Case Report

Trimethoprim-Sulfamethoxazole-induced Hepatotoxicity in a Renal Transplant Patient

Abstract

Drug-induced liver injury (DILI) represents liver damage from various therapeutic drugs. Antimicrobials are among the most common causes of DILI. We report a case of hepatic toxicity due to Trimethoprim-sulfamethoxazole (TMP-SMX) in a patient who underwent renal transplantation. Diagnosis has been made after a careful history taking, exclusion of competing etiologies and reversal of biochemical abnormalities after withdrawal of the antibiotic. TMP-SMX liver toxicity is well known but remains unpredictable and is rarely reported.

Keywords: *Hepatotoxicity, renal transplant, trimethoprim-sulfamethoxazole*

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Introduction

Trimethoprim-sulfamethoxazole (TMP-SMX) is considered a first-line agent for *Pneumocystis jiroveci* pneumonia (PCP) prophylaxis in renal transplant recipients.[1] Gastrointestinal and hepatic adverse events are reported with the use of this antibiotic.[2] Here, we describe a case of drug-induced liver injury (DILI) related to TMP-SMX administration in renal transplantation setting.

Case Report

A 38-year-old male patient received a renal transplant from living donor for end-stage renal disease.

The surgery was completed without any complications, and a fast decrease in serum creatinine was noted. He received his first dose of basiliximab at induction of anesthesia and then a second one on day 4 after the surgery. He was put on tacrolimus and mycophenolate mofetil (Cellcept®) 4 days before surgery. He was also started on corticosteroids, with tapered daily dosage, and on valganciclovir (Valcyte®) and TMP/SMX (Bactrim®) for cytomegalovirus and PCP prophylaxis, respectively. Bactrim was started on the same day of the intervention.

On a routine blood analysis done on the 9th day after the surgery, he had an asymptomatic increase in liver function tests with serum glutamic-pyruvic transaminase level of 375 IU/L and gamma-glutamyl transpeptidase level of 571 IU/L. Bilirubin level as well as prothrombin time were normal. Tacrolimus serum levels were within target ranges. Viral and serologic auto-immune markers as well as Doppler abdominal ultrasound were normal.

When the patient was told about the perturbation of liver enzymes, he mentioned a history during his childhood of icterus secondary to Bactrim® consumption which resolved upon drug discontinuation. Bactrim® was completely withdrawn and we noticed a rapid and progressive improvement in liver tests starting 24 h after stopping the antibiotic [Figure 1]. The patient was then put on inhaled pentamidine for *Pneumocystis* prophylaxis. According to the objective causality assessment by the Naranjo probability scale, Bactrim® was the probable cause of this adverse reaction.[3]

Discussion

DILI represents liver damage from various therapeutic drugs. Antibiotics, central nervous system agents, herbal/dietary supplements, and immunomodulatory agents are the most common causes of DILI.[4] Clinical presentation and course of injury range from asymptomatic transient elevations in liver enzymes to liver failure.

Drug causality of asymptomatic mixed elevation of liver enzymes was established

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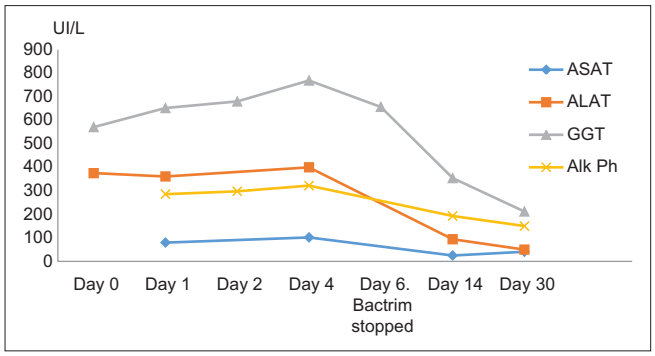

Figure 1: Liver functional tests evolution

based on the clinical history, chronology of exposure and injury, exclusion of competing etiologies, and subjective assessment based on published data. Afterwards, causality assessment using the Naranjo algorithm, or adverse drug reaction probability scale, was undertaken for each newly introduced drug.

Basiliximab and valganciclovir have never been associated with adverse hepatic reactions in adults.[5] Hepatotoxicity of tacrolimus and mycophenolate mofetil at advocated dosages is rarely reported in postrenal transplant setting.[6,7] Elevated transaminase occurring 12 days and above of starting treatment is described in these cases, resolving after discontinuation of tacrolimus or after reducing the dosages of mycophenolate mofetil.

In several prospective studies, TMP-SMX figures among the most common single causative agents of idiosyncratic DILI, along with amoxicillin-clavulanate and antituberculous drugs.[4,8] This fact along with a history of a similar reaction in childhood leads us, in our case, to incriminate Bactrim® as the main drug responsible for abnormal liver enzymes and to stop it, with Naranjo score of 5.

The incidence of TMP-SMX-induced adverse reactions involving the liver is 1/11,000–45,000 adults. Most cases of hepatotoxicity occurred on the 2nd–12th day after initiation of TMP/SMX.[9]

Three forms of TMP-SMX-induced liver damage have been described; the most typical pattern of injury is one of mixed hepatocellular cholestatic but can be cholestasis without inflammation or even hepatocellular necrosis.[8] The severity of/TMP-SMX-induced liver injury can range from mild symptoms with elevated liver enzymes to chronic liver injury,[10] vanishing bile duct syndrome[11] or fulminant hepatic failure.

Two mechanisms have been proposed for TMP-SMX-related hepatotoxicity: allergic response and metabolite-related toxicity.[9] Hypersensitivity is possibly mediated by glutathione metabolism and in the majority of reported cases associated with hypersensitivity reaction symptoms such as fever, rash, and eosinophilia leading to rapid discontinuation of the drug.[12]

In case of metabolite-related toxicity, the rate of acetylation and the status of activity of cytochrome protein 450 isoenzymes (subtype 2C9) are the two factors that have a significant impact on the accumulation of TMP/SMX hepatotoxic metabolite increasing therefore the risk of liver injury.

In the absence of systemic symptoms, reactive metabolite theory for the pathogenesis of idiosyncratic DILI in our patient is favored. We did not find, in the literature, any influence of renal transplant setting *per se* on the occurrence of TMP-SMX metabolite-related toxicity.

TMP-SMX liver toxicity is well known but remains unpredictable and is rarely reported. Its diagnosis requires a careful history taking, vigilance in monitoring symptoms, biochemical tests and exclusion of competing etiologies.

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Conflicts of interest

There are no conflicts of interest.

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