Autoimmune hepatitis (AIH) is a chronic disorder characterised by persisting liver inflammation. The standard treatment for remission induction is prednisolone plus 1 mg/kg/day azathioprine (AZA). This regime is successful in the majority of cases and no other has been shown to be superior. However, about 10% of patients have to reduce or stop AZA because of toxicity and 10-20% of patients fail to achieve biochemical remission on this regime. In patients who do attain biochemical remission, 20-40% have persistent inflammation on follow up biopsy, i.e. fail to achieve histological remission. If possible, steroids are phased out after 2-3 years and AZA monotherapy (2 mg/kg/day, if tolerated) is used long-term to prevent disease relapse. Despite this “optimal” treatment, about 25% of patients with AIH die of liver disease or require liver transplantation over 20 years follow up.

There is sparse data on AZA metabolism in AIH. The aim of this study was to measure the concentration of the active AZA metabolites, 6-thioguanine nucleotides (TGNs), in a cohort of AIH patients. The TGN metabolites have both immunosuppressive and cytotoxic properties. AZA metabolism to TGN metabolites has been extensively studied in inflammatory bowel disease (IBD). A meta-analysis [1] has shown that, in IBD patients, clinical response is associated with TGN concentrations above a threshold of 230-260 pmol/8 x 10^8 red cells.

Blood samples were obtained from AIH patients on long-term AZA at routine clinic visits. Red cell TGN concentrations were measured by established techniques. Over a 9 month period 283 samples were obtained from 84 patients. The duration of AZA was 0.4 to 27, median 7.25, years. Average TGN concentrations were calculated whilst at a constant AZA dose (median 3 assays, range 1 to 7, per patient). Median TGN concentrations were 190 pmol/8 x 10^8 red cells (range 0 to 839) at a median dose of 1.7 mg/kg (range 0.32 to 3.8). Removing a cohort of 11 “new” patients studied during the remission induction 1mg/kg AZA phase, median TGNs (n = 73 patients) were 205 pmol (range 0 to 839) at a median dose of 1.9 mg/kg (range 0.32 to 3.8).

This initial study indicates that over 50% of AIH patients have TGN concentrations that may be considered suboptimal when compared to available data in IBD. Compliance with tablet taking was a problem with a number of patients. The use of TGN metabolite monitoring may enable the optimisation of AZA treatment in this chronic immune disorder.

Reference

[1] Osterman MT et al., Gastroenterology 2006;130:1047-53