The authors declare no conflict of interest.

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Gout and Transplantation: New Treatment Option—Same Old Drug Interaction

Calcineurin inhibitors, particularly cyclosporine, may increase the risk of gout after transplantation. Concomitant use of azathioprine (AZA) and allopurinol is usually avoided in transplant recipients because of the well-known interaction between these two drugs resulting in leukopenia (1–4). Febuxostat (Uloric) is a new, Food and Drug Administration-approved, xanthine oxidase (XO) inhibitor for chronic management of hyperuricemia in patients with gout (5). Although structurally unrelated to allopurinol, febuxostat may have a drug interaction profile similar to allopurinol because of its effect on XO. Detailed drug interaction reports of AZA and febuxostat are scarce. To our knowledge, this is one of the first case reports documenting a likely drug interaction between AZA and febuxostat.

CASE REPORT

A 66-year-old white woman presented to the Transplant Clinic in February 2011 with nausea, vomiting, watery diarrhea, 10 pound weight loss over 1 month, malaise, fatigue, pancytopenia, and an elevated serum creatinine level (1.6 mg/dL, baseline 1.0–1.1). Of note, 6 weeks earlier, the patient presented to her physician’s office with symptoms of recurrent gout and was started on febuxostat (40 mg daily). Her medical history is significant for end-stage renal disease secondary to polycystic kidney disease, deceased donor renal transplant (1995), and gout. Her immunosuppressive regimen included AZA, modified cyclosporine, and prednisone. Before her Transplant Clinic visit, she was seen by a gastroenterologist and hematologist for similar symptoms and to investigate profound pancytopenia. Her initial workup was negative, which led to the scheduling of a bone marrow biopsy. Before her bone marrow biopsy, she was seen in the Transplant Clinic and subsequently admitted to the hospital for further evaluation and management. She appeared acutely ill, and there was concern about potential opportunistic infection or malignancy. So, empiric broad-spectrum antimicrobials were initiated. Imaging studies, tumor markers, stool studies, and cultures were negative except for a nasopharyngeal swab positive for influenza B and trace positive Epstein-Barr virus in the blood (240 copies/mL). Nadir laboratory values during admission were total white blood cell count 700/mm³, absolute neutrophil count 630/mm³, hemoglobin 8.3 g/dL, and platelet count 34,000/mm³. Liver function tests were within normal limits except for a slight increase in total bilirubin (1.7 mg/dL) that returned to normal within 1 week. Serum creatinine and cyclosporine trough levels were 1.9 mg/dL and 125 ng/mL, respectively. AZA and febuxostat were discontinued, and the patient was maintained on modified cyclosporine and prednisone. She received filgrastim to stimulate neutrophil production, blood products to correct anemia, intravenous fluid and electrolyte correction, and marrow supportive measures. The patient’s symptoms improved markedly over the next 3 days, and she was subsequently discharged. Laboratory values at discharge included a total white blood cell count of 5900/mm³, hemoglobin 11.1 g/dL, platelet count 79,000/mm³, serum creatinine 1.2 mg/dL, and cyclosporine level 92 ng/mL. Follow-up clinic visits have documented laboratory values within normal limits, and the patient has remained asymptomatic.

DISCUSSION

Gout can be a challenging clinical problem in solid organ transplant recipients because of potential drug interactions. The combination of AZA and allopurinol may result in AZA toxicity. Nausea, vomiting, and reversible bone marrow toxicity consisting of leukopenia, anemia, and thrombocytopenia are hallmark features of AZA toxicity (2–4,6). AZA is a prodrug of 6-mercaptopurine, which is metabolized through three different pathways (1). Metabolic alterations in this process through XO inhibition can result in increased toxicity from 6-thioguanine nucleotides. Febuxostat is a potent inhibitor of XO and concurrent use with AZA is contraindicated (7). Because febuxostat is structurally unrelated to purine or pyrimidines (like allopurinol), it does not interfere with other enzyme pathways and is selective for XO. In addition, febuxostat inhibits both reduced and oxidized forms of XO (8). This mechanistic advantage produces sustained reductions in serum uric acid levels and may lead to drug-drug interactions caused by XO inhibition.

In the case study described earlier in the text, although influenza B infection or Epstein-Barr viremia could be implicated in the acute development of pancytopenia and gastrointestinal symptoms, the time course of the onset of signs and symptoms relative to the initiation of febuxostat coupled with their rapid resolution after discontinuation of febuxostat and AZA strongly suggests a drug-drug interaction. This commentary highlights the importance of identifying and preventing avoidable drug-drug interactions that may increase morbidity, mortality, and costs. Healthcare providers caring for transplant patients must be aware of the potential for new drug-drug interactions.

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recipients should check for potential drug-drug interactions, particularly with immunosuppressants, and/or inform the transplant program before starting any new medication. We recommend avoiding the simultaneous administration of febuxostat and AZA. If concurrent use is warranted, AZA doses should be reduced and patients monitored closely to prevent toxicity.

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ERRATUM

Glutamine-Enriched Nutrition Does Not Reduce Mucosal Morbidity or Complications After Stem-Cell Transplantation for Childhood Malignancies: A Prospective Randomized Study: Erratum

In the June 27, 2011 issue of Transplantation in the article by Uderzo et al, “Glutamine-Enriched Nutrition Does Not Reduce Mucosal Morbidity or Complications After Stem-Cell Transplantation for Childhood Malignancies: A Prospective Randomized Study”, the author Roberto Masetti should be listed as Riccardo Masetti.

REFERENCE