

ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Diseases

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Pharmacogenomics of IBD Therapies

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G&H How has the study of pharmacogenomics affected IBD therapy?

TD The only area of pharmacogenomics that has influenced inflammatory bowel disease (IBD) clinical practice has been in the use of the thiopurine agents 6-mercaptopurine (6-MP) and azathioprine (AZA). These agents enter competing pathways of inactivation and activation. Thiopurine methyltransferase (TPMT) converts AZA and 6-MP to the inactive metabolites 6-methyl-mercaptopurine ribonucleotides. The enzymatic activity of TPMT is influenced by high and low activity alleles (TPMT^H and TPMT^L) that are inherited in autosomal codominant fashion. Hypoxanthine-guanine phosphoribosyl transferase (HGPRT) and other enzymes are involved in the activation pathway, which leads to the formation of the active and myelotoxic 6-thioguanine nucleotide (6-TGN) metabolites. Several studies have shown that the intracellular concentrations of the 6-TGN metabolites are inversely related to TPMT activity. Approximately 90% of individuals have high TPMT activity. Roughly 10% of patients have intermediate TPMT activity and achieve higher 6-TGN concentrations at standard doses. Furthermore, 3 in 1,000 patients have absent TPMT activity. If treated with thiopurines, such patients will develop very high 6-TGN concentrations, resulting in severe and life-threatening bone marrow toxicity.

TPMT activity may also influence therapeutic response. In a prospective study of 40 AZA-treated patients, our group showed that lower TPMT activity was associated with higher erythrocyte 6-TGN levels and higher response rates. Multivariate analysis showed that baseline TPMT activity and 6-TGN levels were independent predictors of clinical response. Patients with a TPMT level less than 15.3 U/mL blood were 6.2 times

more likely to respond to AZA therapy. A 6-TGN level of greater than 292 pmol/8 × 10⁸ red blood cells was associated with a positive predictive value of clinical response in 85.7% of patients.

There is no evidence supporting a significant contribution of low HGPRT activity to clinical resistance to thiopurines. Decreased activity of another enzyme involved in thiopurine metabolism, inosine triphosphate pyrophosphatase, was associated with AZA intolerance in one study, but two subsequent studies failed to replicate that finding.

G&H How useful is our current knowledge of TPMT pharmacogenomics in establishing optimal doses of the thiopurines?

TD The strongest argument in favor of TPMT testing is the identification of the rare patient with very low or absent TPMT activity. Such patients will invariably develop life-threatening myelosuppression if treated with 6-MP/AZA. The prescribing information for 6-MP and AZA recommends that consideration be given to either TPMT genotype or phenotype testing.

TPMT testing also identifies patients with intermediate TPMT activity, in which standard doses are associated with higher 6-TGN concentrations and a greater risk of myelosuppression. In these patients, lower dosages are theoretically as effective while carrying less toxicity. We treat these patients at half the usual doses (6-MP 0.5 mg/kg/day; AZA 1.0 mg/kg/day).

Nonetheless, TPMT testing is not widely available. Furthermore, in the absence of data from large, prospective studies, some clinicians choose not to test TPMT activity. Most of these clinicians take a conservative approach, starting at a low dose and raising it slowly. Others start at the standard dose and follow the patient carefully. Rationale for the former approach is that lower doses are safer and higher doses are not necessary for response. Clinicians utilizing the latter approach see dose adjustment as a waste of time and prefer to start at a dose with proven efficacy. Patients must be monitored carefully, regardless of prior testing for TPMT and dosage selected. Factors other than TPMT are responsible for most thiopurine toxicity.

An ongoing National Institutes of Health (NIH) trial (ClinicalTrials.gov Identifier NCT00113503) is testing

the hypothesis that AZA dosing adjusted according to a) baseline TPMT and b) 6-TGN levels during therapy is associated with higher efficacy and lower toxicity in the treatment of Crohn's disease. Assuming effectiveness of adjusted thiopurine dosing, the cost-effectiveness of this approach will require evaluation.

Recent research has refined our understanding of 6-MP/AZA metabolism. Neurath and associates correlated AZA responsiveness with the relative concentrations of the different 6-TGNs (mono-, di-, and triphosphates). The 6-thioguanosine triphosphate (TGTP) and 6-thioguanosine diphosphate (TGDP) were the main metabolites within the 6-TGN. The study found that high TGTP levels correlated with both high 6-TGN and clinical response, whereas high TGDP was associated with worse clinical outcomes.

G&H Beyond TPMT levels, how has pharmacogenomic research affected IBD therapy?

TD Pharmacogenomic research has also examined other therapies. One postulated mechanism of action of infliximab is antibody-dependent, cell-mediated cytotoxicity. FcγRIIIa receptors on cytotoxic cells recognize the immunoglobulin G1 portion of infliximab that is bound to tumor necrosis factor (TNF)-α-expressing cells. Cross-linking of the FcγRIIIa receptors signals the cytotoxic cell to kill the target cell by apoptosis. Based on prior work in non-Hodgkin lymphoma, researchers theorized that genetic polymorphisms of FCGR3A, the gene coding for the FcγRIIIa receptor, may influence the efficacy of infliximab. An initial study reported that the FCGR3A-158V/V polymorphism was associated with a better biologic (as measured by levels of C-reactive protein) and perhaps clinical responses to infliximab. A larger follow-up study of a subset of patients from the ACCENT I trial showed a trend towards a greater decrease in C-reactive protein after infliximab in V/V homozygotes versus carriers of one or no V alleles. No association with clinical response was seen.

Other studies have found no association between response to infliximab and several genetic variants, including TNF-α and TNF receptor gene polymorphisms, *NOD2/CARD15* gene mutations, and a haplotype in the TNF-β (lymphotoxin-α) gene. These negative findings reflect the complexity of IBD, as well as the complexity of the drug's therapeutic effects. The effects of any pharmacogenetic variability on the efficacy of infliximab (or similar biologic therapies) may not be strong or discernible.

Another area of investigation has involved drug transporters and receptors. The multidrug resistance 1 (MDR1) gene codes for a drug efflux pump P-glycoprotein 170 (Pgp-170) expressed on the surface of lymphocytes and intestinal epithelial cells. A study found higher Pgp-170 expression in IBD patients who failed medical therapy.

Changes in the expression of the intracellular glucocorticoid receptor do not appear to play a major role in glucocorticoid resistance in IBD. A preliminary study showing that the TT genotype of exon 21 MDR1 polymorphisms is associated with a higher risk of cyclosporine failure in patients with steroid-resistant ulcerative colitis will require replication.

Impaired transport may be a mechanism of resistance to thiopurines in leukemia. Known transporters of nucleoside monophosphates and their analogs include the equilibrative nucleoside transporters, the concentrative nucleoside transporters and members of the multidrug resistance protein family of ATP-dependent efflux pumps. Impaired transport as a mechanism of thiopurine resistance has not been studied in IBD.

G&H What are the challenges of incorporating pharmacogenomics in clinical practice?

TD Genetic variability may affect specific pharmacokinetic and pharmacodynamic properties of individual drugs. At the present time, the impact of pharmacogenomics in clinical practice is limited to thiopurine therapy, where a single, genetically determined factor (TPMT activity) influences to a large extent the toxicity and, perhaps, efficacy of the thiopurines.

However, the complex and multigenic nature of most drug effects, the complexity of IBD pathogenesis itself, and the coarse instruments we use to measure clinical and biologic response present formidable barriers in identifying and replicating genetic variants that influence therapeutic response and/or toxicity. High-throughput genomic methods and sophisticated bio-informatic analyses will be necessary to elucidate the polygenic determinants of drug response and toxicity. Replication studies and well-performed clinical trials will be needed before pharmacogenomics enters clinical practice.

Suggested Reading

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