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Case Report

Use of romiplostim for refractory primary immune thrombocytopenia during pregnancy

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Abstract

Background: Data on the safety and efficacy of thrombopoietin receptor agonists (TRAs) in pregnancy are very limited, although few alternatives exist for patients who are refractory to/ intolerant of corticosteroids and IVIG.

Cases: We report two patients with refractory immune thrombocytopenia (ITP) who received romiplostim during pregnancy. Romiplostim provided effective treatment throughout pregnancy in both cases, although one mother did experience worsened thrombocytopenia requiring additional therapy at week 35, in the setting of preeclampsia. In both cases romiplostim was well tolerated and neither mother nor infant experienced known related adverse effects of romiplostim.

Conclusion: Our cases, in addition to the three previously published, further support the hypothesis that romiplostim can be administered safely in pregnancy. Further investigation is urgently needed.

Introduction

The discovery of thrombopoietin receptor agonists (TRAs) such as romiplostim and eltrombopag has revolutionized management of immune thrombocytopenia (ITP). These agents tend to be well tolerated with fewer side effects than steroids and other immunosuppressive agents and are practical for long term use. While pregnancy in particular presents a challenge in management of ITP, with many common ITP therapies contraindicated during part or all of gestation, the safety of TRAs remains unknown. Three case reports have been published describing use of romiplostim in patients with a history of refractory ITP requiring romiplostim use at baseline [1] or ITP becoming refractory during pregnancy requiring addition of romiplostim [2,3]. Here we describe two patients who received romiplostim during pregnancy without severe complications to the mother or the fetus.

Materials and methods

To evaluate our management regarding this case we conducted a pubmed search using the terms “thrombocytopenia” “romiplostim” and “pregnancy.”

Cases/Results

Case 1

A 32-year-old woman with chronic mixed connective tissue/ lupus –associated ITP became pregnant while receiving romiplostim. She had been diagnosed with ITP at 27 years of age. Initial therapies for her ITP included IVIG and steroids, which produced a temporary response, rituximab which provided a good response for nearly one year but induced an anaphylactic reaction and therefore could not be readministered, and splenectomy which produced no increase in her platelet count. Two years after initiation of romiplostim therapy she became pregnant for the first time. This was noted to be a tubal pregnancy and she was treated with methotrexate to terminate the pregnancy. Six weeks later she suffered a thromboembolic stroke and was started on anticoagulation with warfarin. Romiplostim, along with low dose prednisone for management of her rheumatologic disease, was continued for two years without event until she became pregnant again. As her best response to date had been with romiplostim and her platelet count could not be maintained in a safe range on alternate treatments, romiplostim was continued at a dose of approximately 2 mcg/kg throughout the pregnancy with good response.

She was diagnosed with preeclampsia at approximately 35 weeks of gestation, at which time she was found to be was severely thrombocytopenic with a platelet count of 5×10^9/L. The patient was treated with IVIG and prednisone (40 mg daily) and romiplostim increased to 4 mcg/kg. She delivered a healthy baby boy vaginally at 35 weeks and 5 days gestation with epidural anesthesia, with a platelet count of 369×10^9/L. She reported heavy bleeding with passage of clots for approximately 1.5 weeks post-partum, but did not require transfusions and had no other complications. Her platelet count increased to 800×10^9/L on post-delivery day four. Her romiplostim dose was subsequently adjusted toward a goal platelet count of 100 ×

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10^9/L. She continues on warfarin and romiplostim at this time with a platelet count in the 100 to 200 × 10^9/L range.

The infant had no evidence of bleeding and a normal platelet count of 255 × 10^9/L at birth. Repeat platelet count in the week following birth remained normal (nadir 174 × 10^9/L) and no clinical evidence of thrombocytopenia was noted. He did require hospitalization for phototherapy due to hyperbilirubinemia for approximately five days following delivery but recovered without significant complications. Additionally, he experienced moderate hypoglycemia in the first few days of life (nadir blood glucose of 40 mg/dL), but this quickly resolved and did not recur. The patient did not breastfeed. Her son is currently two and a half years old and is healthy and developmentally normal.

Case 2

A 26-year-old female presented in her 10th week of her first pregnancy due to abdominal pain. She was found to have a urinary tract infection and a platelet count of 17 × 10^9/L. She was treated with antibiotics, prednisone and IVIG. After receiving her third dose of IVIG, she experienced headache and unilateral hemiparesis. Urgent head CT did not show hemorrhage or ischemia. ADAMTS13 activity was normal. Her neurologic symptoms spontaneously resolved within 12 hours. She received several courses of Dexamethasone 40 mg daily for 4 days with only partial responses. Due to the persistence of platelet counts <50 × 10^9/L, she was treated with a course of rituximab between 30-32 weeks. On the day of her third dose of rituximab, her platelet count was <5 × 10^9/L and she had petechiae covering her legs. She finished a course of dexamethasone two days prior to admission. She was transferred to the Medical College of Wisconsin for further management. Because of the recent steroid course, neurologic reaction to IVIG, lack of response to rituximab, and severe thrombocytopenia, she was treated with romiplostim 1 mcg/kg. She experienced pharyngitis, fevers, and severe bone and joint pain. EBV and CMV PCR testing was negative, and her symptoms resolved within 5 days consistent with viral infection. Her platelet count increased to 131 × 10^9/L. Romiplostim was held to determine if her response was secondary to romiplostim or rituximab and her platelet count declined to 48 × 10^9/L. She was treated with an additional dose of romiplostim at 34 and 35 weeks. She did not have recurrence of pharyngitis, fever, or body pain. She underwent induction of delivery at 37 weeks with a pudendal block. Her platelet count remained between 62-92 × 10^9/L. She experienced uterine atony treated with oxytocin and methergine. Estimated blood loss at delivery was 300 milliliters and she did not experience any other bleeding or thrombotic events.

The infant had no bleeding or thrombotic complications. His platelet count at birth was 132 × 10^9/L and increased to 182 × 10^9/L the next day. He experienced a transient hypoglycemia after birth with nadir at 25 mg/dL, but this did not recur. Her son is currently 6 weeks of age and has been growing normally.

Discussion

These patients' cases are similar to those previously reported in the literature [1-3]. In our first case, response to therapy in the nonpregnant state persisted throughout most of her pregnancy. Her dramatic decline in platelet count at 35 weeks likely represents some degree of therapy failure, but also may have been multifactorial given the simultaneous diagnosis of preeclampsia necessitating delivery. While a temporary thrombocytosis may be seen between one to two weeks postpartum in women with preeclampsia (mean platelet count 621 × 10^9/L) [4], the robust degree (800 × 10^9/L) and timing (in the immediate postpartum period) of our patient's thrombocytosis suggests efficacy of the increased romiplostim dose and a possible synergistic effect in combination with IVIG. Additional factors include post-delivery recovery as mentioned above and corticosteroid effect.

The decrease in our patient's platelet count in late pregnancy is not uncommon in pregnancies complicated by ITP and our case suggests that pregnant patients who can only be managed with romiplostim may require dose increases as pregnancy progresses and will benefit from close monitoring.

While an infant's platelet count is often disparate from that of the mother in the case of pregnancy complicated by ITP, preeclampsia is a known risk factor for thrombocytopenia in newborns. However, similar to other reported cases, our patient's infants appeared to tolerate romiplostim use in the mother. They suffered no known related adverse effects and did not experience thrombocytopenia or thrombocytosis. Both infants experienced hypoglycemia which has not been noted in previous reports of romiplostim exposure during pregnancy, but occurs in over 50% of at risk neonates [5]. Infants exposed to romiplostim should be monitored for hypoglycemia, but an association cannot be confirmed due to the limited number of cases that have been reported.

While use of romiplostim in pregnancy cannot be routinely recommended due to a lack of studies in humans and adverse events noted in animal studies [6], ur cases, in addition to those previously published, provide additional data to inform providers in the care of those patients for whom romiplostim may be the only effective ITP therapy during pregnancy.

Authorship and contributions

The corresponding author, B.T.S., had full access to the data and takes full responsibility for the integrity of the data and the accuracy of the data analysis. T.G and L.B.K. contributed substantially to the study design, data analysis and interpretation, and the writing of the manuscript.

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Competing interests

Dr Terry Gernsheimer reports the following conflicts of interest: Amgen – Consultancy and honoraria. Drs Baumann Kreuziger and Samuelson have no conflicts of interest to disclose.

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