suppression when treated with standard or even low-dose therapy.\textsuperscript{12,13}

Concomitant medications may also influence TPMT enzyme activity and can affect the safety and efficacy of thiopurines. It has been demonstrated among IBD patients that 5-ASA-containing compounds cause in vitro inhibition of recombinant human TPMT.\textsuperscript{14} The clinical correlate of this interaction has been reported with both 6-MP and olsalazine.\textsuperscript{15} Caution should be taken when coadministering 5-ASAs and thiopurines, as TPMT inhibition may increase the risk of developing myelosuppression. This effect may also vary depending on the 5-ASA an individual is receiving, such that mesalamine may have the greatest effect on the metabolism of thiopurines.\textsuperscript{16} A recent study suggested that, although an interaction between AZA and 5-ASAs does exist, an alternate mechanism to TPMT inhibition might be responsible for the change in thiopurine pharmacokinetics.\textsuperscript{17} After 5-ASA withdrawal, the mean 6-TGN levels significantly decreased without significant changes in TPMT activity or blood counts. This effect may be additive in patients already genetically determined to produce lower levels of the TPMT enzyme, such that diligent blood count monitoring is necessary. Patients receiving concomitant allopurinol must be carefully monitored as they are at risk of marked myelosuppression given its blockade of xanthine oxidase, an important enzyme for the catabolism of thiopurines. A recent study suggests that certain IBD patients may benefit from adding allopurinol to 6-MP/AZA as an iatrogenic mechanism of altering the metabolite profile in favor of 6-TGN production.\textsuperscript{18}

### ADVERSE EVENTS

The adverse events associated with thiopurines may be categorized as either non dose-dependent (allergic/idiosyncratic) or dose-dependent. Both the Pearson and Cochrane analyses\textsuperscript{19,20} have reported that adverse events severe enough to cause withdrawal from the controlled trials occurred more frequently among 6-MP/AZA treated patients as compared to placebo (9% versus 2%). However, the number needed to treat (NNT) to observe an adverse event in 1 patient was approximately 15.

#### HYPERSENSITIVITY REACTIONS

Approximately 5% to 10% of patients are unable to tolerate thiopurines regardless of what dose is administered and irrespective of their underlying drug metabolism (non dose-dependent). These allergic reactions typically occur within 2 to 4 weeks of initiating therapy and are characterized by a “flu-like” illness, malaise, fevers, nausea, rash, abdominal pain, pancreatitis, and rarely a drug hepatitis. A certain proportion of patients who experienced an allergic reaction initially to AZA may be successfully rechallenged with 6-MP.\textsuperscript{21} The theory is that the patient is reacting to the imidazole ring found on AZA but not 6-MP. This type of “thiopurine switch,” however, is not recommended for patients who experienced pancreatitis. In general, the majority of patients who experienced idiosyncratic reactions require alternate immunomodulators such as methotrexate. Although once a promising alternative for patients allergic to 6-MP/AZA, thioguanine (6-TG), a sister