

Part 2

Medical Treatment: Making the Most of What We've Got – Immunomodulators

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6-Mercaptopurine or azathioprine?

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LEARNING POINTS

6-Mercaptopurine or azathioprine?

- 6-Mercaptopurine (6-MP) and its pro-drug, azathioprine, have subtle differences in their efficacy and tolerability
- Half of patients intolerant of azathioprine are able to take 6-MP but serious toxicity, such as leukopenia and pancreatitis, are common to both
- Azathioprine may be a more powerful immunosuppressant than 6-MP
- Data comparing the two drugs directly in IBD are lacking
- Either drug is a reasonable choice as the first-line thiopurine; azathioprine may be slightly more effective in patients who tolerate it.

Introduction

Azathioprine (AZA) and 6-mercaptopurine (6-MP) are effective cytotoxic therapies and immunosuppressants for organ transplantation, leukemia, and inflammatory conditions. 6-MP was first introduced in 1951 and AZA was synthesized from 6-MP to act as a pro-drug that protected the 6-MP moiety from catabolism (Fig. 13.1). AZA and 6-MP are, for the purposes of meta-analyses and reviews, usually considered as the same drug. For historic reasons, AZA is the thiopurine of choice for the majority of gastroenterologists in the UK and Europe, whereas 6-MP is almost exclusively used in parts of North America. The efficacy of AZA

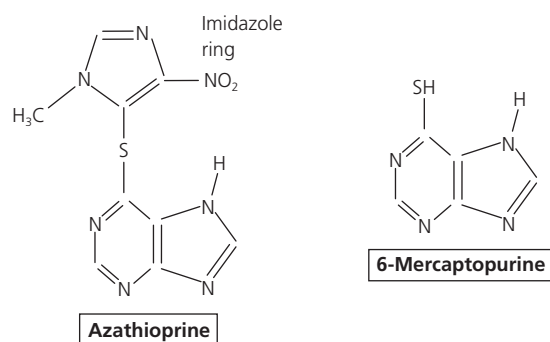


FIG 13.1 Chemical structures of azathioprine and 6-mercaptopurine.

or 6-MP in IBD is beyond doubt [1,2] but evidence from thiopurine therapy in IBD suggests these drugs to be heterogeneous. Important but subtle differences between AZA and 6-MP are revealed by an understanding of thiopurine metabolism and supported by analysis of clinical data.

Thiopurine metabolism

AZA is rapidly converted to 6-MP by a non-enzymatic glutathione-dependent reaction, releasing an imidazole derivative. 6-MP is then subject to metabolism by one of three competing enzymes (see Fig. 12.1) including thiopurine methyltransferase (TPMT) which catalyzes methylation of 6-MP to 6-methyl-mercaptopurine. *TPMT*

mutations are common within the Caucasian population and there is significant interindividual variation in TPMT activity (see Chapter 12). Xanthine oxidase (XO), catalyzes 6-MP to thiourate, and hypoxanthine-guanine-phosphoribosyltransferase (HPRT) leads to the 6-thioguanine nucleotides (6-TGNs), thought to be the most active metabolite of thiopurine therapy. There is less interindividual variation in the activity of XO or HPRT.

Thiopurine intolerance

Three studies have now demonstrated that at least 50% of IBD patients “intolerant” of AZA can tolerate 6-MP [3–5]. 6-MP is 55% of the molecular weight of AZA and 88% of AZA is converted to 6-MP, giving a conversion factor of approximately 50% when converting the dose of AZA to 6-MP. Early AZA intolerance is independent of TPMT activity and much of this intolerance may be caused by the imidazole derivative cleaved when AZA is converted to 6-MP [3]. There are no data suggesting that patients intolerant of 6-MP can accept AZA. Large series examining the toxicity of AZA or 6-MP are rare. An audit of 624 IBD patients from Oxford (in which almost all received AZA) demonstrated that 28% experienced side-effects [6]. In contrast, a study from New York of 356 patients taking 6-MP demonstrated that 15% experienced toxicity [7]. These data might suggest that physicians should consider abandoning AZA in favor of 6-MP but there are other factors to consider.

Is azathioprine more effective than 6-MP?

In vitro evidence suggests that AZA is a more effective immunosuppressant than 6-MP. Examples include the following observations. AZA is more inhibitory than 6-MP in the human mixed lymphocyte reaction (a test of T lymphocyte function) [8] and 24 analogs of AZA lacking the 6-MP analog showed some activity in the human mixed lymphocyte reaction [9]. Furthermore, the cytostatic and cytotoxic properties of 6-MP can be antagonized by exogenous purine administration, but AZA has an additional effect due to imidazole derivatives that is not antagonized by purines [10]. Also of interest is that AZA may have antibacterial properties *in vitro*, which lends a symmetry to the potential immunomodulation by imidazole antibiotics, but this has not been compared with 6-MP [11]. AZA suppresses pro-inflammatory cytokines [9] and suppresses

the human mixed lymphocyte reaction in the Lesch–Nyhan syndrome (HPRT deficiency) more potently than does 6-MP. This indicates that 6-TGNs are not responsible for all thiopurine immunosuppression [12]. Finally, inhibition of T lymphocyte proliferation by 6-MP is dependent on adenine ribonucleotide depletion, while AZA inhibits proliferation independently of this depletion [13]. These data demonstrate that AZA immunosuppression occurs through mechanisms other than those exerted by the mercaptopurine moiety alone and strongly implicate the imidazole derivative as the source of this additional immunosuppression.

Pharmacokinetic factors

Further important differences were highlighted when Cuffari *et al.* [14] compared 6-TGN levels in patients taking branded Imuran, or generic AZA and 6-MP. Patients receiving Imuran or 6-MP achieved significantly higher 6-TGN levels than generic AZA. The improved bioavailability of Imuran and 6-MP compared with generic AZA has implications for dosing and brand choice when considering thiopurine therapy or poor response. Significant differences in urinary thiopurine metabolites were also observed when the same individual was given AZA and then 6-MP, suggesting that AZA and 6-MP undergo metabolism via different pathways [15]. Approximately 12% of oral AZA was excreted in a form that could not have been converted to 6-MP. To add to the debate, the demonstration that a specific thioguanine nucleotide, thioguanosine triphosphate (TGTP) accounts for the mechanism of action through inhibition of Rac-1 signaling and promoting T-cell apoptosis [16], will see the evolution of new thiopurine compounds.

Comparative *in vivo* data

Remarkably, there is only a single *in vivo* comparison between AZA and 6-MP. This study investigated the effect of immunosuppressants on the survival of nephrectomized dogs receiving renal homotransplants. Nine out of 15 dogs treated with AZA survived beyond 20 days with good renal function compared with 6/15 treated with 6-MP. Dogs treated with AZA survived for longer (mean 35 days) than those on 6-MP (22 days), although no formal statistics were performed. Interestingly, this benefit of AZA over 6-MP occurred despite more frequent bone marrow suppression in the 6-MP (5 dogs) than AZA group (1 dog). This suggests

that the additional benefit from AZA may be independent of 6-TGN production.

Nevertheless, in contrast to *in vitro* experiments and the animal data, some clinical evidence suggests that 6-MP may have an advantage over AZA. Herein lies the premise that all thiopurines are not created equal.

The Cochrane meta-analysis of thiopurine therapy for Crohn's disease demonstrated an odds ratio for induction of remission of 2.36 (95% confidence interval [CI] 1.57–3.53) for AZA/6-MP compared with placebo [1]. When trials using 6-MP were removed from the analysis, the odds ratio dropped to 2.04 (95% CI 1.24–3.35), but when AZA was removed the pooled odds ratio of 6-MP versus placebo increased to 3.10 (95% CI 1.55–6.21). These data suggest an increased efficacy of 6-MP over AZA but it is important to note that the odds ratios are still within the 95% confidence intervals.

Conclusions

Why should there be a difference between *in vitro* studies and the clinical evidence? The data illustrate the heterogeneity of AZA and 6-MP. *In vitro* and *in vivo* evidence indicate that the AZA imidazole derivative may contribute to increased immunosuppressive properties, but may also be responsible for increased toxicity. The Cochrane review, however, suggests that 6-MP may be the more effective of the two drugs in clinical practice. We believe that these data are not mutually exclusive. AZA may be the more potent immunosuppressive on a “per protocol” analysis of thiopurine therapy, but as a result of AZA's increased imidazole-related toxicity profile, 6-MP is better tolerated and more efficacious than AZA on an “intention to treat” analysis. At present, clinicians may choose either drug with justification, while recognizing that for those who can tolerate AZA, there may be added value.

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