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A Case Series On Anomalous Presentation Of Eltrombopag Induced Hepatic Dysfunction

[1]Dr. Tintu Thomas *, [2]Dr. Swetha Reba Mathews, [3] Dr. Harikrishnan S , [4]Dr. Jacob Jesuran
[1] Pharm. D Intern, [2]Assistant Professor,Department Of Pharmacology [3]Clinical Pharmacist,Department Of Clinical Pharmacy [4]Head Of Department, Department Of Pharmacology,
Believers Church Medical College Hospital

***Corresponding Author:**
Dr. Tintu Thomas
Pharm.D Intern , Department Of Clinical Pharmacy, Believers Church Medical College Hospital

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Abstract
Eltrombopag is widely used as a thrombopoietin receptor agonist for the treatment of immune thrombocytopenic purpura (ITP) and aplastic anemia. The incidence of Eltrombopag causing hepatic dysfunction such as hyperbilirubinemia, hyperammonemia, and hypertransaminasemia, is rarely reported; therefore, the data available are also sparse. However, the clinical trials reported hepatotoxicity with Eltrombopag. This case series highlights the hepatic dysfunction experienced by our patients on treatment with Eltrombopag at standard dosing and importance of cautious prescription in pediatric patients. It highlights the need for careful monitoring, dosing, diagnosis, and intervention to prevent life-threatening situations.

Keywords: Eltrombopag , thrombopoietin receptor agonist, immune thrombocytopenic purpura, hepatotoxicity, aplastic anemia

Introduction

Eltrombopag is a thrombopoietin receptor (TPO-R) agonist, approved for the management of immune thrombocytopenic purpura and aplastic anemia. Eltrombopag selectively binds to the transmembrane domain of the TPO receptor and stimulates megakaryocytopoiesis through the Janus kinase and signal transducer and activator of transcription (JAK/STAT) signaling pathway, thereby stimulating megakaryocyte proliferation and differentiation and promoting platelet production. Eltrombopag is metabolized in the liver, largely by the cytochrome P450 system (CYP 1A2, 2C8) and by the uridine diphosphate glucuronosyltransferase transport system (UGT1A1 and 1A3); as the liver metabolizes the drug, the adverse effect of the drug will mainly target the liver, causing abnormal liver function and severe hepatotoxicity and rare thromboembolic complications that may develop into a life-threatening situation. [1,2]

The hepatic complications include elevated ammonia and bilirubin levels, transaminase, and thromboembolic complications, including cerebral venous sinus thrombosis (CVST).

Hyperammonemia is a metabolic condition caused by elevated levels of ammonia, a nitrogen-containing compound formed as a byproduct after protein metabolism in the blood when liver function is affected. [3,4] Ammonia is a potent neurotoxin, and elevated levels in the blood can cause neurological signs and symptoms and may lead to encephalopathy. [5]

Specific intervention may be needed in this condition. The proper pathophysiology of Eltrombopag-induced hyperammonemia is not known. It may be due to the impaired urea cycle or portal vein thrombosis, which leads to the decreased ability of the liver to eliminate ammonia from the body leading to hyperammonemia

Hyperbilirubinemia is a condition that occurs due to the excessive accumulation of bilirubin, the end product of heme catabolism, in the blood. The liver converts unconjugated bilirubin into a conjugated form, which is excreted through urine and stool. If the bilirubin level is high in the blood, it will circulate through the blood and reach the brain, causing seizures and brain damage; this condition is known as kernicterus. [6] Normally no specific medications are used; if it is caused by a drug, discontinuation of the drug will resolve hyperbilirubinemia. The pathophysiology includes the inhibition of UDP glucuronosyltransferase (UGT)1A1 and organic anion-transporting polypeptide (OATP)1B1 by Eltrombopag, which can result in indirect hyperbilirubinemia. [7]

Transaminitis refers to the elevation of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP) in the blood. They are considered as biochemical markers of liver function. Any damage to the hepatocytes results in the release of these enzymes into the blood circulation and causes acute elevation of serum liver enzymes. [8]

The management depends on the cause of transaminitis, such as if it is caused by a drug, then withdraw or reduce the dose. The mechanism of injury that might lead to serum liver enzyme elevations during Eltrombopag therapy is not fully known. The thrombosis induced by thrombopoietin receptor agonists might cause a hypercoagulable state resulting in portal vein or hepatic vein thrombosis, and hepatocyte injury may lead to the release of liver enzymes into the blood, resulting in elevated serum transaminase levels. [9]

Case Scenarios

Case No : 01 Eltrombopag Induced Transaminitis And Hyperbilirubinemia -

A 27-year-old female was referred to our hospital with a history of immune thrombocytopenic purpura (ITP), who had complaints of petechial rashes and purpura all over the body and increased vaginal bleeding for 6 days following normal vaginal delivery. On routine blood investigation, she was noted to have severe thrombocytopenia with a platelet count of 3,000, leukocytosis with a total count of 15,900, and Hb of 12.5. In view of thrombocytopenia, she was transfused with multiple pints of RDPs, and steroid therapy continued (T. Prednisolone). In view of the steroid-refractory nature, she was initiated on IVIG 1 g/kg (60 gm) with close cardiac monitoring. She had developed low mood, decreased activity, and anxiety during the hospital stay, and a psychiatry opinion was sought. They advised adding Tab. Tianeptine 12.5 mg HS and Tab. Clonazepam 0.25 mg HS for 2 weeks. Her repeated blood examination showed an increasing trend of platelet counts from 4000 to 17,000 lakhs. In view of the inadequate response to IvIg 1 g/kg, we suggested repeating the dose of IvIg at 2 g/kg. However, her family wanted an alternative management. Hence she was started on Tab. Eltrombopag 50 mg once daily. At the time of discharge, her platelet count was 17,000 lakhs.

After 4 months of treatment with Eltrombopag 75 mg OD, she presented to the outpatient department with complaints of multiple episodes of vomiting for 3 days. A complete blood examination was done, and the report revealed deranged liver function tests (LFTs), the values are summarized in Table No : I

Table No ; I LFT before and after reducing Eltrombopag dose

Liver function test	Bilirubin, total	Bilirubin, direct	Bilirubin, indirect	AST (SGOT)	ALT (SGPT)	Alkaline phosphatase (ALP)
Before dose reduction	6.83 mg/dL	1.53 mg/dL	5.30 mg/dL	353 U/L	322 U/L	136 U/L

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After dose reduction	2.96 mg/dL	0.30 mg/dL	2.66 mg/dL	34 U/L	31 U/L	123 U/L
Normal range	0.20 - 1.00 mg/dL	0.00 - 0.20 mg/dL	0.20 - 1.00 mg/dL	10 - 40 U/L	10 - 40 U/L	30 -120 U/L

Gastroenterology consultation was sought in view of transaminitis and hyperbilirubinemia. They advised reducing the dose of Eltrombopag and prescribed ursodeoxycholic acid (ursocol) 300 mg twice daily for hepatic protection. The dose was reduced from 75 mg to 50 mg and 25 mg on alternate days.

Upon evaluation at our ADR Monitoring Centre, the causality was assessed to be “Probable” using the WHO-UMC causality assessment scale. The type of ADR was classified as "TYPE B” according to the Rawlins- Thompson classification. and severity was assessed as "Level 2” in terms of Modified Hatwig’s scale. As per the WHO criteria, the seriousness of the reaction was categorized as "Other Medically Important." and the outcome of the reaction was"recovering" .Additionally, according to the Schumock and Thornton scale, the ADR was deemed "Probably Preventable". The Assessment of Causality and other attributes of the ADR was conducted using established scales and criteria to ensure comprehensive and standardized evaluation.

After 2 weeks, she returned for follow-up, and blood examination showed improved LFTs.

However, there was a significant drop in her platelet count to 0.15 lakh. As a result, again the dose of Eltrombopag was increased to 50 mg once daily and advised to monitor LFT and continue Ursocol 300 mg twice daily.

Case no : 2 Eltrombopag induced hyperbilirubinemia -

A 54-year-old female came to our hospital for a regular checkup. Later during blood investigation, we found that her bilirubin level was elevated; she was a known case of aplastic anemia and was on Tab. Eltrombopag 50 mg once daily. She was asymptomatic in nature. Taking account of hyperbilirubinemia, Eltrombopag was withheld. The values of LFT is mentioned in the below Table No : II

Table No ; II - LFT before and after withholding Eltrombopag dose

Liver function test	Bilirubin,total	Bilirubin,direct	Bilirubin,indirect
Before withholding Eltrombopag	7.20 mg/dL	0.22 mg/dL	6.98 mg/dL
After withholding Eltrombopag	0.95 mg/dL	0.15 mg/dL	0.80 mg/dL
Normal range	0.20 - 1.00 mg/dL	0.00 - 0.20 mg/dL	0.20 - 1.00 mg/dL

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No conservative treatment was given to the patient for hyperbilirubinemia, and aplastic anemia was managed with Cyclosporin injection 50 mg once daily, followed by Cyclosporin 100 mg and 25 mg once daily.

Upon evaluation at our ADR Monitoring Centre, the causality was assessed to be “Probable” using the WHO-UMC causality assessment scale. The type of ADR was classified as "TYPE B” according to the Rawlins- Thompson classification. and severity was assessed as "Level 3” in terms of Modified Hatwig’s scale. As per the WHO criteria, the seriousness of the reaction was categorized as "Other Medically Important." and the outcome of the reaction was "recovering." Additionally, according to the Schumock and Thornton scale, the ADR was deemed "Probably Preventable". The Assessment of Causality and other attributes of the ADR was conducted using established scales and criteria to ensure comprehensive and standardized evaluation.

After 2 months, she returned for a follow-up and found that her bilirubin levels came within normal range.

Case no: 3 Eltrombopag induced transaminitis, hyperbilirubinemia and hyperammonemia -

An 8-year-old female child came to our hospital with complaints of generalized tiredness and vomiting. She had ITP and was on Tab. Eltrombopag 75 mg and 50 mg OD on alternate days. During the hospital stay, she developed altered sensorium and restlessness. She was managed by Inj. Midazolam 1.5 mg, and Inj. Levipil 300 mg as advised by the pediatrician; later neurology consultations were sought, and a CT brain scan was taken, which showed normal findings. On blood examination, we found a deranged levels of LFT and ammonia and are summarised in below Table No : III and IV

Table No : III - LFT before and after withholding Eltrombopag dose

Liver function test	Bilirubin, total	Bilirubin, direct	Bilirubin, indirect	AST (SGOT)	ALT (SGPT)	Alkaline phosphatase (ALP)
Before dose reduction	4.44 mg/dL	0.28 mg/dL	4.16 mg/dL	71 U/L	58 U/L	137 U/L
After dose reduction	0.57 mg/dL	0.30 mg/dL	0.11 mg/dL	34 U/L	17 U/L	102 U/L
Normal range	0.20 - 1.00 mg/dL	0.00 - 0.20 mg/dL	0.20 - 1.00 mg/dL	10 - 40 U/L	10 - 40 U/L	30 -120 U/L

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Table No : IV - Ammonia level before and after withholding Eltrombopag dose

Ammonia	LEVELS
Before dose reduction	433.10 µmol/L
After dose reduction	41.90 µmol/L
Normal range	10.00 - 47.00 µmol/L

Tab. Eltrombopag was withheld in light of hyperbilirubinemia and hyperammonemia and encephalopathy. A gastroenterology review was sought in view of hyperammonemia and encephalopathy, they advised obtaining an opinion from a pediatric gastroenterologist for further management considering acute liver injury and encephalopathy.

Upon evaluation at our ADR Monitoring Centre, the causality was assessed to be “Probable” using the WHO-UMC causality assessment scale. The type of ADR was classified as "TYPE B” according to the Rawlins-Thompson classification. and severity was assessed as "Level 4b’”in terms of Modified Hatwig’s scale. As per the WHO criteria, the seriousness of the reaction was categorized as "Other Medically Important." and the outcome of the reaction was "recovering." Additionally, according to the Schumock and Thornton scale, the ADR was deemed "Probably Preventable". The Assessment of Causality and other attributes of the ADR was conducted using established scales and criteria to ensure comprehensive and standardized evaluation.

After 1 month she came back for her check-up and found that her LFT and ammonia became normal,and advised to take Romiplostim 170 mcg weekly subcutaneously for ITP management.

An overview of all these 3 cases are summarized in the below Table No : V

Table No ;- V - an overview of the case

Sl.no	**Case no : 01**	**Case no : 02**	**Case no : 03**
Patients details	27-year-old female	54-year-old female	8-year-old girl child
Diagnosis	ITP	Aplastic anemia	ITP
Drug given	Tab.Eltrombopag	Tab.Eltrombopag	Tab. Eltrombopag
Dose	50 mg OD later raised to 75 mg OD	50 mg OD	25 mg raised to 50 mg and then 75 mg and 50 mg OD on alternate days

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Duration of therapy	4 months	3 months	6 months in 50 mg OD and 7 days in 75 mg and 50 mg OD on alternate days
ADR occured	Transaminitis and hyperbilirubinemia	Hyperbilirubinemia	Hyperbilirubinemia , Hyperammonemia and Transaminitis
Action taken	Dose reduced to 50 mg and 25 mg on alternate days	Withdrawn	Withheld
Outcome	Recovered	Recovered	Recovered
WHO-UMC causality assessment scale	Probable	Probable	Probable
Rawlins-Thompson classification	TYPE B	TYPE B	TYPE B
Modified Hatwig's scale	Level 2	Level 3	Level 4b
Schumock and Thornton scale	Probably Preventable	Probably Preventable	Probably Preventable

Discussion

Eltrombopag interacts with the TPO receptor (c-MPL) on stem cells, activating Janus kinases (JAKs) and stimulating megakaryocyte production. Our patients experienced hyperbilirubinemia and transaminasemia with the use of eltrombopag at standard doses for the management of ITP and aplastic anemia. According to the EXTEND study, eltrombopag causes hepatobiliary side effects in approximately 15% of patients. The drug can inhibit UDP-glucuronosyltransferase (UGT) 1A1 and organic anion-transporting polypeptide (OATP) 1B1, which may result in indirect hyperbilirubinemia.

A similar case series was published by Bahar Oztelcan Gunduz et al. [10]. These cases highlight that eltrombopag can cause liver toxicity and emphasize the importance of monitoring serum aminotransferase and bilirubin levels before and during eltrombopag therapy. In clinical trials, patients with ITP showed ALT elevations in 10%–11% of those receiving eltrombopag [9].

One of the case from our case series, also reports hyperammonemia but its proper pathophysiology for

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Eltrombopag-induced hyperammonemia is not known. It may be due to the impaired urea cycle or portal vein thrombosis, which leads to the decreased ability of the liver to eliminate ammonia from the body leading to hyperammonemia.

A pediatric case with acute liver injury and encephalopathy, similar to our case, was published by Erin Hermann et al. [11]. A 2-year-old boy with chronic ITP developed acute liver failure, metabolic acidosis, and encephalopathy while receiving standard doses of eltrombopag. These reports underscore the need for caution in prescribing and dosing eltrombopag in pediatric patients, as long-term safety data in children are limited. Close monitoring of liver function tests during eltrombopag treatment may help reduce the risk of liver injury through early detection.[12]

Conclusion

These cases emphasize that eltrombopag can leads to liver toxicity with hypertransaminesemia and hyperbilirubinemia. And highlights the clinical importance of careful use and monitoring of Eltrombopag and consider initiation and tapering indications.Frequent blood examination after the start of Eltrombopag is an important aid in thwarting episodes of thrombosis and abnormal liver function. It also notes the importance of individualizing the dosing during the treatment to avoid adverse reactions.

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Conflict Of Interest Statement :

The authors have no conflicts of interest to declare. All co-authors have seen and agree with the contents of the manuscript and there is no financial interest to report. We certify that the submission is original work and is not under review at any other publication.

Patient Consent :

The authors certify that they have obtained all appropriate patient consent documents. In the documents, the patient consented for her clinical information to be reported in the journal. The patient understands that her name and initials will not be published, and due efforts will be made to conceal her identity.

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Abbreviations

ITP- Immune Thrombocytopenic Purpura

ALT- Alanine transaminase

AST- Aspartate transaminase

ALP- Alkaline phosphatase

ADR- Adverse drug reaction

RDPs- Random Donor Platelet

CT - Computed Tomography

SGOT - Serum Glutamic Oxaloacetic Transaminase

SGPT - Serum Glutamic Pyruvic Transaminase

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