# A single-center historical control study of eltrombopag combined with immunosuppressive therapy for severe aplastic anemia in children

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**Abstract**

Severe aplastic anemia (SAA) is caused by immune-mediated destruction. Standard immunosuppressive therapy (IST) is effective, but needs to be improved. A total of 115 patients (60 males; median age of 5.77 years and median follow-up time of 45 months) were enrolled in this historical control study. The complete response (CR) rates in the eltrombopag group were 30.3% at 3 months, 50.0% at 6 months, conpared to 8.2% at 3 months, 10.2% at 6 months in the control group. There were significant differences between the two groups at 3 months and 6 months after IST. The overall response rates in the two groups showed no significant differences during the study. There were significant differences in the times separated from granulocyte colony stimulating factor (G-CSF) G-CSF, red blood cell transfusion and Platelet transfusion between the two groups. Overall survival rates were 97.0% in the eltrombopag group and 96.0% in the control group (P=0.998). In the eltrombopag group 10.2% cases relapsed compared to 4.1% in the control group (P=0.703). No case progressed to myelodysplastic syndrome or myeloid leukemia in the eltrombopag group; one patient (2.0%) progressed to myelodysplastic syndrome in the control group. Totally 11 patients (16.7%) showed myeloid gene mutations in the eltrombopag group. Event-free survival (EFS) was 66.6% in the eltrombopag group and 57.1% in the control group. There were no significant differences in EFS between the two groups (P=0.967). In the eltrombopag group the common adverse reactions were transient and reversible hyperbilirubinemia, elevated liver enzymesand hyperuricemia.

**A single-center historical control study ofeltrombopag combined with immunosuppressive therapyfor severe aplastic anemia in children**

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Abbreviations

| | |
|---|---|
| SAA | severe aplastic anemia |
| IST | immunosuppressive therapy |
| CR | complete response |
| G-CSF | granulocyte colony stimulating factor |
| EFS | event-free survival |
| AA | aplastic anemia |
| rATG | rabbit anti-thymocyte globulin |
| CSA | Cyclosporine |
| OR | overall response |
| OS | overall survival |
| FDA | Food and Drug Administration |
| FISH | fluorescence in situ hybridization |
| PNH | paroxysmal nocturnal hemoglobinuria |
| PR | partial response |
| NR | no response |
| VSAA | very severe aplastic anemia |
| HSCT | hematopoietic stem cell transplantation |
| NIH | National Institutes of Health |

**Abstract**

Severe aplastic anemia (SAA) is caused by immune-mediated destruction. Standard immunosuppressive therapy (IST) is effective, but needs to be improved. A total of 115 patients (60 males; median age of 5.77 years and median follow-up time of 45 months) were enrolled in this historical control study. The complete response (CR) rates in the eltrombopag group were 30.3% at 3 months, 50.0% at 6 months, conpared to 8.2% at 3 months, 10.2% at 6 months in the control group. There were significant differences between the two groups at 3 months and 6 months after IST. The overall response rates in the two groups showed no significant differences during the study. There were significant differences in the times separated from granulocyte colony stimulating factor (G-CSF) G-CSF, red blood cell transfusion and Platelet transfusion between the two groups. Overall survival rates were 97.0% in the eltrombopag group and 96.0% in the control group (P=0.998). In the eltrombopag group 10.2% cases relapsed compared to 4.1% in the control group (P=0.703). No case progressed to myelodysplastic syndrome or myeloid leukemia in the eltrombopag group; one patient (2.0%) progressed to myelodysplastic syndrome in the control group. Totally 11 patients (16.7%) showed myeloid gene mutations in the eltrombopag group. Event-free survival (EFS) was 66.6% in the eltrombopag group and 57.1% in the control group. There were no significant differences in EFS between the two groups (P=0.967). In the eltrombopag group the common adverse reactions were transient and reversible hyperbilirubinemia, elevated liver enzymesand hyperuricemia.

**Key points**

Addition of eltrombopag to standard immunosuppressive therapy confers faster hematological response and higher early hematological response in pediatric severe aplastic anemia patients.

Eltrombopag showed a reliable safety, but had no impact on long-term response and prognosis.

**Introduction**

Aplastic anemia (AA) is a bone marrow failure disease, which is mainly characterized by pancytopenia after immune destruction of hematopoietic cells. It is widely admitted that the main cause of AA is the immunological attack of bone marrow hematopoietic cells by dysfunctional T lymphocytes [1]. In North America and Europe, the annual incidence of AA is 2-6 per million [2]; the rate is 2 to 3-fold higher in Asia [3]. For children with severe aplastic anemia (SAA) having a matched sibling donor, allogeneic bone marrow transplantation remains the standard frontline therapy, while other patients should receive frontline immunosuppression therapy (IST) with rabbit anti-thymocyte globulin (rATG) combined with cyclosporine (CSA) [4]. The quality of hematological response to IST is higher than reported by adult studies [4-9], with overall response (OR) rates of 71.2%-74% and complete response (CR) rates of 23%–60%. Overall survival (OS) rates are also high, at 73.6%–93%; however, the CR rate needs to be improved, and long-term complications such as relapse and clonal evolution result in long-term event-free survival (EFS) rates of only 56–64% [5-10].

Eltrombopag is a small molecule thrombopoietin-receptor agonist available for oral administration. It starts a signal cascade reaction through the interaction with the thrombopoietin receptor transmembrane domain, to promote the proliferation and differentiation of bone marrow progenitor cells and induce hematopoiesis. A previous study found that administration of thrombopoietin receptor agonists represented by eltrombopag improves the therapeutic efficacy in aplastic anemia. The combination of eltrombopag and IST has been approved by the United States Food and Drug Administration (FDA) for cases aged [?]2 years as front-line treatment for SAA. Although the application of eltrombopag for SAA treatment in adults is relatively mature[11-13], reports on eltrombopag use in pediatric SAA are still scarce, with conflicting findings[14-16]. Therefore, we conducted a historical control study to evaluate the efficacy and safety of eltrombopag combined with IST for SAA in children.

## Methods

### Study design and implementation

This was a single-center retrospective historical control study to assess whether addition of eltrombopag to IST in SAA could improve the hematological response and long-term efficacy in pediatric patients. This study was approved by the Institutional Review Board of Beijing Children's Hospital, Capital Medical University. All the patients or their legal guardians provided written informed consent.

### Materials and methods

### Patients

Data of pediatric SAA patients treated with IST combined with rATG and CSA were analyzed retrospectively from March 2013 to July 2020 at Hematology Oncology Center, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health.

Inclusion criteria were: <18 years of age; previously untreated SAA. Patients with a diagnosis of an inherited bone marrow failure syndrome were excluded, as well as subjects with a human leukocyte antigen matched sibling who underwent transplantation.

The collected data included age, sex, clinical classification, previous therapy and IST, hematological response, chromosome karyotype and status at the final follow-up, etc. Every pediatric case underwent bone marrow aspirate and biopsy, cytogenetics, fluorescence in situ hybridization (FISH), clonal analysis for paroxysmal nocturnal hemoglobinuria (PNH), telomere flow-FISH analysis and immunological analyses. Follow up was performed for a minimum of 1 year or until death, and was completed in July 2021.

### Classification of severity

The severity of children AA was classified by the following criteria[17]. SAA with: 1) bone marrow karyocyte count <25% or 25%-50% with <25% hematopoietic elements; 2) peripheral blood with at least two of the following factors, including granulocytes $<0.5\times10^9$/L, platelets $<20\times10^9$/L, reticulocytes $<0.2\times10^9$/L or

corrected reticulocyte count ¡1%. Very severe aplastic anemia (VSAA) presenting same as SAA,except for granulocytes <0.2x$10^9$/L.

**Treatment regimen**

IST products for AA in our center included rATG and CSA from March 2013 to July 2020. Before rATG administration, the patients received a subcutaneous test dose to assess potential hypersensitivity. rATG dose was 3.3 – 3.5 mg/kg/day, administered by intravenous injection for 5 consecutive days. Methylprednisone at 2 mg/kg/day was injected intravenously for 5 days (before each rATG), followed by oral prednisone, which was gradually decreased within 14 days. From day 1, G-CSF was injected subcutaneously to maintain granulocytes at 1.0x$10^9$/L; from day 1, CSA was administered orally at a dose of 5 mg/kg/day to maintain the serum trough concentration at about 100-200 mg/dl. Serum CSA levels were measured every 2-4 weeks during drug administration. CSA was administered at full dose for at least 1.5 years, with a decrease at 1.5 years, unless dose reduction or frequent interruption was needed due to toxicity. The selected patients were infused blood products according to institutional policies.

We added eltrombopag to the standard IST since June 2017. The specific usage was as follows: eltrombopag was administered orally on an empty stomach at a dose of 75 mg daily in patients [?]6-years old and 2.5 mg/kg body weight/day in 2-5-year-old individuals. At platelet count > 300x$10^9$/L or toxicity considered to be related to eltrombopag, the drug was discontinued until platelet count dropped to < 100 x $10^9$/L. For responders not meeting the above criteria, eltrombopag was continued indefinitely or stopped at the discretion of the attending physician.

**Definitions**

OS was measured from the first day of IST until death or the date last known alive. Relapse was defined as reduced blood counts that warranted the reintroduction of full-dose CSA. Clonal evolution was defined as progression to myelodysplastic syndrome and acute myeloid leukemia. A PNH clone was considered present if glycophosphatidylinositol hemocytes exceeded 5% according to flow cytometry data. EFS was measured from the start of IST until an event (death, relapse, clone evolution or start of a second therapy for aplastic anemia, either hematopoietic stem cell transplantation or a second course of IST). CR was defined with a bone marrow sample showing <5% myeloblasts with normal maturation of all cell lines and no dysplasia, peripheral blood neutrophil count [?]1x$10^9$/L, hemoglobin [?]10 g/dL, and platelet count [?]100x$10^9$/L. Partial response (PR) was reflected by transfusion independence and G-CSF with ANC [?]0.5x$10^9$/L, hemoglobin [?]8g/dL, and platelet count [?]20x$10^9$/L. OR was defined as at least a PR (PR+CR). No response (NR) was defined as failure in any lineage. These definitions have been previously reported [17]. Response time referred to the time from IST to the first objective response.

**Statistical analysis**

Demographic and baseline clinical data were summarized by descriptive statistics with Excel (Microsoft, Redmond, WA, USA). Normally distributed continuous variables were presented as mean +- standard deviation (SD); non-normally distributed ones were described as median and interquartile range (IQR). Categorical variables were expressed as percentage. The Mann-Whitney U and Pearson v2 tests were used to compare continuous and categorical variables, respectively. Long-term survival odds in patients with categorical and continuous baseline risks were evaluated by the Kaplan-Meier method; the patients lost to follow-up were counted as censored. Median follow-up was determined by the reverse censoring method. $P < 0.05$ indicated statistical significance. Statistical analyses were performed with SPSS 21.0 for Windows (IBM Co., Armonk, NY, USA).

**Results**

**Patient characteristics**

A total of 115 patients with SAA were treated with rATG and CSA from March 2013 to July 2020. Sixty-six patients were administered eltrombopag combined with IST from July 2017 to July 2020, with a median

follow-up of 34 months (range, 18-51 months), including 34 SAA and 32 VSAA cases. The median age was 5.59 years, and the male to female ratio was 1.36:1 in the eltrombopag group. The median disease course before IST was 55 days (range,17-609 days). PNH results were available at diagnosis for 66 patients in the eltrombopag group, and were negative in 40 (60.6%) patients. Totally 7(10.6%) patients had PNH clones between 5.01% and 10% and19 (28.8%) had PNH clones larger than 10% (range, 10.53%-63.59%) in the granulocyte lineage; no patient had clinically evident hemolysis or thrombosis at diagnosis. Forty-nine children with IST treated at our center from March 2013 to May 2017 were assessed as a historical control group; median follow-up was 71 months (range, 53-103 months). The patients included 22 SAA and 27 VSAA cases, with a median age of 6.20 years. The male to female ratio was 0.88:1 in the control group. There were no significant differences in age, sex and disease severity between the two groups (Table 1).

**Hematological response**

The hematological response was evaluated at 3 months, 6 months and 12 months after IST and at the last follow-up in both groups. In the eltrombopag group, the CR and OR rates were 30.3% and 63.6% at 3 months after IST, respectively, versus 8.2% and 49.0% in the control group, respectively. There was a significant difference in CR between the two groups at 3 months (P=0.004). There was no significant difference in OR between the two groups at 3 months (P=0.074). At 6 months, the CR and OR rates were 50.0% and 71.2% in the eltrombopag group, respectively. From 3 to 6 months, 3 NR cases achieved CR, 3 NR cases were converted to PR, 10 PR cases were converted to CR, one PR relapsed, and 18 cases maintained NR. In the control group, the CR and OR rates were 10.2% and 57.1% at 6 months after IST. From 3 to 6 months, one NR case was converted to CR, 9 NR cases were converted to PR, and 16 cases maintained NR. There was a significant difference in CR between the two groups at 6 months (P¡0.001). There was no significant difference in OR between the two groups (P=0.117).

At 12 months after IST, the CR and OR rates were 51.5% and 71.2%, respectively, in the eltrombopag group. From 6 to 12 months, 3 NR cases achieved CR, one NR case was converted to PR, 3 PR cases were converted to CR, one PR and one CR cases relapsed, and 18 cases retained NR. In the control group at 12 months after IST, the CR and OR rates were 42.9% and 65.3%, respectively. From 6 to 12 months, 16 PR cases were converted to CR, one PR case relapsed, and 17 cases retained NR. There were no significant differences in CR (P=0.358) and OR (0.499) between the two groups.

The clinical data were analyzed retrospectively to definite response times in both groups. The median response time was 71 days (interquartile range, 56 to 91 days) in the eltrombopag group. In the control group, the median response time was 90 days (interquartile range, 60 to 135 days). There was a significant difference in response time between the eltrombopag and control groups (P=0.007). The median times to CR in the eltrombopag and control groups were 98 days (interquartile range, 65 to 158 days) and 360 days (interquartile range, 180 to 435 days), respectively, indicating a significant difference between the two groups (p¡0.001). We also compared the times to factor-CSF, red blood cells and platelets between the two groups. There were significant differences between the two groups in these variables (Table 3).

**Long term prognosis**

We evaluated long-term prognosis by comparing OS, relapse, clone evolution and EFS in both groups, as well as factors influencing prognosis. It should be noted that the median follow-up time were 34 months in the eltrombopag group and 71 months in the control group. Unfortunately, 10 patients were lost at the end of follow-up in the control group.

**Overall survival**

OS rates were 97.0% in the eltrombopag group and 96.0% in the control group at the last follow-up. Two patients (3.0%) died in the eltrombopag group, including one who died at 12 months after diagnosis of SAA without hematologic response; the other patient died of hematopoietic stem cell transplantation (HSCT) complications. Two patients (4.1%) died in the control group, including one who died after 2 years without hematologic response; the other case died of transplantation complications. Totally 10 patients (20.4%) were

lost at the end of follow-up in the control group (Table 2). There was no significant difference in OS between the two groups (P=0.999) (Figure 1).

**Relapse**

Of a total of 49 responders in the eltrombopag group, 10.2% relapsed (n=5) compared with 4.1% (n=2) who relapsed in the control group (Table 2). The times to relapse were 5, 9, 11, 12, and 29 months after IST in the eltrombopag group, respectively. Among the relapsed cases of the eltrombopag group, one reached CR after HSCT, and the other four continued oral full-dose CSA with added stanozolol, eltrombopag and traditional Chinese Medicine, and achieved CR (n=1) or partial response (n=3). In the control group, the times to relapse were 10 months and 24 months after IST, respectively. Among the relapsed cases of the control group, one reached CR after HSCT, and the other continued oral full-dose cyclosporine with added stanozolol, showing recovery CR (n=1). There was no significant difference in relapse rate between the two groups (P=0.703).

**Clonal evolution**

No patient evolved to myelodysplastic syndrome or myeloid leukemia in the eltrombopag group. Chromosome karyotypes were monitored regularly during the follow-up, with no positive results. Myeloid gene mutations were monitored regularly. Totally 11 (16.7%) patients showed somatic myeloid gene mutations during the study, including 5 (7.6%) patients showed positive myeloid gene mutation results before treatment; then, three patients (4.5%) remained positive until the endpoint, and the other two patients (3.0%) became negative. Totally 6 patients (9.1%) because positive after IST. In the eltrombopag group, PNH test results showed that 6 months after IST for 33 (78.8%) patients had PNH clones below 5%, 5 (15.1%) cases between 5.01% and 10%, and 2 (6.1%) cases above 10% (range: 44.6%-77.93%). PNH test results were available at 12 months after IST for 32 patients. Totally 28 (87.5%) cases had PNH clones below 5%, 4 (12.5%) between 5.01% and 10%, and none above 10% (Table 4). In the control group, one patient (2.0%) developed clonal evolution and progressed to myelodysplastic syndrome(Table 2).

**Event-free survival**

At the final follow-up in the eltrombopag group, two patients had died, five relapsed, and three (4.5%) received secondary treatment, including oral stanozolol, eltrombopag and traditional Chinese medicine. Totally 12 patients received HSCT, of whom 11 achieved CR and one died of transplantation complications. No patient progressed to myelodysplastic syndrome or myeloid leukemia. Therefore, the EFS rate was 66.6% in the eltrombopag group. In the control group, two patients had died, two relapsed, and 8 (16.32%) showed decreased blood counts and received oral stanozolol and traditional Chinese medicine. Totally 9 patients received HSCT and achieved CR; the remaining patient progressed to myelodysplastic syndrome at 13 months after IST treatment. Therefore, the EFS rate was 57.1% in the control group. There was no significant difference in EFS between the two groups (P=0.967) (Figure 2).

In the eltrombopag group, factors influencing hematological response in the 66 patients were evaluated by logistic regression analysis. It was found that age (P=0.623), gender (P=0.636), absolute neutrophil count (P=0.556) and lymphocyte count (P=0.121) at diagnosis, and PNH clones (P=0.540) and the time from diagnosis to IST treatment (P=0.405) had no effects on prognosis.

**Safety**

In the eltrombopag group, there were no cases of eltrombopag withdrawal due to adverse reactions. The most common adverse events were indirect bilirubin elevation and jaundice (13.6%, 9 patients). Three patients (4.5%) showed transient elevations of liver enzyme levels. One patient showed elevated uric acid (1.5%). The above abnormal laboratory indicators self-resolved or disappeared after eltrombopag withdrawal. None of the patients developed new cataracts or thromboembolic events during the study, and no rashes or myelofibrosis were reported. Adverse events not attributed to eltrombopag by the investigators included neutropenic infections and known toxic effects of rATG and CSA. One patient showed femoral head necrosis at 1 year after IST, which improved after surgery.

## Discussion

Eltrombopag interacts selectively with the thrombopoietin receptor without competing with thrombopoietin; it interacts with the transmembrane domain of human thrombopoietin receptor, initiates a signaling cascade and induces the proliferation and differentiation of bone marrow progenitor cells, and leads to increased proliferation and differentiation of human bone marrow progenitor cells into megakaryocytes and elevated platelet production[18].

The National Institutes of Health (NIH) conducted an adult SAA study, which enrolled 92 consecutive patients in a prospective phase 1–2 study of IST plus eltrombopag as the first line therapy. The CR and OR rates were 39.1% and 87.0% at 6 months, respectively, and the response rate of the eltrombopag group was higher than that of the control group, suggesting that addition of eltrombopag to IST is associated with markedly higher rate of hematologic response among SAA patients[11]. Based on this study, the FDA approved eltrombopag for the first-line treatment of SAA. Meanwhile, the NIH published a prospective study of eltrombopag in children in 2021, with eltrombopag as the first-line therapy for IST of AA, which showed that in the eltrombopag and control groups, the OR rates were 70% and 72%, respectively, at 6 months (P=0.78). CR totaled 30% in the eltrombopag group versus 23% in the control group at 6 months, without statistical significance (P=0.42). This pointed out that addition of eltrombopag to standard IST did not improve outcomes in children with SAA, and eltrombopag in the pediatric population should not automatically be considered the standard of care [14]. On the other hand, a study performed in Greece showed OR and CR rates of 81.8% and 72.7% at 3 months, respectively, indicating addition of eltrombopag to IST is associated with increased hematological response[19]. St. Jude Children's Research Hospital reported in 2021 that addition of eltrombopag to standard IST was well tolerated and resulted in satisfactory hematological response at 6 and 12 months [15]. Olga Goronkova firstly published a multicenter randomized study assessing eltrombopag in combination with standard IST in children with SAA for efficacy and safety in 2022. They concluded that adding eltrombopag to standard IST was well tolerated and increased the CR rate in children [20]. Previous studies assessing children have shown conflicting results. We conducted this study, analyzed SAA cases in children in our center retrospectively, and compared the eltrombopag + IST group with the standard IST group, with comparable baseline features in the two groups. This study showed a faster response in blood count because of the shorter time from G-CSF, red blood cell transfusion and platelet transfusion; meanwhile, eltrombopag reduced the response time. Furthermore, the CR rates were higher in the eltrombopag group compared with the control group at 3 months and 6 months after IST, suggesting that eltrombopag shows a better and earlier hematological response. However, the CR rate at 12 months and the OR rates at 3, 6 and 12 months after IST all showed no significant differences between the two groups. Therefore, in this study eltrombopag combined with IST showed no advantages in OR and long-term CR rates. Whether our findings were affected by loss to follow-up and different follow-up times is unknown.

In a study by the NIH on pediatric SAA, 43% cases relapsed (n=12) in the eltrombopag group versus 27% in the control group, with a trend towards higher relapse rate compared with IST alone. EFS at 1432.5 days (median follow-up time in the eltrombopag group) in 6-month responders was significantly lower in the eltrombopag group (57%) compared with the IST group (69%) [14]. However, other pediatric studies showed no significant differences in relapse rate and EFS between the eltrombopag and control groups[15-16]. In this study, the OS rates were 97.0% in the eltrombopag group and 96.0% in the control group. There was no significant difference in relapse rate between the two groups. Clonal evolution, progression to myelodysplastic syndrome and acute myeloid leukemia were also assessed in this study. Until the end of follow-up, no cases of clonal evolution were found in the eltrombopag group, while one case in the control group progressed to myelodysplastic syndrome. There were few cases of clonal evolution, which may be related to insufficient follow-up time. Long-term EFS rates in this study were 66.6% in the eltrombopag group and 57.1% in the control group, with no significant difference.

The potential toxicity of eltrombopag includes thrombocytosis, thrombosis, reversible bone marrow fibrosis, rebound thrombocytopenia, cataract formation, and reversible hepatic dysfunction[20]. Many studies have reported that eltrombopag shows satisfactory safety in children [4] [11] [14-16]. Eltrombopag was not discon-

tinued because of adverse events in any patient in this study, showing that eltrombopag is well tolerated in children with SAA.

Based on these results, eltrombopag added to IST confers faster hematological response and higher early hematological response rate. Eltrombopag is well tolerated in pediatric aplastic anemia patients. However, it has no impact on long-term response rate and prognosis in this study. A prospective study is required, and long-term survival needs further investigation.

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**Authorship contributions**

Bixi Yang and Lingling Fu designed the study and wrote the manuscript. Hongmin Li, Hui Chen, Rui Zhang, Jiafeng Yao, Liqiang Zhang collected the medical records and conducted data processing. Jie Ma reviewed and corrected this manuscript professionally. All authors reviewed the manuscript and approved the final submission of the manuscript.

**Disclosure of Conflicts of Interest**

The authors declare no competing financial interests.

**Reference**

[1] Young NS. Aplastic anemia. N Engl J Med. 2018;379(17):1643–1656.

[2] Montane E, Ibanez L, Vidal X, et al. Epidemiology of aplastic anemia: a prospective multicenter study. Haematologica. 2008;93(4):518–523.

[3] Helge D Hartung, Timothy S Olson, Monica Bessler. Acquired aplastic anemia in children. Pediatric clinics of North America 2013 Dec;60(6):1311-36.

[4] Scott A Peslak, Timothy Olson, Daria V Babushok. Diagnosis and Treatment of Aplastic Anemia[J]. Current Treatment Options in Oncology, 2017, 18(12):70.

[5] Scheinberg P, Wu C O, Nunez O, et al. Long-term outcome of pediatric patients with severe aplastic anemia treated with antithymocyte globulin and cyclosporine. [J]. Journal of Pediatrics, 2008, 153(6):814-819.e1.

[6] Rogers Z R, Nakano T A, Olson T S, et al. Immunosuppressive therapy for pediatric aplastic anemia: a North American Pediatric Aplastic Anemia Consortium study[J]. Haematologica, 2019.

[7] Yoshida N, Kobayashi R, Yabe H, et al. First-line treatment for severe aplastic anemia in children: bone marrow transplantation from a matched family donor versus immunosuppressive therapy. [J]. Haematologica, 2014, 99(12):1784-91.

[8] Carlo, Dufour, Marta, et al. Outcome of aplastic anemia in adolescence: a survey of the Severe Aplastic Anemia Working Party of the European Group for Blood and Marrow Transplantation. [J]. Haematologica, 2014, 99(10):1574-81.

[9] Garanito M P, Carneiro J D A, Filho V O, et al. Outcome of children with severe acquired aplastic anemia treated with rabbit antithymocyte globulin and cyclosporine A, [J]. Jornal de Pediatria, 2014.

[10] Dufour C, Pillon M, G Socie, et al. Outcome of aplastic anaemia in children. A study by the severe aplastic anaemia and paediatric disease working parties of the European group blood and bone marrow transplant. [J]. British Journal of Haematology, 2015, 169.

[11] Townsley D M, Scheinberg P, Winkler T, et al. Eltrombopag Added to Standard Immunosuppression for Aplastic Anemia[J]. New England Journal of Medicine, 2017, 376(16):1540-1550.

[12] Matthew J Olnes, Phillip Scheinberg, Katherine R Calvo, et al. Eltrombopag and improved hematopoiesis in refractory aplastic anemia. The New England journal of medicine 2012 Jul 05;367(1):11-9.

[13] Regis Peffault de Latour, Austin Kulasekararaj, Simona Iacobelli, et al. Eltrombopag Added to Immunosuppression in Severe Aplastic Anemia. The New England journal of medicine 2022 01 06;386(1):11-23

[14] Emma M. Groarke, Bhavisha A. Patel, Fernanda Gutierrez-Rodrigues, et al. Eltrombopag added to immunosuppression for children with treatment naive severe aplastic anaemia[J]. British Journal of Haematology, 2021, 192, 605–614.

[15] Harry Lesmana, Timothy Jacobs, Michelle Boals, et al. Eltrombopag in children with severe aplastic anemia. Pediatric blood & cancer 2021 08;68(8): e29066.

[16] Olga Goronkova, Galina Novichkova, Tatiana Salimova, et al. Efficacy of combined immunosuppression with or without eltrombopag in children with newly diagnosed aplastic anemia. Blood advances 2022 Apr 21.

[17] Subspecialty Group of Hematology, Society of Pediatrics, Chinese Medical Association The

Editorial Board, Chinese Journal of Pediatrics. Recommendations for diagnosis and treatment of acquired aplastic anemia in children. Zhonghua Er Ke Za Zhi. 2014;52(2):103–106.

[18] Erickson-Miller C. Preclinical activity of eltrombopag (SB-497115), an oral, nonpeptide thrombopoietin receptor agonist[J]. Stem Cells, 2009, 27.

[19] Filippidou M, Avgerinou G, Tsipou H, et al. Longitudinal evaluation of eltrombopag in paediatric acquired severe aplastic anaemia. Br J Haematol. 2020;190(3): e157–e173. doi:10.

1111/bjh.16766.

[20] Kim TO, Despotovic J, Lambert MP. Eltrombopag for use in children with immunethrombocytopenia. Blood Adv. 2018;2(4):454–461. doi:10.1182/bloodadvances.2017010660.

Table 1: Characteristics of the patients at baseline

| Characteristic | Eltrombopag group (N=66) | Control group (N=49) | All patients (N=115) | All patients (N=115) | P value |
|---|---|---|---|---|---|
| Follow-up-month | | | | | |
| Median | 34 | 71 | 45 | | |
| Range | 18-51 | 53-103 | 18-103 | | |
| Age-year | | | | 0.458 | 0.458 |
| Median | 5.59 | 6.20 | 5.77 | | |
| Range | 1.47-16.29 | 2.27-13.88 | 1.47-16.29 | | |
| Sex-no. (%) | | | | 0.258 | 0.258 |
| Male | 38(57.6) | 22(44.9) | 60(52.1) | | |
| Female | 28(42.4) | 27(55.1) | 55(47.9) | | |
| Severity classification-no. (%) | | | | 0.483 | 0.483 |
| SAA | 34(51.5) | 22(44.9) | 56(48.7) | | |
| VSAA | 32(48.5) | 27(55.1) | 59(51.7) | | |

Table 2: Hematologic response in patients treated with immunosuppression and eltrombopag

| | Eltrombopag group | Control group | ALL patients | P value |
|---|---|---|---|---|
| Rate at 3 Mo | | | | |
| No. of patients | 66 | 49 | 115 | |
| Response-no. (%) | | | | |
| CR | 20(30.3) | 4(8.2) | 24(20.9) | 0.004 |
| OR | 42(63.6) | 23(46.9 | 66(57.4) | 0.074 |
| Rate at 6 Mo | | | | |
| No. of patients | 66 | 49 | 115 | |
| Response-no. (%) | | | | |
| CR | 33(50.0) | 5(10.2) | 38(33.0) | ¡0.001 |
| OR | 47(71.2) | 28(57.1) | 75(65.2) | 0.117 |
| Rate at 12 Mo | | | | |
| No. of patients | 66 | 49 | 115 | |
| Response-no. (%) | | | | |
| CR | 34(51.5) | 21(42.9) | 55(47.8) | 0.358 |
| OR | 47(71.2) | 32(65.3) | 79(68.7) | 0.499 |
| Rate at the end of follow-up | | | | |
| Relapse | 5(7.6) | 2(4.1) | 7(6.1) | 0.703 |
| Death | 2(3.0) | 2(4.1) | 4(3.5) | |
| Clonal evolution | 0(0) | 1(2.0) | 1(0.9) | |
| Lost to follow up | 0(0.0) | 10(20.4) | 10(8.7) | |

Table 3: Response times in the two groups

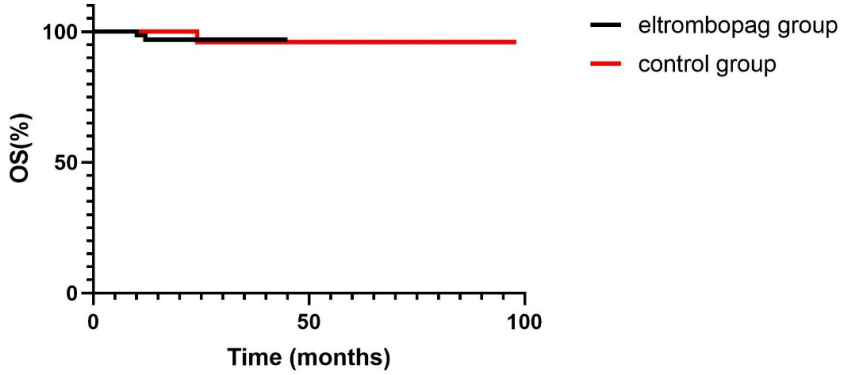
| Time after IST | Eltrombopag group | Control group | P value |
|---|---|---|---|
| OR-days | | | 0.007 |
| Median | 71 | 90 | |
| Interquartile range | 56-91 | 60-135 | |
| CR-days | | | ¡0.001 |
| Median | 98 | 360 | |
| Interquartile range | 65-158 | 180-435 | |
| Separated from G-CSF-days | | | 0.003 |
| Median | 68 | 105 | |
| Range | 34-139 | 25-187 | |
| Separated from Red Blood Cells-days | | | 0.001 |
| Median | 45 | 46 | |
| Range | 12-110 | 13-156 | |
| Separated from Platelets-days | | | ¡0.001 |
| Median | 45 | 54 | |
| Range | 16-122 | 21-150 | |

Table 4: PNH clones in the eltrombopag group

| | Baseline-no. (%) (N=66) | 6 Months-no. (%) (N=33) | 12 Months-no. (%) (N=32) |
|---|---|---|---|
| Below 5% | 40(60.6) | 26(78.8) | 28(87.5) |
| 5.01-10% | 7(10.6) | 5(15.1) | 4(12.5) |

| | Baseline-no. (%) (N=66) | 6 Months-no. (%) (N=33) | 12 Months-no. (%) (N=32) |
|---|---|---|---|
| Above 10% | 19(28.8) | 2(6.1) | 0(0) |

**Figure 1: OS in both groups**



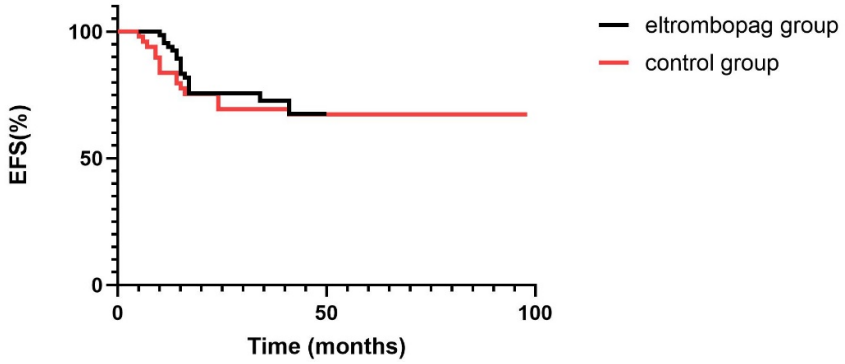




**Figure 2: EFS in both groups**