Thiopurine methyltransferase screening before azathioprine therapy.

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Br J Ophthalmol. 2006 Jul;90(7):923-4.

Azathioprine is used to treat various inflammatory eye conditions such as uveitis and dysthyroid orbitopathy. Despite good overall clinical response rates, particularly when used as steroid sparing agent, adverse effects such as severe myelosuppression can lead to early withdrawal in approximately a quarter of patients.[1,2]

Thiopurine methyltransferase (TPMT) is a cytosolic enzyme that metabolises azathioprine in vivo. The risk of azathioprine induced myelosuppression may be predicted by detecting patients with intermediate or low TPMT activity. The human TPMT gene exhibits genetic polymorphism that is evident in all populations studied to date.[3] Population studies have shown 89% of white people have high TPMT activity, 11% have intermediate, and 0.3% have low TPMT activity.[2,4] People heterozygous for TPMT mutations have intermediate activity while those homozygous for the mutation have low activity and are therefore at a higher risk of thiopurine induced myelosuppression. Conversely, individuals with very high levels of TPMT activity are known to have the homozygous wild type phenotype, in which the clinical response to thiopurines is less likely.[3] This in turn suggests that pretreatment TPMT levels may be used to titrate the starting dose of azathioprine.

Some debate still exists regarding the best method of monitoring TPMT activity—namely genotyping or assay assessment. At present, there is no conclusive evidence suggesting that either alone is predictive of the myelosupressive effects without regular blood monitoring. Genotyping can predict the one in 220 individuals who is TPMT deficient,[5] including those with intermediate activity. However, this method cannot yet predict those individuals with high TPMT activity.[2] There are also uncertainties regarding the interpretation of allelic polymorphisms in different racial groups.[6] Phenotype testing is able to quantify the biological enzyme activity and is hence thought to be a more reliable reflection of in vivo events.[6] Sies *et al*[7] have established the

normal range of TPMT to be 9.3–17.6 units/ml red blood cells. However, these results can have considerable inconsistencies as a result of factors such as recent blood transfusions, certain medications, alcohol, and interlaboratory variation.[8] Oh *et al*[8] report that polymerase chain reaction genotyping of the TPMT polymorphism produces a rapid result and is accepted to have a 95% concordance with blood enzyme activity. Hence, performing both, genotype and phenotype TPMT tests is likely to be a more reliable predictor of the myelosuppressive effects of azathioprine. It must, however, be emphasised that these tests do not obviate the need for regular haematological monitoring during azathioprine therapy.

The direct cost of hospital treatment in the United Kingdom of an azathioprine related myelotoxicity episode was estimated at £3200 in 1997.[9] Studies have since shown the cost effectiveness of pretreatment TPMT screening.[8,10]

To the best of our knowledge, TPMT screening has not been considered in the ophthalmic literature to date. We would like to raise awareness in the ophthalmic community that screening for the TPMT enzyme, genotypically or phenotypically, may help titrate the starting dosage of azathioprine and help prevent potentially fatal side effects. We suggest that ophthalmologists should consider the incorporation of TPMT testing in the routine investigations performed before starting immunomodulatory therapy with thiopurines.

At present, the TPMT test most readily available in the United Kingdom is the phenotypic enzyme assay which is offered by laboratories at Guy's Hospital, London; The John Radcliffe Hospital, Oxford; and City Hospital, Birmingham

PMID: 16782959 [PubMed - indexed for MEDLINE]