LETTER TO THE EDITOR
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Successful Treatment with Romiplostim After Eltrombopag-Induced Liver Injury in Immune Thrombocytopenic Purpura

İmmün Trombositopenik Purpurada Eltrombopag ile Oluşan Karaciğer Hasarının Ardından Romiplostim ile Başarılı Tedavi

Eren Arslan Davulcu
University of Health Sciences Türkiye, İstanbul Bakirkoy Dr. Sadi Konuk Training and Research Hospital, Clinic of Hematology, İstanbul, Türkiye

Eren Arslan Davulcu, M.D., University of Health Sciences Türkiye, İstanbul Bakirkoy Dr. Sadi Konuk Training and Research Hospital, Clinic of Hematology, İstanbul, Türkiye
erenarslan85@yahoo.com
0000-0001-9262-2883

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Dear Editor,

Immune thrombocytopenia (ITP) is an acquired autoimmune hematologic disorder defined by isolated thrombocytopenia in the peripheral blood, resulting from increased platelet destruction and/or impaired platelet production, and associated with a heightened bleeding diathesis (1). The age-adjusted prevalence of ITP was 9.5 per 100,000 persons (2). Management of the disease follows a stepwise therapeutic approach, guided by the patient's clinical response to prior lines of treatment. Corticosteroids are first-line therapy, followed by thrombopoietin receptor agonists (TPO-RAs) and rituximab as second-line options, and progressing to splenectomy and other immunosuppressive modalities for refractory cases. Intravenous immunoglobulin may be incorporated into the treatment regimen in cases where corticosteroids are contraindicated or in urgent clinical scenarios requiring rapid platelet elevation (3). While all therapies carry their own adverse effect profiles, eltrombopag—a thrombopoietin receptor agonist—requires close monitoring due to its potential for hepatotoxicity.

A 33-year-old female patient was evaluated for isolated thrombocytopenia, with a platelet count of 51,000/mm³. Other hematological parameters, coagulation tests, and biochemical profiles were within normal limits. Physical examination was unremarkable, except for intermittent petechial lesions observed on the lower extremities. To exclude secondary causes, the following investigations were conducted and yielded negative results: antinuclear antibodies, lupus anticoagulant, anti-β2-glycoprotein I antibodies (IgG and IgM), anticardiolipin antibodies (IgG and IgM), antiphospholipid antibodies, serological tests for hepatitis B and C viruses, human immunodeficiency virus, and stool antigen test for *Helicobacter pylori*. Additionally, abdominal ultrasonography and chest radiography revealed no abnormalities. Following the exclusion of secondary etiologies, the patient was classified as having primary ITP (3).

Approximately 1.5 years post-diagnosis, the patient presented to the emergency department with a petechial rash and menorrhagia. Laboratory evaluation revealed severe thrombocytopenia with a platelet count of 4,000/mm³. First-line therapy with methylprednisolone at a dose of 1 mg/kg/day was initiated. A complete response was achieved within three weeks, with the platelet count rising above 100,000/mm³, prompting a tapering regimen of methylprednisolone at a rate of 8 mg per week. Due to the development of significant metabolic adverse effects—including weight gain, Cushingoid features, and hyperglycemia—steroid therapy was appropriately tapered and subsequently discontinued after 18 weeks of treatment. Three months later, the patient experienced a relapse with a platelet count of 5,000/mm³, prompting initiation of second-line therapy with eltrombopag at a dose of 50 mg/day. After 15 days of treatment, laboratory tests revealed elevated transaminases (aspartate aminotransferase: 475 U/L, alanine aminotransferase: 980 U/L) with a total bilirubin of 0.75 mg/dL, consistent with drug-induced liver injury. The patient was not receiving any concomitant medications or hepatotoxic substances. Eltrombopag was promptly discontinued, and the patient was admitted for close inpatient monitoring. Viral, ischemic, and autoimmune hepatitis were excluded through comprehensive diagnostic workup, including imaging modalities (abdominal ultrasonography, portal Doppler ultrasonography, abdominal magnetic resonance imaging, and echocardiography) and extensive laboratory testing encompassing serologic assays for hepatotropic viruses and autoimmune markers such as antinuclear antibody, anti–smooth muscle

antibody, anti–mitochondrial antibody, liver microsomal antibody, and immunoglobulin quantification. During inpatient follow-up, intravenous N-acetylcysteine and methylprednisolone were administered, although their clinical efficacy remained uncertain (4). Methylprednisolone was administered at a dose of 100 mg/day for three consecutive days, followed by 1 mg/kg/day, which was subsequently tapered and discontinued within a three-week period. Hepatotoxicity attained its maximum severity approximately 13 days following eltrombopag discontinuation (Table 1, Graphic 1), with biochemical parameters returning to baseline levels by day 28. Due to persistent refractory thrombocytopenia, weekly administration of rituximab at a dose of 375 mg/m² was initiated as third-line therapy; however, the patient exhibited no clinical response. Given the patient's refusal to undergo splenectomy, an another thrombopoietin receptor agonist romiplostim was initiated as a subsequent line of therapy at a starting dose of 1 mcg/kg/week. The dosage was titrated up to a maximum of 2 mcg/kg/week, then maintained at 1 mcg/kg/week with subsequent dose adjustments guided by serial platelet count measurements. To date, no laboratory abnormalities or clinical adverse effects have been observed in the patient, who has been maintained on this therapy for over three months.

Although infrequent, severe hepatotoxicity has been documented in association with eltrombopag therapy even in the standard doses (5,6). It has been reported that alanine aminotransferase elevations occurred in 10% to 11% of eltrombopag-treated patients compared to 3% to 7% in placebo-treated subjects. These elevations were usually mild and transient, resolving once eltrombopag was discontinued and sometimes even with continued use (7). In a study comorbid type 2 diabetes mellitus or noninflammatory hepatobiliary disorders—including cholelithiasis, gallbladder polyps, hepatic cysts, and hepatic steatosis—were significantly associated with eltrombopag-induced hepatotoxicity (8).

Romiplostim, eltrombopag, avatrombopag, lusutrombopag, and hetrombopag are classified as TPO-RAs, a class of agents that stimulate platelet production by activating the thrombopoietin receptor (TPO-R). However, unlike the other orally administered TPO-RA that bind to the transmembrane domain of the TPO-R, romiplostim is administered subcutaneously and exerts its effect by competitively binding to the extracellular domain of the TPO-R, mimicking the natural ligand thrombopoietin (9). Romiplostim has not been associated with clinically significant hepatotoxicity (7). The variation in hepatotoxicity observed between romiplostim and eltrombopag may be explained by differences in their pharmacokinetic profiles, including route of administration and receptor binding mechanisms. However, no cases of hepatotoxicity have been reported with TPO-RAs exhibiting a binding mechanism similar to that of eltrombopag, including avatrombopag, lusutrombopag and hetrombopag. Furthermore, lusutrombopag and avatrombopag likewise approved for the management of thrombocytopenia secondary to chronic liver disease (9, 10). Potential explanations for the differences among oral TPO-RA may include variability in hepatic metabolism, specifically the involvement of different cytochrome enzymes, as well as distinct elimination pathways. For example, eltrombopag is metabolized by CYP1A2, CYP2C9, UGT1A1, and UGT1A3. Avatrombopag is primarily metabolized by the cytochrome CYP3A4 and CYP2C9. In contrast, lusutrombopag undergoes limited hepatic metabolism, mainly via oxidation and glucuronidation processes (7). The successful transition to romiplostim without adverse hepatic effects in our patient suggests that alternative TPO-RA with differing pharmacokinetic and receptor-binding profiles may offer safer therapeutic options in patients at risk of liver injury.

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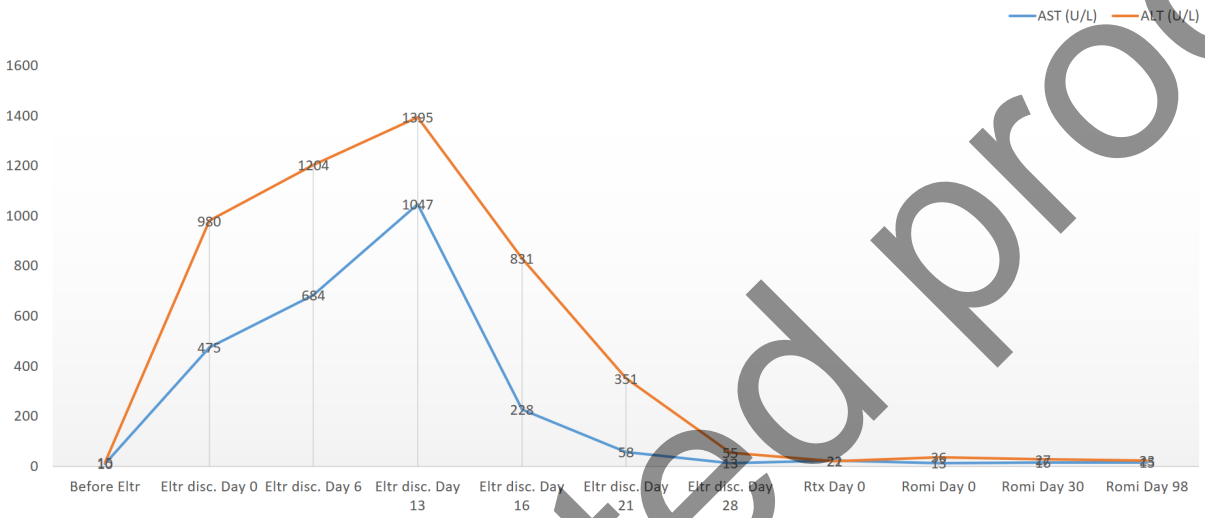

Graphic of a time-based ALT/AST trends