

A Multicenter Retrospective Study Comparing Immunosuppressive Therapy Combined with Eltrombopag to Immunosuppressive Therapy Alone as Frontline Treatment for Pediatric Severe Aplastic Anemia

Pediyatrik Ağır Aplastik Anemide İlk Basamak Tedavide Eltrombopag ile Birlikte İmmünosüpresif Tedavinin Sadece İmmünosüpresif Tedavi ile Karşılaştırılması: Çok Merkezli Retrospektif Çalışma

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Abstract

Objective: Eltrombopag (EPAG) added to standard immunosuppressive therapy (IST) has been associated with higher overall response (OR) and complete response (CR) rates in adult patients with treatment-naïve severe aplastic anemia (SAA), but clinical evidence on the efficacy of EPAG in children with acquired aplastic anemia is limited and controversial. This retrospective study aimed to determine the efficacy and safety of EPAG combined with IST in pediatric patients with SAA compared to a standard IST group.

Materials and Methods: We compared the efficacy and safety of EPAG combined with IST (n=38) versus IST alone (n=57) as frontline treatment for pediatric patients with SAA.

Results: The EPAG+IST group had higher CR and OR rates at 3 and 6 months, although the 1-year OR, CR, and partial response rates showed no significant difference between the two groups. Older age at diagnosis (>8.95 years) was associated with a higher OR rate at 6 months and 1 year in the EPAG+IST group (p=0.007 and p=0.005, respectively). The addition of EPAG to IST did not achieve superiority over IST alone in terms of overall survival (OS) and event-free survival (EFS) in this study, with 1-year EFS of 81.1% for EPAG+IST and 71.3% for IST, and 1-year OS of 89.2% versus 80.4%, respectively.

Conclusion: EPAG+IST induced a faster response compared to IST alone without increasing toxic effects, but EPAG did not confer additional benefits regarding OS or relapse rates in children. Notably, older age at diagnosis was significantly associated with improved response rates in the EPAG+IST group.

Keywords: Eltrombopag, Immunosuppression, Treatment, Severe aplastic anemia

Öz

Amaç: Standart immünoşüpresif tedaviye (IST) eklenen eltrombopag (EPAG), yetişkinlerde tedavi görmemiş ağır aplastik anemisi (SAA) olan hastalarda daha yüksek genel (OR) ve tam yanıt (CR) oranları ile ilişkilendirilmiştir, ancak edinisel aplastik anemisi olan çocuklarda EPAG'nin etkinliğine ilişkin klinik kanıtlar sınırlı ve tartışmalıdır.

Gereç ve Yöntemler: Çalışmada SAA'lı pediatrik hastalarda ilk basamak tedavi olarak IST ile kombine EPAG'nin (n=38) etkinliği ve güvenliği tek başına IST (n=57) alan hasta grubu ile karşılaştırıldı.

Bulgular: EPAG+IST grubu 3 ve 6 aylarda daha yüksek CR ve OR oranlarına sahipti, ancak 1 yıllık OR, CR ve parsiyel yanıt oranları iki grup arasında anlamlı bir fark göstermedi. EPAG+IST grubunda tanı anında daha büyük yaşta olmak (>8,95 yaş), 6 ay ve 1 yılda daha yüksek OR oranları ile ilişkiliydi (sırasıyla p=0,007, p=0,005). Bu çalışmada EPAG'nin IST'ye eklenmesi, genel sağkalım (OS) ve olaysız sağkalım (EFS) açısından tek başına IST'ye göre üstünlük göstermedi (1 yıllık EFS EPAG+IST için %81,1 ve IST için %71,3 ve 1 yıllık OS %89,2'ye karşı %80,4).

Sonuç: EPAG toksik etkileri artırmadan tek başına IST alanlara kıyasla daha hızlı yanıt almayı sağladı. Ancak IST'ye EPAG eklenmesi çocuklarda OS veya relaps oranları açısından tek başına IST'ye göre ek fayda sağlamadı. Tanı sırasında daha büyük yaşta olan çocuklarda özellikle IST'ye EPAG eklenmesi daha iyi yanıt oranları ile önemli ölçüde ilişkiliydi.

Anahtar Sözcükler: Eltrombopag, İmmünoşüpresyon, Tedavi, Ağır aplastik anemi

Introduction

Acquired aplastic anemia is an immune-mediated bone marrow (BM) failure where marrow disruption is driven by a cytotoxic T-cell-mediated autoimmune attack against hematopoietic stem cells. The current treatment approach for severe aplastic anemia (SAA) consists of immunosuppressive therapy (IST) or hematopoietic stem cell transplantation (HSCT) [1,2]. The standard IST protocol involves the use of anti-thymocyte globulin (ATG) and cyclosporine A (CSA), with studies indicating that horse ATG is superior to rabbit ATG in terms of both short-term response and long-term survival [3,4,5,6,7].

Studies have shown that all patients with SAA have significantly decreased levels of early progenitor cells and hematopoietic stem cells [8,9]. It has also been reported that thrombopoietin (TPO) can stimulate the hematopoietic capacity of primitive hematopoietic stem cells in the BM [9,10]. As an agonist of TPO receptors, eltrombopag (EPAG) has been found to significantly restore trilineage hematopoiesis in patients with refractory aplastic anemia, which can be sustained even upon discontinuation of the drug [8,11,12]. Numerous studies have demonstrated its efficacy in patients with SAA refractory to immunosuppression [13,14,15]. However, findings on the effects of EPAG in pediatric patients with SAA remain controversial and

limited. Data from adults indicate that the addition of EPAG resulted in considerable increases in response rates to >80%, but the same outcome did not occur in children [16,17]. Therefore, we conducted a retrospective study to determine the efficacy and safety of EPAG combined with IST in pediatric patients with SAA in comparison to a standard IST group.

Materials and Methods

This multicenter retrospective study assessed the safety and efficacy of EPAG combined with IST for pediatric patients with SAA in comparison to a standard IST group. Sixteen pediatric hematology centers participated in the study. Group 1 comprised pediatric patients who received EPAG+IST as frontline treatment for SAA. A historical pediatric treatment group that received standard IST as frontline therapy served as Group 2. We also conducted subgroup analysis based on the median age of 8.95 years in our study to assess the impact of age on treatment outcomes.

This study was approved by the Ethics Committee of the Acıbadem University Faculty of Medicine (no: 2024-5/166, date: 28 March 2024). Informed consent was obtained from all patients and/or their legal guardians according to the Declaration of Helsinki.

Definitions

SAA was defined as BM cellularity of <25% and at least two of the following: absolute neutrophil count (ANC) of $<0.5 \times 10^9/L$, platelet count of $<20 \times 10^9/L$, or reticulocyte count of $<20 \times 10^9/L$ (or corrected reticulocyte count of <1%), according to the Camitta criteria [18]. Very severe cases of SAA were identified using the same criteria applied for SAA with the following modification: neutrophil count of $<0.2 \times 10^9/L$.

Overall response (OR) was defined as no longer meeting the criteria for SAA in the absence of recent transfusions and without the administration of granulocyte colony-stimulating factor (G-CSF). Complete response (CR) required all of the following criteria to be satisfied: ANC of $\geq 1.0 \times 10^9/L$, hemoglobin of ≥ 10 g/dL, and platelet count of $\geq 100 \times 10^9/L$. Partial response (PR) was defined as an overall outcome where the patient did not meet the criteria for CR but still achieved transfusion independence, with ANC of at least $0.5 \times 10^9/L$, hemoglobin of at least 8 g/dL, and platelet count of at least $20 \times 10^9/L$. Patients who did not complete 6 months of initial IST due to death or HSCT or who underwent a second course of IST or failed to achieve a response by 6 months were considered to have had no response.

Treatment Protocol

Patients with previously untreated SAA without matched sibling donors were eligible for inclusion in this study. Patient histories and clinical and laboratory tests were used to screen for classical inherited BM failure syndromes. The diepoxybutane test was applied to rule out Fanconi anemia. Paroxysmal nocturnal hemoglobinuria (PNH) clones were assessed by flow cytometry. Standard cytogenetic analysis and fluorescence in situ hybridization for monosomy 7 were performed to exclude clonal abnormalities. In the group treated with standard IST, patients received horse-derived ATG at 40 mg/kg per day (ATGAM, Pfizer, New York, NY, USA) for 4 days and oral CSA at 3-5 mg/kg per day (Sandimmun Neoral, Novartis, Basel, Switzerland) starting on day 1 to maintain whole blood trough concentrations of 150 to 300 ng/mL. In addition, methylprednisolone was administered intravenously at 1 mg/kg per day on days 1 to 4, followed by administration of oral prednisolone at 1 mg/kg per day for 10 days without tapering. CSA was continued for ≥ 18 months after achieving a hematological response plateau, followed by tapering by 5% to 10% of the daily dose per month.

In the EPAG+IST group, the patients additionally received EPAG (Revolade, Novartis) at an initial daily dose of 150 mg for patients aged ≥ 12 years, 75 mg for those aged 6-11 years, and 2.5 mg/kg for those aged 2-5 years starting on day 1 of the ATG administration. These doses were subsequently adjusted according to the results of complete blood counts. The duration of EPAG treatment was ≥ 120 days, and in the absence of at least PR at 3 months, EPAG was discontinued and patients received second-line treatment.

Response Evaluation

The primary endpoints were responses, including CR and PR, at the following timepoints: 3, 6, and 12 months, as well as at the end of treatment. Secondary indexes included times of transfusion independence for G-CSF, red blood cells, and platelets.

The secondary endpoints were safety parameters including the tolerability and toxicities of EPAG, relapse rate, overall survival (OS), and event-free survival (EFS).

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics 22.0 (IBM Corp., Armonk, NY, USA). For data that were not normally distributed, findings were presented as medians and ranges. The Kaplan-Meier method was used to analyze OS and duration of responses. The Mann-Whitney U test and Pearson chi-square test were used to compare continuous and categorical variables with a level of statistical significance of $p < 0.05$. Fisher's exact test was used to compare categorical variables between groups when the expected cell frequencies were < 5 . Variables with a p value of less than 0.2 in univariate analysis were included in the multivariate analysis. Multivariable Cox proportional hazard regression models were used to analyze the factors influencing both OS and EFS.

Results

Patient Characteristics

A total of 95 pediatric patients aged between 1.2 and 18 years (median: 8.95 years) were included in this study. The duration of EPAG treatment was a median of 28 (4-106) weeks. The median follow-up period was 41.73 (1.10-88.77) months in the EPAG+IST group and 69 (1.03-344.13) months in the IST group.

Hematological Response

Patients in the EPAG+IST group had higher probabilities of CR and OR at 3 months and 6 months ($p=0.02$; Table 2). The CR rate was 15.6% at 3 months and 48.1% at 6 months in the EPAG+IST group compared to 1.8% and 13.3% in the IST group, respectively ($p=0.01$ and $p=0.002$, respectively). Additionally, the number of non-responding patients was higher in Group 2 at 3 months (66.1%) and at 6 months (48.9%). However, the response rates at the end of therapy and at 1 year were not statistically significantly different between the groups in terms of OR, CR, PR, or NR.

Relapse and Clonal Evolution

Of the 17 patients in Group 1 with CR, 11.7% relapsed compared to 11.1% in Group 2. The time to relapse was 4 and 18 months following the cessation of EPAG therapy for the relapsed patients in Group 1, while it was 30 and 48 months following the cessation of IST for the relapsed patients in Group 2. The

Table 1. Patients' characteristics.

	EPAG+IST (Group 1, n=38)	IST (Group 2, n=57)	p
Age at diagnosis, years, median (range)	10.42 (1.42-17.50)	8.75 (1.2-18)	0.65
Laboratory values, median (range)			
Hemoglobin, g/dL	7.1 (3.2-12.3)	6.9 (1.5-11.5)	0.06
Absolute neutrophil count, x10 ⁹ /L	0.13 (0-3.2)	0.1 (0-1.8)	0.27
Platelet count, x10 ⁹ /L	6 (1-68)	10 (1-76)	0.02
Median duration of follow-up, months	41.73 (1.1-88.77)	69 (1.03-344.13)	0.11

EPAG: Eltrombopag; IST: immunosuppressive therapy.

Table 2. Hematological responses in each of the treatment groups.

	EPAG+IST (Group 1, n=38)	IST (Group 2, n=57)	p
3-month response, n (%)			
OR	19 (59.4)	19 (33.9)	0.02
CR	5 (15.6)	1 (1.8)	0.01
PR	14 (43.8)	18 (32.1)	
NR	13 (40.6)	37 (66.1)	
Off-study*	6	1	
6-month response, n (%)			
OR	22 (81.5)	23 (54.8)	0.02
CR	13 (48.1)	6 (13.3)	0.002
PR	9 (33.3)	17 (37.8)	
NR	5 (18.5)	22 (48.9)	
Off-study	11	12	
1-year response, n (%)			
OR	20 (80)	25 (78.1)	0.86
CR	16 (64)	14 (43.8)	0.23
PR	4 (16)	11 (34.4)	
NR	5 (20)	7 (21.9)	
Off-study	13	25	
Response at end of therapy, n (%)			
OR	23 (60.5)	27 (47.41)	0.20
CR	17 (39.5)	18 (31.6)	0.38
PR	6 (15.8)	9 (15.8)	
NR	15 (39.5)	30 (52.6)	
Relapse/responders, n	2/23	2/27	0.83
Clonality, n (%)	4 (10.52)	11 (19.30)	0.27
Time to platelet transfusion independence, days, median (range)	60 (14-171)	64.5 (3-550)	0.38
Time to RBC transfusion independence, days, median (range)	49 (14-171)	77 (28-751)	0.05
OS			
1-year OS, %	89.2	80.4	0.26
2-year OS, %	86.5	74.7	
5-year OS, %	82.6	72.2	
EFS			
1-year EFS, %	81.1	71.3	0.14
2-year EFS, %	78.4	65.4	
5-year EFS, %	74.3	53.5	

EPAG: Eltrombopag; IST: immunosuppressive therapy; OR: overall response; CR: complete response; PR: partial response; NR: no response; RBC: red blood cell; OS: overall survival; EFS: event-free survival.

*Off-study: Patients were off-study at 3 months, 6 months, and 1 year for a variety of reasons including EPAG stopped due to toxicity, alternate treatment such as repeated IST or hematopoietic stem cell transplantation, death, or being lost to follow-up. Patients who were deemed non-responders at 3 or 6 months were not routinely monitored for late response beyond this timepoint as they were deemed off-study.

cumulative incidence of relapse did not differ significantly between the groups.

The most frequent clonal evolution was the development of PNH clones. Ten patients developed PNH during follow-up, while progression to myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML) was observed in 5 patients. In Group 1, clonality was observed in 4 patients, including 3 with PNH and 1 with MDS. The PNH clone appeared in those 3 patients at 4, 11, and 12 months after therapy, while MDS was detected 3 months after therapy. In Group 2, clonality was observed in 11 patients, including 7 with PNH, 3 with MDS, and 1 with AML. The PNH clone appeared in those 7 patients between 8 and 84 months after therapy. MDS was detected in 3 patients at 4, 12, and 22 months after therapy, and AML was detected in 1 patient 9 months after therapy. No PNH-related clinical manifestations were detected. HSCT was performed for all patients who developed MDS or AML. The rates of clonal evolution did not significantly differ between the groups.

OS and EFS

Twenty-three patients died during the course of the study, including 6 patients in Group 1 and 17 patients in Group 2. Three patients in Group 1 and 4 patients in Group 2, who were non-responders, died due to post-HSCT complications including graft-versus-host disease and infection. Three patients in Group 1 and 13 patients in Group 2 died due to cytopenia related to an infection or bleeding complications. The EFS rate was similar between Group 1 and Group 2 ($p=0.142$; Table 2, Figure 1). Similarly, no difference was found in the OS rates of the two groups ($p=0.26$; Table 2, Figure 1).

Subgroup Analysis

Subgroup analysis showed that the OR rates at 6 months and 1 year were significantly better in the subgroup of children aged >8.95 years respectively ($p=0.012$, $p=0.010$, Table 3). This observed significance was only applicable for patients in the

EPAG+IST group. However, the response rate at 6 months and 1 year was significantly higher in the whole EPAG+IST group compared to the subgroup of patients younger than 8.95 years ($p=0.007$ and $p=0.005$, respectively).

While there was no difference in OS between the two subgroups, EFS was statistically significantly better in younger patients compared to older patients ($p=0.01$; Figure 2). However, this significance was only observed for the patients receiving IST therapy ($p=0.006$).

Clonality was statistically more frequent in children older than 8.95 years (25.5% vs. 6.4%; $p=0.01$). A higher occurrence of clonality was observed in children aged >8.95 years who received IST alone. Detailed treatment responses and survival analysis results are summarized in Table 3.

Predictors of Response

Details of the multivariable analyses are provided in Table 4. In multivariable analysis, randomization groups, patient age at diagnosis, and initial platelet counts were the only three factors associated with response. Patients in the EPAG+IST group had a higher probability of OR at 3 months and at 6 months. Higher initial platelet counts were significantly related to higher rates of OR at 3 months. Younger age at diagnosis was associated with lower rates of OR at 6 months and 1 year.

Multivariate analysis was also performed for OS in terms of randomization groups, age at diagnosis, hemoglobin at diagnosis, ANC at diagnosis, platelet count at diagnosis, 3-month responses, 6-month responses, 1-year responses, and not receiving G-CSF therapy. This analysis showed that none of these factors significantly affected OS, but being a non-responder significantly correlated with worse OS ($p=0.004$).

For EFS, being a non-responder, not receiving G-CSF therapy, and older age at diagnosis were confirmed as risk factors ($p=0.017$, $p=0.048$, and $p=0.008$, respectively; Table 4).

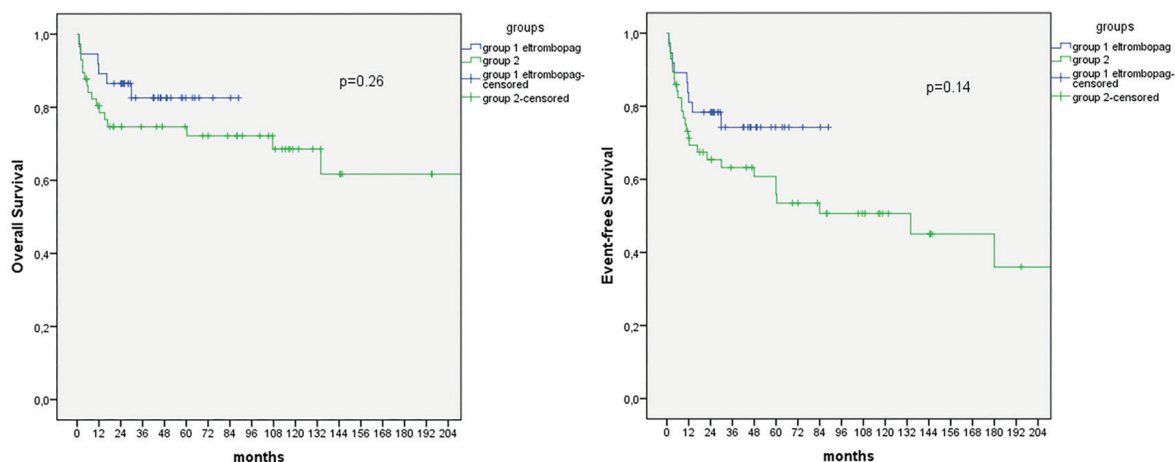


Figure 1. Comparisons of overall survival and event-free survival between treatment groups.

Table 3. Comparison of hematological responses between subgroups according to age at diagnosis.

	Subgroup 1, age of <8.95 years (n=47)	Subgroup 2, age of >8.95 years (n=48)	p
3-month response, n (%)			
OR	16 (37.2)	22 (47.7)	0.29
CR	2 (4.7)	4 (9.1)	0.48
PR	14 (32.6)	18 (40.9)	
NR	27 (62.8)	22 (50)	
Off-study*	4	4	
6-month response, n (%)			
OR	17 (50)	27 (79.4)	0.012
CR	7 (20.6)	11 (30.6)	0.02
PR	9 (26.5)	17 (47.2)	
NR	18 (52.9)	8 (22.2)	
Off-study	13	12	
1-year response, n (%)			
OR	18 (64.3)	27 (93.1)	0.010
CR	14 (56)	16 (55.2)	0.013
PR	4 (16)	11 (37.9)	
NR	7 (28)	2 (6.9)	
Off-study	22	19	
Response at end of therapy, n (%)			
OR	21 (44.7)	28 (60.4)	0.15
CR	14 (29.8)	21 (43.8)	0.28
PR	7 (14.9)	8 (16.7)	
NR	26 (55.3)	19 (39.6)	
Relapse/responders, n	1/21	3/28	0.42
Clonality, n (%)	3 (6.4)	12 (25.5)	0.01
Time to platelet transfusion independence, days, median (range)	109.5 (14-730)	70.5 (3-875)	0.07
Time to RBC transfusion independence, days, median (range)	120 (14-730)	79 (20-852)	0.10
OS			0.74
1-year OS, %	84.8	82.8	
2-year OS, %	80.3	78.5	
5-year OS, %	76	75.7	
EFS			0.01
1-year EFS, %	82.7	67.6	
2-year EFS, %	78.1	63.1	
5-year EFS, %	69.7	49.2	

OR: Overall response; CR: complete response; PR: partial response; NR: no response; RBC: red blood cell; OS: overall survival; EFS: event-free survival.
*Off-study: Patients were off-study at 3 months, 6 months, and 1 year for a variety of reasons including EPAG stopped due to toxicity, alternate treatment such as repeated IST or hematopoietic stem cell transplantation, death, or being lost to follow-up. Patients who were deemed non-responders at 3 or 6 months were not routinely monitored for late response beyond this timepoint as they were deemed off-study.

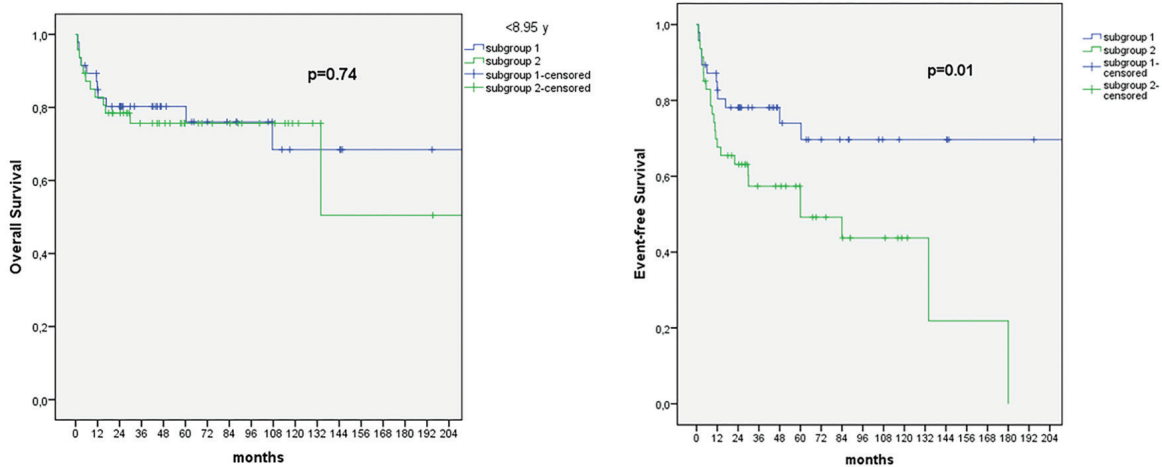


Figure 2. Comparisons of overall survival and event-free survival between subgroups according to median age (subgroup 1: age of <8.95 years; subgroup 2: age of >8.95 years).

Table 4. Multivariate analysis of factors associated with favorable outcomes.		
Outcomes	Odds ratio (95% CI)	p
Overall response 3 months after treatment		
Group (EPAG+IST vs. IST)	0.136 (0.035-0.531)	0.004
Platelet count at diagnosis	1.000 (1.000-1.000)	0.030
Overall response 6 months after treatment		
Patient age at diagnosis	1.147 (1.026-1.283)	0.016
Group (EPAG+IST vs. IST)	0.274 (0.081-0.927)	0.037
Overall response 1 year after treatment		
Patient age at diagnosis	1.321 (1.096-1.592)	0.003
Outcomes	Hazard ratio (95% CI)	p
Overall survival		
Overall response after treatment	0.122 (0.029-0.516)	0.004
Event-free survival		
Patient age at diagnosis	1.167 (1.041-1.308)	0.008
Overall response after treatment (no vs. yes)	0.255 (0.083-0.786)	0.017
G-CSF treatment (no vs. yes)	0.341 (0.118-0.990)	0.048

CI: Confidence interval; EPAG: eltrombopag; IST: immunosuppressive therapy; G-CSF: granulocyte colony-stimulating factor.

Safety Data

EPAG was well tolerated, with no serious adverse events observed related to the therapy. Four patients had reversible liver function abnormalities possibly attributable to EPAG. The most common adverse event was indirect bilirubin elevation. Fifteen patients in the EPAG group (44.7%) had indirect hyperbilirubinemia, which was temporary and controllable for 9 patients with dose reduction. Seven patients, who were also non-responders or PRs, discontinued their medication due to grade 2 indirect hyperbilirubinemia.

Discussion

SAA is primarily an immune-mediated, acute-onset, rapidly progressive disease. Studies, particularly those involving adults, have shown that the addition of EPAG to standard IST improves the rate, rapidity, and strength of hematological response in previously untreated patients with SAA without adding further toxic effects. The EBMT phase III study comparing first-line ATG and CSA with or without EPAG for SAA (RACE trial) showed a significant increase in CR with EPAG [14]. The addition of EPAG increased the rate of CR at 3 months, OR at 6 months, and shorter median times to response compared to standard IST.

Two-year OS rates were similar between the two arms. However, the efficacy of frontline concomitant IST and EPAG in pediatric patients is still unclear. In a study of 40 pediatric patients, Groarke et al. [16] found no improvement at 6 months in terms of OR and CR compared to a historical IST cohort. Goronkova et al. [19] conducted a randomized prospective study to compare the efficacy and safety of IST with (n=49) or without (n=49) the addition of EPAG in children with SAA and they reported no significant difference in OR at 4 months between the groups, although the rate of CR at 4 months was higher in the IST+EPAG group. No difference in survival was observed between the groups. In our study, patients in the EPAG+IST group had higher CR and OR rates at 3 and 6 months compared to those treated with IST alone. More non-responders were found in the IST group than the EPAG+IST group at 3 months and 6 months. Long-term response rates showed no significant difference between the groups, but the addition of EPAG to IST provided patients with the opportunity to respond in an earlier period. Prolonging treatment beyond 3-6 months for patients with PR did not lead to CR. While long-term CR rates were higher in the EPAG+IST group than the IST group (64% vs. 43.8%), this finding was not statistically significant.

Previous pediatric studies have also addressed the impact of age on treatment outcomes, suggesting that younger children may not experience the same benefits from EPAG. Groarke et al. [16] found that younger children (<12 years) had lower response rates than adolescents when treated with EPAG, with OR and CR rates of 63% versus 78% and of 6% versus 46%, respectively. Similarly, Zhao et al. [17] demonstrated that younger children (<14 years) had lower response rates compared to adolescents, with OR rates of 50.0% versus 85.7% and CR rates of 12.5% versus 85.7%. Our subgroup analysis based on median age revealed higher OR rates in older children (>8.95 years) at 6 months (50% vs. 79.4%) and 1 year (64.3% vs. 93.1%). However, statistical significance was only achieved for older patients treated with EPAG+IST (p=0.007 and p=0.005, respectively). Due to the small sample size of our study, these conclusions require further verification, and it is essential to investigate the potential mechanisms underlying the differences in responses between younger children and adolescents.

The addition of EPAG to IST did not yield superiority compared to IST alone in terms of OS and EFS in this study. However, EFS was statistically significantly better in younger patients receiving IST. Further analysis of the factors influencing EFS revealed a higher incidence of clonality in children older than 8.95 years (25.5% vs. 6.4%). While age did not affect clonality development in patients treated with EPAG+IST, a higher occurrence of clonality was noted in older patients who received only IST. Future studies involving larger patient populations would clarify this matter. In our cohort, with a median follow-up duration of 44.5 months,

adding EPAG to IST treatment did not reduce relapse frequency, consistent with the findings of previous pediatric studies.

The ability to identify patients who have a higher probability of hematological response is important. None of the previously reported baseline hematological characteristics were associated with the OR rate in our study [20,21]. Our findings indicated that the addition of EPAG to IST therapy, older age at diagnosis, and higher initial platelet counts were the only three factors significantly associated with hematological response in multivariate analyses. Additionally, being a non-responder was significantly correlated with worse OS.

Conclusion

In our pediatric study, EPAG induced a faster response compared to IST alone without increasing the rate of toxic effects. However, the question of which SAA patients will benefit most from the addition of EPAG to their therapy remains unresolved. The retrospective nature of this study limited its power. Due to the varying results obtained for different pediatric groups, it remains uncertain whether concomitant EPAG+IST is superior to IST alone. These outcomes should be further validated with large, prospective, multicenter studies in the future.

Ethics

Ethics Committee Approval: This study was approved by the Ethics Committee of the Acibadem University Faculty of Medicine (no: 2024-5/166, date: 28 March 2024).

Informed Consent: Informed consent was obtained from all patients and/or their legal guardians according to the Declaration of Helsinki.

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