Avatrombopag Treatment of Severe Aplastic Anemia With Liver Injury: a Case Report

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Case Report

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Abstract

At present, avatrombopag has not obtained a clinical license and is not accepted as a standard clinical treatment of Severe aplastic anemia. Here, We present a case of SAA treated with avatrombopag. Our patient was intolerant to eltrombopag, demonstrating elevated transaminase levels, but avatrombopag treatment was well tolerated with high effectiveness. Therefore, avatrombopag may not cause hepatotoxicity compared with other TPO receptor agonist for SAA treatment, and its combination with CsA may be a possible safe and effective treatment for long-term SAA management. Our case highlights the importance of recognizing TPO-RAS as a safe and effective treatment of SAA and adds avatrombopag to this list.

Introduction

Severe aplastic anemia (SAA) is considered to be an immune-mediated destruction of hematopoietic stem cells, accompanied by pancytopenia, which can be successfully treated with either immunosuppressive therapy (IST) or hematopoietic stem-cell transplantation (HSCT)[1].Treatment with IST using the combination of anti-thymocyte globulin (ATG) and cyclosporine A (CsA), with the more recent addition of thrombopoietin receptor agonist (TPO-RAS) has been shown to be an effective regimen.In order to break through the bottleneck of SAA treatment and improve the first-line efficacy, the new therapy of TPO-RAS has become a new hope. Currently, the TPO-RAS used clinically for the treatment of SAA is mainly eltrombopag, but it can cause a variety of adverse events in treatment, including increased liver enzymes, thromboembolic events and cataracts[2]. Once hepatotoxicity occurs, it is even worse for patients with extremely low platelets, which will also aggravate the psychological burden, affect the drug response and patient compliance. Due to the adverse reactions, these patients are even forced to stop the drug, affecting the overall therapeutic benefits seriously.

Therefore, it is particularly important to find other alternative treatments. We report a 41 year old female with newly treated SAA whose transaminases were increased due to the treatment of eltrombopag. After the replacement treatment with avatrombopag, the transaminase gradually returned to normal and the effect of promoting hematopoiesis was significant. Now the treatment process is reported as follows.

Case Report

Investigations

A 41-year-old man presented to our hospital with ecchymosis on the skin. She was found to be profoundly pancytopenia. The patient had no medical history.

Diagnosis

The worst laboratory tests showed white blood cell count (WBC) 2.02×109/L, hemoglobin (Hb) concentration 58 g/L, neutrophil count 1.23×109/L, platelet (Plt) count 2×109/L and absolute reticulocyte count 17.2×109/L. Bone marrow biopsy revealed hypoplastic myelodysplasia, reduced granulocyte to

erythrocyte ratio (G/E), and visible megakaryocytes with normal count and morphology. There was no significant increase in blasts by CD117 and CD34 staining, no significant increase in B- or T-cells by CD20 and CD3 staining, and no significant increase in plasma cells by CD138 staining. CK was negative and reticular fiber staining was Grade 0. Bone marrow smear revealed G/E = 2.81/1, reduced tri-lineage counts, and elevated lymphocyte ratio. Membrane antibody, platelet antibody, myelodysplasia–FISH panel, and PNH clones were negative, detected by flow cytometry. Chromosomal karyotype was normal. Prognostic leukemia genes were PPMID 20.61%, ASXL1 52.44%. Thrombopoietin receptor (TPO-R) expression rates on T-cell subsets were determined by flow cytometry as 19.82%, 62.45%, and 11.87% on CD4+, CD8 + and Treg cells, respectively. PET-CT revealed multiple hypermetabolic foci in the bone marrow, considered as a hematologic disease. The results of liver, renal function, and electrolyte tests were all within the normal range. Ferritin, folic acid, and vitamin B12 were not deficient. CMV-DNA and EBV-DNA were negative. Antinuclear antibody spectrum, tumor markers, and free thyroid function were normal.

After excluding other causes of pancytopenia, the patient met the criteria for severe aplastic anemia (SAA).

Treatment

Considering the nephrotoxicity of cyclosporin A (CsA), She refused the immunosuppression therapy (IST) but received methylprednisolone (24 mg, three times daily) to regulate immunity. Moreover, she received hematopoietic therapy, including eltrombopag (50 mg daily), recombinant human erythropoietin (6000 IU, once every other day), and G-CSF (0.6 mL, daily), adjusted according to routine blood results. In addition, the patient was intermittently infused with red blood cells and platelets. Polyene phosphatidylcholine were provided to protect hepatocytes from toxic damage. After 2 weeks of treatment, her transaminase level increased significantly (AST, 27 U/L; ALT 79 U/L), possibly caused by eltrombopag-induced hepatotoxicity.

Eltrombopag was then replaced by avatrombopag, 40 mg daily, based on experience. Two weeks later, the transaminase level gradually returned to normal, and the patient tolerated the regimen well without any other side effects. The patient was then started on cyclosporin A (CsA; 50 mg, three times daily), with the concentration periodically monitored to adjust the dose. Peripheral hemogram characteristics improved slowly, and the frequency of component transfusion decreased over the treatment time. After 9 weeks of treatment, peripheral hemogram characteristics were significantly improved, red blood cell transfusions were no longer needed, and the platelet transfusion frequency was significantly reduced. Methylprednisolone dose was reduced to 12 mg per day, CsA was continued to correct the immune environment, and avatrombopag promoted bone marrow hematopoiesis. At 13 weeks of treatment, platelet transfusion was not necessary. The patient had an ongoing tri-lineage hematopoietic response at 1 month after the patient was completely free from blood transfusion. At that time, blood workup demonstrated Hb, 106 g/L; Plt, 50×10^9/L; ANC, 11.9×10^9/L; and Ret, 107.2×10^9/L. Bone marrow hyperplasia was significantly active, G/E was almost normal, dominant in mature cells and fewer megakaryocytes, and no special morphology was observed. TPO-R expression on T-cells was 48.76%,

25.50%, and 33.33% in CD4+, CD8+, and Treg cells, respectively, indicating that immune indicators were improved.

Follow-up and outcomes

Before report submission, the patient continued to receive avatrombopag and CsA treatment, and was in stable condition with a good quality of life.

Discussion

TPO is usually produced by the liver, which regulates hematopoietic and megakaryocyte growth by binding to its receptor c-Mpl and triggering activation of the Janus kinase 2 (JAK2) / signal transducer and activator of transcription (STAT) pathway[3, 4]. Many preclinical studies have confirmed the beneficial effect of TPO on the activation and maintenance of hematopoietic stem cells. Therefore, TPO-RAS seem to be ideal therapeutic agents for enhancing bone marrow function, which has greatly contributed to the progress of clinical treatment of SAA[5]. TPO-Ras simulates endogenous TPO, regulates the proliferation and maturation of megakaryocytes in bone marrow and increases platelet production [6, 7].

In the last decade, the introduction of TPO-Ras has opened up new possibilities for the treatment of AA. The TPO-RAS romiplostim, eltrombopag, avatarmbopag and lusutrombopag have unique indications approved by the US Food and Drug Administration (FDA) and the European Drug Administration (EMA) and may be used in a variety of conditions to increase platelet counts [5]. Romistine competes with endogenous TPO to bind the extracellular segment of TPO receptor; eltrombopag and avatrombopag are non competitively combined with endogenous TPO and have potential superimposed platelet raising effect[5]. Eltrombopag, a second-generation platelet receptor agonist, has been shown to be satisfactorily effective in the treatment of AA in numerous clinical trials. Nevertheless, it has been well documented that eltrombopag may cause hepatotoxicity[2], commonly manifested by elevated transaminases, particularly in those patients with type 2 diabetic disease and hepatobiliary disease[8].Although most of the liver damage is mild and moderate, the drug can be reversible after withdrawal, but the incidence rate is high. It will seriously increase the psychological burdens on patients and affect compliance with medication. In the event of liver damage, there may even be a risk of potentially fatal liver injury. Patients with severe hepatotoxicity need to discontinue the drug in a timely manner, which will severely compromise disease management.

Avatrombopag has notable advantages. It does not need to monitor abnormal liver function routinely during treatment. It can be used in combination with multivalent cations such as calcium, magnesium and iron, and lacks food drug interaction[9]. To date, no published clinical studies have mentioned the association of avatrombopag with hepatotoxicity. In addition, a pharmacodynamic experiment conducted by Abe et al. Suggests that the pharmacological effect of avatrombopag may be stronger than that of eltrombopag [10]. TPO-RAs will be an important treatment for patients with AA, and their high efficiency and long-term safety will improve their health and quality of life When toxicity or diminished efficacy of

one TPO-RAs occurs, a choice to another TPO-RAs may be considered. Subtle mechanistic differences between different TPO-Ras may explain why switching TPO-Ras may have clinical advantages in some cases.

During the course of the consultation in this case, the patient was unable to tolerate etrombopag and had an adverse event of increased transaminases. Subsequently, she was treated with avatrombopag replacement therapy and the platelet count increased safely and effectively, with good tolerance and promising results. Avatrombopag offers a new treatment option for patients with SAA, avoiding the potential risks associated with platelet transfusions and alleviating the shortage of blood products.

Learning points

With its low side-effect burden, absence of hepatotoxicity, ease of use as an oral medication, and lack of food-drug interactions, avatrombopag is a favorable option for SAA, though there is a lack of long-term safety data. Although a greater amount of clinical data on the use of avatrombopag in SAA is certainly required, our results suggest that avatrombopag may be a favorable option in the treatment of SAA. We look forward to further expanding the sample and completing the clinical trial of avatrombopagl in the treatment of SAA.

Declarations

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Financial Disclosure

None to declare.

Conflict of Interest

None to declare.

Informed Consent

Informed consent was obtained.

Author Contributions

Study conception and design: Chenchen Liu, chunyan Liu, Zonghong Shao, Rong Fu; data collection: Chenchen Liu, chunyan Liu; anal-ysis and interpretation of results: Chenchen Liu, chunyan Liu, Zonghong Shao, Rong Fu; draft manuscript preparation: Chenchen Liu, chunyan Liu, Zonghong Shao. All authors reviewed the results and approved the final version of the manuscript.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

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Figures

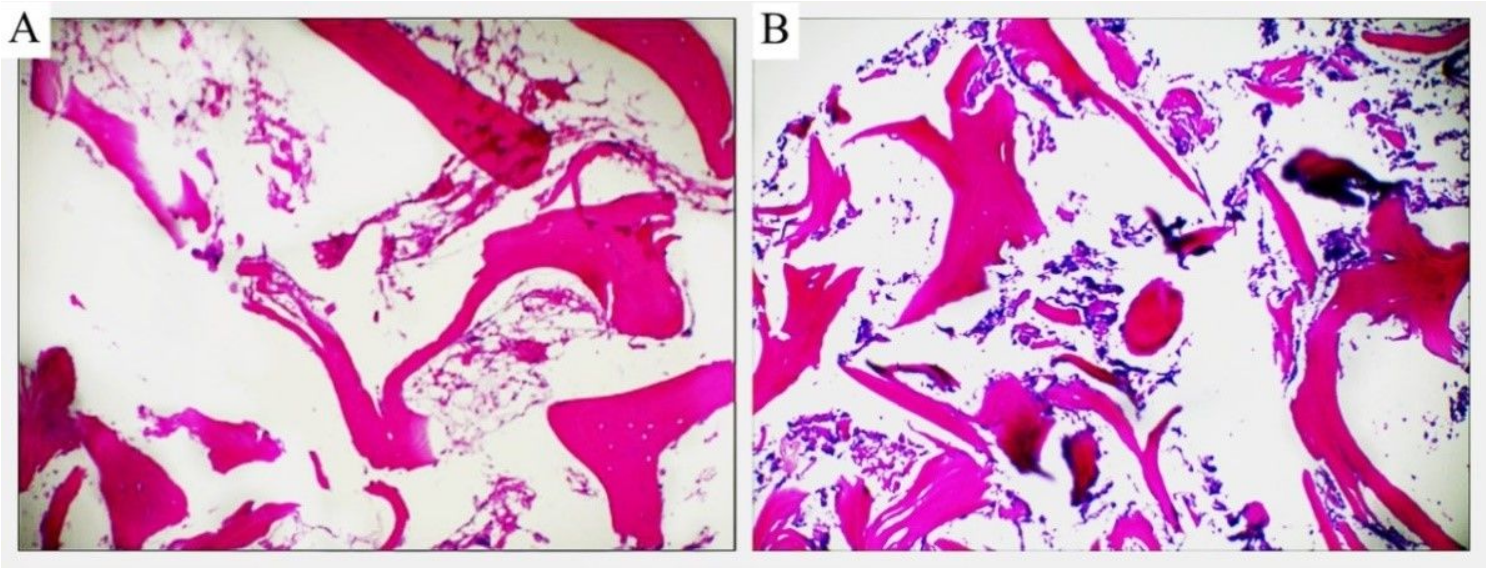

Figure 1

Bone marrow biopsy

A. Bone marrow biopsy at the time of the first diagnosis showed severe hypoplasia.

B. Bone marrow biopsy after avatrombopag therapy revealed granulocyte, erythrocyte, and megakaryocyte were all hyperplasia.(Wright-Giemsa stain, original magnification, × 100).

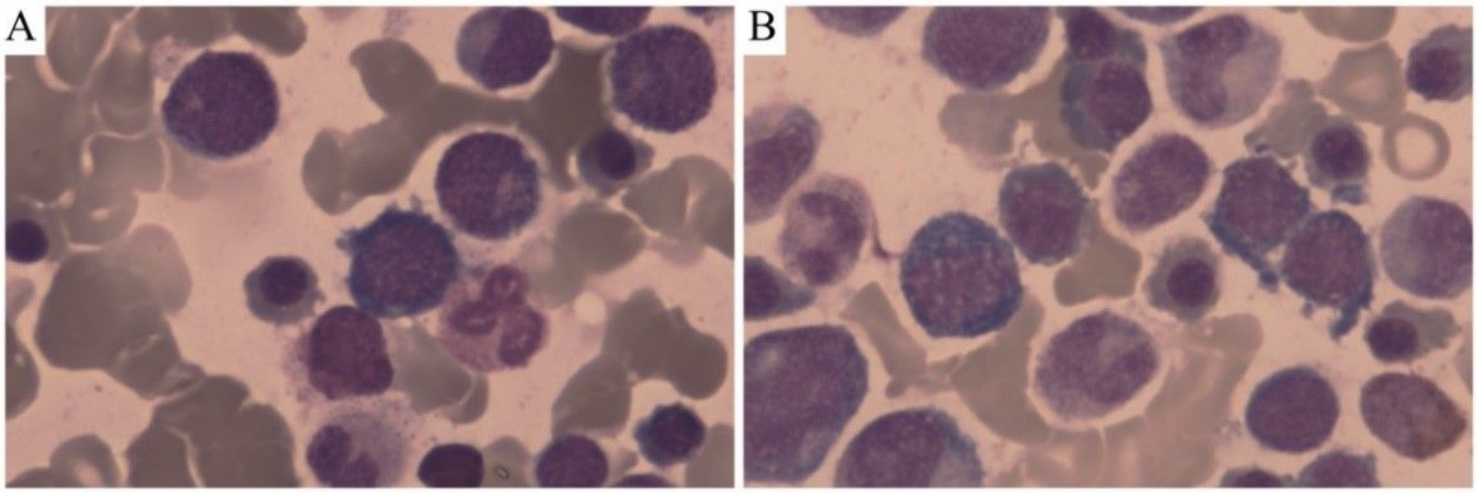

Figure 2

Comparison of bone marrow smear after 5 months of treatment.

(A: before; B: after avatrombopag therapy)

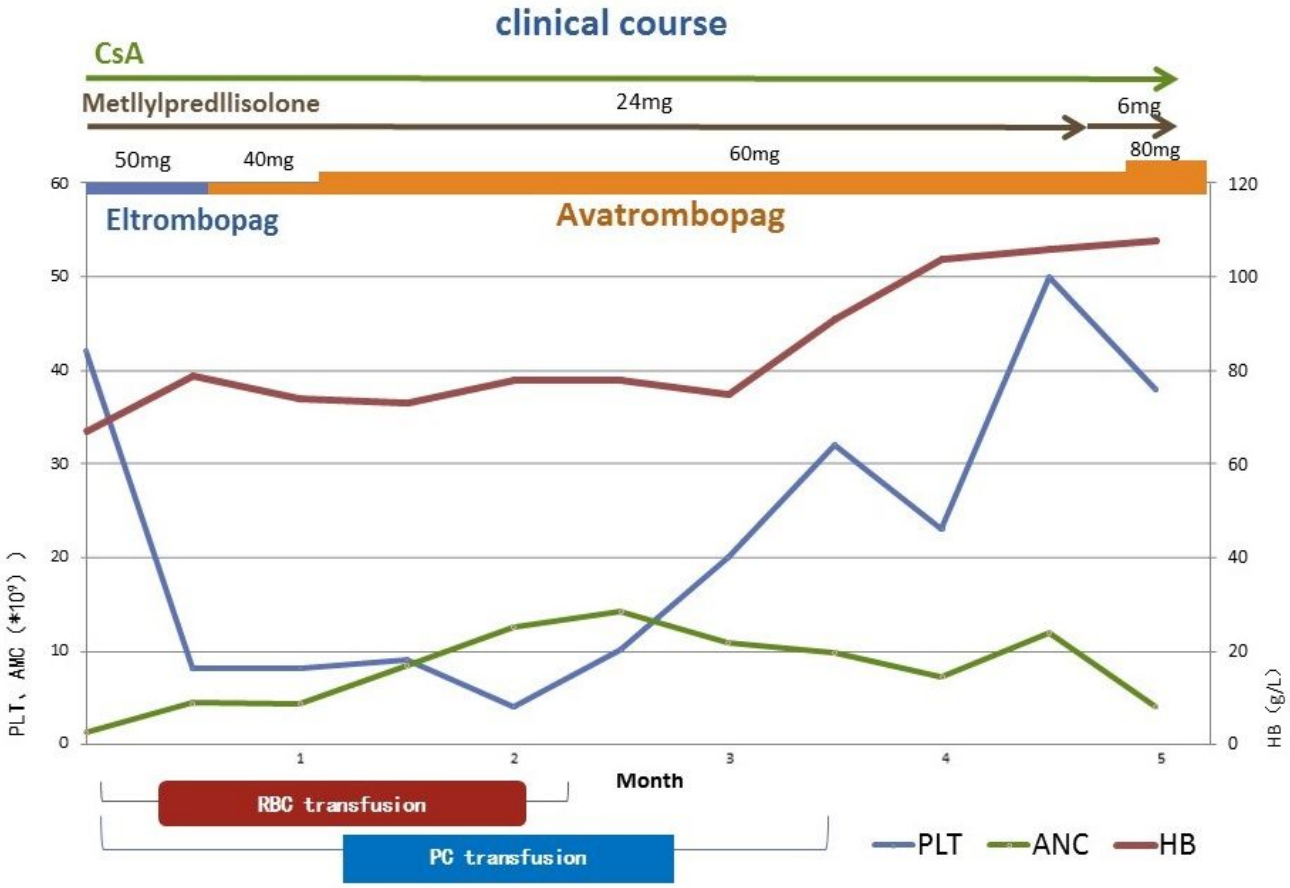

Figure 3

Clinical Course summarizes her hematologic responses to avatrombopag over time.

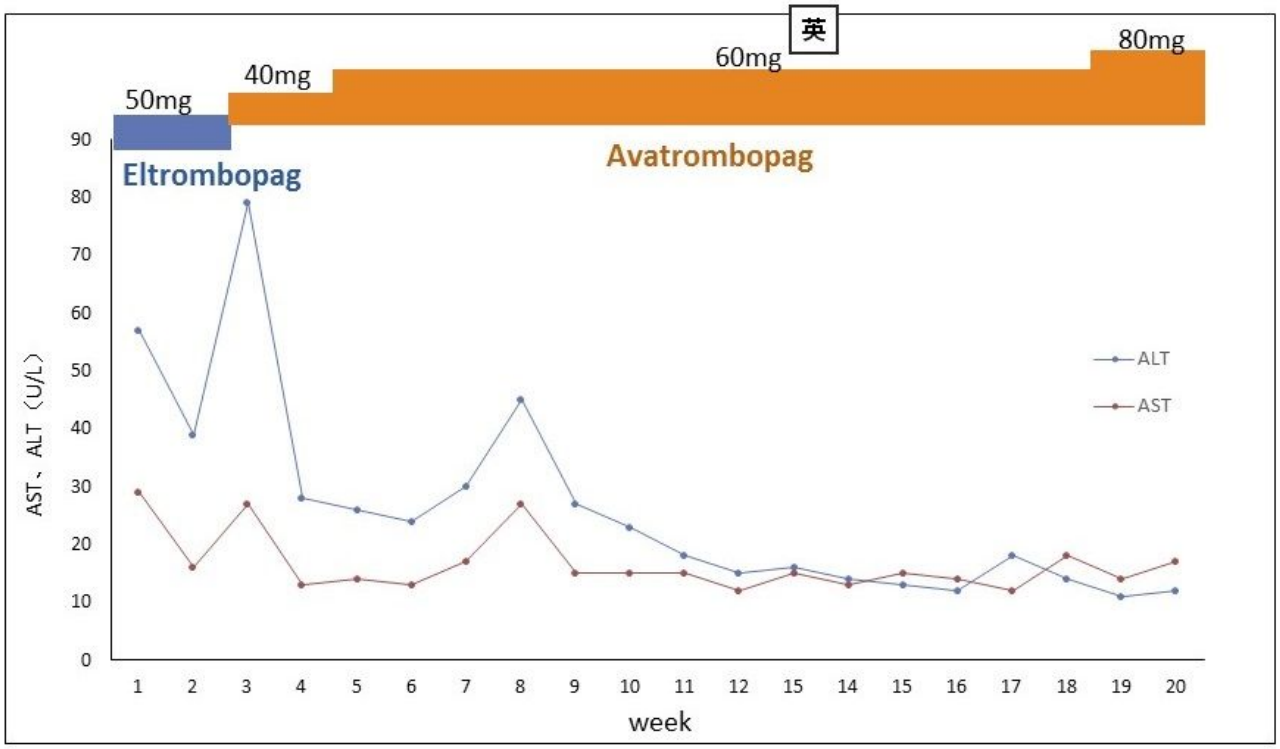

Figure 4

Graph of the timeline of liver function tests in response to avatrombopag.