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Predictive Pharmacogenomics of thiopurine therapy in Inflammatory Bowel Disease

Azathioprine is a drug commonly prescribed for the treatment of inflammatory bowel disease. The drug is generally an effective therapy in about two-thirds of cases. However, in one-third, the drug has to be withdrawn because of side effects or lack of response. Recently, studies have highlighted the importance of tests which can help to predict the development of side effects to azathioprine prior to commencing treatment. The best-known of these is the level of an enzyme called thiopurine methyl transferase (TPMT). As a result of genetic variation, 1 in 300 of the population have a total lack of this enzyme and are at very high risk of severe toxicity if given azathioprine. 1 in 10 individuals have half the level and are also at increased risk of side effects. Prior knowledge of the enzyme level can therefore permit either avoidance of the drug or use at a lower dose to avoid side effects.

However, variations in the TPMT gene only explain a proportion of the side effects seen with Azathioprine treatment. We have recently shown an association between genetic variation the level of a different enzyme called inosine triphosphate pyrophosphatase or ITPase and a significant risk of side effects an azathioprine treatment. Interestingly, this appears to predict many of the side effects not predicting by differences in TPMT. Little is know about the role of TIPase deficiency and this study therefore aims to test this further by assessing in much more detail what happens in patients who do or do not develop side effects on azathioprine.

Other genetic factors may also result in variation in the level of TPMT in different individuals and alter the risk of side effect. In particular, genetic variation in the way individuals handle the vitamin, folate, can be predicted to influence activity of the TPMT enzyme. Interestingly, genetic differences folate handling might also affect the way individuals tolerate another drug used for inflammatory bowel disease called Methotrexate. Also, genetic variation in the way the TPMT gene is controlled (the gene promoter) may also influence the level of the enzyme. This may be particularly important in individuals who are noted to have a very high level of TPMT enzyme activity as previous studies have shown a link between this high level and development of adverse effects on the liver.

We are currently conducting a separate study to assess in detail the role of TPMT measurement before and during treatment with Azathioprine for inflammatory bowel disease. This will be completed in the early part of 2003. In the study, patients have blood taken before undergoing treatment with Azathioprine and are then monitored for the occurrence of side effects. In the study proposed in this application, we would like to use these blood tests to assess the role of ITPase, folate handling and variation in the TPMT gene promoter. We will also study folate handling in a separate group of patients who have undergone treatment with Methotrexate. As a result of this study, we hope to provide much more insight into the risk of side effects in patients being considered for azathioprine or Methotrexate. Ultimately, this should allow us to tailor treatments much better to individuals and avoid unnecessary and unpleasant side effects.