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Jude Howaidi
Clinical Pharmacy Department, King Fahad Medical City, Riyadh, Saudi Arabia, jude.howaidi@gmail.com

Abdullah M. AlRajhi
Clinical Pharmacy Department, King Fahad Medical City, Riyadh, Saudi Arabia

Ali Howaidi
College of Medicine, Imam Muhammad Ibn Saud Islamic University, Riyadh, Saudi Arabia

Fouad H. AlNajjar
Clinical Pharmacy Department, King Fahad Medical City, Riyadh, Saudi Arabia

Imran K. Tailor
Comphrensive Cancer Center, King Fahad Medical City, Riyadh, Saudi Arabia

REVIEW ARTICLE

Use of Thrombopoietin Receptor Agonists in Pregnancy: A Review of the Literature

Jude Howaidi [a,*], Abdullah M. AlRajhi [a], Ali Howaidi [b], Fouad H. AlNajjar [a], Imran K. Tailor [c]

[a] Clinical Pharmacy Department, King Fahad Medical City, Riyadh, Saudi Arabia
[b] College of Medicine, Imam Muhammad Ibn Saud Islamic University, Riyadh, Saudi Arabia
[c] Comphrensive Cancer Center, King Fahad Medical City, Riyadh, Saudi Arabia

Abstract

The management of immune thrombocytopenic purpura (ITP) involves several lines of therapy such as corticosteroids and intravenous immunoglobulin. With the emergence of novel therapies such as thrombopoietin receptor agonists (TPO-RAs), there has been a shift in treatment modalities. Eltrombopag and romiplostim have proven to be effective in the management of ITP through clinical studies, but their safety in pregnancy remains uncertain. The purpose of the study is to review the literature to evaluate the safety of TPO-RAs in pregnant women. Ten case reports and a cohort study pertaining to the use of TPO-RAs in pregnancy were obtained. According to the reported cases and prospective study, the use of eltrombopag and romiplostim appears to be relatively safe in the first, second, and third trimesters, as there were no reported congenital malformations. Low fetal birth weight has been observed following the administration of eltrombopag during the second trimester, whereas preterm birth has occurred following the administration of eltrombopag in the third trimester. Eltrombopag and romiplostim seem relatively safe. Further studies are necessary to clarify their safety during pregnancy.

Keywords: Eltrombopag, Newborn, Pregnancy, Romiplostim, Thrombopoietin mimetics, Thrombocytopenia

1. Introduction

Immune thrombocytopenia (ITP) is an autoimmune disorder characterized by a low production in platelets, which places an individual at risk of bleeding [1]. The pathophysiology behind ITP involves an antibody-mediated destruction of platelets through the glycoprotein IIa/IIIa receptor on platelet cell surface that results in reduced platelet production [2–4]. A normal platelet level ranges between 150 and 450×10^9/L, whereas in patients with ITP, the platelet count is usually below 100×10^9/L [1].

The management of ITP involves several lines of therapy. First-line treatment options include corticosteroids or intravenous immunoglobulin (IVIG) [5]. In patients with refractory or chronic ITP, second-line treatment options include different modalities such as splenectomy or the use of rituximab [1,6]. With the emergence of novel therapies such as thrombopoietin receptor agonists (TPO-RAs) that include avatrombopag, eltrombopag, lusutrombopag, and romiplostim, splenectomy rates have fallen drastically, which shifted the placement of splenectomy from a second-line to a third-line treatment option [7]. According to the American Society of Hematology (ASH) guideline, TPO-RAs are given to patients diagnosed with ITP for ≥3 months who are either steroid-dependent or refractory to first-line agents such as IVIG [8]. Eltrombopag is Food and Drug Administration (FDA) approved for the treatment of aplastic anemia

Abbreviations: ASH, American Society of Hematology; FDA, Food and Drug Administration; ITP, immune thrombocytopenia; IVIG, intravenous immunoglobulin; TPO-Ras, thrombopoetin receptor agonists

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* Corresponding author at: Clinical Pharmacy Department, King Fahad Medical City, Postal Code 11564, Makkah Al Mukarramah Branch Road, As Sulimaniyah, Riyadh, Saudi Arabia.
E-mail address: jude.howaidi@gmail.com (J. Howaidi).

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and ITP, avatrombopag is FDA approved for ITP and thrombocytopenia associated with chronic liver disease, lusutrombopag is only approved for thrombocytopenia associated with chronic liver disease, whereas romiplostim is only approved for ITP [9–12]. TPO-RAs bind to and activate TPO receptors, which are found on the cell surface of platelets. After their activation, intracellular signal transduction transpires causing an elevation in platelet count [13,14]. They proved to be effective in the management of thrombocytopenia through clinical studies [15–21].

Data regarding the safety of TPO-RAs in pregnancy are limited. Preclinical animal-based studies conducted on female pregnant rats and rabbits have observed low birth weight at higher doses of eltrombopag, avatrombopag, and lusutrombopag, whereas the administration of romiplostim led to thrombocytosis and mortality in pups [9–12]. Our objective is to evaluate the safety of TPO-RAs in pregnant women through a review of the literature.

2. Methods

Articles pertaining to the use of eltrombopag and romiplostim in pregnancy were retrieved through a comprehensive literature search by using several databases. Studies involving avatrombopag and lusutrombopag were not available. The databases used include PubMed, Scopus, Cochrane library, and Web of Science. Search terms such as eltrombopag, romiplostim, pregnancy, thrombopoietin receptor agonists, and thrombopoietin mimetics were used during database search to target comparable articles. Only 10 case reports and one cohort study were found and retrieved. Two case reports described the use of eltrombopag and romiplostim through the first trimester, whereas two case reports described the use of eltrombopag and one case report described the use of romiplostim during the second trimester. Two and three case reports described the use of eltrombopag and romiplostim during the third trimester, respectively. Regarding the cohort study, the study was prospective and assessed the use of TPO-RAs during all trimesters.

3. Results

3.1. Thrombopoietin receptor agonists use during the first trimester of pregnancy

3.1.1. Eltrombopag

The use of eltrombopag during the first trimester of pregnancy has been described in one case report, which focused on a previously diagnosed 25-year-old female with ITP who was on maintenance therapy with 8 mg/day prednisolone. While she was on prednisolone, her platelet count was at 10×10^9/L. The patient's obstetric history included two induced abortions because of the reduced level of platelet count that was unsuccessfully controlled by transfusion. After the administration of 12.5 mg/day eltrombopag prior to pregnancy, her platelet count remained above 50×10^9/L. Eltrombopag was continued after conception and throughout the pregnancy. During the pregnancy, the patient's platelet count remained at 60×10^9/L; however, it dropped to 19×10^9/L at 36 weeks of gestation. She was then diagnosed with gestational hypertension (blood pressure, 150 mmHg) at 37 weeks of gestation. The patient gave birth to a low birth weight baby (1670 g) with no congenital malformations. The newborn, whose platelet count was 416×10^9/L, remained in good health 1 month after delivery.

3.1.2. Romiplostim

An additional report described the use of romiplostim in a 28-year-old woman with a history of refractory ITP. The patient was previously treated with IVIG, prednisone, azathioprine, and rituximab. Five months prior to conception, the patient was initiated on romiplostim. During gestation, romiplostim was continued at a dose of 3 μg/kg/week. Dexamethasone and IVIG were administered after 14 weeks of gestation because of a relapse episode resulting in a platelet count of 7×10^9/L. Her platelet count stabilized thereafter while the patient remained on romiplostim. At 33 weeks of gestation, induction of labor was initiated because of persistently severe incidents of thrombocytopenia experienced by the patient. During labor, the patient's platelet count was $200–300 \times 10^9$/L after the administration of intravenous hydrocortisone at 50 mg every 6 hours. The patient gave birth to a male newborn with a low birth weight of 1910 g and a platelet count of 70×10^9/L. The neonate was born with phimosis and suspected adrenal insufficiency. The newborn's platelet count was 186×10^9/L. Eight hours after delivery, the neonate's platelet count dropped to 33×10^9/L, which prompted the administration of IVIG that stabilized his platelet count to 116×10^9/L. Ten months after delivery, the baby's health condition was normal.

3.2. Thrombopoietin receptor agonists use during the second trimester of pregnancy

3.2.1. Eltrombopag

Two case reports described the use of eltrombopag during the second trimester of pregnancy. The first case report involved a 33-year-old female with a

history of chronic idiopathic thrombocytopenic purpura. At 25 weeks of gestation, she was hospitalized because of ITP relapse with severe decline in platelet count reaching a level of 3×10^9/L. During her admission, she was initiated on a glucocorticoid that resulted in a substantial increase of platelet count. One week later she was initiated on IVIG, which had a similar effect to corticotherapy utilization (30×10^9/L). As the patient's platelet count remained below normal levels, further treatment was warranted. Azathioprine was administered; however, at 27 weeks of gestation the patient developed hematuria. After treatment failure, the patient was initiated on eltrombopag at a dose of 50 mg/day starting at 27 weeks of gestation. After the administration of eltrombopag, the patient's platelet count increased to 70×10^9/L. Eltrombopag dose was reduced to 25 mg/day after the patient was discharged at 29 weeks of gestation. Because her platelet count was further increased to a normal level of 346×10^9/L during the 30th week, eltrombopag was discontinued. A female newborn with a low birth weight of 2400 g was delivered. The neonate presented with no bleeding and congenital deformities.

The second case report focused on the use of eltrombopag in a 27-year-old woman who was previously diagnosed with ITP. Her obstetric history included five pregnancies and three abortions. At 26 weeks of gestation, she was admitted because of a relapse of ITP. Her platelet count was 10×10^9/L despite being on 50 and 40 mg of azathioprine and prednisolone, respectively. Because of her poor response to prednisolone and azathioprine, the patient received platelet transfusions. After failing several treatment options, the patient was started on eltrombopag 25 mg daily and at 29 weeks of gestation. One week later, eltrombopag dose was titrated to 50 mg/day. Her platelet count increased to 30×10^9/L. Her levels were maintained at 30×10^9/L throughout the remainder of her pregnancy. She had preterm labor at 36 weeks of gestation and gave birth to a male newborn with low birth weight (1860 g) and platelet count (145×10^9/L). At discharge, the newborn's platelet count was 249×10^9/L. Her platelet count after delivery was 55×10^9/L, which led to the discontinuation of eltrombopag. At 6 weeks postpartum, the mother's platelet count stabilized at 70×10^9/L.

3.2.2. Romiplostim

A case of a 34-year-old female diagnosed with immune thrombocytopenia at 17 weeks of gestation was reported. Her platelet count upon admission was 20×10^9/L. She was started on prednisone 1 mg/kg/day, which was discontinued because of lack of improvement in platelet counts (10×10^9/L) after 3 weeks of administration. IVIG, which was given at a dose of 1 g/kg/day, showed comparable results to prednisone on platelet count. Clinical and laboratory findings were indicative of poor prognosis; the patient's platelet count dropped significantly to 4×10^9/L with signs and symptoms of gingival bleeding and headache. As the patient was refractory to initial therapy with prednisone and IVIG, romiplostim was initiated at 4 μg/kg/week. Her platelet count significantly improved to 110×10^9/L 5 days after administration. Treatment with romiplostim was continued throughout pregnancy with a maintenance dose of 3 μg/kg/week. At 39 weeks of gestation, she gave birth to 3480 g female newborn with no evidence of malformation.

3.3. Thrombopoietin receptor agonists use during the third trimester of pregnancy

3.3.1. Eltrombopag

The reported case involved a 41-year-old female with an inherited form of thrombocytopenia mediated by a mutation in the *MYH9* gene denoted as p.Met1934TrpfsX14. The patient's obstetric history included complicated labor because of uterine atony that resulted in severe postpartum hemorrhage with subsequent hemoglobin (Hgb) level of 6.5 g/dL. Her platelet count through her first pregnancy was 26×10^9/L. During her second pregnancy, eltrombopag was initiated after 36 weeks of gestation at 50 mg/day. The patient was considered eligible because of her previous complicated delivery and platelet count of 26×10^9/L obtained prior to labor. The safety of eltrombopag was evaluated by assessing thrombopoietin levels as well as any evident physical finding. In terms of efficacy, 19 days after the administration of eltrombopag, the patient's platelet count peaked at 179×10^9/L compared to her platelet level of 30×10^9/L prior to eltrombopag administration, whereas the safety profile during treatment remained insignificant. Eltrombopag was discontinued on Day 24 as a result of premature labor that required a cesarean section. The patient successfully gave birth without requiring transfusion; however, her Hgb level was 10.2 g/dL postpartum. The newborn weighed 3145 g with no congenital deformity. The baby inherited the *MYH9* genetic mutation and had a platelet count of 62×10^9/L.

Another report described a case of a 24-year-old female with ITP, for which she was diagnosed during her first pregnancy. Her platelet count was 9×10^9/L. She is gravida 3, para 2 + 0. She was

initiated on IVIG and dexamethasone. After a suboptimal response to IVIG and corticotherapy, she was given eltrombopag during her last trimester for which her platelet count has stabilized. During her third pregnancy, the patient was admitted for preterm labor. She had a relapse episode of ITP with platelet count 41 $\times$ 10^9/L and Hgb 10.2 g/dL. She was given 50 mg/day of eltrombopag, 40 mg of dexamethasone, and transfusion during the third trimester. She gave birth to a newborn with severe thrombocytopenia. Six weeks postpartum, she experienced vaginal bleeding. She received IVIG for 2 days, dexamethasone for 14 days, and rituximab. Eltrombopag dose was titrated to 75 mg/day.

3.3.2. Romiplostim

A 34-year-old female with a platelet count of 55×10^9/L and clinical findings of epistaxis and bruising at 8 weeks of gestation was diagnosed with ITP 2 years ago. At 12 weeks' gestation, her platelet count was 36×10^9/L; she was therefore initiated on prednisone (1 mg/kg/day). Four weeks after the administration of prednisone, the patient's platelet count remained at 36×10^9/L. IVIG (1 g/kg) was administered, resulting in an increase in platelet count of 50×10^9/L. At 28 weeks of gestation, romiplostim was given at 4 μg/kg/week because of the decreased platelet count (26×10^9/L) after 3 months of IVIG administration. On Day 15 after initiation with romiplostim, her platelet count increased to 100×10^9/L. Her platelet count was maintained between 50 and 100×10^9/L with romiplostim maintenance dose of 3 μg/kg/week. At 38 weeks of gestation, she gave birth to a 2640 g female newborn without any congenital malformation. The newborn's platelet count was 90×10^9/L but returned to normal levels 5 days after delivery.

An additional report described a case of a 34-year-old female who is gravida 6 para 5. She was admitted because of petechiae, hematuria, epistaxis, and gingival bleeding. Her platelet count was 3×10^9/L, which confirmed a diagnosis of ITP. She was given IVIG 2 g/kg with 20 mg of IV dexamethasone. After treatment with IVIG and dexamethasone, the patient's platelet count remained between 2 and 5×10^9/L. Further treatment options were given because of platelet count instability that included: rituximab 375 mg/m^2/week, pulsed 500 mg cyclophosphamide, and 50 mg of eltrombopag with dose titration of 75 mg/day. Because the patient was near term, romiplostim 3 μg/kg/week was given to accelerate platelet response prior to labor. Six days after the administration of romiplostim, her platelet count was 65×10^9/L, which further increased to 91×10^9/L a week later. Owing to fluctuations in platelet response, induction of labor was implemented at 34 weeks of gestation. During labor, her platelet count was 52×10^9/L. She gave birth to a healthy female newborn with normal platelet level.

Another 34-year-old female was admitted at 29 weeks of gestation (twin pregnancy) because of hematuria, petechiae, mucosal blisters, and a platelet count of 1×10^9/L, which confirmed the diagnosis of ITP. She was given 1 mg/kg prednisolone and 0.4 g/kg IVIG for 5 days. Her platelet count increased to 12×10^9/L. Her platelet count reached 7×10^9/L 10 days after discharge. Her platelet count further declined to 1×10^9/L and IVIG was administered. Anti-D immunoglobulin 250 IU/kg was given; however, her platelet count decreased to 3×10^9/L. Owing to the lack of response to anti-D, azathioprine was given at 50 mg/day and was titrated to 100 mg/day. At 32 weeks of gestation, optimizing the platelet count became necessary because the patient was reaching term. Romiplostim (2 μg/kg) as a single dose was given. No further doses of romiplostim were administered. The patient's condition did not improve, leading to seven plasma exchanges. Further doses of 1 g/kg of IVIG were administered. Her platelet count then rose to 37×10^9/L. During labor, her platelet count was 79×10^9/L. She gave birth to twins with a platelet count of 20×10^9/L who were both treated with 0.4 g/kg IVIG for 5 days.

3.4. Prospective studies

A prospective cohort study assessed the safety and efficacy of both romiplostim and eltrombopag in 15 pregnant women with chronic ITP who had 17 pregnancies (with one twin pregnancy) and 18 neonates. Eight pregnant women received eltrombopag with doses of 25–100 mg/day. Eltrombopag was initiated during the first trimester and continued for 9–12 weeks in three pregnancies, whereas five pregnant women received eltrombopag during the third trimester and continued till delivery. Pregnant women on eltrombopag had received two to seven treatment-lines prior to eltrombopag administration, including splenectomy in three women. Prior to eltrombopag initiation, the platelet count was $2–15 \times 10^9$/L; however, the platelet count at the time of delivery was $23–169 \times 10^9$/L. Four neonates whose mothers were on eltrombopag developed neonatal thrombocytopenia ($6–34 \times 10^9$/L) and two had different events: neonatal thrombocytosis (555×10^9/L) and intracranial hemorrhage.

Moreover, seven women received romiplostim during pregnancy with doses of 3–10 μg/kg.

Romiplostim was initiated during the third trimester for all pregnancies (31–39 weeks) and continued for 1–6 weeks. Pregnant women had received two to seven treatment-lines prior to romiplostim administration including splenectomy in three women. The platelet count prior to romiplostim administration was $1–20 \times 10^9$/L, by contrast, the platelet count during delivery was $6–250 \times 10^9$/L. Two neonates developed neonatal thrombocytopenia (4×10^9/L and 20×10^9/L) whereas one neonate had pulmonary artery stenosis. One neonate had trisomy 8 and died on Day 7 after delivery.

4. Discussion

Our review highlights the use of TPO-RAs in pregnant women to further identify their safety profile. The use of TPO-RAs in pregnancy has been deemed challenging because of the lack of information pertaining to their utilization. The case reports and cohort study present the administration of eltrombopag and romiplostim during pregnancy while considering the risks and benefits. All case reports have mentioned the use of eltrombopag and romiplostim in patients who were refractory to first-line treatment options such as IVIG, corticotherapy, azathioprine, cyclophosphamide, rituximab, and transfusion.

Animal studies pertaining to the use of TPO-RAs in pregnancy were reported. Regarding eltrombopag, doses of 10, 20, and 60 mg/kg/day were administered to female rats during the embryonic stage. At higher doses, low fetal birth weight was observed in addition to implantation loss. High dose eltrombopag in rats resulted in 6–7% decrease in fetal weight. In an embryo developmental study on rabbits, serum plasma levels of eltrombopag was detected in the fetus after administering 30, 80, and 150 mg/kg/day. The doses administered did not lead to fetotoxicity or teratogenicity. Several animal studies pertaining to romiplostim were reported. Romiplostim was found to cross the placenta in pups, which led to loss of implantation, thrombocytosis, and mortality. Moreover, doses that were 11 and 82 times higher were administered to female rats and rabbits, respectively. This increase in the recommended dose administered in humans has not caused any fetal harm [9,12].

According to the FDA, counseling pregnant women regarding the potential harmful effects of eltrombopag during pregnancy is essential. The FDA recommends appropriate contraception (by utilizing contraceptive methods that would result in < 1% pregnancy rates) with the use of eltrombopag during pregnancy and for 7 days after the last dose. Regarding romiplostim, the FDA urges pregnant women to apply to the pregnancy registry. The administration of eltrombopag or romiplostim in pregnant women should only be implemented if the benefits outweigh the risks as stated by the FDA [9,12]. A common approach mentioned in the case reports was the utilization of several treatment options such as glucocorticoid therapy (prednisolone, prednisone, or dexamethasone), azathioprine, IVIG, rituximab, cyclophosphamide, anti-D, and platelet transfusion prior to initiating a TPO-RA. The case reports highlighted the use of eltrombopag and romiplostim as a last line of therapy after obtaining consent from patients.

The approved dosage of romiplostim starts at 1 μg/kg/week, with titration of up to 10 μg/kg/week depending on platelet levels. The approved eltrombopag dosage starts at 50 mg/day, with titration down to 25 mg/kg or up to 75 mg/kg based on platelet response [9]. In the case reports, during the first trimester, romiplostim dosage was 3 μg/kg/week, whereas that of eltrombopag was 12.5 mg/day. During the second trimester, the doses of eltrombopag administered ranged between 25 and 50 mg/day, whereas romiplostim was administered at 4 μg/kg/week. During the third trimester, eltrombopag dosage ranged between 50 and 75 mg/day and that of romiplostim ranged from 2 to 4 μg/kg/week.

According to the reported cases and prospective study, use of eltrombopag and romiplostim appears to be relatively safe in the first trimester, as there were no reported congenital malformations. However, in one case report, the newborn's weight was 1670 g with the administration of eltrombopag, which is considered low [22]. Both case reports demonstrated insignificant outcomes in terms of maternal health. Moreover, use of eltrombopag during the second trimester resulted in abnormal fetal weight. In both case reports pertaining to eltrombopag, the fetal weight was 2400 and 1860 g. As for romiplostim, the fetal weight was 3480, which is considered above the normal fetal weight of 2500 g [22]. In addition, the administration of eltrombopag and romiplostim during the second trimester did not result in congenital malformations. The administration of eltrombopag and romiplostim during the third trimester has been demonstrated through the prospective study and several case reports. In both case reports pertaining to eltrombopag, both pregnancies have been preterm and the fetal birth weight was not affected. Meanwhile, romiplostim administration during the third trimester did not show significant fetal/maternal outcomes.

Our review has several limitations. Data regarding the use of eltrombopag and romiplostim in

pregnancy are limited. There were no clinical trials demonstrating the safety of both medications in pregnancy, which led to the retrieval of case reports and a prospective study for the review. Moreover, certain case reports did not mention the outcome on maternal and fetal health.

5. Conclusion

The administration of eltrombopag and romiplostim during all trimesters of pregnancy seems relatively safe. However, there seems to be an association between the administration of eltrombopag during the first/second trimester and low fetal birth weight. This finding may seem confounded by the administration of other drug classes such as rituximab, IVIG, azathioprine, or corticotherapy. Further studies showcasing the safety of eltrombopag and romiplostim during pregnancy are necessary to classify TPO-RAs as either safe or harmful during pregnancy.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] Khan AM, Mydra H, Nevarez A. Clinical practice updates in the management of immune thrombocytopenia. P T 2017;42:756–63.
[2] Abadi U, Yarchovsky-Dolberg O, Ellis MH. Immune thrombocytopenia: recent progress in pathophysiology and treatment. Clin Appl Thromb Hemost 2015;21:397–404.
[3] Godeau B. Immune thrombocytopenic purpura: major progress in knowledge of the pathophysiology and the therapeutic strategy, but still a lot of issues. Presse Med 2014;43:e47–8.
[4] Nugent D, McMillan R, Nichol JL, Slichter SJ. Pathogenesis of chronic immune thrombocytopenia: increased platelet destruction and/or decreased platelet production. Br J Haematol 2009;146:585–96.
[5] Raj AB. Immune thrombocytopenia: pathogenesis and treatment approaches. J Hematol Transfus 2017;5:1056–65.
[6] Lambert MP, Gernsheimer TB. Clinical updates in adult immune thrombocytopenia. Blood 2017;129:2829–35.
[7] Cooper KL, Fitzgerald P, Dillingham K, Helme K, Akehurst R. Romiplostim and eltrombopag for immune thrombocytopenia: methods for indirect comparison. Int J Technol Assess Health Care 2012;28:249–58.
[8] Neunert C, Terrell DR, Arnold DM, Buchanan G, Cines DB, Cooper N, et al. American Society of Hematology 2019 guidelines for immune thrombocytopenia. Blood Adv 2019;3:3829–66.
[9] Novartis. Promacta (eltrombopag) [package insert]. U.S Food and Drug Administration. http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/022291s006lbl.pdf. [accessed 22 June 2019].
[10] Dova Pharmaceuticals. Doptelet (avatrombopag) [package insert]. U.S Food and Drug Administration. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210238s000lbl.pdf. [accessed 19 December 2020].
[11] Shionogi & Company. Mulpleta (lusutrombopag) [package insert]. U.S Food and Drug Administration. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210923s000lbl.pdf. [accessed 19 December 2020].
[12] Amgan. Nplate (romiplostim) [package insert]. U.S Food and Drug Administration. https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/125268s077lbl.pdf. [accessed 22 June 2019].
[13] Kaushansky K. The molecular mechanisms that control thrombopoiesis. J Clin Invest 2005;115:3339–47.
[14] Imbach P, Crowther M. Thrombopoietin-receptor agonists for primary immune thrombocytopenia. N Engl J Med 2011;365:734–41.
[15] Peck-Radosavljevic M, Simon K, Iacobellis A, Hassanein T, Kayali Z, Tran A, et al. Lusutrombopag for the treatment of thrombocytopenia in patients with chronic liver disease undergoing invasive procedures (L-PLUS 2). Hepatology 2019;70:1336–48.
[16] Li C, Li X, Huang F, Yang J, Wu A, Wang L, et al. Efficacy and safety of avatrombopag in patients with thrombocytopenia: a systematic review and meta-analysis of randomized controlled trials. Front Pharmacol 2019;10:829.
[17] Shirasugi Y, Ando K, Miyazaki K, Tomiyama Y, Okamoto S, Kurokawa M, et al. Romiplostim for the treatment of chronic immune thrombocytopenia in adult Japanese patients: a double-blind, randomized Phase III clinical trial. Int J Hematol 2011;94:71–80.
[18] Frey N, Jang JH, Szer J, Illes A, Kim HJ, Ram R, et al. Eltrombopag treatment during induction chemotherapy for acute myeloid leukaemia: a randomised, double-blind, phase 2 study. Lancet Haematol 2019;6:e122–31.
[19] Bussel JB, de Miguel PG, Despotovic JM, Grainger JD, Sevilla J, Blanchette VS, et al. Eltrombopag for the treatment of children with persistent and chronic immune thrombocytopenia (PETIT): a randomised, multicentre, placebo-controlled study [published correction appears in Lancet Haematol 2015;2:e407]. Lancet Haematol 2015;2:e315–25.
[20] Siegal D, Crowther M, Cuker A. Thrombopoietin receptor agonists in primary immune thrombocytopenia. Semin Hematol 2013;50:S18–21.
[21] Saleh MN, Bussel JB, Cheng G, Meyer O, Bailey CK, Arning M, et al. Safety and efficacy of eltrombopag for treatment of chronic immune thrombocytopenia: results of the long-term, open-label EXTEND study. Blood 2013;121:537–45.
[22] Cutland CL, Lackritz EM, Mallett-Moore T, Bardaji A, Chandrasekaran R, Lahariya C, et al. Low birth weight: case definition & guidelines for data collection, analysis, and presentation of maternal immunization safety data. Vaccine 2017;35:6492–500.