

Effective treatment of refractory acquired pure red blood cell aplasia with eltrombopag and sirolimus: a case report

Yuzhou Huang, Xianyong Jiang and Bing Han^{ID}

Ther Adv Hematol

2020, Vol. 11: 1–6

DOI: 10.1177/
2040620720940144

© The Author(s), 2020.
Article reuse guidelines:
sagepub.com/journals-
permissions

Abstract: Acquired pure red cell aplasia (aPRCA) is a kind of anemia characterized by severe reticulocytopenia and reduced bone marrow erythroblastic cells. For patients who are refractory to the first-line therapy (cyclosporin A with/without glucocorticoids), second-line therapy is considered less effective. We report on a patient with primary aPRCA who was refractory to cyclosporin A, glucocorticoids, and several second-line regimens. The patient was treated with sirolimus for 10 months with no improvement in hemoglobin but complete response was achieved after adding eltrombopag at a dosage of 25 mg/day. Eltrombopag was well tolerated with no evidence of clonal evolution at the end of follow up. This case provided a new attempt at treating patients with refractory/relapse aPRCA with eltrombopag, probably in combination with sirolimus.

Keywords: acquired pure red cell aplasia, eltrombopag, refractory, sirolimus

Received: 26 March 2020; revised manuscript accepted: 11 June 2020.

Introduction

Acquired pure red blood cell aplasia (aPRCA) can be primary or secondary to other diseases or drugs. Primary aPRCA is mainly caused by immune dysfunction that interrupts erythroid differentiation.^{1,2} The main treatment for aPRCA focuses on immunosuppression. Cyclosporin A (CsA), with or without glucocorticoids (GS), is currently the most effective treatment option.^{1,2} However, for some patients this treatment is ineffective or patients are intolerant to it, and second-line therapies are required, including cyclophosphamide (CTX), methotrexate, antihuman thymocyte immunoglobulin, rituximab, bortezomib, etc.¹

Eltrombopag, an oral thrombopoietic receptor agonist, is firstly approved to treat patients with immune thrombocytopenic purpura.^{3,4} Recently, it has shown a promising effect on refractory severe aplastic anemia (SAA) and SAA not eligible for hematopoietic stem cell transplantation (HSCT).^{4–7} It works not only on megakaryopoiesis, but also on granulocytic hematopoiesis and

erythropoiesis in patients with aplastic anemia. Apart from the hematopoiesis stimulation effect, it can also regulate immune function.⁷ As far as we know, there has been only one report where eltrombopag was effective in treating erythroid aplasia and transfusion dependence after HSCT in two patients who had not benefited from multiple previous treatments.⁸ Here we report a successful case of refractory primary aPRCA treated with eltrombopag after the failure of almost all second-line therapies.

Case presentation

A 45-year-old Chinese man came to our clinic because of hypodynamia in July 2015. His past medical history included reflux esophagitis, and physical examination revealed only anemia. Laboratory examinations indicated a moderate anemia with hemoglobin (Hgb) of 76 g/L and the reticulocyte percentage as 0.23%. The level of ferritin was 468 ng/ml with no other abnormalities indicated for iron, folic acid, and vitamin B12. The liver and renal function tests were within the

Correspondence to:
Bing Han
Department of
Hematology, Peking Union
Medical College Hospital,
Chinese Academy of
Medical Sciences & Peking
Union Medical College,
Shuaifuyuan No. 1,
Dongcheng District,
Beijing 100730, China
Hanbing_li@sina.com.cn
Yuzhou Huang
Xianyong Jiang
Department of
Hematology, Peking Union
Medical College Hospital,
Chinese Academy of
Medical Sciences & Peking
Union Medical College,
Beijing, China

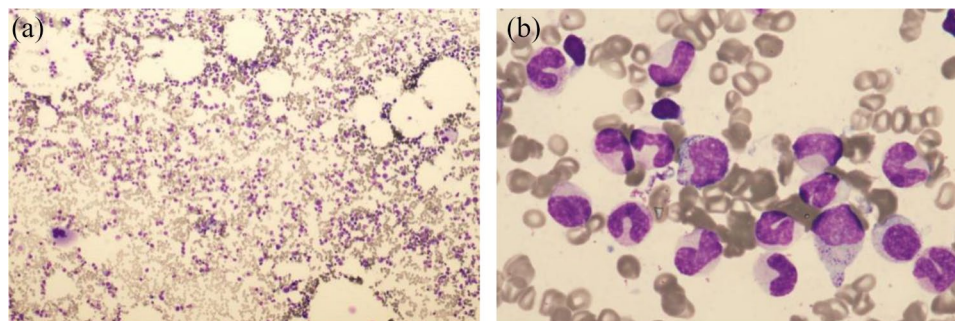


Figure 1. Bone marrow smear showing decreased erythropoiesis (a) and the precursors of other lineages showing no other abnormalities (b) in July 2015.

reference ranges [including lactate dehydrogenase (LDH) and bilirubin]. The results of Coombs test, urine (Rous), free hemoglobin, and schistocytes were unremarkable. Infections were excluded after screening for viral (including cytomegalovirus, Epstein–Barr virus, herpes simplex virus 1 and 2, and parvovirus B19) and other infections. Immunity results showed no significant abnormalities in antinuclear antibodies, rheumatoid factors, and immunoglobulins. Following tumor screening, the tumor markers were all negative and the results of chest computed tomography scan and abdominal ultrasonography showed no clear prompts for solid tumor. Flow cytometry tests for lymphoproliferative diseases and paroxysmal nocturnal hemoglobinuria (PNH) were normal. The results of bone marrow morphology showed decreased erythropoiesis with a myeloid/erythroid ratio of 25:1, whereas precursors of other lineages were well detected without abnormalities (Figure 1). Bone marrow immunophenotyping and karyotype were both negative. He was diagnosed with primary aPRCA after secondary causes had been carefully ruled out.

Immunosuppression therapy (IST) combining with CsA (200 mg/day) and prednisone (50 mg/day) was initiated in 2015, and the plasma concentration of CsA was maintained at 120–600 ng/ml. After a 7-month treatment of IST, GS were stopped and the patient achieved a complete response (CR). However, when the CsA was tapered to 75 mg/day, the disease relapsed in February 2017, at which point CsA was administered at 200 mg/day. From February 2017 to December 2018, recurrence occurred four times after drug tapering and the patient recovered each time when the dose was increased (Figure 2). The

erythropoietin level was within the normal range at diagnosis, and recombinant human erythropoietin (rhEPO) was added at 10,000 U qod for 4 months from August 2018 when the patient was transfusion dependent. Bone marrow morphology, chromosome, fluorescence *in situ* hybridization (FISH) tests, and immunotyping were repeated several times, and he was diagnosed with primary aPRCA with no evidence of myelodysplastic syndrome or PNH.

The patient became transfusion dependent (Hgb level 54 g/L) in December 2018 when CsA was still being administered at full dose and steroids were no longer administered. The therapy was switched to sirolimus at 2 mg/day with a trough concentration of 6–8 ng/ml, combined with CTX (500 mg/week for 6 months) and rhEPO (10,000 U qod for 6 months). The Hgb level was between 30 g/L and 50 g/L after 3 months of treatment. Sirolimus was shortly replaced by bortezomib (2.6 mg/week) for 4 weeks in combination with rituximab 500 mg once in February 2019, followed by sirolimus + CTX + rhEPO and then sirolimus alone. The Hgb level was maintained within 50–60 g/L during this period (Figure 2).

In October 2019, when sirolimus had been administered for 10 months (but interrupted when bortezomib and rituximab were administered), the Hgb level dropped to 30–45 g/L. Repeated workup including bone marrow smear, bone marrow biopsy, chromosome tests, FISH tests, immunotyping, etc., confirmed the diagnosis of primary aPRCA at that point. Serum ferritin level was 2023 ng/ml but the patient refused iron chelation therapy due to financial difficulties. Eltrombopag 25 mg/day was combined with sirolimus. Surprisingly, after 1 week of treatment,

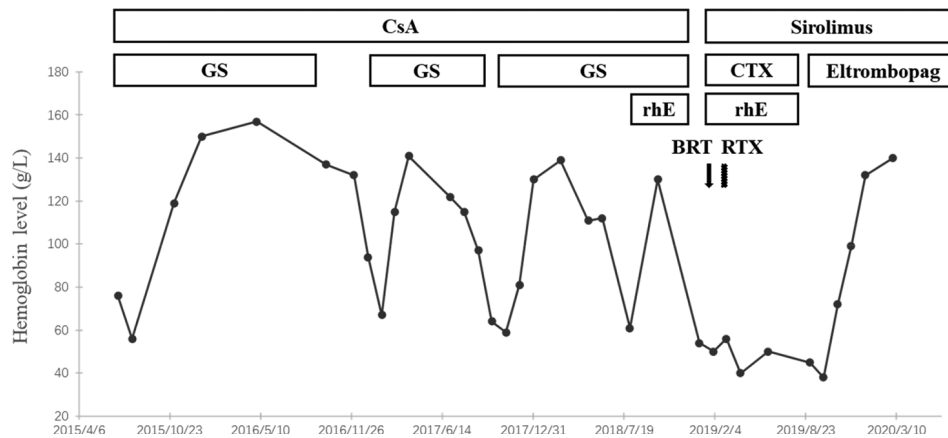


Figure 2. Change of Hgb level from when immunosuppression therapy with CsA and GS was started in July 2015. BRT, bortezomib; CsA, cyclosporin A; CTX, cyclophosphamide; GS, glucocorticoids; Hgb, hemoglobin; rhE, recombinant human erythropoietin; RTX, rituximab.

the patient's Hgb level, which had been persistently low for 8 months, gradually increased. After 1 month, Hgb level increased to 72 g/L and the patient became transfusion independent. Hgb increased to 99 g/L after 2-month therapy and finally increased to 132 g/L in January 2020. The highest platelet level was $323 \times 10^9/L$ and remained normal for most of the time. During follow up, the patient came back to our clinic in March 2020 with an Hgb level of 140 g/L, a normal platelet level, and without any overt symptoms (Figure 2). No notable side effects were found after careful physical examination and laboratory evaluations. Serum ferritin level was 1099 ng/ml. Repeated bone marrow and other laboratory tests showed no evidence of clone evolution or myelofibrosis. By the end of submission, eltrombopag had been administered for 7 months with a constant dosage of 25 mg/day. We will reduce the dosage to 25 mg qod in May 2020 if the Hgb level is still within the normal range.

Discussion

CsA and/or GS¹ are still the first choice for treatment of patients with primary aPRCA. It has been reported that CsA and GS appear to have a 77% and 40% response rate (CR + partial response), respectively.^{1,9,10} For patients unresponsive to GS or CsA, cytotoxic agents, such as azathioprine and CTX, and other immunosuppression compounds like tacrolimus were commonly considered, but the effects were limited.^{1,11,12} In our previous study sirolimus was reported to produce a nearly 76% response rate in

patients with refractory/relapsed aPRCA.^{13,14} The median onset time was 4 months with a range of 2–7 months. Previous reports have shown rituximab and bortezomib to be effective for refractory/relapsed aPRCA, either as single agents or in combination.^{15–17} However, strong and long-term use of IST may carry high risks for infection, which is the leading cause of death in most patients.¹⁸

Eltrombopag was approved to treat SAA, in both refractory and newly diagnosed patients, combined with IST.⁴ Obvious effects were noticed on the platelets, white blood cells, and Hgb. Based on these properties, Busca *et al.*⁸ used eltrombopag to treat two patients with aPRCA secondary to major ABO incompatible HSCT, who were resistant to multiple first- and second-line therapies. The Hgb levels of both patients improved after 1 month and eventually reached CR after 6 months of treatment.

Our patient was diagnosed as primary aPRCA after other diseases and possible secondary causes were ruled out. He responded to first-line therapy with CsA and GS, but became refractory after nearly 3 years of full-dose therapy and suffered from severe anemia even with the use of CsA. Second-line therapies including CTX, sirolimus, rhEPO, rituximab, and bortezomib had been attempted over a long period with few noticeable therapeutic effects. However, the Hgb level increased rapidly after eltrombopag was added and the patient achieved CR at 3 months. Although the late response of sirolimus could not

be completely excluded, eltrombopag definitely accelerated the recovery of this patient.

The mechanism by which eltrombopag has moderate effects on the recovery of erythropoiesis remains unknown. According to the literature, c-MPL is expressed on the surface of hematopoietic stem (progenitor) cells. Eltrombopag binds to the c-MPL transmembrane domain to activate the downstream janus kinases/signal transducers and activators of transcription, STAT (JAK/STAT) signal transduction pathway and thus promotes multilineage hematopoiesis.^{5,19} On the other hand, Alvarado *et al.* found that eltrombopag can evade IFN γ -mediated inhibition of hematopoietic stem cells and activate the c-MPL downstream signal transduction pathway.²⁰ Other reports showed that the immunoregulatory properties of eltrombopag may be related to its positive effects on immune-mediated cytopenia.²¹ Eltrombopag exerts immunomodulatory effects through increasing regulatory T cells and B cells, secreting TGF β , reducing the release of IFN γ and TNF α , inhibiting dendritic cell differentiation, and increasing Treg activity.^{7,22} All these mechanisms illustrate potential therapeutic value for aPRCA, which is also an immune-related anemia disease.

Of note, we cannot fully exclude the late effects of sirolimus although most of our patients responded to sirolimus by month 4 and the latest response occurred at month 7 in our previous reports.¹⁴ In this case, the Hgb level remained consistently low after 10 months of sirolimus and even declined dramatically before eltrombopag started to be administered. Based on our clinical experience, we believed that sirolimus alone might not be the reason for disease improvement, although a synergistic effect could not be excluded because sirolimus also moderates immune function through suppressing Th1 immune responses, eradicating pathogenic CD8+ T cells, stimulating immunosuppressive Treg cells, and protecting hematopoietic stem and progenitor cells.^{14,23,24} The literature on SAA has shown that the combination of eltrombopag and IST is better than using eltrombopag alone,^{4,25} so we continued the treatment of sirolimus with eltrombopag. Since other second-line therapies had been ceased for at least 6 months when eltrombopag was added, their positive effects on erythropoiesis were negligible.

Existing data suggest that iron chelation therapy is able to induce an erythroid response,²⁶

unfortunately this patient did not receive any iron chelators. However, after the effective treatment of anemia, the serum ferritin level also dropped significantly, probably due to the improvement of ineffective hematopoiesis²⁷ and the possible iron chelation effect of eltrombopag.²⁸

In this case, eltrombopag was well tolerated with mild and transient thrombocytosis. In the literature, commonly observed side effects of eltrombopag include headache, nausea, diarrhea, high fever, fatigue, joint pain, and abnormal laboratory indicators for the liver and gallbladder, all of which were not seen in this patient. Rare side effects including cataract, bone marrow fibrosis, thrombosis, and clonal evolution^{3,6,22,29} were not discovered either, although the follow-up period was only short.

To our knowledge this is the first case report on the treatment of primary aPRCA with eltrombopag. We provided a novel potential treatment for refractory/relapse primary aPRCA, however, a longer follow up is needed to evaluate the long-term therapeutic effects and the potential long-term side effects.

Authors' contribution

BH managed the therapy for the patient; BH and YH collected the data and edited the paper; XJ confirmed the results of bone marrow tests.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was supported by grants from the Beijing Natural Science Foundation (7192168), the Chinese Academy of Medical Sciences innovation fund for medical sciences (2016-I2M-3-004), and the Non-profit Central Research Institute Fund of the Chinese Academy of Medical Sciences (2019XK 320047).


Conflict of interest statement

The authors declare that there is no conflict of interest.

Informed consent and ethic statement

Written informed consent was obtained from the patient and the study was approved by the ethics committee of Peking Union Medical Colleague Hospital.

ORCID iD

Bing Han  <https://orcid.org/0000-0002-9717-217X>

References

1. Means RT Jr. Pure red cell aplasia. *Blood* 2016; 128: 2504–2509.
2. Sawada K, Fujishima N and Hirokawa M. Acquired pure red cell aplasia: updated review of treatment. *Br J Haematol* 2008; 142: 505–514.
3. Kim TO, Despotovic J and Lambert MP. Eltrombopag for use in children with immune thrombocytopenia. *Blood Adv* 2018; 2: 454–461.
4. Fattizzo B, Levati G, Cassin R, *et al.* Eltrombopag in immune thrombocytopenia, aplastic anemia, and myelodysplastic syndrome: from megakaryopoiesis to immunomodulation. *Drugs* 2019; 79: 1305–1319.
5. Gill H, Wong RSM and Kwong YL. From chronic immune thrombocytopenia to severe aplastic anemia: recent insights into the evolution of eltrombopag. *Ther Adv Hematol* 2017; 8: 159–174.
6. Lengline E, Drenou B, Peterlin P, *et al.* Nationwide survey on the use of eltrombopag in patients with severe aplastic anemia: a report on behalf of the French Reference Center for Aplastic Anemia. *Haematologica* 2018; 103: 212–220.
7. Scheinberg P. Activity of eltrombopag in severe aplastic anemia. *Hematology Am Soc Hematol Educ Program* 2018; 2018: 450–456.
8. Busca A, Dellacasa C, Giaccone L, *et al.* Eltrombopag for the treatment of refractory pure rbc aplasia after major ABO incompatible hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant* 2018; 24: 1765–1770.
9. Fujishima N, Sawada K, Hirokawa M, *et al.* Long-term responses and outcomes following immunosuppressive therapy in large granular lymphocyte leukemia-associated pure red cell aplasia: a nationwide cohort study in Japan for the PRCA collaborative study group. *Haematologica* 2008; 93: 1555–1559.
10. Means RT Jr, Dessypris EN and Krantz SB. Treatment of refractory pure red cell aplasia with cyclosporine A: disappearance of IgG inhibitor associated with clinical response. *Br J Haematol* 1991; 78: 114–119.
11. Sawada K, Hirokawa M and Fujishima N. Diagnosis and management of acquired pure red cell aplasia. *Hematol Oncol Clin North Am* 2009; 23: 249–259.
12. Yoshida S, Konishi T, Nishizawa T, *et al.* Effect of tacrolimus in a patient with pure red-cell aplasia. *Clin Lab Haematol* 2005; 27: 67–69.
13. Chen Z, Liu X, Chen M, *et al.* Successful sirolimus treatment of patients with pure red cell aplasia complicated with renal insufficiency. *Ann Hematol* 2020; 99: 737–741.
14. Long Z, Yu F, Du Y, *et al.* Successful treatment of refractory/relapsed acquired pure red cell aplasia with sirolimus. *Ann Hematol* 2018; 97: 2047–2054.
15. Auner HW, Wolfler A, Beham-Schmid C, *et al.* Restoration of erythropoiesis by rituximab in an adult patient with primary acquired pure red cell aplasia refractory to conventional treatment. *Br J Haematol* 2002; 116: 727–728.
16. D’Arena G, Vigliotti ML, Dell’Olio M, *et al.* Rituximab to treat chronic lymphoproliferative disorder-associated pure red cell aplasia. *Eur J Haematol* 2009; 82: 235–239.
17. Shahan JL and Hildebrandt GC. Successful treatment of refractory pure red cell aplasia with bortezomib after allogeneic hematopoietic cell transplantation in a patient with alpha-beta subcutaneous panniculitis-like T cell lymphoma. *Transfus Med* 2015; 25: 342–344.
18. Hirokawa M, Sawada K, Fujishima N, *et al.* Long-term outcome of patients with acquired chronic pure red cell aplasia (PRCA) following immunosuppressive therapy: a final report of the nationwide cohort study in 2004/2006 by the Japan PRCA collaborative study group. *Br J Haematol* 2015; 169: 879–886.
19. Sun H, Tsai Y, Nowak I, *et al.* Eltrombopag, a thrombopoietin receptor agonist, enhances human umbilical cord blood hematopoietic stem/progenitor cell expansion and promotes multi-lineage hematopoiesis. *Stem Cell Res* 2012; 9: 77–86.
20. Alvarado LJ, Huntsman HD, Cheng H, *et al.* Eltrombopag maintains human hematopoietic stem and progenitor cells under inflammatory conditions mediated by IFN-gamma. *Blood* 2019; 133: 2043–2055.
21. Teachey DT and Lambert MP. Diagnosis and management of autoimmune cytopenias in childhood. *Pediatr Clin North Am* 2013; 60: 1489–1511.
22. Lum SH and Grainger JD. Eltrombopag for the treatment of aplastic anemia: current perspectives. *Drug Des Devel Ther* 2016; 10: 2833–2843.
23. Li Y, Shi Y, Liao Y, *et al.* Differential regulation of Tregs and Th17/Th1 cells by a sirolimus-based regimen might be dependent on STAT-signaling

- in renal transplant recipients. *Int Immunopharmacol* 2015; 28: 435–443.
24. Chaoul N, Fayolle C, Desrues B, *et al.* Rapamycin impairs antitumor CD8+ T-cell responses and vaccine-induced tumor eradication. *Cancer Res* 2015; 75: 3279–3291.
25. Townsley DM, Scheinberg P, Winkler T, *et al.* Eltrombopag added to standard immunosuppression for aplastic anemia. *N Engl J Med* 2017; 376: 1540–1550.
26. Oliva EN, Ronco F, Marino A, *et al.* Iron chelation therapy associated with improvement of hematopoiesis in transfusion-dependent patients. *Transfusion* 2010; 50: 1568–1570.
27. Cazzola M, Della Porta MG and Malcovati L. Clinical relevance of anemia and transfusion iron overload in myelodysplastic syndromes. *Hematology Am Soc Hematol Educ Program* 2008; 1: 166–175.
28. Punzo F, Tortora C, Argenziano M, *et al.* Iron chelating properties of Eltrombopag: investigating its role in thalassemia-induced osteoporosis. *PLoS One* 2018; 13: e0208102.
29. 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.

Visit SAGE journals online
[journals.sagepub.com/
home/tah](http://journals.sagepub.com/home/tah)

 SAGE journals