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Progress Report

Thiopurines in inflammatory bowel disease: pharmacogenetics, therapeutic drug monitoring and clinical recommendations

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Abstract

There is a growing interest in the use of thiopurines (azathioprine, 6-mercaptopurine and 6-thioguanine) for the management of inflammatory bowel disease. The genetically controlled thiopurine (*S*)-methyltransferase enzyme is involved in the metabolism of these agents and is hypothesised to determine the clinical response to thiopurines. Diminished activity of this enzyme decreases the methylation of thiopurines, theoretically resulting in potential overdosing, while high thiopurine (*S*)-methyltransferase status leads to overproduction of toxic metabolites and ineffectiveness of azathioprine and 6-mercaptopurine. In practice, controversies exist regarding the utility of standard thiopurine (*S*)-methyltransferase pheno- and genotyping. Current pharmacogenetic insights suggest that another enzyme system may participate in the efficacy and toxicity of thiopurines; inosine triphosphate pyrophosphatase. Other topics discussed in this review are the utilisation of therapeutic drug monitoring and the experimental use of 6-thioguanine in the treatment of inflammatory bowel disease. 6-Thioguanine has a less genetically controlled metabolism and skips genetically determined metabolic steps. On theoretical basis, 6-thioguanine might therefore have a more predictable profile than azathioprine and 6-mercaptopurine. However, the use of 6-thioguanine has been associated with an increased risk of nodular regenerative hyperplasia of the liver and veno-occlusive disease. Further research is warranted before 6-thioguanine can be considered as a treatment option for inflammatory bowel disease.

Keywords: Azathioprine; IBD; ITPase; 6-Mercaptopurine; Pharmacogenetics; Therapeutic drug monitoring; 6-Thioguanine; Thiopurines; TPMT

1. Introduction

The treatment of ulcerative colitis (UC), Crohn's disease (CD) and indeterminate colitis aims to induce and subsequently maintain clinical remission of the disease. Glucocorticosteroids and aminosalicylates are currently the first-line treatment for the induction of remission in CD and UC, respectively. However, for patients with chronic recurrent disease, glucocorticosteroids are not effective as maintenance therapy and their long-term side-effects are unacceptable [1–3]. Moreover, about 50% of CD patients treated with steroids develop steroid-resistance or steroid-dependency [4]. For such patients, steroid-sparing immunosuppressive treatment with thiopurines (azathioprine [AZA] or 6-mercaptopurine [6-MP]) is indicated.

AZA and 6-MP have gained a prominent place as maintenance therapy of inflammatory bowel disease (IBD) [5].

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However, their therapeutic role is often discussed, because of toxicity and therapeutic failure. In clinical practice, 25% patients may not respond to AZA or 6-MP, 30% may relapse during treatment, and side-effects may occur in 15–30% of the patients [6–12]. The adverse effects of AZA and 6-MP can be subdivided into two types: allergic and non-allergic [10,12,13]. The allergic-type adverse reactions are dose-independent and occur within weeks following the introduction of the drug. These reactions include: pancreatitis, hepatitis, skin rash, fever, arthralgias, malaise, nausea, diarrhoea and abdominal pain. The non-allergic adverse reactions are dose-dependent and are thought to be related to the (intracellular) concentration of thiopurine metabolites and include myelosuppression and hepatotoxicity. Myelosuppression is of major concern, as it is accompanied by an increased risk of infections and sepsis [14–17].

The genetically controlled thiopurine (*S*)-methyltransferase (TPMT) enzyme is involved in the metabolism of these agents. TPMT is known to modulate the clinical response to thiopurines in children with acute lymphoblastic leukaemia [18]. The United States Food and Drug Administration (FDA) has recently approved a safety labelling change for 6-thioguanine (6-TG) as a chemotherapeutic agent (Tabloid®), alerting prescribers to the possibility of TPMT status measurement, to reduce the risk of developing life-threatening myelosuppression in patients found to be TPMT deficient [19]. However, the benefit of performing TPMT status measurement in clinical IBD practice is a matter of ongoing debate. Recently, a theory has been proposed concerning the role of the dephosphorylating enzyme inosine triphosphate pyrophosphatase (ITPase) in AZA and 6-MP metabolism. An impaired activity of ITPase may lead to pancreatic toxicity, rash, neutropoenia and gastro-intestinal complaints probably due to the accumulation of a metabolite, 6-thioinosine triphosphate [20].

It has been hypothesised that 6-TG (a third thiopurine) is less intensively metabolised by TPMT and that ITPase is probably not involved in its metabolism. Theoretically, 6-TG may therefore be beneficial in patients with high TPMT status (extensive methylators) or in patients with impaired ITPase activity. However, 6-TG is probably associated with an increased risk of nodular regenerative hyperplasia (NRH) of the liver and veno-occlusive disease as seen in patients with acute lymphoblastic leukaemia [21,22] and IBD [23,24].

In this review, the pharmacogenetic aspects of the thiopurine cascade, therapeutic drug monitoring (TDM) and clinical implications for IBD practice are specifically addressed. Furthermore, the possible use of 6-TG for IBD is discussed.

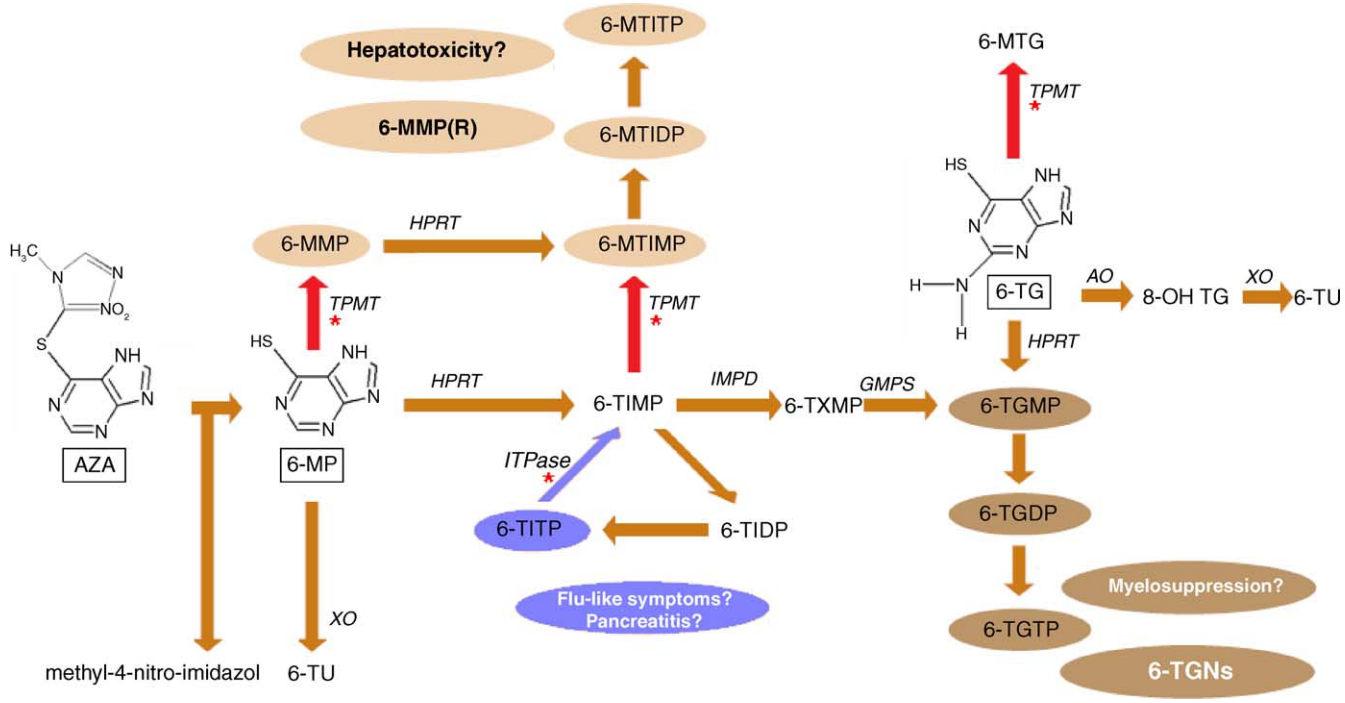

Fig. 1. Schematic presentation of proposed metabolism pathways of AZA, 6-MP and 6-TG. Asterisk (*) denotes pathways of possible pharmacogenetic relevance. Abbreviations: AO: aldehyde oxidase, AZA: azathioprine, GMPS: guanosine monophosphate synthetase, HPRT: hypoxanthine phosphoribosyl transferase, IMPD: inosine monophosphate dehydrogenase, 6-MTIMP: 6-methyl thioinosine 5′-monophosphate, 6-MMP: 6-methylmercaptopurine, 6-MMPR: 6-methylmercaptopurine ribonucleotide, 6-MP: 6-mercaptopurine, 6-MTG: 6-methyl thioguanine, 6-MTIDP: 6-methylthioinosine 5′-diphosphate, 6-MTIMP: 6-methylthioinosine 5′-monophosphate, 6-MTITP: 6-methylthioinosine 5′-triphosphate, 8-OHTG: 8-hydroxythioguanine, 6-TG: 6-thioguanine, 6-TGDP: 6-thioguanine 5′-diphosphate, 6-TGMP: 6-thioguanine 5′-monophosphate, 6-TGTP: 6-thioguanine 5′-triphosphate, 6-TGNs: 6-thioguanine nucleotides, 6-TIDP: 6-thioinosine 5′-diphosphate, 6-TIMP: 6-thioinosine 5′-monophosphate, 6-TITP: 6-thioinosine 5′-triphosphate, TPMT: thiopurine (*S*)-methyltransferase, 6-TU: 6-thiouric acid, 6-TXMP: 6-thioxanthosine 5′-monophosphate and XO: xanthine oxidase.