



Case Report

Short-term dose-escalated romiplostim for preparing an adult patient with persistent newly diagnosed primary immune thrombocytopenia for splenectomy



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Introduction

Treatment of newly diagnosed primary immune thrombocytopenia (ITP) is aimed at obtaining a safe platelet count in order to prevent major bleeding with minimal side effects. Treatment is recommended for patients with a platelet count of $<30,000$ platelets/mm³, associated with bleeding or $<20,000$ platelets.¹

The American Hematology Society (ASH) 2011 guidelines² recommend oral prednisone 1 mg/kg/day for 21 days and subsequently tapered off, rather than dexamethasone 40 mg intravenous/oral for 4 days every two weeks. In case of hemorrhage, intravenous immunoglobulin (IVIG) 1 gm/kg/day for two days is recommended.² Platelet transfusions for life-threatening bleeding have a better response if used after IVIG infusion due to increased platelet survival.² For patients who do not respond to steroids/IVIG, intravenous dexamethasone

alone,¹ or in combination with rituximab, is recommended.³ The combination provides a sustained response rate of 58% at six months and is superior to mono-therapy.⁴ Splenectomy is indicated for patients failing first- and second-line treatment.¹ IVIG plus platelet transfusions may increase the platelet count sufficiently to decrease the risk of hemorrhage and permit surgery.¹ The use of thrombopoietin receptor agonists (TPO-RAs) has been used in chronic ITP to increase the platelet count, permitting the splenectomy. There is little published data on the short-term use of TPO-RAs in patients refractory to the initial treatment for the subsequent splenectomy.

We present the case of a 27-year-old woman with newly diagnosed ITP who had persistent severe thrombocytopenia after treatment with steroids, intravenous immunoglobulin and rituximab; to enable the splenectomy, she was treated with short-term dose-escalated TPO-RA.

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Clinical case

A 27-year-old woman presented with generalized petechiae and epistaxis at the local Emergency Service. Five months earlier, the patient had undergone a cholecystectomy and had a normal platelet count. An abdominal ultrasound did not show splenomegaly and an upper gastrointestinal (GI) endoscopy was reported to be normal and without evidence of *Helicobacter pylori*. There was no family, or personal, history of thrombocytopenia.

Initial blood tests showed a platelet count of $5,000/\text{mm}^3$, the rest of the full blood count was normal. Peripheral blood smear showed thrombocytopenia, with no platelet aggregates and normal platelet size. The liver function tests, TSH, prothrombin time and activated partial thromboplastin time were normal. The tests were negative for human immunodeficiency virus (HIV), hepatitis B and C, antinuclear antibodies, anti-DNA antibodies and endo-nuclear antibodies and the polymerase chain reaction (PCR) tests for cytomegalovirus (CMV) and Epstein-Barr virus (EBV) were negative. A CT scan of the thorax-abdomen and pelvis was normal, with no evidence of splenomegaly or lymphadenopathy.

Primary ITP was diagnosed and the treatment was started with intravenous dexamethasone 40 mg daily. On the third day, the platelet count was $4000/\text{mm}^3$, associated with mild macroscopic hematuria and epistaxis, for which the patient was transfused with six units of platelets and intravenous immunoglobulin at a dose of 1 gm/kg/day for two days. The patient continued with 40 mg daily of intravenous dexamethasone for a total of seven days when the steroids were changed to oral prednisone at the dose of 1.5 mg/kg/day .

Three weeks later the platelet count remained below $10,000/\text{mm}^3$ and the hematuria continued. Weekly rituximab (375 mg/m^2) for four cycles was commenced; five weeks later, the platelet count remained $<20,000/\text{mm}^3$. Due to the lack of response, a bone marrow aspirate was performed, which showed an increased number of megakaryocytes and a very low CD20 lymphocyte count (post-rituximab).

On day 58, the patient was treated with a second cycle of IVIG, transfused with six units of platelets and transferred to our hospital.

The patient was re-assessed on arrival; on further questioning, the patient reported a self-limiting “viral illness” characterized by nausea, vomiting and diarrhea two weeks prior to the petechial rash. The patient was Cushingoid in appearance, with ecchymosis and petechial rash in the lower and upper limbs; both nasal fossa had been packed to treat the epistaxis. The platelet count was $20,000/\text{mm}^3$, the rest of the full blood count was normal and the peripheral blood smear showed some macro-platelets, but no other abnormalities. The presence of macro-platelets was not constant, as in only 3/23 full blood counts analyzed were macro-platelets detected. The therapy on arrival was 120 mg/day of oral prednisone (1.5 mg/kg/day) plus folic acid 5 mg/day . To prevent menstruation, the patient had been treated with an estrogen-containing (levonorgestrel) intrauterine device (IUD).

Prophylaxis with cotrimoxazol was started for the low CD20 count, along with high-dose steroids. The stool test for *Helicobacter pylori* was negative.

In summary, the patient was eight weeks post-diagnosis, without a response to steroids, IVIG or rituximab. Over the next two days, the platelet count decreased to $4000/\text{mm}^3$ and the oral steroids were decreased due to lack of response. The management plan was to proceed to splenectomy after achieving a safe platelet count. To achieve this, romiplostim was started at a dose of $4\text{ }\mu\text{g/kg/week}$ subcutaneously and decreased to a dose of $2\text{ }\mu\text{g/kg/week}$, in order to obtain a platelet count of $>100,000/\text{mm}^3$. Daily platelet counts were taken, at one, two and three weeks after starting romiplostim; the platelet counts were $32,000$, $56,000$ and $112,000/\text{mm}^3$ with a dose of 4, 6 and $8\text{ }\mu\text{g/kg/week}$, respectively. Laparoscopic splenectomy was performed without excessive hemorrhage or adverse effects.

The platelet counts were $320,000/\text{mm}^3$, $636,000/\text{mm}^3$ and $1,320,000/\text{mm}^3$ at 24 h, 5 and ten days post-splenectomy, respectively. Thrombo-prophylaxis with low molecular weight heparin and aspirin 100 mg/day were started at 24 h post-surgery. Over the next three weeks, the platelet count decreased to normal, and steroids were decreased until they were discontinued. Six months later, the patient retains a normal platelet count and has no need for steroids.

Discussion

The sequence of treatment in patients not responding to first-line treatment is not well defined in ITP. Failure to respond to steroids, immunoglobulins and rituximab, as a monotherapy or in combination, and a persistent platelet count of $<5,000/\text{mm}^3$ presents a treatment dilemma. Splenectomy is the treatment of choice for these patients, although an International Consensus recommended deferring splenectomy until the chronic phase of ITP.⁵

In patients with thrombocytopenia, it is necessary to determine whether the low platelet count is a result of hypo-production or hyper-destruction. Hypo-production is seen in the inherited thrombocytopenia, infiltration of the bone marrow, aplastic anemia or post-chemotherapy, while hyper-destruction is seen in ITP, disseminated intra-vascular coagulopathy and thrombotic thrombocytopenic purpura. The presence of macro-platelets and higher mean platelet volume (MPV) and distribution width (PDW), measured by automated blood analyzers, are associated with hyper-destruction. The MPV and PDW vary according to the analyzer used; the Sysmex XN1000® analyzer, used at our hospital does not calculate these parameters with $<10,000/\text{mm}^3$.

The absence of macro-platelets may be explained as follows: in the acute phase of ITP, the hyper-destruction of platelets is greater and, as such, macro-platelets are detected. With treatment, the decrease in hyper-destruction may result in more normal-sized platelets. Autoantibodies in ITP patients also inhibit platelet production by affecting megakaryocyte production and maturation, resulting in normal or suppressed platelet production with normalization of the platelet size.⁶

The use of platelet parameters obtained on automated analyzers in the evaluation of suspected ITP is not recommended.²

In this clinical case, the lack of family history, a previously normal platelet count, normal coagulation tests and later bone marrow aspiration were consistent with ITP.

Romiplostim, a TPO-RA, is started at a dose of 1 $\mu\text{g/kg/week}$, adjusting the dose according to the response, which generally requires between 7–15 days. It is used as long-term maintenance therapy in persistent/chronic ITP, with little reported evidence on its use in the short term to improve the platelet count prior to splenectomy. In 31 adult patients with persistent or chronic ITP treated with TPO-RAs prior to splenectomy, there was a 77% response rate. Median platelet counts increased from 11,000/ mm^3 to 114,000 platelets/ mm^3 , although it was necessary to maintain treatment with steroids and/or intravenous immunoglobulins in 61% of the cases. This permitted splenectomy in 94% of the cases, although the authors reported that an increased risk of thromboembolic events post-splenectomy could not be ruled out.⁷

An escalated dose of romiplostim has been reported in a small case series with eight patients, who failed to respond to steroids and IVIG, and were started at a dose of 3 $\mu\text{g/kg}$ per week, reaching a dose of 6–9 $\mu\text{g/kg/week}$, and achieving >30,000 platelets/ mm^3 within two weeks.⁸ Using a higher initial dose, the time to achieve >30,000 platelets/ mm^3 was shorter and the response rate higher.⁹ Management of refractory ITP remains a challenge and the optimal sequence of treatment is not known, nor is the role of the combination therapy well defined. After failing second-line therapy, the use of a TPO-RA at an escalated dose was proposed. No side effects from the dosage regime were recorded and within three weeks the platelet count was sufficient to proceed to splenectomy.

Reactive post-splenectomy thrombocytosis is reported in approximately 80% of the cases and may reach extreme levels in some 20% of the patients.⁹ The use of TPO-RAs is also reported to be associated with thrombosis due to thrombocytosis.¹⁰ In this report, the platelet count reached 1,300,000 platelets/ mm^3 ten days post-surgery. Thromboprophylaxis was started 24 h after surgery, with a combination of low molecular weight heparin and aspirin 100 mg/day, as has been suggested.⁹

With romiplostim, the platelet count increases in a dose-dependent fashion, however its pharmacokinetics are non-linear and there is significant patient response variation, despite its weight-based dosing.¹⁰ Suspension of the drug 7–10 days prior to splenectomy is suggested to avoid postsurgical thrombocytosis,¹⁰ but the data on the temporal relationship between romiplostim administration and extreme thrombocytosis post-splenectomy (four days in our report) is minimal.

In the post-surgery, no further romiplostim was necessary and steroids were slowly tapered off; six months post-surgery the patient maintained a platelet count of between 200,000/ mm^3 and 250,000/ mm^3 and is off steroid therapy.

Concerning the initial management of the patient, seven days of intravenous dexamethasone and then oral prednisone is not a suggested schedule and it could be argued that mild macroscopic hematuria and epistaxis are not life-threatening events and that platelet transfusions and intravenous immunoglobulin are not indicated. Local treatment of the cause of epistaxis may have been sufficient.

Rituximab, which causes long-term immunosuppression, was used early in this case; the time response for steroids is from 3 to 30 days and thus, the period for an expected response to steroids had not been completed. This emphasizes that an experienced medical team should manage patients with severe thrombocytopenia or that they be transferred early to a medical center with the appropriate specialists.

Conclusions

Short-term escalated dose romiplostim may improve platelet counts sufficiently to perform splenectomy, without an increased risk of bleeding in patients who have failed previous treatments. It is crucial to closely monitor platelet counts post-splenectomy, administer thrombo-prophylaxis and antiplatelet therapy, if necessary. For extreme thrombocytosis, platelet-apheresis may be warranted and thus, hospitalization and close monitoring are essential. Although TPO-RAs are efficacious, they are costly and in the local environment, this may be prohibitive.

Conflict of interest

The authors declare no conflicts of interest.

REFERENCES

1. Ribeiro RA, Neto AS, Furtado AS, Albuquerque LL, Kubrusly MS, Kubrusly ES. Proposal of treatment algorithm for immune thrombocytopenia in adult patients of a hematology service at a referral centre in Northeastern Brazil. *Hematol Transfus Cell Ther.* 2019, <http://dx.doi.org/10.1016/j.htct.2018.10.005>. In press.
2. Nuenert C, Lim W, Crowther M, Cohen A, Solberg L Jr, Crowther MA. The American Society of Hematology 2011 evidence based practice guidelines for immune thrombocytopenia. *Blood.* 2011;117(16):4190–207.
3. Patel VL, Mahevas M, Lee SY, Stasi R, Cunningham-Rundles S, Godeau B, et al. Outcomes 5 years after response to rituximab therapy in children and adults with immune thrombocytopenia. *Blood.* 2012;119(25):5989–95.
4. Wang J, Chong Wang YL, Zhang Y, Gao C, Lang H, Chen X. Efficacy and safety of the combination treatment of rituximab and dexamethasone for adults with primary immune thrombocytopenia (ITP): a meta-analysis. *Biomed Res Int.* 2018, <http://dx.doi.org/10.1155/2018/1316096>.
5. Provan D, Stasi R, Newland AC, Blanchette VS, Bolton-Maggs P, Bussell JB, et al. International consensus report on the investigation and management of primary immune thrombocytopenia. *Blood.* 2010;115:168–86.
6. Negash M, Tsegaye A, Medhin AG. Diagnostic predictive value of platelet indices for discriminating hypo productive versus immune thrombocytopenia purpura in patients attending a tertiary care teaching hospital in Addis Ababa, Ethiopia. *BMC Hematol.* 2016;16:18, <http://dx.doi.org/10.1186/s12878-016-0057-5>.
7. Zaja F, Barcellini W, Cantoni S, Carpenedo M, Caparrotti G, Carrai V, et al. Thrombopoietin receptor agonists for preparing adult patients with immune thrombocytopenia to splenectomy: results of a retrospective, observational GIMEMA study. *Am J Hematol.* 2016;91:E293–5.

8. Contis A, Lazaro E, Greib C, Pellegrin JL, Viillard JF. Romiplostim as early treatment for refractory primary immune thrombocytopenia. *Int J Hematol.* 2013;98:520–4.
9. Zimmerman J, Norsworthy KJ, Brodsky R. Balancing therapy with thrombopoietin receptor agonists and splenectomy in refractory immune thrombocytopenic purpura: a case of postsplenectomy thrombocytosis requiring plateletpheresis. *Case Rep Hematol.* 2016;2016:5403612.
10. Yang BB, Doshi S, Arkam K, Franklin J, Chow AT. Development of romiplostin for treatment of primary immune thrombocytopenia from a pharmacokinetic and pharmacodynamics perspective. *Clin Pharmacokinet.* 2016;55:1045–58.