

## Hepatic Toxicity and Clopidogrel-Induced Systemic Inflammatory Response Syndrome

### To the Editor,

Clopidogrel, an adenosine biphosphate receptor antagonist, inhibits platelet aggregation and is widely used to prevent thrombotic complications of atherosclerosis or after percutaneous coronary stent placement.

Various studies have shown that clopidogrel is as safe as aspirin and better tolerated than ticlopidine.<sup>1,2</sup> The most common adverse effects are gastrointestinal discomfort, exanthema, and pruritus. Other more serious, but rare, effects are aplastic anemia, thrombotic thrombocytopenic purpura, hemolytic-uremic syndrome, and severe hypersensitivity with systemic inflammatory response syndrome.<sup>2</sup> We present a case of severe clopidogrel-induced liver toxicity.

A 63-year-old man was admitted for abdominal pain, fever, and abnormal liver profile. He was allergic to sulfamides, ex-smoker since 8 years ago, with an alcohol intake of less than 25 g a day, and had hypertension, hypercholesterolemia, and chronic gastritis. Thirty days earlier, he had an anterolateral myocardial infarction and was revascularized by percutaneous transluminal coronary angioplasty (PTCA) with a conventional bare-metal coronary stent in the left anterior descending artery. A 300-mg loading dose of clopidogrel was administered. Afterwards, dual antiplatelet therapy with acetylsalicylic acid (100 mg/day) and clopidogrel (75 mg/day) was started. The patient's pre-infarction therapy was: lisinopril (10 mg/day), atorvastatin (80 mg/day), carvedilol (18.75 mg/12 h), and bromazepam (1.5 mg/day). Two weeks later, the patient began to experience an increase in the number of liquid stools (6-8 a day), without pathological products, episodes of severe epigastric pain, and fever peaks of up to 39°C, symptoms that persisted intermittently until admission.

Blood pressure was 130/70 mm Hg, heart rate, 100 bpm, and temperature, 38°C. The patient's overall condition was good and he was eupneic. Cardiopulmonary auscultation was normal, but the abdomen was painful to palpation in the right hypochondrium, with no peritonism. There was no swelling in the extremities.

The results of the admission analyses were as follows: GOT 133 U/L, GPT 204 U/L, GGT 766 U/L, ALP 682 U/L, total bilirubin 1 mg/dL, amylase 95 U/L. Hemogram: hemoglobin 13.8 g/dL, platelets 216 000  $\mu$ L, leukocytes 8390/ $\mu$ L (normal leukocyte differential). The coagulation study, routine urinalysis, and chest x-ray were normal. On the basis of suspected biliary tract infection, empirical treatment with intravenous piperacillin-tazobactam was started. The abdominal sonography, abdominal scan, and magnetic resonance cholangiography were all normal. Blood cultures and serology tests for hepatotropic viruses were negative. Stool cultures, *Clostridium difficile* toxin, and fecal parasites were also negative. The rest of the liver disease study was negative. The patient did not improve, the cholestasia worsened, and a considerable increase of peripheral blood

eosinophils (3037/mL) was observed. On the fifth day of antibiotic treatment, drug-induced toxicity was suspected, and clopidogrel and atorvastatin were discontinued. The fever, diarrhea, and abdominal pain disappeared, and the eosinophil, bilirubin, and transaminase levels gradually returned to normal. At 6 months, the patient was asymptomatic and had normal analyses.

Drug-induced liver toxicity appears in 1:1000 to 1:10 000 exposed patients<sup>3</sup> and accounts for 5% of all cases of jaundice and 10% of all patients with acute hepatitis admitted to a hospital.<sup>4</sup>

The diagnosis is based on clinical suspicion, a detailed pharmacological history, the temporal relationship between drug exposure and clinical symptoms, and the exclusion of other diagnoses.<sup>4</sup> Rechallenge is considered the most specific test, but may be hazardous and should be avoided.<sup>4</sup> In some cases, liver biopsy is indicated to rule out other diseases and support the drug-related etiology.

In our patient, there was a temporal, but not immediate, relationship between use of clopidogrel and the onset of the clinical symptoms (20-30 days). In the cases found in the scientific literature, toxicity appeared 4 days to 3 months after the drug was started, with mixed hepatocellular and cholestatic alterations. In one case, clopidogrel rechallenge caused recurrence of the liver damage.<sup>5</sup> Only the patient described by the Mayo Clinic<sup>2</sup> also experienced a systemic response, with fever, skin rash, tachycardia, and leukocytosis.

The statin was also discontinued, although the patient had been taking this drug for some time. Clopidogrel was not reintroduced for ethical reasons, and liver biopsy was not done because the patient was on antiplatelet therapy. After applying the most widely accepted causality scales for drug-induced liver damage (CIOMS and Maria et al), we obtained a result of "probable" toxicity.<sup>4</sup>

The mechanism of this hepatotoxicity is unknown. Clopidogrel is oxidized by cytochrome P450 (CYP3A4), producing an active metabolite that inhibits platelet aggregation.<sup>6</sup> Oxidation yields active intermediate products (free radicals, reduced oxygenated species, epoxides, etc.) that cause tissue lesions and contribute to oxidative stress. Atorvastatin is also a CYP3A4 substrate and, due to its greater affinity, can displace clopidogrel and alter its metabolism. Interaction with metabolites of the drug could also lead to neoantigens or autoantibodies, triggering an immune response in liver tissue ("immune mechanism").

Our patient represents a new case of drug-induced liver toxicity, with systemic inflammatory response. Any patient receiving clopidogrel antiplatelet therapy should discontinue treatment when there are any liver profile changes, jaundice, or evidence of systemic inflammatory response.

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