UpToDate® Official reprint from UpToDate®
www.uptodate.com ©2015 UpToDate®

Wolters Kluwer

6-mercaptopurine (6-MP) metabolite monitoring and TPMT testing in the treatment of inflammatory bowel disease with 6-MP or azathioprine

Author
Richard P MacDermott, MD

Section Editor
Paul Rutgeerts, MD, PhD, FRCP

Deputy Editor
Shilpa Grover, MD, MPH

INTRODUCTION

The therapeutic efficacy, bone marrow toxicity, and liver toxicity of azathioprine (AZA) and 6-mercaptopurine (6-MP) may be related to their metabolites: 6-thioguanine (6-TG) and 6-methylmercaptopurine (6-MMP). AZA is a prodrug that is metabolized to 6-MP, which is then further metabolized along an anabolic pathway to several metabolites including 6-TG and 6-MMP. Two enzymes are responsible for catalyzing these reactions: thiopurine methyltransferase (TPMT) and hypoxanthine phosphoribosyl transferase (figure 1). 6-TG levels between 230 and 400 may correlate with response and remission of inflammatory bowel disease. Bone marrow suppression may correlate with elevated levels of 6-TG greater than 400, while elevated levels of 6-MMP levels greater than 5700 may correlate with liver toxicity, manifested as increased liver enzymes.

TPMT ENZYME DETERMINATION

Thiopurine methyltransferase (TPMT) enzyme activity is a major factor determining azathioprine (AZA) and 6-MP metabolism, and therefore 6-thioguanine (6-TG) and 6-methylmercaptopurine (6-MMP) levels. Approximately 89 percent of the population has wild type TPMT, which is associated with normal or "high" TPMT enzyme activity, while 11 percent are heterozygous and have corresponding low TPMT enzyme activity [1,2]. Most importantly, 0.3 percent (1 in 300) of the population is homozygous for mutations of TPMT and thus have negligible activity, which causes 6-MP to be preferentially metabolized to produce high levels of 6-TG, which then leads to bone marrow suppression. Intermediate and normal metabolizers can have up to a threefold difference in initial target doses of AZA and 6-MP to achieve therapeutic 6-TG concentrations [3].

TPMT genotyping — Genetic polymorphism of TPMT causes some individuals to be particularly vulnerable to side effects and makes empiric dose-adjustments of AZA and 6-MP riskier. Measurement of TPMT genotypes and/or TPMT enzyme activity before instituting AZA or 6-MP may help prevent toxicity by identifying individuals with low or absent TPMT enzyme activity, which may lead to increased risk of myelosuppression [1,2,4-6]. (See "Overview of pharmacogenomics".)

Dosing strategies involving such testing may be cost-effective [5-7]. Multiple studies have described the use of TPMT genotyping or measurement of activity in predicting toxicity. As a general rule, these have demonstrated that prediction of toxicity is possible in some patients but is not consistently reliable. An illustrative report included 67 patients receiving AZA for rheumatic disease, six of whom were heterozygous for mutant TPMT alleles [4]. Five of these patients had to discontinue therapy within one month because of leukopenia, while the sixth did not adhere to therapy. In comparison, the median duration of therapy was 39 weeks in those with wild type alleles.