Understanding Nutrient-Gene Interaction to Reduce Azathioprine-Induced Toxicity in Pediatric Inflammatory Bowel Disease

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Inflammatory bowel disease (IBD) is characterized by a dysregulated immune response to tissue injury that can be characterized by chronic inflammation. Pediatric IBD patients are at risk of impaired nutrition status, growth retardation symptoms that disrupt normal life and surgical intervention. Adverse side effects may occur from use of medication to control the diseases. Azathioprine (AZA) is an immunomodulator used in the treatment of IBD. Approximately 20% of children with IBD have a polymorphism in the gene that codes for the enzyme thiopurine methyltransferase (TPMT). Polymorphisms that result in low TPMT activity are correlated with increased risk of AZA-induced genotoxicity that can result in significant myelosuppression. To personalize patient response to AZA, TPMT genotyping and phenotyping are often conducted in concordance with clinical decision making. It has been proposed that supplemental folic acid can modulate AZA toxicity since TPMT-mediated inactivation of AZA is regulated by methylation reactions. **Purpose.** Characterize the frequency of genotype and phenotype testing and use of folic acid supplementation in pediatric IBD patients on AZA to improve treatment outcomes. **Methods.** Data was obtained from the *ImproveCareNow* dataset (May 2019), which contains anonymized patient data from over 20,000 pediatric IBD patients in over 100 clinics worldwide. R was used compute descriptive statistics including means, medians, and frequencies. Treatment success was defined as achieving remission while on AZA. **Results.** 4,780 of 22,661 patients (17%) in the dataset had been prescribed AZA. 29.9% of patients on AZA were genotyped for polymorphisms in TPMT and 66.0% were phenotyped for relative TPMT activity. For genotype, 90% of patients were homozygous dominant, 8.5% were heterozygous, and 1.5% were homozygous recessive. For phenotype, 77% had high activity, 18% had intermediate activity, and 5% had low/no activity. In total, 35% of patients did not achieve remission while on AZA. Of these patients, 73.7% had never completed genotype testing and 31.5% had never completed phenotype testing. Folic acid supplementation was found to reduce AZA genotoxic metabolite 6-thioguanine nucleotides (6-TGN) by 6%, from a mean of 249 to 235 pmol/8×108 erythrocytes. **Conclusions.** It is speculated that phenotyping is used more frequently than genotyping as it provides information on the observed activity of TPMT as influenced by both genetics and environment. Folic acid supplementation reduced genotoxic 6-TGN levels, suggesting great potential to use adjunct treatment strategies in combination with drugs and nutrition. The dataset did not contain outcomes related to myelosuppression, therefore future clinical study warrants investigation in using folic acid to enhance use of AZA by reducing incidence of AZA-related genotoxicity.