

## Successful treatment of severe aplastic anemia with eltrombopag

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### Abstract

Aplastic anemia is a clinical syndrome characterized by peripheral pancytopenia and deficiency of hematopoietic precursors in the bone marrow. Allogeneic hematopoietic stem cell transplantation (AHSCT) should be considered as first line treatment for young patients with an available donor. However, alternative therapy options are scant in patients who are not candidates for transplantation. Here, we report the efficacy of eltrombopag in a case of severe aplastic anemia. Case Presentation: Twenty-two years old female patient was admitted to the Marmara University Hospital because of severe aplastic anemia. There was not an available HLA-matched sibling donor and immunosuppressive treatment with horse-derived ATG (40 mg per day for 5 days) and cyclosporine (5 mg/kg per day) was started. At the sixth month of therapy she was still in need of transfusion. Eltrombopag was prescribed at a dose of 50 mg and the dose was increased up to 150 mg per day in 2 months. Successful response was noted within 2 weeks of 150 mg dosage and this response was sustained at the 4th month following discontinuation of drug. Conclusion: Eltrombopag provides good and permanent clinical response in refractory severe aplastic anemia.

**Key words:** Eltrombopag, Aplastic anemia

### Introduction

Aplastic anemia is an autoimmune disease of the bone marrow characterized by deficiency of hematopoietic precursors and peripheral pancytopenia (1). It was suggested that activated cytotoxic T cells expressing inhibitory cytokines like Interferon- $\gamma$  and Tumor Necrosis Factor- $\alpha$  (TNF  $\alpha$ ), take role in the immune destruction of hematopoietic stem cells (2). The standard treatment of patients who are ineligible for transplantation consists of immunosuppressive treatment with ATG and cyclosporine. Hematologic response is achieved in about two thirds of the patients with this treatment. However, AHSCT is recommended for those bellow age 40, if HLA-matched sibling is available.

During the course of aplastic anemia, infections following neutropenia may lead to death or fatal hemorrhages can occur because of thrombocytopenia (4). Although immunosuppressive treatment improves the outcomes, pancytopenia persists in about 30 % of patients after ATG and cyclosporine (3,5,6). AHSCT is an option where donor is available; however there is high risk of infections, graft versus host disease (GvHD) and graft failure (5). Treatment options other than AHSCT are limited with growth factors, supportive care and androgens (6).

Salvage treatment with immunosuppressive drugs may be effective in some patients, but intensification with rabbit-derived ATG, sirolimus or mycophenolate mofetil does not improve response rates (7,8).

Thrombopoietin is the main regulator of thrombocyte production via c-MPL receptor in megakaryocytes. Activation of the pathway results in maturation and release of thrombocytes (9). Stimulation of c-MPL signal may overcome the decrease in hematopoietic stem cells in aplastic anemia. Eltrombopag is an oral Thrombopoietin receptor agonist, which binds c-MPL ligand and enhances release of thrombocytes from mature megakaryocytes. It was approved by FDA (US Food and Drug Administration) for treatment of chronic ITP (10). The critical role of thrombopoietin in the growth and differentiation of hematopoietic stem cell is demonstrated in a form of congenital bone marrow failure due to c-MPL deficiency (11). Regarding this observation, a prospective phase 2 study was designed to evaluate the efficacy of eltrombopag in aplastic anemia and it was shown to be effective in patients non-responsive to immunosuppressive agents.

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In this study, the normalization of all three lines in the bone marrow was observed and in 44% of patients hematologic response was achieved in at least one line (12).

In this case, we aimed to report our successful results with eltrombopag in a transplant ineligible patient who is unresponsive to immunosuppressive drugs.

### Case

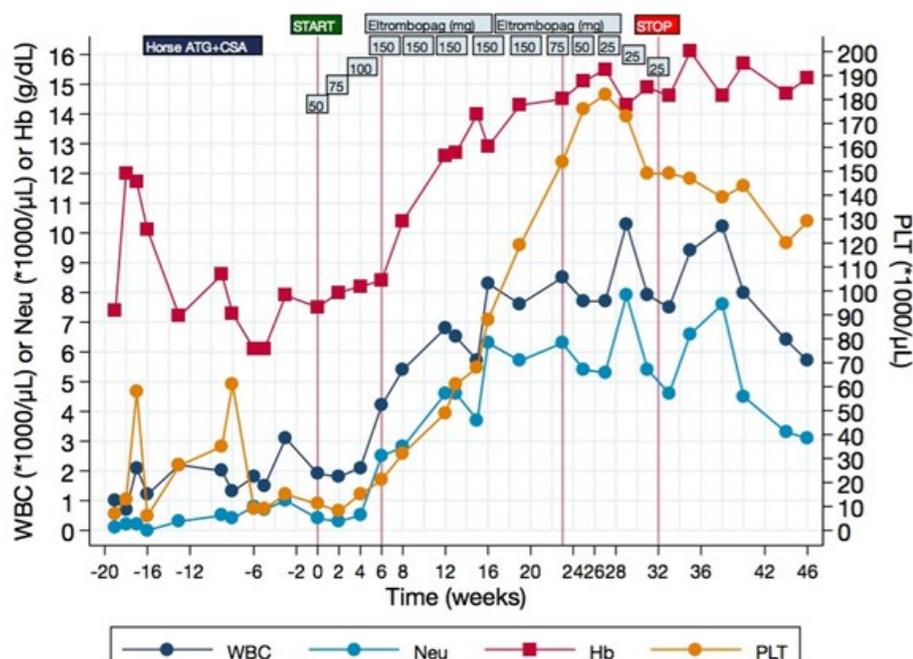
Twenty-two years old female patient was admitted to the emergency unit of Marmara University Hospital in September 2013, because of ecchymosis on the arm and bleeding gums. She also had menorrhagia. These complaints existed for the last one-week. Her physical examination was normal. Laboratory tests revealed pancytopenia and slightly increased transaminases (AST:54, ALT:85).

Other biochemical tests were in normal ranges. Her blood group was A Rh negative. The patient was hospitalized at our hematology clinic. Peripheral blood smear examination showed 16 bands, 14 neutrophils, 69 lymphocytes, anisochromia, anisocytosis and microcytosis and average number of thrombocytes in each field was 1-2.

There was no atypical cell. Direct and indirect coombs were negative. Erythrocyte sedimentation rate was normal. PNH clone was negative. Bone marrow biopsy showed severe hypocellularity. Considering bone marrow biopsy and pancytopenia on the peripheral blood, the diagnosis of severe aplastic was established.

HLA typing was done for the patient and her siblings, however a HLA-matched sibling donor was not available. Horse-derived ATG (ATGAM) (40 mg per day for 5 days) and cyclosporine (5 mg/kg per day) was given starting at day 12.11.2013. The documentation of blood count follow-up after immunosuppressive therapy is shown in the figure 1.

At the sixth month of therapy with ATGAM and cyclosporine, there was not enough response, transfusion requirement was continuing and cyclosporine related side effects like hirsutism and gum hypertrophy were emerging. After taking the required permissions from the government, eltrombopag was prescribed at a dose of 50 mg per day. Blood count was controlled every 2 weeks and the dose was increased by 25 mg. There was no response at the doses of 50, 75 and 100 mg per day. However, 2 weeks after practicing 150 mg per day, there was increase in the number of neutrophils and thrombocytes. Response assessment was done by bone marrow biopsy, which was taken at the end of the first month with eltrombopag. The cellularity was increased to 50 % and the maturation of all three series was normal. During the follow-up, after the dose was increased to 150 mg per day, cytopenias have begun resolving. However, the dose was decreased to 75 mg per day when the thrombocyte number was 154 000. Two weeks later, the dose was decreased to 50 mg and then to 25 mg per day. Later then, the treatment was terminated since the blood count was in normal range. Eltrombopag did not cause any increase in transaminases during the therapy and the response was preserved at the 4th month of discontinuation.



**Figure 1:** Progress of blood counts during follow-up

## Discussion

It is thought that severe aplastic anemia develops after an autoimmune attack to the bone marrow, which results in paucity of hematopoietic stem cells and progenitor cells (7). Standard treatment of the disease is immunosuppressive therapy with ATG and cyclosporine. With this treatment, hematologic response is achieved in two thirds of the patients (3). However, allogeneic hematopoietic stem cell transplantation (AHSCT) is recommended for those younger than 40 years, if there is an available donor (4).

Most of the patients are in need of repeated transfusions which may result in hemosiderosis, alloimmunization or transfusion related infections. Therefore, novel therapies are required for patients who are not candidates for AHSCT and unresponsive to immunosuppressive agents. Eltrombopag is a low molecular weight synthetic agonist of thrombopoietin receptor and it may improve hematopoiesis by stimulating c-MPL receptor in refractory aplastic anemia.

Olnes et al. reported clinical improvement of thrombocytes, erythrocytes and neutrophils in 11 of 25 patients who used eltrombopag continuously. Moreover, they detected normalization of cellularity in all 3 series of bone marrow (12). Similarly, Desmond et al. observed decreased transfusion need and significantly increased blood counts in 40% of patients with severe aplastic anemia resistant to immunosuppressive drugs. In this study, they determined hematologic recovery in at least one serial among 17 (40%) of 43 patients, while recovery in all 3 series determined in 7 (16.3%). In addition, at the 12th month after discontinuation of eltrombopag, cellularity of the bone marrow was still normal in 5 patients (13).

The disease relapse is expected after discontinuation of eltrombopag in patients with ITP (14). However, continuous treatment may not be necessary in severe aplastic anemia in order to maintain permanently sufficient hematopoiesis. Eltrombopag may have different mechanisms of action in these two diseases. In ITP, the stimulation of megakaryocytes with eltrombopag is greater than physiologic stimulus (13). As indicated previously, the direct stimulation of stem cells restores the number of hematopoietic cells in severe aplastic anemia (13).

The required dosage of drug in ITP is lower than the doses required in severe aplastic anemia. In the study by Desmond the lowest dose for response is 100 mg (13). Similarly, our patient did not respond to

treatment with doses 50, 75 and 100 mg respectively. Then, the use of 150 mg per day resulted in improvement in all 3 series within 4 weeks. The complete response was sustained at 4 months after discontinuation of eltrombopag.

Similar to the presented literature above, in our patient we also have experienced successful results with eltrombopag. However, it should be kept in mind that there was only 6 weeks between the cessation of cyclosporine and the beginning of eltrombopag and we cannot clearly rule out the possibility of a late response by immunosuppressive treatment.

In addition, severe aplastic anemia bears a risk of clonal bone marrow dysfunction like cytogenetic abnormality and leukemic transformation. Although, there is no clear evidence of an increased clonal transformation with eltrombopag, in a large observational study, 15% of patients were reported to have risk of clonal transformation (15). So, there is need for more controlled studies.

In conclusion, eltrombopag provides good clinical responses in refractory severe aplastic anemia and may be used in patients who don't have any other treatment option. Since, it is possible to gain permanent response, the treatment should be discontinued with close follow-up after sufficient clinical response is obtained.

**Conflict of Interest:** The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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