the 1/1 wild type genotype and normal enzyme activity. 10%-11% of the patients have a reduced enzyme activity due to the heterozygous 1/3 (TPMT3A or 3C) genotype. Only 1 in 300 patients carries the homozygous 3/3 genotype with absent TPMT activity. Together this distribution in a population follows a classical trimodal pattern[80], although very high metabolizers superimpose this view without clinical relevance. The TPMT status can be determined by measuring enzyme activity (radiochemical or HPLC) or by genotyping. Allelic frequencies in IBD may be somewhat higher[81-83]. In patients with TPMT deficiency a tiny dose of thiopurines (1/10) can be used under careful monitoring. Patients with intermediate TPMT activity should receive half or one third of the initial dose, normal to high TPMT activity is in need of up to very high doses. Other adverse drug effects are unrelated to TPMT pheno- or genotype. However, a recent finding is the association of some type 2 adverse events (flu-like illness, rash) and inositol pyrophosphohydrolase (ITPase, ITPA) polymorphisms. This has not been implemented in the recommendations so far but warrants attention[84]. At present determination of TPMT activity is questionable in the clinical setting although cost effectiveness has been noted. A recent position paper summarizes the recommendations of TPMT testing and monitoring of 6-TGN levels[85].

Monitoring metabolites

Metabolite monitoring is not mandatory for patients with IBD who are treated with thiopurines. Although several trials have observed an association between high 6-TGN levels and a favourable response this has not been unequivocally reproduced (summarized in[86]). However, monitoring is particularly useful in those patients that do not respond to a standard dose of thiopurine drugs after a meaningful duration of treatment. The combination of erythrocyte 6-TGN and 6-MMP concentrations can

be helpful to detect the reason for a lack of response. Absent 6-TGN and 6-MMP levels unmask poor compliance. If the concentration of both metabolites is low, the patient is probably under-dosed. A low 6-TGN level in conjunction with a high 6-MMP concentration identifies a patient who may respond to a rechallenge with low dose AZA in combination with allopurinol. Otherwise he has to be termed thiopurine resistant. In case of high concentrations of both metabolites the patient suffers from thiopurine refractory disease.

TIOGUANINE AS AN ALTERNATIVE TO AZA AND MP-REAL BENEFIT?

In order to overcome problems of toxicity and delayed action of thiopurines, tioguanine, originally established for treatment of leukemias mainly in children, was investigated for remission induction and maintenance in IBD. It serves as a direct precursor to 6-TGN, the proposed active metabolite of thiopurines. In one group with 37 patients with active CD tioguanine appeared to be effective with acceptable short-term toxicity[87,88]. 6-TGN levels were far above those documented for classical thiopurines. However, neither toxicity nor efficacy increased. Recent data has shown that hepatotoxicity does not reoccur during tioguanine treatment in most IBD patients who failed conventional thiopurines due to 6-MMP associated hepatotoxicity. Hence, tioguanine appears to be a justifiable alternative in these IBD patients[89]. Another investigation by Dubinsky *et al*[42] found opposing results and stated that NRH is a common finding in tioguanine treated patients with IBD. As progression or reversibility of NRH remains unknown the authors do not recommend tioguanine therapy for patients with IBD. Tioguanine related hepatotoxicity in the Dubinsky study was surprisingly frequent whereas in other studies this rate is nearly comparable to that of AZA as NRH has been described under therapy with AZA as well (see chapter hepatotoxicity). A lower dose of 10-20 mg tioguanine for remission maintenance has been proposed to be safe in the long term[90]. Accordingly, tioguanine should not be abandoned but more surveillance data are needed.

CONCLUSION

The role of conventional thiopurines, 6-MP and AZA, still evolves in the treatment of patients with IBD. The above stated data underline the important role of thiopurines in remission maintenance. Understanding the metabolic pathways has greatly optimized treatment and lead to greater safety and efficacy. Long-term observational studies regarding the still controversial issues of hepatotoxicity, nodular regenerative hyperplasia and malignant potential of the drugs are still warranted. Tioguanine may be an effective alternative in patients who are intolerant to AZA or MP but the incidence and fate of NRH is still unresolved.

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