Randomized Clinical Trial of the Use of Eltrombopag in Children with Aplastic Anemia

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ABSTRACT

ABSTRACT: Severe aplastic anemia is a life - threatening disorder that requires prompt treatment. For children not eligible for Hematopoietic Stem Cell Transplantation (HSCT), the Standard Immunosuppressive Therapy (IST) consisting of Antithymocyte Globulin (ATG) and Cyclosporine (CSA) is the ideal treatment for patients with Severe Aplastic Anemia (SAA). The addition of ELTROMBOPAG (E - PAG) with IST shows good improvement in the response rates, a rise of blood cell counts, and recovery of trilineage hematopoiesis. The purpose of this study was to compare the efficacy and safety of E - PAG combined with CsA and immunosuppressive mono therapy of CsA for treatment in children with SAA.

METHOD: This was a prospective clinical trial with a patient sample of $^{2}0$ children diagnosed with SAA. Half of the participants were treated with CsA monotherapy. The other half was treated with combined E - PAG + CsA. All patients were evaluated for hematological response, complete response, and partial response at 3, 6, and 12 months. We also measured treatment safety and tolerability.

RESULTS: The overall response rate for the E - PAG patients was 40 % after three months of therapy. At six months, this had increased to 80 %, and the percentage of patients showing a complete response (40 %) was significantly higher than in the CsA group ($p = 0.006$). After a year of regular treatment, the complete response rate for the E - PAG regimen had increased to 60 % and the overall response rate to 90 %, compared to a rate of 20 % in the CsA group ($p = 0.01$). The survival rate at 12 months was 100 % in the E - PAG group compared to 80 % in the CsA cohort. In conclusion, combined treatment with CsA + E - PAG was found to be a safe, well - tolerated and effective alternative treatment for children with SAA.

KEYWORDS
Severe aplastic anemia, Children, Cyclosporine, Eltrombopag

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INTRODUCTION

Aplastic Anemia (AA) is a life - threatening condition, a rare disorder characterized by pancytopenia and hypo cellular bone marrow in the absence of major dysplastic signs and marrow fibrosis.[1] The incidence of acquired AA is about two per million children per year in Europe and North America but the incidence is 2 - 3 times higher in East Asia.[2] Both males and females are equally affected. AA occurs in all age groups with a small peak in incidence in childhood. Half of the cases of AA present in the first three decades of life.[3] the pathogenesis of AA are multifactorial and it involves an abnormal hematopoietic microenvironment, hematopoietic stem cell / progenitor cell deficiencies, immunity disorder, and mutation in genes controlling hematopoiesis. Any of these factors causes primary defects in or damage to the stem cell or the marrow microenvironment.[4] the clinical presentation of AA is anemia, usually with an increased requirement for frequent red blood cell transfusions and the associated neutropenia and thrombocytopenia that can lead to potentially life - threatening infections and bleeding, respectively.[5] There is a clinical challenge to distinguish between acquired and inherited disease. Inherited causes of aplastic anemia are responsible for at least 25 % of children with this condition. Acquired causes of aplastic anemia form 80 % of cases and include Idiopathic (> 80 %), Post - infectious 15 % particularly after hepatitis, Epstein - Barr virus, human immune deficiency virus, parvovirus, and mycobacteria, Drug - induced and toxins (4 %). All patients should be screened to rule out hypoplastic myelodysplasia / leukemia, congenital marrow failure, infections, and Paroxysmal Nocturnal Haemoglobinuria (PNH). The Hematopoietic Stem Cell Transplantation (HSCT) from an HLA Matched Sibling Donor (MSD) considers a definitive and potentially curative therapy for AA and it shows excellent results. The drawbacks of HSCT are only 30 % of patients have a suitably matched donor in addition to the Graft – Versus - Host Disease (GVHD) that causes great morbidities and mortality with the affection of long - term quality of life. Also, the remote complication of HSCT comprises an increased risk of malignancy and infertility related to HSCT conditioning therapy. The alternative treatment in about two - thirds of cases is Immunosuppressive Therapy (IST) which consists of anti - thymocyte globulin (horse or rabbit) and cyclosporine (CsA). IST carries a satisfactory long - term response but 30 – 40 % of patients do not respond to immunosuppressive therapy and continue to have pancytopenia after therapy or may have persistent thrombocytopenia even with an improvement in their life - threatening neutropenia. HSCT and IST regimens can control the manifestation of AA effectively but both have limitations. HSCT costs a lot on the other hand, many patients are unsuitable. IST may leave a significant number of patients having persistent cytopenias. Actually, the treatment of these patients is regular transfusion, which is expensive, inconvenient, and associated with serious side effects related to iron overload. Thrombopoietin (TPO) is a glycoprotein class 1 hematopoietic cytokine, manufactured mainly in the liver. It is an essential regulator of hematopoiesis. It acts through the TPO receptor, called c - Mpl that is expressed on hematopoietic stem and progenitor cells. Its action causes signal transduction events that prevent apoptosis, improve cell viability, promote growth, and possibly increase differentiation. Eltrombopag (E - PAG) is an oral thrombopoietin mimetic that selectively binds to c - MPL at the transmembrane and juxtamembrane domains of the thrombopoietin receptor. There is no competition between the native molecule and E - PAG for binding sites as it attaches in a distinct position from the binding site of TPO. It promotes thrombopoiesis and the release of platelets from mature megakaryocytes. It also can promote other hematopoietic stem cell differentiation. E - PAG got the approval of the Food and Drug Administration (FDA) in 2008 as the first oral platelet growth factor. This approval is for its use in adult patients with chronic Immune Thrombocytopenic Purport (ITP). On this approval was extended to include the children group who are aged 1 to 17 with chronic ITP. In addition, it has been recently shown a brilliant result in AA with trilineage responses in some patients and many achieving transfusion independence.[6] It has licensed by the European Medicines Agency for this indication in the National Institutes of Health (NIH) made E - PAG a standard of care in aplastic anemia. Due to these encouraging early preliminary results in addition to low toxicity and ease of administration of this drug, we started a study to explore the effectiveness and safety of E - PAG in sever aplastic anemia patients and comparing between E - PAG added to CsA versus CsA only.[7]

MATERIAL AND METHODS

Design

The current study was an interventional, prospective clinical trial, achieved at Assiut University children Hospital in Egypt. This study enrolled 20 patients between 1 and 18 years with aplastic anemia our sample comprised two groups. 10 patients received CsA monotherapy (CsA group). 10 patients treated with E - PAG + CsA (E - PAG group). Pre - treatment evaluations included a complete medical history and physical examination, Complete Blood Count (CBC) with differential, serum chemistry, bone marrow aspiration and biopsy, viral serology, peripheral blood flow cytometer for PNH antigens (CD_{55} and CD_{59}) chromosomal breakage to exclude Franconia anemia, and inherited bone marrow failure panel.[8] Patient follow - ups were performed every 2 – 4 weeks and included a CBC and monitoring of kidney and liver function.[9]

Eligibility Criteria

Children with newly - diagnosed and previously untreated SAA and adequate hepatic and renal functions who met the modified Camitta criteria for SAA were eligible for inclusion in this study. According to these criteria, a diagnosis of SAA may be made if bone marrow cellularity is < 25 % and / or at least two of the following criteria are met: (i) the absolute neutrophil count is below 0.5×10^9 / L (ii) the platelet count is below 20×10^9 / L, (iii) the reticulocyte count is below 20×10^9 / L. The exclusion criteria were inherited bone marrow failure, myelodysplasia, AA secondary to infection or organ failure, underproduction anaemias secondary to B_{12}, foliate or iron deficiency, or with other reversible causes. Patients with documented hypersensitivity to any of the component medications were also excluded.[10]

Treatment Plan

Patients have received Eltrombopag at an initial oral dose of 25 mg once daily in patients aged 1 - 5 years and 50 mg / day in patients aged ≥ 6 years. It must be administered on an empty stomach, 1 h before or 2 h after a meal, and not within 4 h of taking other medications, such as antacids, or supplements containing polyvalent cations (iron, calcium,

aluminum, magnesium, selenium, and zinc). The initial dosage is reduced to 25 mg once daily in patients with hepatic impairment with no change of dosage in patients with renal impairment After 2 weeks, the dose was increased by 25 mg every 2 weeks to a maximum of 75 mg in a patient aged from one year to five years and 150 mg in patients aged older than five years if the platelet count had not increased by 20,000 per cubic millimeter from baseline or platelet - transfusion requirements had not decreased. The dosage should be decreased by 25 mg / day for 2 weeks if the platelet count increases at any time to between 200,000 and 400,000 / lL and should be suspended for 1 week if the platelet count exceeds 400,000 / lL, with reintroduction 1 - Patients have received E - PAG at an initial oral dose of 25 mg once daily in patients aged 1- 5 years and 50 mg / day in patients aged ≥ 5 years. It must be administered on an empty stomach, 1 h before or 2 h after a meal, and not within 4 h of taking other medications, such as antacids, or supplements containing polyvalent action (iron, calcium, aluminum, magnesium, selenium, and zinc). The initial dosage is reduced to 25 mg once daily in patients with hepatic impairment with no change of dosage in patients with renal impairment. After 2 weeks, the dose was increased by 25 mg every 2 weeks to a maximum of 75 mg in a patient aged from one year to five years and 150 mg in patients aged older than five years if the platelet count had not increased by 20,000 per cubic millimeter from baseline or platelet - transfusion requirements had not decreased. The dosage should be decreased by 25 mg / day for 2 weeks if the platelet count increases at any time to between 200,000 and 400,000 / lL and should be suspended for 1 week if the platelet count exceeds 400,000 / lL, with reintroduction at a 25 mg - lower dose once the platelet count reduces to 150,000 / lL. If the platelet count remains above 400,000 / lL after 2 weeks of treatment at the lowest dose, then E - PAG should be discontinued. It must be also discontinued if no hematologic response has happened after 16 weeks of therapy or excessive platelet count responses or important liver test abnormalities. In case of tri - lineage response, including transfusion independence, lasting 8 weeks, the dose may be reduced by 25 % and continued on the reduced dose if counts remained stable after 8 weeks then discontinue and monitor blood counts. If platelets counts drop to < 30,000 / mm^3, hemoglobin to < 9 g / dL, or ANC to < 500 / mm^3, may reinitiate at the prior effective dose. 2 - Oral CsA treatment in both groups was initiated at 5 – 10 mg / kg / day and the dose adjusted to maintain trough levels of 170 – 270 ng / ml. CsA was continued for at least six months as tolerated and, in those who responded, continued at a fixed daily dose for at least an additional six months before weaning. Serum CsA levels were measured every two to four weeks while patients were receiving the drug.[11-14]

Supportive Therapy: Supportive therapy was allowed throughout the study when required. This included granulocyte colony - stimulating factor (G -CSF), iron chelation, or platelet transfusion (if the count was < 10,000 / µL with an apparent bleeding tendency or < 20,000 / µL with fever) and Red Blood Cell (RBC) Transfusion (if hemoglobin was < 7 g / dL or in the presence of (significant symptoms, such as exertional dyspnea or anemic heart failure)

Primary Outcome Measures

Outcomes were evaluated at the following time points: 3, 6, and 12 months. The primary outcome of the current study was to evaluate the efficacy of the combination of E - PAG with CSA using Hb, ANC, and Platelet at study time points and treatment outcomes were categorized as No Response (NR) and Overall Response (OR) which was further categorized as CR or Partial Response (PR).[15]

Response Criteria

- **Platelet Count:** measuring increase of platelet count from baseline by 20,000 / microliter or more (in the absence of platelet transfusion), or independence from platelet transfusions for a minimum of 8 weeks in patients who were previously transfusion - dependent.
- **Hemoglobin:** measuring the following: Increase from baseline by 1.5 gram g / dL or more when the baseline hemoglobin level is < 8.5 g / dL and no Red Blood Cell (RBC) transfusion at baseline. A decrease of at least four units in RBC transfusions in the post - treatment 8 - week period compared to the pre - treatment 8 - week period
- **Absolute Neutrophil Count (ANC):** measuring the increase in the ANC of more than 500 per cubic millimeter
- No Response (NR) was defined as failure in any lineage. Participants who received transfusions of packed red blood cells (PRBCs) or platelets within less than 8 weeks
- Partial Response (PR) was defined as blood count no longer meeting Camitta criteria for Severs Aplastic Anemia in case of SAA
- **Complete Responders (CR) met the following criteria:** Hb ≥ 100 g / l, platelet count ≥ 100 × 109 / L, and ANC ≥ 1 × 109 / L. additionally, patients had to be transfusion and growth factor independent
- An overall response (or) was defined as at least a PR.

Secondary Outcome Measures

Secondary outcomes were the tolerability, safety and toxicities of the combination, time to achieve a response and duration of response.[16]

Statistical Analysis

Data entry, cleaning, and analysis were carried out using SPSS version 20 Descriptive statistics is expressed as frequencies with percentages for categorical data. Continuous variables are expressed as median values with inter quartile range (IQR Q_1 to Q_3) as the sample size was small. Categorical data were compared between the groups using Chi - Square test and Fisher's exact test when the expected frequencies were less than 5. Continuous variables were compared between the groups using non parametric method Mann - Whitney U test. A p - value < 0.05 indicates statistical significance.[17]

RESULTS

Patient Characteristics

A total of 20 patients were enrolled in this study: 10 patients (CsA group) received CSA alone and the other 10 patients (E - PAG group) received CSA and E - PAG. Baseline patient characteristics as regard to age and sex were similar between the two treatment cohorts with p value of age and sex were 0.97 and 0.12 respectively. There is no significant difference in baseline CBC data before treatment between the two groups (Table1).

Character	E - PAG Group (n = 10)	CsA Group (n = 10)	P - value
Age (median)	11.5 (6.5 - 12.5)	10.5 (7.5 - 12.7)	0.97
Sex			

- Male	6 (60 %)	9 (90 %)	0.12
- Female	4 (40 %)	1 (10 %)	
Baseline CBC			
WBC (109 / L)	1.75 (1 - 3)	1.8 (1.35 - 2.15)	0.93
ANC (cell / ul)	255 (186.7 - 523.7)	260 (196.7 - 636.2)	0.94
RETIC (%)	0.4 (0.1 - 0.8)	0.25 (0.1 - 0.4)	0.41
Hg (g / dl)	5 (4.7 - 5)	4.25 (4 - 5)	0.11
PLT (109 / L)	8.5 (6.7 - 16.7)	8.5 (5.7 - 19.7)	0.93

ANC: Absolute Neutrophil Count; HB: Hemoglobin (g/L); PLT: Platelet Count; RETIC: Absolut Reticulocytic Count. Data are expressed as the number of cases (%) or median with inter-quartile range. Note: p-Value is calculated to compare both cohorts using Mann-Whitney test.

Table 1. Baseline Patient Demographic Characteristics in Each Group.

Primary Outcomes (The Efficacy of Therapy)

All 20 patients were evaluated for the hematological response to treatment. The follow - up end point was 3 month, 6 month and 12 month.

At 3 Month after Therapy Initiation Follow up CBC

Follow up CBC: A significant p value of 0.02 was seen in ANC, also hemoglobin level showed significant difference in both groups with p value equal to 0.01. The rise of platelet count was considerable in E - PAG with highly significant P value of 0.004 (Table 2).

Character	E - PAG Group (n = 10)	CsA Group (n = 10)	P - value
After 3 months			
WBC	3.7 (2.7 – 4.9)	2.9 (1.9 – 4)	0.14
ANC	790 (675 - 1492.5)	623 (274.7 - 800.7)	0.02
RETIC	1.1 (0.9 - 1.3)	0.7 (0.2 - 1)	0.02
Hg	7.7 (6.4 - 9.2)	6 (5 - 6.7)	0.01
PLT	44 (33.7 - 114.5)	27.5 (16.5 – 38.2)	0.004
After 6 months (E - PAG group, n = 10 - CsA group, n = 9)			
WBC	4 (2.9 – 4.9)	3 (2.4 – 4)	0.15
ANC	850 (595 - 1620)	500 (435 - 800)	0.01
RETIC	1.1 (0.9 - 1.2)	1 (0.9 – 1.1)	0.38
Hg	8.3 (6.5 - 11)	6.8 (5.5 - 7)	0.03
PLT	90 (67.5 - 136.2)	25 (20 – 31.5)	0.001
After 12 months (E – PAG group, n = 9 - CsA group, n = 8)			
WBC	6 (3.4 – 6.9)	4.1 (2.3 – 5)	0.08
ANC	1900 (775- 2600)	640 (470 - 1625)	0.03
RETIC	1.3 (1 - 1.5)	1.2 (1 – 1.6)	0.76
Hg	11 (7.7 - 12)	7 (6 – 10.9)	0.05
PLT	150 (85 - 185)	38 (30.7 – 92.5)	0.007

Data are expressed as the number of cases (%) or median and inter - quartile range. Note: p - Value is lasted to compare both cohorts using Mann - Whitney test.

Table 2. CBC Follow up at 3, 6 and 12 Month.

The Need for Red Cell and Platelet Transfusion: The need for transfusion in patients of E - PAG was lower than the other group. There was significant difference in both groups as regard the number of patient received with red cell and platelet transfusion with P value of 0.02 and 0.002 respectively (Tables 3,4).

Character	E - PAG Group (n = 10)	CsA Group (n = 10)	P - value
After 3 months			
Less than 1 week	0 (0 %)	5 (50 %)	0
Every 2 week	1(10 %)	3 (30 %)	
Every 4 week	2 (20 %)	2 (20 %)	
Every 6 week	5 (50 %)	0 (0 %)	
Every 8 week	1 (10 %)	0 (0 %)	
No need	1 (10 %)	0 (0 %)	
After 6 months (E - PAG group, n = 10 - CsA group, n = 9)			
Every 2 week	1 (10 %)	2 (20 %)	0
Every 4 week	0 (0 %)	4 (40 %)	
Every 6 week	2 (20 %)	2 (20 %)	
Every 8 week	1 (10 %)	1 (10 %)	
No need	6 (60 %)	0 (0 %)	
After 12 months (E - PAG group , n = 9 - CsA group, n = 8)			
Every 2 week	0 (0 %)	1 (10 %)	0.1
Every 4 week	0 (0 %)	2 (20 %)	
Every 6 week	0 (0 %)	2 (20 %)	
Every 8 week	2 (20 %)	1 (10 %)	
No need	7 (70 %)	2 (20 %)	

Table 3. The Number of Patients Recived Rbcs Transfusion.

Character	E - PAG Group (n = 10)	CsA Group (n = 10)	P - value
After 4 months			
Less than 1 week	0 (0 %)	5 (50 %)	0
Every 2 week	0 (0 %)	2 (20 %)	
Every 4 week	0 (0 %)	2 (20 %)	
Every 6 week	6 (60 %)	1 (10 %)	
No need	4 (40 %)	0 (0 %)	
After 6 months (E - PAG group, n = 10 - CsA group, n = 9)			
Every 2 week			
Every 4 week	0 (0 %)	3 (30 %)	
Every 6 week	1 (10 %)	2 (20 %)	
Every 8 week	2 (20 %)	1 (10 %)	
No need	7 (70 %)	0 (0 %)	
After 12 months (E - PAG group , n = 9 - CsA group, n = 8)			
Every 2 week			
Every 4 week	0(0 %)	1 (10 %)	
Every 6 week	0 (0%)	2 (20 %)	
Every 8 week	0 (0 %)	1 (10 %)	
No need	9 (100 %)	3 (30 %)	

Note: p-Value is calculated to compare both cohorts using *Chi-square* test.

Table 4. The Number of Patient's Received Platelets Transfusion.

End Result Response: A complete response in E - PAG group was observed in one patient and a partial response in 3 (30 %), for an overall response rate of 40 % (4 of 10) with P - value of 0.02 (Table 5).

A - PAG group(n = 10)						CSA group (n = 10)					P value
	OR N / %	CR N / %	PR N / %	NR N / %	Death (N / %)	ORR N /%	CR N / %	PR N / %	NR	Death	
At 3 months	4(40 %)	1(10 %)	3(30 %)	6(60 %)	-	0 (0 %)	0	0	10(100 %)	-	*0.02
At 6 moth	A - PAG group(n = 10)					CSA group (9)					
	8(80 %)	4(40 %)	4(40 %)	2(20 %)	-	2(20 %)	0	2(20 %)	8(80 %)	1(10 %)	*0.007
	At 12 Months					CSA group (n = 8)					
	9 (90 %)	6(60 %)	3(30 %)	1(10 %)		4(50 %)	2(25 %)	2(25 %)	4(50 %)	1 (10 / %)	*0.01
OR: Overall response; CR: complete response; PR: partial response. Note: P - Value is calculated to compare both cohorts using Chi - square test.											

Table 5. Response Rat and Overall Survivors in the Studied Groups.

At 6 Month after the Initiation of Therapy

Follow up CBC: The difference in response between the two groups was statistically significant, the E - PAG group had a significantly higher median hemoglobin concentration (8.3 g / dL *vs.* 6.8 g / dL for the CSA:P = 0.03) and ANC (0.850 $\times 10^9$ / L *vs.* 0.500 $\times$ 10^9 / L for the CSA: P = 0.01) and a strikingly higher median platelet count of 90 $\times$ 10^9 / L as compared with 25 $\times$ 10^9/L for the CSA group (P = 0 .001) (Figure 1).

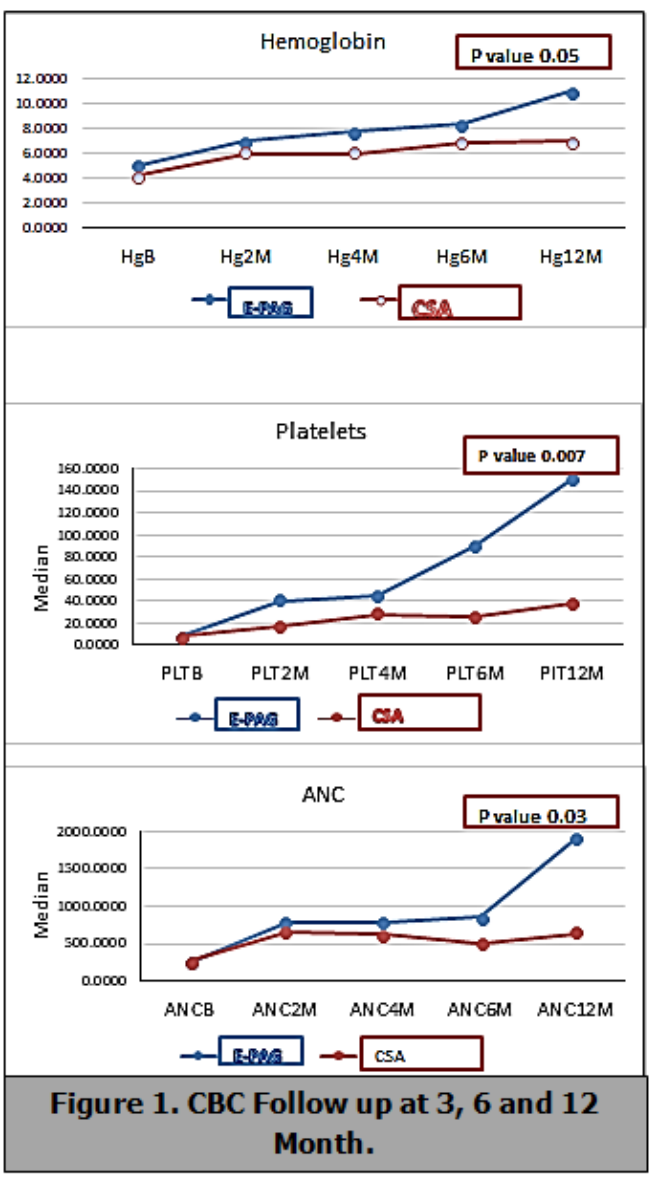

Figure 1. CBC Follow up at 3, 6 and 12 Month.

The Need for Red Cell and Platelet Transfusion: In E - PAG group, Platelet transfusion independence was observed in 7 patients (70 %) (P = 0.008) and red cell transfusion independence was detected in 6 patient (60 %) (P = 0.03).

End Result Response: A complete response in E - PAG group was observed in 4 patients (40 %) and a partial response in 4 (40 %), for an overall response rate of 8 (80 %) with P - value of 0.007. In contrast, in the CSA group, patients did not had a complete response and 2 (20 %) had a partial response for an overall response rate of 20 % (2 of 10).

Long - Term Outcomes (At 12 Month)

At the 1 - year evaluation in E - PAG group, the OR rate was 90 % compared to 50 % in CsA group (12 - month ORR P = 0.01). Complete responders totaled 60 % (6 / 10) in E - PAG compared to 25 % (2 / 10) in the CsA group. Response rates at 1 year were significantly different between the CSA - EPAG and CSA groups, however, one patient from E - PAG group who failed to achieve a response at 12 months was underwent allogeneic HSCT. Two patients from CsA group were excluded from the study and died, one as result of an intracranial hemorrhage and the other from infection.[18]

Secondary Outcomes (Safety and Tolerability of Therapy)

All patients were eligible for evaluation of toxicity. Overall, both treatment arms had acceptable toxicities. As regard to cyclosporine, three patients (15 %) from both cohorts experienced hirtutism and mild renal dysfunction was seen in one patient with recovery after decreasing dose to 5 mg / kg in 2 weeks. Asymptomatic gum hypertrophy was noted in one patient while on therapy and he did not require decrease in drug dosage. E - PAG was not discontinued because of adverse events in any patient. The most common adverse events were indirect bilirubin elevation and jaundice (30 %, 3 patients). One patient (10 %) showed transient elevations in liver enzyme levels and one patient showed Myalgia and headache. The above abnormal laboratory indicators were self - resolved or disappeared after transient E - PAG withdrawal. None of the patients developed new cataracts or thromboembolic events or shin reaction during the study.[19]

DISCUSSION

Severe aplastic anemia is a life - threatening disorder, characterized by failure of bone marrow which is manifested by pancytopenia and hypo cellularity of bone marrow. For children not eligible for matched sibling donor - HSCT, The standard Immunosuppressive Therapy (IST) consisting of Antithymocyte Globulin (ATG) and CsA (CSA) is the optimal treatment. For those treated with IST, responses are satisfactory but relapse, treatment failure and clonal evolution remain concerns. ATG cause immediate and late side effects. Rabbit ATG is less effective than Horse ATG and cause more profound immunosuppression, which might be responsible for

the higher incidence of severe infections. However Horse ATG is globally unavailable. Now, the emerging E - PAG, a thrombopoietin receptor agonist, seems to be effective in adult patients with AA. Addition of E - PAG to IST show good tolerability, improvement in the response rates, recovery of blood cell counts and restoration of trilineage hematopoiesis, even after drug discontinuation. E - PAG has been recently approved for use as first - line treatment for adult patients with SAA in combination with standard IST. Reports evaluating the use of E - PAG in pediatric SAA are rare and confusing. Most of these studies assess its use of E - PAG with standard IST of ATG + CsA as (Table 6). This was the first prospective study to confirm the efficacy and safety of E - PAG in combination with CsA alone in pediatric patients with severe AA. Study in adult and evaluate the use of E - pag and CSA as first line therapy in Patients with SAA. This was a prospective clinical trial with a patient sample of 20 children diagnosed with SAA. Half of the participants were treated with CsA immunotherapy. The other half was treated with combined E - PAG + CsA. The present study showed that the mean age of patients was 11.5 in CSA E - PAG group and 10.5 in CSA group which is in agreement with the previous studies done by Leman. The median age of the cohort at the time of diagnosis was 6.5 and 7.1 years respectively. In the present study, OR rate of CSA plus E - PAG was 40 % after 3 month of therapy but a CR was observed in one patient and a partial response in 3 of patient. After 6 month of therapy, CR in E - PAG group was observed in 4 patients and a partial response in 4 (40 %), for OR rate of 80 %. additionally, Platelet transfusion independence was observed in 7 patients (70 %) of E - PAG group and red cell transfusion independence was detected in 6 patient (60 %). In contrast, in the CSA group, patients did not had a complete response and 2 (20 %) had a partial response for an OR rate of 20 %. At the 1 - year evaluation in the group A, the OR rate was 90 % compared to 50 % in CsA group. Complete responders reached 60 % (6 / 10) in E - PAG group compared to 25 % (2 / 10) in CsA group. The survival rate at 12 months was 100 % compared to 80 % in the CsA cohort. Studied cohorts of 25 patients, 16 were treated with standred IST and 9 of patient were treated with IST and E - PAG. No significant difference in CR and OR rate was found at 6 month (CR was 29 % in both group, ORR: 77.7 % *vs* 71%, p 0.25) and 12 month (CR: 58 % *vs* 29 %, p 0.35, ORR was 100 % in both group). However the hematological response and Event Free Survival (EFS) were better in the IST and E - PAG treatment group (Overall survival was 100 % *vs* 88 % and EFS was 100 *vs* 75). These results were somewhat similar to our own, which may suggest that E - PAG and CsA exert similar effects to E - PAG and IST (24 %). Studied a cohort of 57 pediatric patients with AA treated with ATG and E - PAG (18 of 57). They found the OR rate was 77.7 % *vs* 56.4 %, p > 0.05 and the CR was 22.2 % *vs* 12.8 % p > 0.05 (95 % CI 0.18 – 0.24) in in patients treated with IST and E - PAG compared to IST alone. Also, Response rates were significantly higher (CR: 50 % *vs* 17.9 %, p < 0.05, ORR: 94.4 % *vs* 69.2 %, p < 0.05) at 6 months in patients treated with IST and E - PAG compared to IST alone conducted their cohort of 14 pediatric patients with AA treated with rabbit ATG and E - PAG. The male - to - female ratio was around 1.3:1 (8 males and 6 females). This study found CR and OR rates of 3 month were 7.1 % (1 / 14) and 35.7 %(5 / 14), respectively, and 64.3 % (9 / 14) of cases showed no response. The CR and ORR was 64.3 % and 78.6 %, respectively at 6 months studies a cohort of 92 adult and pediatric patients, 19 of patients were children, who treated in a prospective study of IST and E - PAG. This study was divided the patients in to 3 cohorts according to the day when patients in each cohort started E - PAG. In the 3rd cohort that initiated E - PAG from day one reported the ORR of 80 % and 87 % in 3 and 6 month respectively while the CR was 30 % at 3 and 6 months? This study found that the beneficial effect of E - PAG is directly proportionate to the length of exposure to the drug. In addition to hematologic response, the bone marrow also showed presence of populations highly enriched in hematopoietic stem cells and multipotent progenitors at 3 or 6 months after therapy. The use of E - PAG in children with SAA has to date conflicting results, in recent study of 40 pediatric patients less than 18 years did not result in obvious therapeutic benefits. Reported that there was no significant difference in either the or rate or CR rate at 6 months (ORR 70 % in EPAG group, 72 % IST, P = 0.78). In comparison with adults had a significantly improved ORR of 82 % with EPAG compared to 58 % with IST (P < 0.001) our results differ from those found in studies of CsA treatment for adults with SAA? Studied 20 patients who received CsA alone. The age of the patients ranged from 10 to 65 years. Male to female ratio was 1.8:1. In this study the ORR was 56.2 % after 3 month studied 54 treatment - naïve adults with severe aplastic anemia were given E - PAG and CsA for 6 month. The median age of the patients was 55 years, 63 % were male. The OR rate of 3 and 6 months was 40.7 % and 46.3 % of patients respectively (Table 6).[20-32]

Follow up number ()	Presnt study e – pag + csa (10 / 10)	Jie et al.2021 e – pag + ist (14 children)	Fang et al.2021 e - pag+ ist (18 / 57 children)	Lesmana et al.2020 e – pag + ist (9 / 25 children)	Groarke et al. 2021 e – pag + ist (40 / 87 children)	Scheinberg et al. 2017 e – pag + csa (54 adult)
Three month						
ORR (%)	40%	35.70%	77%	-	68%	40.70%
CRR (%)	14.3	7.10%	22.20%	-	23%	-
Six month						
ORR (%)	80%	78.50%	94.40%	77.70%	70%	46.30%
CRR (%)	66.70 %	64.30%	50%	29%	30%	5.40%

CRR, complete response rate; CsA, cyclosporine; E-PAG, eltrombopag; IST, immunosuppressive therapy; ORR, overall response rate.

Table 6. Comparison of Research Evaluating Eltrombopag + Immunosuppressive Therapy as a Treatment for Severe Aplastic Anemia.

CONCLUSION

CRR, Complete Response Rate, CsA, cyclosporine, E - PAG, eltrombopag IST immunosuppressive therapy, ORR, Overall Response Rate. In order to evaluate the safety and tolerability of E - pag, the present study showed that the main adverse effect of E - PAG was the slightly too moderately elevated bilirubin levels which was temporary and controllable, accounting for about 30 % (3 / 10) of patients. This percentage was higher in other studies as (66.6 %) and (64.3 %). The second common side effect was transient transaminemia, which subsided after dose reduction and recorded in one patient (10 %) in our study. Three patients (21.4 %) of study and one patient (11.1 %) of study showed transient elevation in liver enzyme levels. As regarded to the adverse effect of CsA, in the present study three patients (15 %) from both cohorts experienced hirtutism while mild renal dysfunction was seen in one patient of CSA group with recovery after decreasing dose to 5 mg / kg in 2 weeks. Asymptomatic gum hypertrophy was noted in one patient

while on therapy and he did not require decrease in drug dosage. Showed that renal insufficiency was more common in patients receiving the combination of IST and E - PAG than those receiving IST (67 %, 6 / 9 *vs* 6 %, 1 / 16, p = .003). Combined cyclosporine + eltrombopag were found to be an effective, well tolerated and safe alternative treatment for pediatric SAA. This study was limited by its small sample size and the lack of similar studies in pediatric groups. A larger prospective study with longer follow - up is essential to evaluate response stability.

ETHICAL STATEMENT

This study was conducted in accordance with the tenets of the Declaration of Helsinki 1964. The study was approved by Assiut University's Ethical Committee for Clinical Research. Signed statements of informed content to participation and publication were obtained from the guardians of trial participants before the study. The consent requirement was waived for retrospective participants by the above-named ethics committee.

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