

CASE REPORT

Eltrombopag in long-term management of pediatric thrombocytopenia

Sanjay J. Shah  | Michael M. Ettl Jr

Phoenix Children's Hospital, Phoenix, Arizona

CorrespondenceSanjay J. Shah, Phoenix Children's Hospital, Phoenix, AZ.
Email: sshah2@phoenixchildrens.com**Funding information**

Editorial support for the preparation of this manuscript was provided by ClinicalThinking, Inc, Hamilton, NJ, USA and was funded by Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA. Novartis did not influence the content of the manuscript, nor did the authors receive financial compensation for their contribution in writing the manuscript.

Key Clinical Message

Eltrombopag is a thrombopoietin receptor agonist that may be effective in a broad range of thrombocytopenias of distinct etiology. We have observed rapid, robust, and sustained responses to eltrombopag in two young patients with refractory thrombocytopenia, one with primary immune thrombocytopenia and the other with Evans syndrome.

KEYWORDS

acute medicine, critical care medicine, emergency medicine, hematology, pediatrics and adolescent medicine

1 | INTRODUCTION

Thrombocytopenia, the primary manifestation of immune thrombocytopenia (ITP), increases the risk of uncontrolled bleeding with injury and rare spontaneous bleeding events that may be fatal if they occur in vital organs.^{1,2} Platelet count is an important factor determining the risk of bleeding and need for therapy in patients with thrombocytopenia. In adults, treatment is critical to manage the risk of bleeding when the platelet counts are $<30 \times 10^9/L$, and the goal of treatment is usually to maintain platelet levels in the range of $30 \times 10^9/L$ to $50 \times 10^9/L$, rather than $>150 \times 10^9/L$, which is the lower end of the normal range.^{1,2} In children, clinically significant bleeding symptoms are less frequent, and severe spontaneous bleeding events are usually not observed when the platelets counts are $>10 \times 10^9/L$.³ Thus, in contrast to the guidelines for the adult disease, treatment guidelines for pediatric ITP do not have clear-cut platelet count thresholds for treatment decisions and require consideration of psychosocial and quality-of-life factors.^{2,3} Indeed, withholding treatment based solely on platelet counts may have a negative impact on the lives of certain children, particularly the ones who

participate in sports and have active lifestyles, rendering them more prone to play- or sports-related injury.^{4,5}

Intravenous immunoglobulin (IVIg) is an expensive treatment that is commonly used due to its efficacy in rapidly increasing platelet counts. Steroid therapy is another common treatment choice because it is a relatively low-cost option with reasonable efficacy and is very well known to physicians due to its use in numerous immune-mediated diseases. However, IVIg and steroid therapy usually do not yield durable responses and are associated with potential serious adverse events.^{6,7} Eltrombopag is a thrombopoietin receptor agonist that may promote thrombopoiesis and proliferation of hematopoietic stem cells in the bone marrow.^{10,11} It is indicated in patients with chronic ITP and in adult patients with severe aplastic anemia, in whom it may help restore bone marrow cellularity and improve multilineage responses.^{10,11,13} In addition, eltrombopag has shown activity in a broad range of primary and secondary thrombocytopenias; studies in transplant, chemotherapy, hepatitis C virus-associated thrombocytopenia, and certain hereditary thrombocytopenias have provided preliminary evidence for the efficacy of eltrombopag in these conditions.^{14,15}

About a decade after its initial approval for adult chronic ITP, eltrombopag is now also approved for the treatment of pediatric patients with chronic ITP. We report our experience treating two children with refractory ITP who had not benefited from conventional therapy. Both patients tolerated the treatment well and rapidly achieved a robust response to eltrombopag, which was maintained at the time of the preparation of this publication. We will also share our experience with potential practical issues regarding proper administration and patient adherence.

2 | CASE 1

2.1 | Case history/examination

In April 2014, a 5-year-old girl was brought to our clinic with complaints of bruising over 3-4 weeks, small red dots on her face for 3-4 days, and an episode of epistaxis 2 weeks before presentation. She also complained of nasal congestion and cough for 3-4 days.

The initial physical examination revealed scattered ecchymosis over the upper and lower extremities, with larger ecchymosis over her lower back, anterior hips, and right shin; 1-2 mm nonblanching petechiae scattered over her face and coalescing over her chin were noted. Her spleen, liver, and lymph nodes

appeared normal. Laboratory results showed that the patient had a normal white blood cell count at diagnosis (6900/ μ L; range, 4000-12 000/ μ L), with normal differential, severe thrombocytopenia (platelets, 14×10^9 /L), mild anemia (hemoglobin, 10.7 g/dL), and normal reticulocyte count (1.6%; range, 0.5%-2%).

2.2 | Differential diagnosis, investigations, and treatment

There was no evidence of leukemia, aplastic anemia, or any other hematologic disorder that may lead to thrombocytopenia. A potential diagnosis of autoimmune hemolytic anemia was ruled out by a negative direct Coombs test. Serum uric acid level was normal. ITP was diagnosed based on the patient's clinical presentation and the lack of any evidence suggesting an alternative diagnosis.

The patient was treated with IVIg 1 g/kg immediately after diagnosis (April 2014) and received additional doses (a total of 10) as needed over the next 16 months—many times for associated epistaxis. However, the responses were not durable (2-4 weeks), and severe headaches and vomiting were observed with the last several doses, suggestive of aseptic meningitis. In July 2014, Rh₀(D) IVIg (75 μ g/kg) was administered, but the response was insufficient (platelets, 6×10^9 /L to 28×10^9 /L) and lost within 3 weeks.

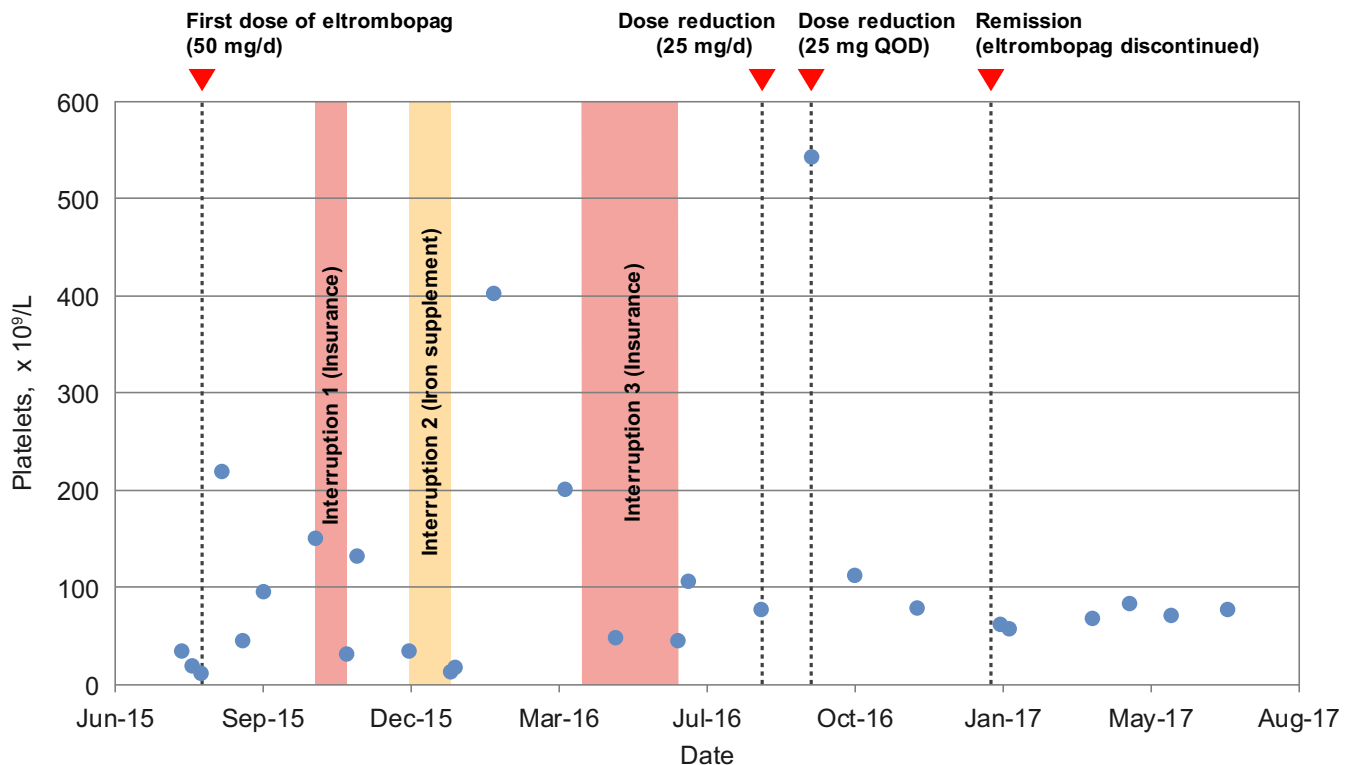


FIGURE 1 Platelet counts of patient 1 after initiation of eltrombopag therapy on 3 August 2015, are shown. The therapy was interrupted twice due to insurance-related problems (periods shown in red) and once due to an administration error (shown in orange). Platelet counts were low at the end of each interruption but recovered quickly after reinitiation of eltrombopag therapy. On 17 January 2017, eltrombopag was successfully discontinued, and the patient has since been in remission with stable platelet counts. QOD, every other day

Following the failure of Ig-based treatments, the patient received corticosteroid therapy with prednisone (2 mg/kg, tapered to 1 mg/kg) between August and November 2014. A platelet count of $193 \times 10^9/L$ was achieved, but there were significant adverse events: weight gain and emotional lability, which led to the discontinuation of the prednisone treatment. Immunosuppressive therapy was resumed for 9 months (January to September 2015) with cyclosporine A (starting dose of 6 mg/kg, titrated to reach 100–300 ng/mL serum concentration). Although cyclosporine A appeared to augment the effects of IVIg, treatment was not sustainable due to nausea, poor appetite, hirsutism, and emotional lability.

During her treatment, the patient received two 4-week courses of rituximab 375 mg/m^2 weekly, beginning in October 2014 and May 2015. The treatment was well tolerated, but no apparent therapeutic benefit was noted.

After failure of immunosuppressive therapies, eltrombopag 50 mg/d was initiated in August 2015 because the patient had a platelet count of $12 \times 10^9/L$. Within 2 weeks, the patient demonstrated a robust response, with her platelet count increasing to $220 \times 10^9/L$ (Figure 1). Because the treatment was well tolerated, the response could be maintained with continued exposure to eltrombopag. There were three periods during which the patient did not receive the correct dose of eltrombopag, and the changes in platelet counts during these periods demonstrated the significant therapeutic effect of eltrombopag.

Insurance-related and financial issues led to two interruptions in eltrombopag treatment between 19 October 2015 and 9 November 2015, and 15 April 2016 and 20 June 2016. During both periods, a substantial decrease in platelet counts was observed ($151 \times 10^9/L$ to $32 \times 10^9/L$ and $201 \times 10^9/L$ to $49 \times 10^9/L$, respectively), but platelet counts recovered 1–2 weeks after eltrombopag treatment was restarted.

The third interruption in effective treatment was a result of not adhering to administration instructions. The patient was prescribed an oral iron supplement after receiving a diagnosis of iron deficiency on the basis of low hemoglobin level (10 g/dL), normal reticulocyte count (0.7%; range, 0.5%–2%), and low ferritin level (6 ng/mL; range, 10–150 ng/mL). Following approximately 1 month of concomitant use of the prescribed iron supplement and eltrombopag, the patient's platelet counts decreased to $14 \times 10^9/L$. The patient was provided written instructions not to coadminister iron supplements and eltrombopag. Upon discussion with the patient's caregiver, it was determined that the timing of the iron supplements was not coordinated properly with eltrombopag administration. The instructions for administration preclude the use of supplements and foods rich in divalent cations (eg, iron, calcium, and magnesium) 2 hours before or 4 hours after eltrombopag dosing.¹⁰ It is plausible that coadministration with the iron supplement interfered with absorption of oral eltrombopag and reduced the effective dose, thereby causing a decrease in platelets. The iron supplement was discontinued upon

improvement of the patient's iron levels, and subsequently, platelet counts started to increase and reached safe levels within 3 weeks.

The initial dose of eltrombopag 50 mg/d was reduced to 25 mg/d after her platelet counts were maintained at $>50 \times 10^9/L$ for nearly 2 months ($107 \times 10^9/L$ and $78 \times 10^9/L$ in June and August 2016, respectively). While she received the 25 mg/d dose, the patient's platelet count increased to $543 \times 10^9/L$, which prompted a dose reduction. In November 2016, the patient had a platelet count of $79 \times 10^9/L$ while receiving eltrombopag 25 mg every other day.

2.3 | Outcome and follow-up

Eltrombopag was stopped on 17 January 2017, and the patient has since maintained a platelet count of $>50 \times 10^9/L$ without any therapy. At her last follow-up on 19 January 2018, her platelet count was $115 \times 10^9/L$, without any bleeding manifestations.

This case not only exemplifies a robust platelet response and durable remission in a pediatric patient with highly refractory chronic ITP but also demonstrates the importance of patient and caregiver education. A failure to understand and follow instructions for administration may decrease treatment efficacy, mimic a state of treatment failure, and put patients at risk of bleeding.

3 | CASE 2

3.1 | Case history/examination

In May 2000, a 2-year-old girl presented with pancytopenia and hepatosplenomegaly. A bone marrow examination showed borderline low megakaryocyte count and a developmental arrest of the erythroid and myeloid series.

3.2 | Differential diagnosis, investigations, and treatment

There was no evidence for malignancy, and bone marrow cytogenetics and immunophenotyping were normal. After a positive direct Coombs test and a platelet response—albeit limited—to IVIg, an autoimmune pancytopenia, Evans syndrome, was diagnosed. With time, the splenomegaly, anemia, and thrombocytopenia resolved, but the neutropenia persisted.

The initial diagnosis of Evans syndrome was reevaluated due to the patient's persistent neutropenia; however, after an extensive workup looking for an underlying collagen vascular disease, autoimmune lymphoproliferative syndrome (ALPS), cyclic neutropenia, and common variable immunodeficiency, Evans syndrome remained the most likely diagnosis. A genetic workup for inherited neutropenia was not available. In 2004, a spontaneous

remission in neutropenia was noted, and the patient was discharged from the clinic with a normal complete blood count.

After resolution of the immune cytopenias, the patient appeared to be in complete remission and was generally healthy, apart from hay fever-type symptoms, which were treated with cetirizine and intranasal fluticasone, and occasional urinary tract infections. In keeping with the natural history of Evans syndrome, a relapse in thrombocytopenia was discovered when the patient presented with the symptoms of sinusitis and a complete blood count showed a platelet count of $41 \times 10^9/L$. Between 2009 and 2014, the patient was mostly thrombocytopenic and also had occasional neutropenia. Starting in February 2014, her platelet counts stabilized at $<50 \times 10^9/L$, and she became severely neutropenic (absolute neutrophil count [ANC], $0.2 \times 10^9/L$). The patient received a variety of regimens but did not have a good response (IVIg) or had severe toxicity (hyperglycemia with steroids and serum sickness with rituximab). After approximately 19 months of persistent or worsening thrombocytopenia and neutropenia, she was treated with eltrombopag in September 2015 and had a remarkably good response: an increase in platelet count from $17 \times 10^9/L$ to $510 \times 10^9/L$ within 2 weeks (Figure 2). Elevated platelet counts were maintained, and the starting dose of 50 mg/d was decreased to 25 mg every other day

within the first year of treatment and to 25 mg every third day in March 2017. The patient's neutropenia also improved during the course of eltrombopag treatment (Figure 2). However, the onset of neutrophil response was approximately 8-9 months after the onset of platelet response.

3.3 | Outcome and follow-up

At the patient's last two visits in May 2017 and December 2017, she had platelet counts of $300 \times 10^9/L$ and $322 \times 10^9/L$ and ANC of $5.0 \times 10^9/L$ and $3.9 \times 10^9/L$, respectively, in contrast to the platelet count of $17 \times 10^9/L$ and ANC of $0.9 \times 10^9/L$ in September 2015, before the start of eltrombopag therapy.

This case exemplifies the potential use of eltrombopag in patients with autoimmune pancytopenia who are not eligible for, or do not respond to, immunosuppressive therapy.

4 | DISCUSSION

We described two children with immune cytopenias who did not benefit from standard treatments but achieved and maintained a robust response with eltrombopag.

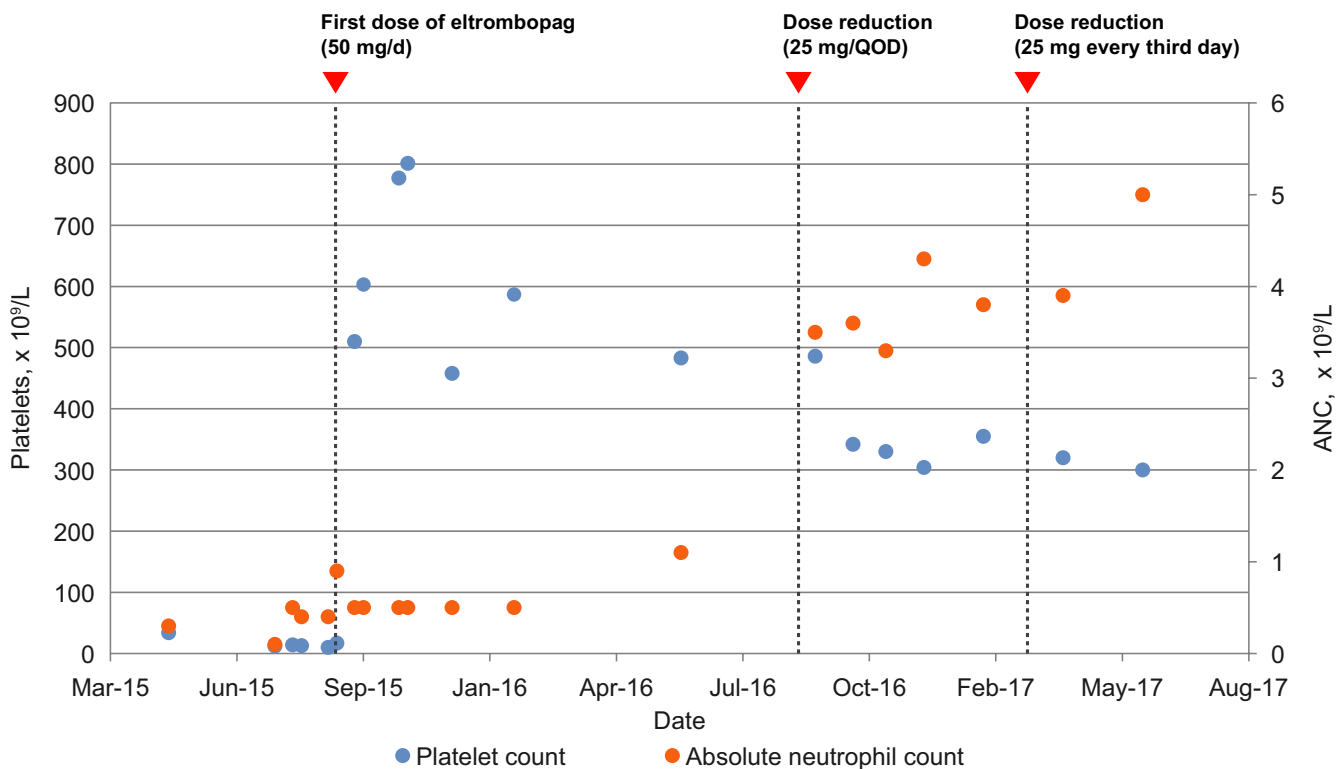


FIGURE 2 Available platelet (blue) and absolute neutrophil (orange) count results for patient 2 after initiation of eltrombopag therapy on 2 September 2015, are shown. Platelet counts rapidly improved after initiation of eltrombopag therapy and were maintained at $>200 \times 10^9/L$ throughout the treatment. Absolute neutrophil counts (ANCs) increased approximately 8-9 mo after the initiation of eltrombopag therapy and continued to improve throughout the therapy. At the patient's last several visits, she had absolute neutrophil and platelet counts in the normal range. QOD, every other day

The first patient had chronic ITP and quickly showed a significant response to eltrombopag treatment, which was maintained after discontinuation of all other ITP therapies, including eltrombopag itself. Eltrombopag has been shown to induce long-term remissions in a proportion of patients with ITP,¹⁶ but we do not know whether the remission in this case was induced by eltrombopag or was spontaneous. Importantly, this case also demonstrated the vital role of patient and caregiver education. The efficacy of eltrombopag may be severely reduced when administered with food or supplements that are rich in divalent cations. If patients are using concomitant supplements that include divalent cations (eg, iron), it is particularly important to not only inform them of the proper administration timing but also confirm that they fully understand these instructions. It should be stressed that eltrombopag and the supplement must be taken at different times during the day (eg, one in the morning and the other at night). Secondly, even if platelet counts had been stable previously, it may be helpful to assess platelet counts again within 2 weeks of supplement initiation to ensure that the platelet count had not been affected by the concomitant supplement. It is important to clarify with patients that supplements and foods rich in divalent cations do not need to be avoided during eltrombopag therapy, but the administration timing instructions must be followed.

Our experience with the second patient suggests that eltrombopag may also have some benefit in patients with multilineage immune cytopenias. The patient was diagnosed with Evans syndrome and had severe thrombocytopenia and neutropenia with borderline megakaryocyte count and a developmental arrest of the erythroid and myeloid series in the bone marrow. Eltrombopag enabled a very rapid and robust platelet response, which was maintained at the time of the preparation of this article. Interestingly, the patient's persistent neutropenia also improved while on eltrombopag. Although the causative factors behind this improvement are not fully clear, published clinical data in patients with bone marrow dysfunction¹³ support the possibility that this may be an effect of eltrombopag; the significant improvement in ANC in this patient was noted approximately 8-9 months after the initiation of eltrombopag treatment, while the platelet response was observed within 2 weeks. In a clinical trial of eltrombopag in patients with severe aplastic anemia, many patients who eventually achieved multilineage responses with eltrombopag had only a single-lineage response at weeks 12 and 16, indicating that such responses may occur many months after the first dose of eltrombopag.¹³

Regular monitoring is an important requirement for patients receiving eltrombopag to enable dose adjustments in case of thrombocytosis or hepatic abnormalities.¹⁰ Indeed, in both patients, we noted periods of thrombocytosis that required a reduction in the eltrombopag dose. However, patient adherence may sometimes be a limiting factor. After living

with low platelet counts that require extensive monitoring due to the risk of bleeding, patients who start taking eltrombopag and are told their risk of bleeding is under control due to their improved platelet counts may feel they do not require any monitoring. It is vital to remind patients and caregivers of the importance of continued monitoring to avoid thrombocytosis, limit toxicity and maximize adherence to dosing guidelines.

These case reports exemplify the potential benefits of eltrombopag in children with thrombocytopenia who have had experienced a poor response or poor tolerability with immunosuppressive therapy. Increasing platelet count in case 1 allowed normal play activity without restrictions, thus improving her quality of life. Both patients demonstrated a rapid and robust platelet response to eltrombopag and maintained this response at the time of this publication, and both patients tolerated the treatment well. One has been off treatment for a year and is in remission; for the other patient, we were able to reduce the dose to 25 mg once every 3 days. We find the outcomes of these cases consistent with previous clinical data¹⁴ and our overall experience with eltrombopag, and thus believe eltrombopag may be a viable option for the long-term management of thrombocytopenia in children and young adults. The use of eltrombopag in acute, severe, and refractory nonimmune thrombocytopenia associated with bleeding complications should also be explored in future clinical trials.

CONFLICT OF INTEREST

The authors have no conflict of interests to declare.

AUTHOR CONTRIBUTIONS

All listed authors meet the criteria for authorship set forth by the International Committee of Medical Journal Editors. SJS: was involved with the management of patient 1; MME: was involved with the management of patient 2. SJS and MME: were involved with manuscript concept, preparation, editing, and review, data acquisition, and quality control of data.

ORCID

Sanjay J. Shah  <http://orcid.org/0000-0001-7762-598X>

REFERENCES

1. Abrams C. Thrombocytopenia. In: Goldman L, Schafer A, eds. *Goldman-cecil medicine*. Philadelphia: Saunders Elsevier; 2011:1124-1131.
2. Neunert C, Lim W, Crowther M, et al. The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. *Blood*. 2011;117:4190-4207.

3. Provan D, Stasi R, Newland AC, et al. International consensus report on the investigation and management of primary immune thrombocytopenia. *Blood*. 2010;115:168-186.
4. Kumar M, Lambert MP, Breakey V, et al. Sports participation in children and adolescents with immune thrombocytopenia (ITP). *Pediatr Blood Cancer*. 2015;62:2223-2225.
5. Heitink-Pollé KM, Haverman L, Annink KV, Schep SJ, de Haas M, Bruin MC. Health-related quality of life in children with newly diagnosed immune thrombocytopenia. *Haematologica*. 2014;99:1525-1531.
6. Arnold DM. Positioning new treatments in the management of immune thrombocytopenia. *Pediatr Blood Cancer*. 2013;60(suppl 1):S19-S22.
7. Harris E, Tiganescu A, Tubeuf S, Mackie SL. The prediction and monitoring of toxicity associated with long-term systemic glucocorticoid therapy. *Curr Rheumatol Rep*. 2015;17:513.
8. Duhem C, Dicato MA, Ries F. Side-effects of intravenous immune globulins. *Clin Exp Immunol*. 1994;97(suppl 1):79-83.
9. O'Brien SH, Ritchey AK, Smith KJ. A cost-utility analysis of treatment for acute childhood idiopathic thrombocytopenic purpura (ITP). *Pediatr Blood Cancer*. 2007;48:173-180.
10. PROMACTA (eltrombopag) [package insert]. East Hanover, NJ. Novartis Pharmaceuticals Corporation;2017.
11. Townsley DM, Scheinberg P, Winkler T, et al. Eltrombopag added to standard immunosuppression for aplastic anemia. *N Engl J Med*. 2017;376:1540-1550.
12. Di Buduo CA, Currao M, Pecci A, Kaplan DL, Balduini CL, Balduini A. Revealing eltrombopag's promotion of human megakaryopoiesis through AKT/ERK-dependent pathway activation. *Haematologica*. 2016;101:1479-1488.
13. Desmond R, Townsley DM, Dumitriu B, et al. Eltrombopag restores trilineage hematopoiesis in refractory severe aplastic anemia that can be sustained on discontinuation of drug. *Blood*. 2014;123:1818-1825.
14. Rodeghiero F, Carli G. Beyond immune thrombocytopenia: the evolving role of thrombopoietin receptor agonists. *Ann Hematol*. 2017;96:1421-1434.
15. González-López TJ, Alvarez-Román MT, Pascual C, et al. Use of eltrombopag for secondary immune thrombocytopenia in clinical practice. *Br J Haematol*. 2017;178:959-970.
16. González-López TJ, Pascual C, Álvarez-Román MT, et al. Successful discontinuation of eltrombopag after complete remission in patients with primary immune thrombocytopenia. *Am J Hematol*. 2015;90:E40-E43.

How to cite this article: Shah SJ, Etzl MM Jr. Eltrombopag in long-term management of pediatric thrombocytopenia. *Clin Case Rep*. 2019;7:196–201. <https://doi.org/10.1002/ccr3.1916>