Azathioprine co-therapy with allopurinol for inflammatory bowel disease: trials and tribulations

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Summary

Although the employment of thiopurine metabolites profiles to decide on allopurinol co-therapy is intellectually appealing, their use in determining dosing decisions or use of allopurinol co-therapy is based on assumptions which are of unproven clinical importance. If decisions are based on metabolic profiling it is likely to deny many patients the benefits of low dose azathioprine with allopurinol co-therapy (LDAAC). Conversely, the measurement of thiopurine methyl transferase appears to be of benefit as it allows tailored dosing which is of particular importance with LDAAC. Poor response or side effects to full dose azathioprine (FDA) is common (up to 60%) in inflammatory bowel disease (IBD) and results in the need for monoclonals ($15-20,000/patient/year), surgery ($10,000/patient/surgery), hospitalisations ($7,000/patient/admission) (UK costs) and steroid dependency. With an increasing incidence of IBD in developing nations (surpassing the West) this will place a significant strain on these economies. Evidence emerging from centres in the UK, Australia and North America indicate an improvement in efficacy of using LDAAC over FDA for IBD. These observations include by-passing hepatotoxicity, non-pancreatitis side effects and importantly increasing the numbers of patients likely to benefit from FDA. If these observations are confirmed LDAAC will result in health improvements for IBD patients and significant cost saving for health commissioners and patients. The use of LDAA should similarly benefit patients who require azathioprine for other disorders including hepatology, childhood IBD and dermatology.

Keywords: Azathioprine; mercaptopurine; allopurinol; inflammatory bowel disease, Crohn's disease.

Resumo

Coterapia com azatioprina e alopurinol para doença inflamatória intestinal: experiências e tribulações

Embora o emprego de perfis de metabólitos tiopurina para decidir sobre o alopurinol coterapia seja intelectualmente atraente, seu uso nas decisões de dosagem ou utilização de alopurinol coterapia baseia-se em suposições cuja importância clínica não foi comprovada. Se as decisões baseiam-se em perfil metabólico é possível que sejam negados a muitos pacientes os benefícios da coterapia com baixa dose de azatioprina e alopurinol (CBDAA). Por outro lado, a medição de metiltransferase tiopurina parece ser benéfica, pois permite a dosagem sob medida, particularmente importante com CBDAA. É comum a ocorrência de resposta insatisfatória ou de efeitos adversos à dose completa de azatioprina (DCA) (mais de 60%) na doença inflamatória intestinal, resultando na necessidade de monoclonais ($15-20,000/paciente/ano), de cirurgia ($10,000/pacientes/cirurgia), e de internações ($7,000/paciente/admissão) (custos Reino Unido) e na dependência de esteroides. O aumento da incidência de DII em países em desenvolvimento (ultrapassando o Ocidente) demandará um esforço ainda maior dessas economias. Novas evidências de centros no Reino Unido, na Austrália e nos EUA indicam uma melhoria na eficácia do uso CBDAA e DCA para DII. Essas novas considerações incluem a superação da hepatotoxicidade e dos efeitos colaterais da pandreatite além de considerável aumento no número de pacientes propensos a beneficiarem-se da DCA. Se estas observações forem confirmadas, a CBDAA gerará melhorias na saúde para pacientes com DII e economia significativa de custos para os orgãos de saúde e para os pacientes. O uso de CBDAA deve beneficiar também os pacientes que necessitam de azatioprina para outros distúrbios, incluindo hepatologia, DII infantil e dermatologia.

Unitermos: Azatioprina; mercaptopurina; alopurinol; doença inflamatória intestinal; doença de Crohn.

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Introduction

Inflammatory bowel disease (IBD; comprising Crohn's disease and ulcerative colitis) is a chronic relapsing lifelong disorder of unknown aetiology, affecting the gastrointestinal tract. IBD is more common in Northern Europe and developed nations, although the numbers of sufferers in developing nations may well exceed that in the West[1,2]. IBD has a spectrum of disease severity which mainly determines its treatment and long-term natural history. Crohn's disease (CD) often progresses to non-curative surgery (50% in 10 years, 80% in a lifetime), and the use of immunosuppressives is steadily increasing (up to 70%) to meet this challenge[3]. In Northern Europe and the USA, rates of surgery for ulcerative colitis (UC) in the past two decades have decreased from over 30% to 5-11%. During that time there has been an increase in the intake of immunosuppressive or biological agents, from about 3% from 1960-1979 to 20% for the period 1980-2001[4].

The thiopurine drugs 6-mercaptopurine (6MP) and its pro-drug azathioprine (AZA), have well known long-term safety profiles and are often used as first-line immunosuppressives in IBD. There have been conflicting reports about the impact of thiopurines on the natural history of CD[3,5,6]. However, several encouraging reports have recently emerged. A Cardiff cohort demonstrated a significant reduction in surgery and steroid use since thiopurines have been more extensively used in CD[5]. Falling rates of surgery following earlier and more aggressive use of AZA/6MP have also been reported for a paediatric population[6] and a large cohort from Copenhagen[7]. As IBD most commonly affects patients during their reproductive years the long-term safety of thiopurines in pregnancy has been a therapeutic advantage. Failure to respond to thiopurine can have significant consequences for a patient. For CD, failure to respond to thiopurines frequently leads to the use of expensive 'biological' therapy (monoclonal antibody drugs) – if affordable for the patient – in preference to other immunosuppressants such as methotrexate partly due to the teratogenicity. However for UC, thiopurine failure leads to a colectomy in up to 88% of cases[8].

Adverse drug reactions (ADRs) to thiopurines result in stopping treatment and loss of the possibility of gaining the benefits from a thiopurine response, while noting that gastric ADRs to AZA/6MP maybe exacerbated by IBD disease factors[9]. However, it is likely that the frequency of side effects to these thiopurines are far higher than previously determined by retrospective studies[10,11] that reported thiopurine ADRs in approx. 15% of patients, with a recent prospective study suggesting an ADR rate up to 40%[12]. The commonest ADR is gastrointestinal intolerance (especially nausea); others are much less common include flu-like symptoms, hepatotoxicity, rash, pancreatitis and myelotoxicity. Some of these side effects can have a dose-dependant element, e.g. hepatotoxicity occurs in 25-30% of patients who receive supra-therapeutic doses of AZA of > 2 mg/kg[13]. Gastric intolerance, myelotoxicity and flu-like symptoms can occur both as the dose of AZA/6MP is slowly bought to therapeutic levels or when increased to supra-therapeutic levels when pursuing a positive response. Pancreatitis and rash appears to have an idiosyncratic or allergic quality and may reoccur on re-exposure to AZA/6MP.

Several studies have evaluated the impact of modern use of immunosuppressives including thiopurines. A study by Cosnes et al.[3] did not find any reduction in surgical rates between 1978-2002 for patients receiving thiopurines, but the half of the group that would have been predicted to have a lower rate of surgery started the AZA/6MP less than three months before surgery, and AZA/6MP takes at least 12 weeks to work, i.e. surgery was undertaken among the patient cohort too soon for them to benefit from thiopurines. In contrast, a large Cardiff cohort in which AZA/6MP was started earlier had significantly reduced surgical rates[5].

Failure to respond or adverse reactions to thiopurines can have a high cost. Patients who cannot take AZA/6MP have a high probability of hospitalisations, surgery, nutritional therapies, monoclonal therapies and occasionally parenteral nutrition. A hospital bed in the UK in 2011 costs £ 600-800/patient/day, while monoclonal therapies costs range from £ 10.000-15.000/patient/year: these therapies are thus expensive but far cheaper than hospitalisation. However, monoclonals suffer from significant loss of response each year of treatment, limiting their long-term use.

The genetics of thiopurine response are concerned with the activation and inactivation of the parent drugs (Figure 1). Genetic polymorphism of thiopurine methyltransferase (TPMT) can produce raised levels of the cytotoxic and immunosuppressive metabolites of AZA/6MP, the thioguanine nucleotides (TGNs), accompanied by low levels of methylated-6MP (6MeMP); this has been well-documented as producing myelotoxicity. However, the therapeutic value of erythrocyte TGN levels in predicting a positive response to AZA/6MP has yet to be confirmed with prospective studies: the value of TGN levels in erythrocytes is limited as they do not reflect levels in the target cells, the T-lymphocytes[14]. The cytotoxicity of TGNs has always been assumed to be concentrated on the bone marrow, however a prospective study has shown that nausea is also a common early adverse reaction accompanying low TPMT activity and raised TGNs[12]. Polymorphic deficiency of the inosine triphosphate pyrophosphohydrolase (ITPA) gene, which is associated with accumulation of an unusual thiopurine metabolite thio-ITP was initially reported as associated with flu-like symptoms[12], but this gene has also been linked to other thiopurine-induced adverse events in IBD patients[15].

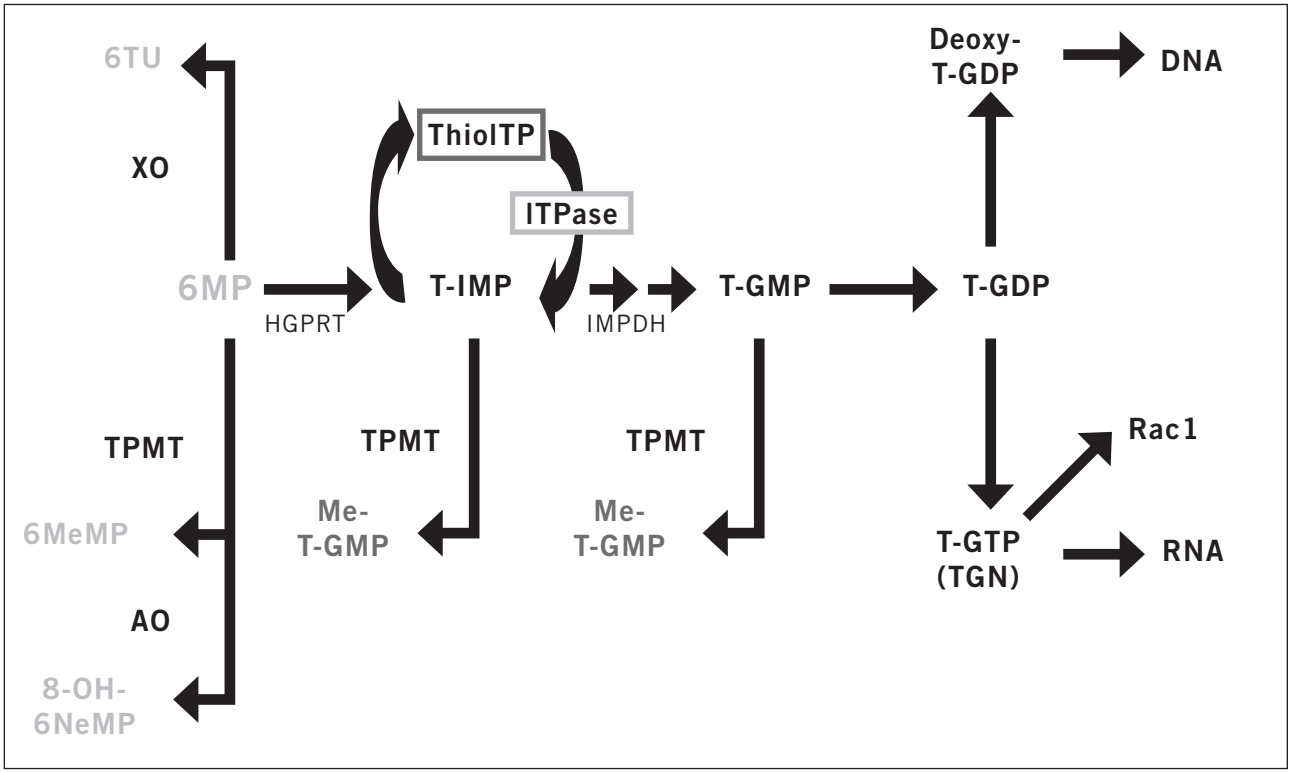

Figure 1 – Metabolic activation and targets of thiopurines. TPMT, thiopurine methyl-transferase; AO, aldehyde oxidase; XO, xanthine oxidase; HGPRT, hypoxanthine guanine phosphoribosyl-transferase; ITPase, inosine triphosphate pyrophospho-hydrolase; IMPDH, inosine monophosphate dehydrogenase; 6MP, 6-mercaptopurine; 6MeMP, methyl-6MP; 8-OH-6MeMP, 8-hydroxy-6MeMP; 6TU, 6-thiouric acid.

The association of hepatotoxicity with thiopurines is well established. Although 6MP is thought to be less hepatotoxic than AZA[16], no difference in hepatotoxicity rates was found between the two drugs in a meta-review[17]. In addition, a prospective evaluation found the rate of hepatotoxicity in IBD was high (13% abnormal liver function, 10% hepatotoxicity)[18], suggesting under-reporting in retrospective studies.

The concept of hepatotoxicity related to high methylated thiopurines (and thus high TPMT) has been around since 1967 when 6MeMP was tested as a therapy for leukaemia[19], and others have since provided evidence for this association[20,21]. However, similar to TGNs, measurement of erythrocyte 6MeMP may be limiting in its clinical application, due to two factors. First, most assays do not distinguish between inert 6MeMP and metabolically active 6-thio-IMP. Second, erythrocyte levels of 6MeMP have been demonstrated to be quite different to leucocytes (i.e. the target cells) and presumably other 'by-stander' cells such as hepatocytes. As a result, erythrocytes may be poor markers of hepatotoxicity: 90% of patients with high 6MeMP have no hepatotoxicity and conversely 40% of patients with hepatotoxicity have low 6MeMP[18].

Other genetic factors affecting thiopurine response may emerge. Xanthine oxidase effects have been studied and appear to have little correlation with response, although its role is far from clear[22]. Aldehyde oxidase polymorphism may be related to some side effects of AZA and requires further study[23] as does IMP dehydrogenase[24]. For the present, the usefulness of erythrocyte metabolite levels as a guide to thiopurine treatment has been shown to be limited[25], and other parameters (clinical response, CRP, ESR, leucocyte count and liver function tests) remain more reliable for routine monitoring.

Tribulations: allopurinol co-therapy for thiopurines

Allopurinol has a short half-life (2-3 hrs) and is weak completive inhibitor of xanthine oxidase (XO). Oxypurinol is generated by the action of aldehyde oxidase and XO on allopurinol, resulting in a longer-lived (18-30 hrs) metabolite that has a more potent non-completive inhibition of XO. Interestingly, allopurinol was originally designed as a XO inhibitor to improve bioavailability and the therapeutic index of 6MP[26]. Studies confirmed a 3-4x improvement in 6MP bioavailability, but there was a lack of improvement in the therapeutic index for leukemia. Subsequently, allopurinol's effect on lowering uric acid levels in patients receiving cytotoxic therapy lead to its more famous role in treating gout.

The synergistic effect of allopurinol on thiopurine therapy was recognised early in the development of renal transplantation as based on the bioavailability studies of

Elion[26] – kidney transplant patients receiving allopurinol for gout were determined to require an AZA dose of only one-third normal until the oxypurinol was eliminated[27]. However, the strong synergism of allopurinol with thiopurines paradoxically led to it being contra-indicated in pharmaceutical practice, with numerous reports of toxicity or death arising from inadvertent thiopurine/allopurinol co-prescription. As a result, deliberate co-therapy was not considered.

Co-therapy of allopurinol with azathioprine was first revived by Chocair in 1993[28], who reported a significantly higher graft survival among renal transplants. A similar improvement in heart graft survival was found by Chrzanowska and Krzymański[29] who were first to link allopurinol effects to changes in patterns of AZA metabolites, noting that for a given AZA dose erythrocyte TGN levels were greatly increased while 6MeMP levels were lowered. This contradicted the generally accepted mechanism for allopurinol interaction with thiopurines, which had previously been attributed to XO inhibition, despite the fact that XO has little affinity for 6MP[30], particularly at low doses[22]. The thiopurine metabolite effects of allopurinol imply inhibition of TPMT, but work done by Sparrow et al. could not find direct inhibition of TPMT in patients receiving allopurinol[31]. Recently, Marinaki et al. have reported that thioxanthine, which accumulates during allopurinol therapy, inhibits TPMT: whether this explains the mechanism requires further investigation[32].

Sparrow et al. were the first to report the deliberate use of thiopurine/allopurinol co-therapy for IBD patients who were showing poor thiopurine response accompanied by a specific metabolic profile (high 6MeMP and low TGN)[33]. A significant positive response was demonstrated in this sub-set of patients, with clinical improvement in almost 70% of those treated with reduced dose AZA/6MP plus allopurinol. Sparrow has further developed the concept of preferential methylation as a basis for justifying allopurinol co-therapy[31,34], and this has been supported by others[35,36].

The concept linking lack of response to excessive methylation was also supported by our prospective study that showed genetically wild-type TPMT patients who tolerated 2mg/kg AZA but had very high erythrocyte activity were at risk of poor outcome (43% response) compared with patients with normal TPMT activity (81% response)[12], echoing an earlier retrospective study[37], but others have pointed out that the positive predictive value of thiopurine metabolite ratios is poor[18].

An open-labelled trial: azathioprine-allopurinol co-therapy

To examine the outcome of using allopurinol co-therapy in IBD patients with poor response and without prior metabolite monitoring, an open-labelled trial was performed[38]. Clinical and blood monitoring was standard as used for thiopurine monotherapy. Patients were given 100mg allopurinol in combination with an AZA dose that was approximately a third of a TPMT-corrected dose of 2mg/kg (wild-type) or 1mg/kg (partial TPMT deficiency), i.e. 0.7 mg/kg for TPMT wild-type and 0.35mg/kg AZA for partial deficiency.

Of the 25 patients treated, an unusually high proportion (73%) had a full clinical response. During an 18-month evaluation period, 4 patients had reversible side effects: 2 episodes of myelotoxicity were detected and both responded to a simple reduction of AZA dose, while 2 patients had myalgia which responded to reduction of allopurinol dose (from 100 to 50mg) without loss of clinical response.

Long-term allopurinol co-therapy with thiopurines

Our first long-term treatment with AZA/allopurinol was reported for a patient who had been on co-therapy for 5 years[22]. Initially, we restricted co-therapy to patients who had experienced hepatotoxicity on AZA or 6MP following dose escalation, with excellent long-term results[38]. However, since 2000 we have expanded the use of allopurinol co-therapy beyond overcoming hepatotoxicity, to unselected non-responders, and the clinical response has ranged between 70-80%[39,40], similar to that recorded in this open-label trial and approximately double the usual long-term success rate observed with AZA or 6MP alone.

Metabolite profiling selection

Sparrow et al.[31,33] were first to demonstrate that with thiopurine-allopurinol co-therapy a positive response was achievable in over 70% of IBD patients who previously had poor response accompanied by hepatoxicity upon dose escalation, identified as a subset of patients exhibiting preferential erythrocyte methylation (high 6MeMP levels and low TGN). This was similar to Chrzanowska and Krzymanski[29], who showed that co-prescription of allopurinol significantly increased erythrocyte TGN levels and reduced 6MeMP in heart transplant patients receiving AZA immunosuppression.

The strategy developed by Sparrow relies on at least two assumptions: 1) erythrocyte TGNs are predictive of clinical response, and 2) high erythrocyte 6MeMP levels predict a diversion of metabolism away from activation to TGN. As a result, restricting allopurinol use to erythrocyte metabolic profiles identified as 'high methylators' (or 'shunters') has led inadvertently to allopurinol co-therapy being recommended only for non-responders with a specific metabolic profile[41]. This approach also suffers from at least two additional restrictions: 1) the proportion of patients not responding to AZA/6MP who fit this profile is not known, and 2) the facility to measure metabolites to identify this subset of patients is restricted to a few developed nations.

Conclusions

The more universal use of co-therapy – as advocated here – thus increases the number of patients eligible for allopurinol, especially as they do not require prior metabolic profiling. In addition, direct co-therapy bypasses the lengthy (minimum 3 months) waiting period required for a positive response to classical thiopurine therapy that can add to the significant morbidly and suffering associated with symptoms from active and severe inflammatory bowel disease.

Potential patients can therefore be divided into:

A. Prior thiopurine exposure: This includes patients who have hepatotoxicity[38] non-pancreatic adverse drug reactions[39] or poor thiopurine response without prior metabolite profiling/monitoring[40].

B. Thiopurine naive: IBD patients in this group include those exhausted with frequent flares and/or other disease activity, and prefer to avoid any chance of early reactions or poor response[41]. Ulcerative colitis patients with high risk of colectomy, including colitics exhausted with poor response to steroids and 5ASA's, and those with acute severe disease acute requiring infliximab/cyclosporine.

There are two constraints to co-therapy. First, it is reasonable to consider the predictive value of TPMT activity/genotype, and calculate an appropriately lowered dose (50% normal dose for TPMT carriers), then the dose is reduced to one third of the lower dose when allopurinol is included. Second, there will be a small proportion of patients who are hypersensitive or intolerant of allopurinol: this is relatively rare in European populations but is a significant among Han Chinese[42].

Interestingly, hepatotoxicity and neutropenia have been by-passed with allopurinol co-therapy in patients who are TPMT heterozygotes, and this suggests that allopurinol co-therapy may reduce toxicity in other ways in addition to lowering high 6MeMP, perhaps through a simple dose-lowering mechanism.

In conclusion, it is important to note that while thiopurines offer a cheap, safe and long-term treatment option for IBD, they suffer from significant rate of poor response and side effects. In particular, poor responders prescribed a higher dose of AZA from the beginning of therapy or are dose escalated, have 25-30% chance of developing hepatotoxicity, with an uncertain clinical outcome. Alternatively, low dose AZA/6MP with allopurinol co-therapy is potentially be less toxic and can achieve at least 70% clinical response among poor responders.

But co-therapy does not need to be restricted to a poor responder subset: it can be used from the initiation of therapy for most patients who are to be treated with thiopurines. Allopurinol co-therapy offers the hope of reducing side effects and improving clinical efficacy of thiopurines without any significant risk or cost. If this promise is borne out then there will be an improvement in patient experience with IBD and commissioning for health care costs. As allopurinol co-therapy appears to significantly lower the chance of side effects and increases the probability of a positive response, this may also significantly reduce patients' therapeutic uncertainties and improve their experience of thiopurines.

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