Poor Response to Thiopurine in Inflammatory Bowel Disease: How to Overcome Therapeutic Resistance?

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CASE

A 24-year-old woman (53 kg) with a 5-year history of steroid-dependent ulcerative colitis with mild and extensive ulcerations presented to the gastroenterology clinic for symptom recurrence. She was given 100 mg/day (1.9 mg · kg^{-1} · day^{-1}) azathioprine (AZA) for 1 month, after which the dose was increased to 125 mg/day (2.3 mg · kg^{-1} · day^{-1}). Four months later, the patient was tapered off steroid therapy. Her symptoms persisted after 7 months of AZA therapy, however, and she experienced gastrointestinal side effects. The patient was switched to another thiopurine drug, 6-mercaptopurine (6-MP), at 75 mg/day (1.4 mg · kg^{-1} · day^{-1}), which was well tolerated but similarly ineffective (8 stools daily). A brief course of steroid therapy rapidly produced a substantial but short-lived clinical improvement.

To understand this patient's unresponsiveness to 2 thiopurine agents, we quantified thiopurine metabolites *(1)* 1 year after initiating AZA therapy. Intraerythrocyte concentrations of 6-thioguanine nucleotides (6-TGNs) were low (132 pmol/8 · 10^8 erythrocytes; therapeutic interval, 230–400 pmol/8 · 10^8 erythrocytes), and 6-methylmercaptopurine ribonucleotides (6-MMPRs) were very high (11 666 pmol/8 · 10^8 erythrocytes; therapeutic interval, <5800 pmol/8 · 10^8 erythrocytes). A second quantification of thiopurine metabolites 3 months later confirmed these results (6-TGNs, 127 pmol/8 · 10^8 erythrocytes; 6-MMPR, 26 304 pmol/8 · 10^8 erythrocytes). The patient had an unusual and extremely high thiopurine *S*-methyltransferase (TPMT) activity in erythrocytes [61.5 nmol · h^{-1} · (mL erythrocytes) $^{-1}$; reference interval, 8.5–15 nmol · h^{-1} · (mL erythrocytes) $^{-1}$]. The lack of clinical efficacy for 6-MP, together with the evidence of pharmacologic resistance, prompted discontinuation of 6-MP therapy. Thereafter, we administered the tumor necrosis factor-α (TNF-α) antagonist adalimumab, but we quickly replaced it with infliximab, which has a good clinical efficacy and safety profile.

Reference

1. Dervieux T, Boulieu R. Simultaneous determination of 6-thioguanine and methyl 6-mercaptopurine nucleotides of azathioprine in red blood cells by HPLC. Clin Chem 1998;44: 551–5.

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Questions to Consider
• What is the clinical utility of assessing the TPMT phenotype or genotype?
• What is the rationale for therapeutic drug monitoring of thiopurines?
• What causes of resistance should be considered before switching to another drug class in patients with apparent thiopurine resistance?
• How can thiopurine treatment be optimized in patients with a very high TPMT activity?

Final Publication and Comments

The final published version with discussion and comments from the experts will appear in the July 2013 issue of *Clinical Chemistry*. To view the case and comments online, go to http://www.clinchem.org/content/vol59/issue7 and follow the link to the Clinical Case Study and Commentaries.

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