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Management of pregnant women with Refractory Immune Thrombocytopenia Purpura (ITP) receiving eltrombopag therapy at Sanjiwani Hospital, Gianyar, Indonesia



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ABSTRACT

Background: Immune Thrombocytopenia Purpura (ITP) is an autoimmune disease characterized by a low level of platelets in the blood caused by accelerated platelet destruction or disruption of the thrombopoiesis due to antibodies to platelets. Drugs with similar functions to thrombopoietins (TPO) such as eltrombopag and romiplostim have been widely used and have been shown to be quite successful in treating ITP in nonpregnant patients. This case study aims to evaluate eltrombopag therapy's role in managing the refractory ITP in pregnant women.

Case Presentation: A 25-year-old patient, a housewife, presented to the obstetrics clinic at Sanjiwani Hospital for the first time at a gestational age of 13 weeks for her third pregnancy, with a history of two abortions. ITP was diagnosed in 2017 during the second abortion treatment. The platelet examination results were between 32,000-66,000/ μ l, with platelet count during delivery planning at 34 weeks

of 41,000/ μ l. The patient was diagnosed with chronic refractory ITP and was considered for second-line drug administration. Intravenous Immunoglobulin Therapy (IVIg) and anti-D administration as second-line drugs were not possible due to cost. The patient was given 50 mg eltrombopag per day for a week. The platelet counts increased to 202,000/ μ l a week after therapy. The patient then underwent vaginal delivery with a baby weight of 2,850 gram, Apgar Score of 8-10. The baby was exclusively breastfed and subjected to clinical monitoring and laboratory tests. The patient's clinical condition was favorable and the platelets fell to 20,000/ μ l nineteen days after delivery.

Conclusion: In this case, the patient with chronic ITP refractory to steroid therapy showed an immediate response to eltrombopag. However, the platelet level decreased two weeks after the treatment cessation. More studies are needed on the use of eltrombopag in pregnant women.

Keywords: Immune Thrombocytopenic Purpura, Pregnancy, Eltrombopag

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INTRODUCTION

Immune Thrombocytopenic Purpura (ITP) is an acquired autoimmune disorder characterized by a low platelet count and caused by accelerated platelet destruction and disruption of thrombopoiesis due to circulating antiplatelet antibodies in maternal blood circulation, which will damage platelet glycoproteins.¹ ITP is estimated to occur in about 1 in 10,000 of the general population and about half of the cases occur during childhood. The incidence of ITP during pregnancy is reported to be 1-2 per 1,000 deliveries.² ITP is responsible for 4-5%

of thrombocytopenia in pregnancy.³ The most important fetal or neonatal complication of ITP in pregnancy is Neonatal Alloimmune Thrombocytopenia (NAIT).³

The approach to managing ITP during pregnancy differs from that of nonpregnant women because of the potential drug adverse reactions that may complicate fetal development and the course of the pregnancy.⁴ Glucocorticoids are an option for initial therapy in the absence of life-threatening bleeding. Other treatment options include IVIG, which is safe for the fetus but is included

as secondary treatment because of maternal adverse reactions and high cost. Studies investigating anti-Rh (D) therapy in pregnant women remain limited.⁴ Thrombopoietin (TPO) drugs such as eltrombopag and romiplostim have been used successfully in many nonpregnant patients with ITP, but research and trials regarding their effects on pregnancy are limited.⁵ Based on those mentioned above, this case study aims to evaluate the ITP refractory to steroid treatment and was given secondary treatment with an eltrombopag as current management in pregnant women.

CASE REPORT

A pregnant woman initially presented to the Department of Obstetrics and Gynecology at 13 weeks of gestational age with early pregnancy and a history of ITP in her second pregnancy in 2017 observed during pregnancy evacuation due to abortion. The patient did not complain of spontaneous bleeding but bruises after collisions. There were no abnormalities found during physical examination. Blood laboratory examination showed a platelet count of 66,000/ μl , as shown in Table 1.

Other tests conducted to rule out other secondary causes such as HIV, hepatitis B, hepatitis C and *Helicobacter pylori* IgG were negative. The patient was subjected to peripheral blood smear examination, bone marrow aspiration and examination for antiplatelet antibodies. The diagnosis of ITP was confirmed based on clinical features and further studies, excluding other possible causes. Since the patient has a history of two abortions, she was screened for anti-cardiolipin antibodies (ACA) for the possible anti-phospholipid syndrome (APS) and the results were negative. The patient was also consulted to the internal department and was prescribed an increasing dose of methylprednisolone with a target platelet level of 50,000/ μl .

On the third trimester examination, the platelet count was 41,000/ μl which did not reach the platelet level target with methylprednisolone. The alternatives discussed at the team meeting included IVIG administration, platelet transfusions at delivery and administration of TPO.

IVIG administration was not possible due to cost. Eltrombopag was more likely to be affordable because even though it is expensive and is not covered by insurance, the hospital may cover the drug. It took time to get the drug ready. The eltrombopag oleamin was then given at a dose of 50 mg/

day for a week. Platelet counts a week after therapy was 212,000/ μl (Figure 1). The patient was planned for vaginal delivery and the patient gave birth spontaneously at Sanjiwani Hospital. The newborn weight, length, and APGAR score were 2850 grams, 150 cm, and 8-10, respectively.

Table 1. Laboratory examination of case study

Blood Examinations	Results	Normal value
Hemoglobin (g/dL)	13.1	11-16
WBC ($10^3/\mu\text{l}$)	11.7	4-10
Thrombocyte (Plt) ($10^3/\mu\text{l}$)	66	150-450
Bleeding Time (BT) (Minutes)	1'30	2-6
Clotting Time (CT) (Minutes)	7'30	6-15
PT	8.0	11.6
APTT	21.5	

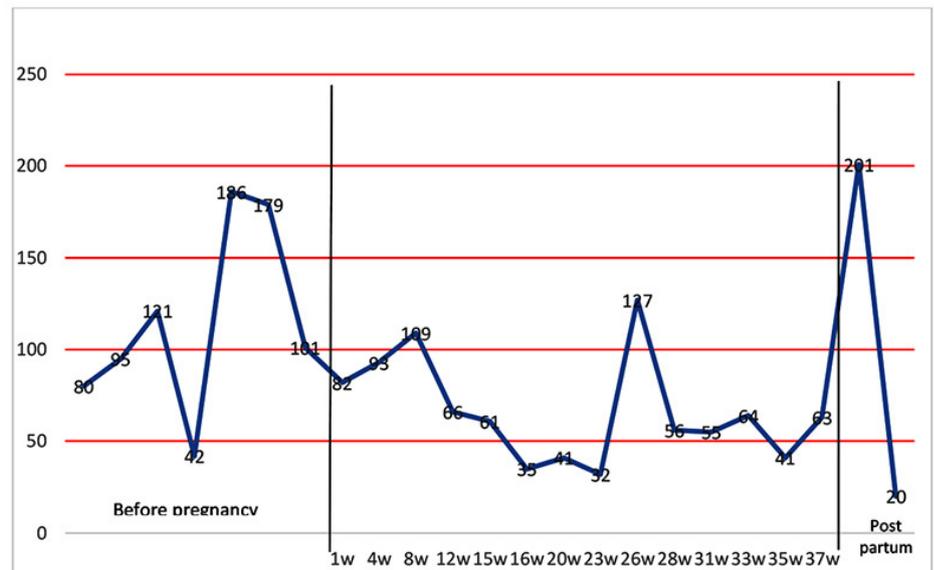


Figure 1. Thrombocytes ($10^3/\mu\text{l}$) counts during pregnancy and delivery

Table 2. Liver Function Examinations Before and After Administration of Eltrombopag

Liver function parameters	Before Eltrombopag administration	After Eltrombopag administration	Normal value	Reference
SGOT (u/L)	14	19		<31
SGPT (u/L)	10	19		<31
Total bilirubin (mg/dL)		0.91		0.1 – 1.2
Direct bilirubin (mg/dL)		0.17		<0.2
Indirect bilirubin (mg/dL)		0.34		<0.75
ALP (IU/L)		79		42-141
APTT (seconds)	24.4	24.3	25.2 – 36.2 s	
PT (seconds)	97	8.9	11.6 – 18.9 s	
INR	0.9	0.82		

SGOT: Serum glutamic oxaloacetic transaminase; SGPT: Serum glutamic pyruvic transaminase; ALP: Alkaline Phosphate; APPT: Activated Partial Thromboplastin Time; PT: Prothrombin Time; INR: International Normalized Ratio

The postpartum bleeding was estimated to be around 300 cc and no problems were found during the puerperium. The patient exclusively breastfed her baby. The platelet count 19 days after delivery was 20,000/ μ l, with no bleeding tendency (Figure 1). The patient was subsequently treated with steroids. Based on the liver function test, there is no abnormal sign following eltrombopag administration, as depicted in Table 2.

DISCUSSION

Immune Thrombocytopenic Purpura (ITP) is caused by the circulation of antiplatelet antibodies, namely Platelet-Associated immunoglobulins (PAIg), which bind to glycoproteins (GP) IIb/IIIa complex or GPIb/IX complex or other glycoprotein complexes.⁶ These antibody-coated platelets are destroyed by tissue macrophages which are mainly located in the spleen.^{6,7} Decreased platelet production occurs in acute and chronic ITP because autoantibodies to platelet glycoproteins interfere with megakaryocytic maturation.^{8,9}

The differential diagnosis for ITP includes gestational thrombocytopenia, which occurs in 5-8% of pregnancies.¹⁰ Gestational thrombocytopenia occurs physiologically in pregnant women, decreasing the platelet count of 70,000-100,000/ μ l during the third trimester of pregnancy without complications. ITP generally causes thrombocytopenia, while ITP generally occurs in the first trimester. ITP may progress during pregnancy and possibly back to pre-pregnancy platelet counts after delivery.⁵

Drug adverse reaction is an essential part to be considered in the management of ITP because it may affect pregnancy and fetal development. A multidisciplinary approach must be carried out by involving a team of hematologists, obstetricians and neonatologists based on the previous study.⁵

Glucocorticoids are considered for initial therapy in the absence of life-threatening bleeding.⁵ Glucocorticoids are non-teratogenic, but they may induce gestational diabetes or hypertension. Cytotoxic drugs, such as the vinca alkaloids, azathioprine and cyclophosphamide, are potentially teratogenic.⁵ For our case,

treatment with cytotoxic drugs was not carried out because of possible adverse reactions. Our patient did not respond to steroid administration. Hence, a secondary drug was considered to be given in the form of TPO.¹¹ IVIG was not considered possible due to high cost and no signs of bleeding were found. Although IVIG is safe for the fetus, it is often associated with maternal adverse reactions, temporary effects, and not cost-effectiveness. We did not prescribe anti- (Rh) D therapy because we had no previous experience with this treatment.⁴

In this patient, we planned the delivery by cesarean section with durante platelets administration during surgery to expect that the platelet count would increase by 80,000/ μ l. However, considering that the platelet count could be increased up to 80,000/ μ l, vaginal delivery was planned.

Eltrombopag olamine is a thrombopoietin receptor agonist indicated for the treatment of thrombocytopenia in patients with chronic immune thrombocytopenia who are less responsive to corticosteroids, immunoglobulins, or splenectomy.⁵ Eltrombopag is a nonpeptide thrombopoietin receptor agonist for oral administration. Eltrombopag interacts with the transmembrane domain of the thrombopoietin receptor (c-Mpl), leading to increased platelet production. This triggers megakaryocytic growth and differentiation.⁵

Eltrombopag treatment starts at a dose of 50 mg/day for most patients with chronic ITP. The initial dose can be reduced in patients with liver disorders. The dose is adjustable to maintain a platelet count of $\geq 50 \times 10^9 / L$. Daily dose should not exceed 75 mg.⁵

Eltrombopag belongs to the C category of drug for pregnancy according to the Food and Drug Administration (FDA).⁵ There are no adequate and well-controlled studies on the use of eltrombopag in pregnancy. Eltrombopag can be used in pregnancy only if the benefits outweigh the risks.⁵ There was evidence of embryonic mortality and reduction in fetal weight at doses exceeding maternal toxic doses in animal studies and developmental toxicity.⁵ In our case, this drug was started during the third trimester, so there was no concern about embryo death based on the previous guidelines.^{5,12}

Our patient showed an increase in platelets to normal values after one-week administration of 50 mg/day eltrombopag. This result is in line with Psaila B and Bussel JB showing a platelet increase of 70% normal value.¹³ A study on eltrombopag therapy's effectiveness and safety was conducted in a multi-center, retrospective study in Spain, including 164 subjects who had previously received treatment but did not show favorable response.¹⁴ Eltrombopag was shown to be very effective in these patients and was well-tolerated, where 88.8% of patients responded well. The bleeding in these patients ceased and there was no specific intervention after 8 weeks of drug administration with a median platelet response time of 12 days. Grade 1 and 2 side effects were observed in less than 2% of patients.¹⁴ In our case, the eltrombopag was discontinued, and subsequently, a decrease in the platelet count to the initial level was observed within 19 days after the last drug administration. The discontinuation will decrease platelet count to the initial level within 2 weeks, requiring careful monitoring for possible bleeding. For this reason, it is recommended that platelet measurements must be carried out every week for 4 weeks after drug discontinuation and it is recommended to continue ITP treatment according to existing guidelines. In this patient, we continued treatment with 16 mg/day of methylprednisolone. Our patient kept breastfeeding her baby.

The most common adverse reactions are nausea, vomiting, diarrhea, upper respiratory tract infections, myalgia, urinary tract infections, oropharyngeal pain, pharyngitis, back pain, influenza, paresthesia and rash.⁵ However, our patient did not show any of such reactions.

We encouraged our patient to keep breastfeeding her baby. To date, it remains unclear whether eltrombopag is excreted in breast milk. Animal studies showed that eltrombopag was secreted into breast milk; hence, breastfeeding risk cannot be excluded. The decision to either discontinue breastfeeding or continue treatment is based on breastfeeding's advantages and disadvantages.¹²

The most important complication of this drug is hepatotoxicity. Therefore,

monitoring of liver function before and during therapy is essential. Eltrombopag may inhibit the UDP-glucuronosyltransferase (UGT) -1A1 enzymes and organic anion-transporting polypeptide (OATP) 1P1, leading to increased hyperbilirubinemia.⁵ If abnormalities occur during treatment, they should be discontinued. For our patient, liver function tests were performed before starting the eltrombopag therapy, repeated every 2 weeks, and performed before the patient was discharged from the hospital based on the previous treatment.⁵

CONCLUSION

Eltrombopag can be considered as a treatment option in pregnant patients with ITP who have failed steroid therapy. The therapeutic response was significant and fast, but an imminent decrease in platelet count should be monitored for possible complications.

CONFLICT OF INTEREST

The authors declare that there is no competing interest regarding the manuscript.

ETHICS CONSIDERATION

Ethics approval has been obtained from the Ethics Committee, Faculty of Medicine, Universitas Warmadewa, Sanjiwani Hospital, Gianyar, Bali, Indonesia, prior to the study being conducted.

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AUTHOR CONTRIBUTIONS

The authors equally contributed to the study from the conceptual framework, data gathering, and data analysis until interpreting the study results on publication.

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