Clinical Drug Investigation (2023) 43:315–324
https://doi.org/10.1007/s40261-023-01266-7

SYSTEMATIC REVIEW

Efficacy of Eltrombopag with Immunosuppressive Therapy Versus Immunosuppressive Therapy Alone on Severe Aplastic Anaemia: A Systematic Review and Meta-analysis

Senlin Zhang[1] · Qingwei Wang[1] · Kai Cui[1] · Bingjie Cheng[2] · Junjie Fan[1] · Shaoyan Hu[1]

Accepted: 2 April 2023 / Published online: 11 May 2023

Abstract

Background and Objective Severe aplastic anaemia (SAA) is a syndrome of bone marrow failure caused by T cell-mediated destruction of haematopoietic stem cells and progenitor cells. Whether patients with SAA should be treated with eltrombopag (EPAG) and immunosuppressive therapy (IST) or IST alone remains debatable. Therefore, we conducted this meta-analysis to compare the efficacy of eltrombopag + IST with that of IST alone in patients with SAA and to assess the difference in the efficacy of eltrombopag in adults and children.

Methods We performed this meta-analysis by retrieving studies that met the inclusion and exclusion criteria from PubMed, EMBASE, and the Cochrane Library up to 1 January 2023. We used a random-effects model to calculate odds ratios (ORs) with 95% confidence intervals (CIs) for primary and secondary outcomes. I^2 statistics were used to evaluate the heterogeneity of the included studies.

Results Six studies involving a total of 699 patients were included. In terms of the primary outcomes, our pooled results indicated that patients treated with EPAG + IST had a higher 6-month overall response rate (OR = 2.25; 95% CI, 1.60–3.16; $p < 0.00001$), a higher 6-month complete response rate (OR = 2.61; 95% CI, 1.82–3.74; $p < 0.00001$), and a lower 6-month nonresponse rate (OR = 0.32; 95% CI, 0.19–0.52; $p < 0.00001$). However, there was no significant difference in the rate of 6-month partial response (OR = 0.94; 95% CI, 0.49–1.81; $p = 0.85$).

Conclusion This meta-analysis indicated that patients treated with additional eltrombopag for IST may have a higher rate of haematological response.

Key Points

Our meta-analysis indicates that patients treated with an additional eltrombopag to IST may have a higher rate of haematologic response.

Our study suggests that the application of eltrombopag in treatment can be beneficial to patients with SAA.

1 Introduction

Severe aplastic anaemia (SAA), a syndrome of bone marrow failure that is a significant threat to human health and can be fatal if left untreated, manifests as marrow hypoplasia and peripheral blood cytopenia [1–3]. Historically, treatment approaches for SAA involved immunosuppressive therapy (IST) and haematopoietic stem cell transplantation (HSCT) [4]. Currently, in patients with SAA aged ≤40 years and with a human leukocyte antigen (HLA) identical sibling donor, HSCT is still the preferred treatment for patients with SAA, with a

✉ Junjie Fan
jjiefan@126.com

✉ Shaoyan Hu
hushaoyan@suda.edu.cn

[1] Department of Haematology and Oncology, Center of Jiangsu Pediatric Haematology and Oncology, Children's Hospital of Soochow University, No. 92, Zhongnan Street, Suzhou 215000, China

[2] Department of Nephrology, Wuhan Children's Hospital (Wuhan Maternal and Child Healthcare Hospital), Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430000, China

high overall survival rate of more than 80% [5, 6]. However, patients are often unfit for HSCT because of their poor physical condition or donor unavailability. Furthermore, HSCT may be accompanied by complications, such as graft-versus-host disease (GVHD) and infection, which can compromise the quality of life of a patient [7]. Standard IST, including anti-thymocyte globulin (ATG) and cyclosporin A (CSA), may be an alternative treatment option for patients with no appropriate donor or for those who are ineligible for HSCT [8, 9]. In 2020, a study reported that the haematological response rate of patients treated with IST ranged from 60 to 70% [10]. However, more than 25% of patients fail to respond to IST, and approximately 75% have unsatisfactory long-term outcomes [11].

Eltrombopag (EPAG), an oral synthetic thrombopoietin receptor agonist, has been reported to be effective for both refractory and newly diagnosed SAA in adults [12, 13]. One possible mechanism is that thrombopoietin (TPO) enhances the haematopoietic stem cell function. Another possible mechanism is that TPO induces platelet maturation and release by binding to the c-MPL receptor on megakaryocytes [14]. However, adverse events such as liver toxicity and clone [15, 16] evolution of EPAG limited its use in patients with SAA [17]. Some studies have reported that patients with SAA treated with EPAG + IST have a higher haematological response rate than those not treated with EPAG [18–20]. However, a study conducted by Groarke et al reported that the addition of EPAG to IST did not improve the overall response rate at 6 months in children [21]. Moreover, two studies reported the overall response rates at 3 months in children and adults treated with EPAG + IST are 35.7% and 59.0%, respectively [22, 23]. The efficacy of EPAG is still disputable, and there have been some differences in the haematologic response rate between adults and children who were treated with EPAG. Therefore, we conducted this systematic review and meta-analysis to compare the efficacy of EPAG + IST with that of IST alone in patients with SAA and assessed the differences in the efficacy of EPAG in adults and children.

2 Methods

This study was performed, and the results are reported in accordance with the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [24].

2.1 Literature Search Strategy

Relevant articles up to 1 January 2023 were independently retrieved by two authors (Zhang and Wang) from PubMed, EMBASE, and the Cochrane Library. A combination of 'Aplastic Anaemia' and 'Eltrombopag' was used as the search term to retrieve relevant studies. The search strategy for PubMed is described in the Supplementary file. Moreover, we manually searched the references of all included studies to identify any other relevant studies. A third author (Junjie Fan) was consulted to address any disagreements.

2.2 Outcomes and Study Selection

The primary outcomes were as follows: overall response at 6 months (defined as complete response or partial response); complete response at 6 months (defined as an absolute neutrophil count [ANC] $\geq 1.0 \times 10^9$/L, haemoglobin [Hb] levels ≥ 100 g/L and a platelet count $\geq 100 \times 10^9$/L); partial response at 6 months (defined in each included study); and nonresponse at 6 months (defined as failing to achieve a response by 6 months). The secondary outcomes were overall response at 3 months, complete response at 3 months, partial response at 3 months, and nonresponse at 3 months. Two authors (Wang and Cui) independently screened the titles and abstracts of all studies and subsequently examined the full texts of eligible studies. If there were any disagreements in the study selection process, a consensus was reached through group discussion with a third author (Shaoyan Hu). The studies included in this meta-analysis had to meet the following criteria: (1) patients were divided into two groups: the EPAG + IST group and the IST alone group; (2) each clinical trial included more than five patients; (3) all patients with SAA were diagnosed according to the WHO diagnostic criteria; (4) retrospective or prospective original studies. Studies were excluded if they met any of the following criteria: (a) reviews, letter, meeting abstract, supplement, comment, or case report; (b) single-arm study; (c) different studies used the same datasets; (d) studies that did not report clinical outcomes of patients with SAA.

2.3 Data Extraction and Quality Assessment

Two authors (Zhang and Cheng) independently collected the baseline characteristics of each included study using a standardised Excel table. The baseline characteristics were as follows: first author, publication year, study design, number of patients, median age, number of females, disease severity, and paroxysmal nocturnal haemoglobinuria (PNH) clone. Two authors (Fan and Wang) independently used the Newcastle-Ottawa Scale (NOS) to evaluate the quality of nonrandomised controlled trials (RCTs). In contrast, the Cochrane Collaboration tool was used for RCT. Any disagreements in this process were addressed through discussion or adjudication by a third author (Shaoyan Hu).

2.4 Statistical Analysis

We used RevMan version 5.4 to perform the statistical calculations involved in this meta-analysis. A random-effects model was used to calculate odds ratios (ORs) with 95% confidence intervals (CIs) for primary and secondary outcomes. Moreover, we used I^2 statistics to evaluate the heterogeneity of all the included studies. When I^2 was greater than 50%, significant heterogeneity was observed among the included studies. Publication bias in primary outcomes was evaluated using funnel plots. Additionally, we performed a subgroup analysis based on age (children vs children and adults) (patients aged 0–18 years were defined as "children").

3 Results

3.1 Study Selection and Study Characteristics

Initially, 847 potential clinical articles were retrieved and extracted through literature search. Of these, 197 were excluded after finding duplicates. A further 608 studies were excluded after reading the titles and abstracts of the remaining 650 studies according to the exclusion criteria. We then read the full texts to screen the remaining 42 articles, and 8 studies met the inclusion criteria. However, only 6 studies were ultimately included in our meta-analysis [22, 23, 25–28] because 2 studies [29, 30] included the same patients who were treated with EPAG + IST as one of our included studies [25]. A selection flowchart of the included studies is shown in Fig. 1. Of the included studies, three were prospective studies (two were RCTs) [23, 25, 28] and three were retrospective studies [22, 26, 27]. In total, 699 patients with SAA were included in our meta-analysis, including 364 treated with EPAG + IST and 335 treated with IST alone. The baseline characteristics of each study are summarised in Table 1. The results of the primary outcomes and their subgroup analyses are presented in Table 2, and those of the secondary outcomes and their subgroup analyses are shown in Table 3. There was no significant bias in the primary outcomes across the included studies because the funnel plots were roughly symmetrical (Supplementary Figs 1–4). The quality assessments of non-RCTs and RCTs are shown in

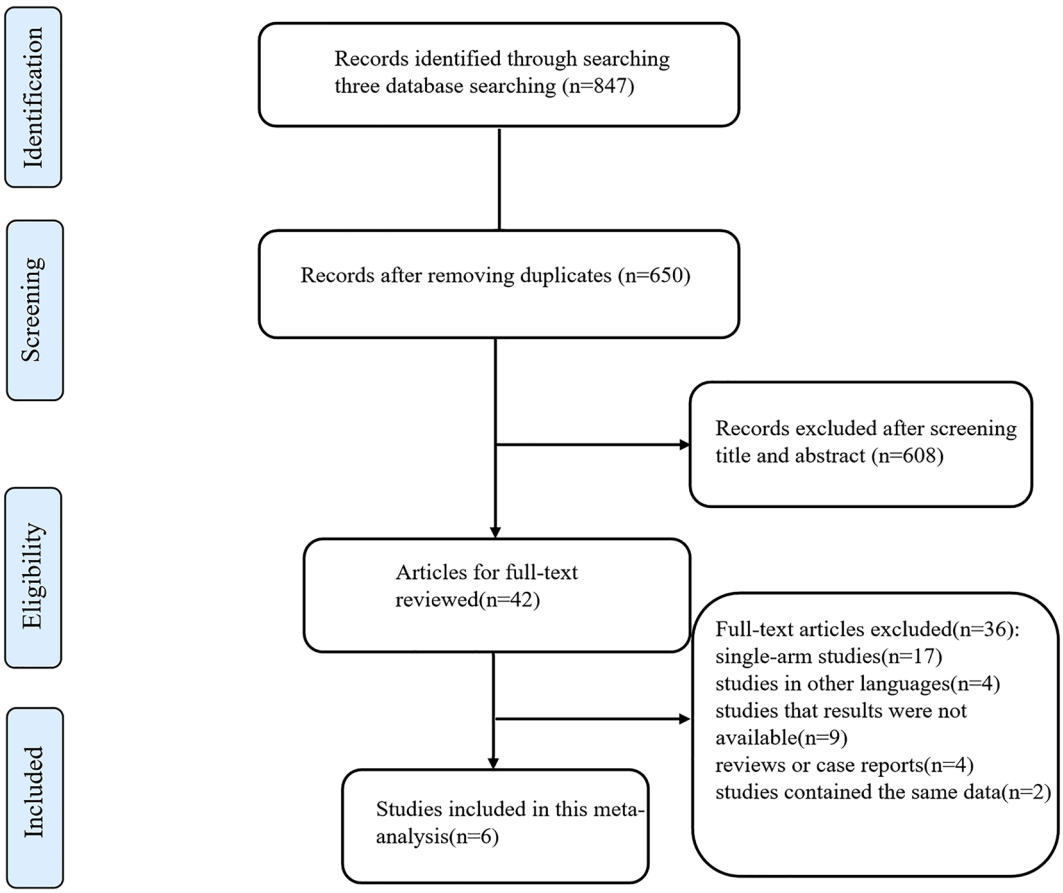

Fig. 1 The selection flow chart of included studies

Table 1 Baseline characteristics of each study included in this meta-analysis

Author	Year	Total no.	Study design	EPAG + IST					IST				
				Patients (*n*)	Age (Median)	Female	Disease severity	PNH clone (+)	Patients (n)	Age (Median)	Female	Disease severity	PNH clone (+)
Fang [26]	2021	57	Retrospective observational study	18	6.5Y	8	VSAA/SAA:6/12	NA	39	7Y	18	VSAA/SAA:14/25	NA
Peffault de Latour [23]	2022	197	RCT	96	55Y	40	VSAA/SAA:34/62	33	101	52Y	49	VSAA/SAA:34/67	44
Jie [22]	2021	42	Retrospective observational study	14	86M	6	NA	9	28	NA	NA	NA	NA
Goronkova [28]	2022	98	RCT	49	10.5Y	14	VSAA/SAA:31/18	14	49	8.7Y	19	VSAA/SAA:28/21	19
Patel [25]	2022	280	Prospective observational study	178	NA	NA	VSAA/SAA:76/102	60	102	NA	NA	VSAA/SAA:35/67	43
Lesmana [27]	2021	25	Retrospective observational study	9	11Y	2	NA	4	16	11.5Y	12	NA	1

EPAG eltrombopag, *IST* immunosuppressive therapy, *M* month, *NA* no report, *PNH* paroxysmal nocturnal haemoglobinuria, *RCT* randomised controlled trial, *SAA* severe aplastic anaemia, *V* very, *Y* year

Table 2 Evaluation of AA at 6 months for studies included in this meta-analysis

Treatment response at 6 months	Number of included studies	EPAG + IST/IST	Pooled effects			Heterogeneity	
			OR	95% CI	*p* value	I^2,%	*p* value
Overall response	6	272/189	2.25	[1.60,3.16]	< **0.00001**	0%	0.43
Children	4	62/80	1.63	[0.87,3.05]	0.13	0%	0.41
Children and adults	2	210/109	2.58	[1.72,3.86]	< **0.00001**	0%	0.42
Complete response	6	135/63	2.61	[1.82,3.74]	< **0.00001**	0%	0.50
Children	4	36/26	2.91	[1.56,5.41]	**0.0008**	0%	0.43
Children and adults	2	99/37	2.45	[1.44,4.17]	**0.0009**	30%	0.23
Partial response	4	129/108	0.94	[0.49,1.81]	0.85	68%	**0.03**
Children	2	18/36	0.61	[0.30,1.24]	0.17	0%	0.62
Children and adults	2	111/72	1.25	[0.44,3.59]	0.68	86%	**0.008**
No response	4	62/124	0.32	[0.19,0.52]	<**0.00001**	30%	0.23
Children	2	16/34	0.28	[0.03,2.60]	0.26	60%	0.11
Children and adults	2	46/90	0.28	[0.18,0.43]	<**0.00001**	0%	0.55

Bold values indicate statistically significant values at $p < 0.05$

AA aplastic anaemia, *CI* confidence interval, *EPAG* eltrombopag, *IST* immunosuppressive therapy

Table 3 Evaluation of AA at 3 months for studies included in this meta-analysis

Treatment response at 3 months	Number of included studies	EPAG + IST/IST	Pooled effects			Heterogeneity	
			OR	95% CI	*p* value	I^2,%	*p* value
Overall response	3	76/71	1.52	[0.39,6.00]	0.55	80%	**0.006**
Children	2	19/40	0.92	[0.11,7.75]	0.94	81%	**0.02**
Children and adults	1	57/31	3.30	[1.83,5.94]	< **0.0001**	NA	NA
Complete response	3	26/18	2.14	[1.09,4.23]	**0.03**	0%	0.55
Children	2	5/8	1.43	[0.42,4.94]	0.57	0%	0.43
Children and adults	1	21/10	2.55	[1.13,5.74]	**0.02**	NA	NA
Partial response	2	46/38	2.10	[1.21,3.65]	**0.008**	0%	0.60
Children	1	10/17	1.62	[0.53,4.98]	0.40	NA	NA
Children and adults	1	36/21	2.29	[1.21,4.31]	**0.01**	NA	NA
No response	2	43/87	0.31	[0.18,0.53]	< **0.0001**	0%	0.78
Children	1	4/17	0.37	[0.10,1.33]	0.13	NA	NA
Children and adults	1	39/70	0.30	[0.17,0.55]	< **0.0001**	NA	NA

Bold values indicate statistically significant values at $p < 0.05$

AA aplastic anaemia, *CI* confidence interval, *EPAG* eltrombopag, *IST* immunosuppressive therapy

Supplementary Tables 1 and 2, indicating medium and high quality, respectively.

3.2 Overall Response at 6 Months

The overall response at 6 months was evaluated in six studies, including 699 patients with SAA. Our analysis showed that the overall response rate of patients in the EPAG + IST group was higher than that of patients in the IST-alone group. (OR = 2.25; 95% CI, 1.60–3.16; $p < 0.00001$, $I^2 = 0\%$) (Fig. 2). In the subsequent subgroup analysis, we found that the results in the "children and adults" subgroup were consistent with the initial pooled results (OR = 2.58; 95% CI, 1.72–3.86; $p < 0.00001$, $I^2 = 0\%$), whereas no significant difference was identified in the children subgroup (OR = 1.63; 95% CI, 0.87–3.05; $p = 0.13$, $I^2 = 0\%$) (Table 2).

3.3 Complete Response at 6 Months

The complete response at 6 months was evaluated in 6 studies that included 699 patients with SAA. Our analysis results of 6 studies suggested that the complete response

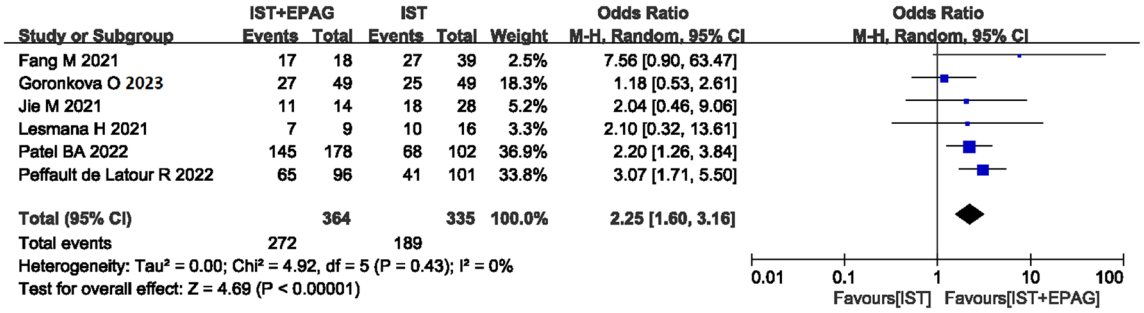

Fig. 2 Overall response at 6 months. *CI* confidence interval, *EPAG* eltrombopag, *IST* immunosuppressive therapy

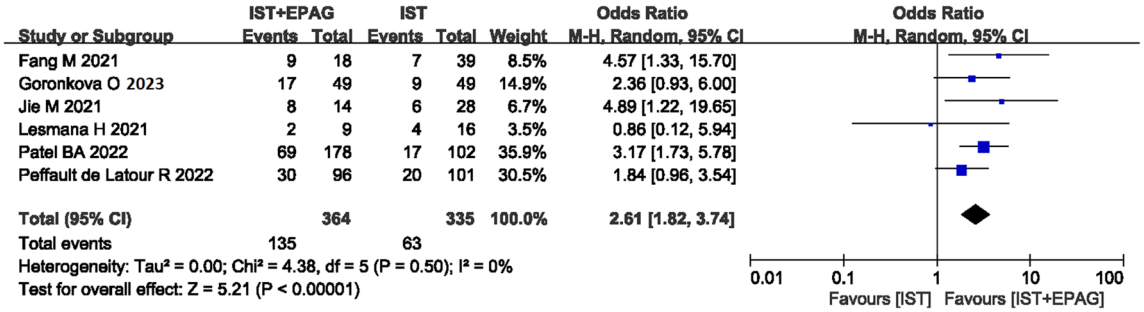

Fig. 3 Complete response at 6 months. *CI* confidence interval, *EPAG* eltrombopag, *IST* immunosuppressive therapy

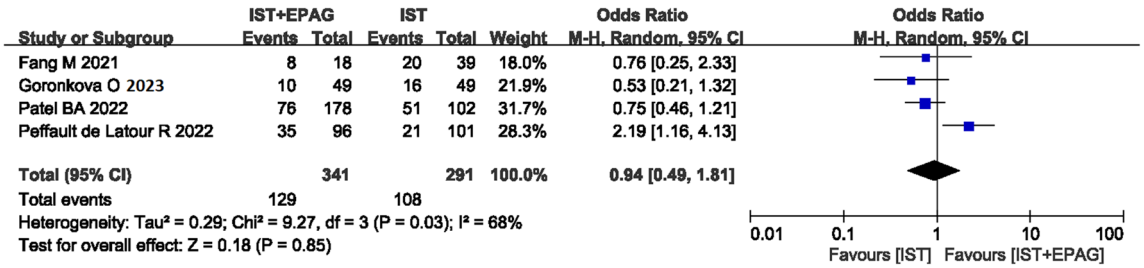

Fig. 4 Partial response at 6 months. *CI* confidence interval, *EPAG* eltrombopag, *IST* immunosuppressive therapy

rate was higher in the EPAG + IST group than in the IST alone group (OR = 2.61; 95% CI, 1.82–3.74; $p < 0.00001$, $I^2 = 0\%$) (Fig. 3). Then, the results of both the children and "children and adults" subgroups were similar to the previous analysis results (Table 2).

3.4 Partial Response at 6 Months

Partial response at 6 months was evaluated in 4 studies, including 632 patients with SAA. There was no significant difference between the EPAG + IST group and the IST alone group according to the pooled results (OR = 0.94; 95% CI, 0.49–1.81; $p = 0.85$, $I^2 = 68\%$) (Fig. 4). The results of subgroup analysis were similar to those of the previous analysis (Table 2).

3.5 No Response at 6 Months

No response at 6 months was reported in 4 studies that included 632 patients with SAA. We found that the non-response rate of the EPAG + IST group was lower than that of the IST alone group according to the pooled results (OR = 0.32; 95% CI, 0.19–0.52; $p < 0.00001$, $I^2 = 30\%$) (Fig. 5). The results of the subgroup analysis in the "children and adults" subgroup were similar to our previous analysis results. By contrast, no significant differences were identified in the children subgroup (Table 2).

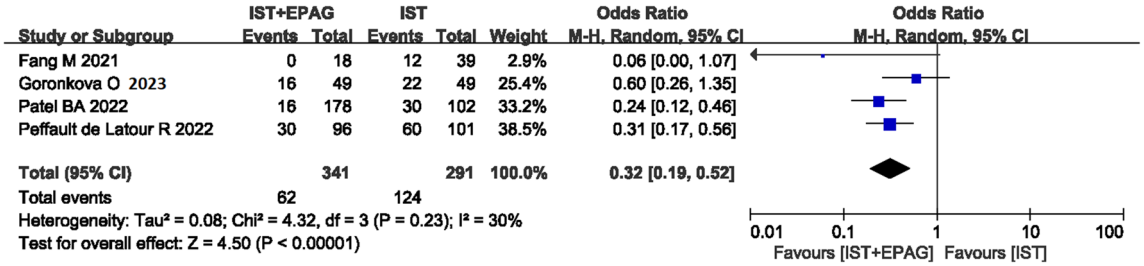

Fig. 5 No response at 6 months. *CI* confidence interval, *EPAG* eltrombopag, *IST* immunosuppressive therapy

3.6 Secondary Outcomes of this Meta-Analysis

Our analysis results suggested that there was no significant difference between the EPAG + IST group and the IST alone group in the 3-month overall response (OR = 1.52; 95% CI, 0.39–6.00; $p = 0.55$, $I^2 = 80\%$). In the subsequent subgroup analysis, the results for the children subgroup were consistent with the initial pooled results. In contrast, the occurrence rate of the 3-month overall response in the "children and adults" subgroup was higher in the EPAG + IST group.

Moreover, our pooled analysis indicated that the 3-month complete response rate (OR = 2.14; 95% CI, 1.09–4.23; $p = 0.03$, $I^2 = 0\%$) and 3-month partial response rate (OR = 2.10; 95% CI, 1.21–3.65; $p = 0.008$, $I^2 = 0\%$) were higher in the EPAG + IST group between the two groups. The subgroup analysis indicated that the 3-month complete response rate and 3-month partial response rate in the "children and adults" subgroup were consistent with the initial pooled results, whereas significant difference was noted in the results of the children subgroup between the two treatment groups.

In addition, the 3-month nonresponse rate was lower in the EPAG + IST group according to the pooled results (OR = 0.31; 95% CI, 0.18–0.53; $p < 0.0001$, $I^2 = 0\%$). The results in the "children and adults" subgroup were consistent with the initial pooled evidence, but no significant difference was noted in the results of the children subgroup (Table 3).

3.7 Adverse Events

Adverse events reported in patients treated with EPAG include elevated liver enzymes, infection, bilirubin increase, jaundice, hypertension, seizure, febrile neutropenia, rash, diarrhoea, gastrointestinal disorders, myalgia and joint pain, renal failure, cardiac disorders, skin hyperpigmentation, blurred vision, and ileus. The most common adverse events are gastrointestinal disorders, increased bilirubin, and elevated liver enzyme levels [22, 23, 26–28]. In a study conducted by Goronkova et al. [28], the incidence of liver abnormalities was higher in the EPAG group. A study conducted by Lesmana et al. [27] indicated that the incidence of renal insufficiency was higher in patients treated with EPAG.

Most studies did not report the discontinuation of EPAG due to severe adverse events. A study conducted by Peffault et al. [23] indicated that EPAG was discontinued in ten patients because of elevated liver enzymes (four patients), bone marrow reticulin deposition, cytomegalovirus infection, rhabdomyolysis, pulmonary embolism, and skin toxidermia. The study conducted by Goronkova et al. [28] reported that the only adverse events that led to the discontinuation of EPAG were liver test abnormalities. Liver toxicity could be a crucial adverse event of EPAG and the primary reason for its discontinuation. Therefore, monitoring liver function during EPAG administration is important.

4 Discussion

In 2019, Hong et al. conducted a meta-analysis to explore the efficacy and safety of EPAG for aplastic anaemia (AA) and found that EPAG was effective for both refractory AA and ATG-naïve AA. In addition, their study indicated that EPAG had different effects in patients with AA treated with different regimens, accompanied by clone evaluation and adverse effects (such as haemorrhage and infection) during the treatment period [31]. Several studies have reported the safety and efficacy of EPAG + IST versus IST alone for the treatment of SAA [22, 23, 25–28]. Their findings are disparate, and the application of EPAG in children and adults remains controversial. Therefore, we performed this meta-analysis to compare the efficacy of EPAG + IST with IST alone in patients with SAA. Our meta-analysis included six studies involving 364 patients with SAA in the EPAG + IST group and 335 patients with SAA in the IST alone group. Most comparison outcomes were significantly different. Based on the primary and secondary outcomes, we concluded that the efficacy of IST+ EPAG is superior to that of IST alone. We noted that the overall response rate, an important efficacy evaluation indicator, differed when analysed at 6 and 3 months. The 6-month overall response rate was better than that at 3 months. This difference can be

explained by the fact that the onset time of EPAG on SAA may be relatively long, and it can be used for longer than 3 months, even if no improvement is achieved [32].

Subgroup analysis was performed to investigate whether there was a difference in efficacy between children and adults (children vs children and adults). The reason we divided the patients into the children and "children and adults" subgroups was that four of our included articles studied children, and two of them studied the combination of children and adults. Nevertheless, we can still estimate how age affects the efficacy of EPAG using a subgroup analysis. The results of the subgroup analysis indicated that EPAG + IST could be better than IST alone in adult patients with SAA; however, for paediatric patients, the addition of EPAG may not significantly improve the efficacy. We speculate that this discrepancy may be due to the initial ANC. As reported, patients with SAA and a higher initial ANC responded better than those with a lower ANC, whereas more adult patients with SAA had a higher ANC [30]. Another possible reason is that paediatric patients respond better to IST than adult patients. Subsequently, based on the IST, an additional EPAG can further improve the efficacy in adult patients [33–36]. This difference between different age groups may be helpful for future protocols and decision making regarding SAA treatment.

The addition of EPAG resulted in a better response, especially in adult patients with SAA. The adverse effects of EPAG, such as liver toxicity and clone evolution, should not be ignored. Because EPAG plays a role in haematopoietic stem cell proliferation, patients with SAA treated with EPAG + IST may be more vulnerable to other haematological diseases, such as PNH, acute myeloid leukaemia, and myelodysplastic syndrome [20]. A prospective study conducted by Townsley et al. [12] reported that 18% of patients who underwent EPAG + IST had liver test abnormalities, indicating that medical staff should regularly monitor the liver function of patients. Relapse is another complication of EPAG + IST. Another prospective study published in *BLOOD* reported that patients with SAA treated with EPAG + IST relapsed with a cumulative rate of 39%, mostly occurring within the first 2 years after the use of anti-thymocyte globulin [25]. Therefore, preventive strategies should be further investigated to reduce the rate of relapse.

Recently, several studies have explored the efficacy of other thrombopoietin receptor agonists such as romiplostim and avatrombopag in patients with AA. One multicentre study indicated that the haematological response rates of 27 weeks and 53 weeks in refractory patients with SAA treated with romiplostim were 84% and 81%, respectively [37]. Another retrospective study conducted in France reported only one response among 14 patients with refractory SAA, but no severe adverse events arising from the application of romiplostim [38]. A retrospective single-centre study conducted by Chi et al. [39] explored the efficacy of avatrombopag in chemoradiotherapy-induced AA and found that the overall response rates to avatrombopag at 3 and 6 months were 55.9% and 58.8%, respectively. However, studies on the efficacy of other thrombopoietin receptor agonists in patients with AA are still lacking and should be further investigated.

Moderate heterogeneity existed in several outcomes, such as the 6-month partial response and 3-month overall response, which could limit the reliability of our results. However, we could not further analyse the source of heterogeneity because of the limited number of studies included. We assumed that the baseline data differences among the included studies, such as the PNH clone and initial absolute reticulocyte count (ARC), may be the source of heterogeneity. In 2021, Tu et al. conducted a meta-analysis to evaluate the role of PNH clones in patients with AA. The pooled results showed that the 6-month overall response rate in the PNH clone-positive group was higher than that in the PNH clone-negative group, which may indicate that the PNH clone is predictive of the haematologic response in patients with AA [40]. Moreover, another recent retrospective study reported that patients with SAA who responded to EPAG + IST had a higher initial ARC than those who did not, suggesting that the initial ARC of patients treated with EPAG + IST may be related to these haematological responses [30]. Unfortunately, not all data were available in the included studies; therefore, we could not avoid heterogeneity caused by these factors.

This meta-analysis had some limitations that should be emphasised. First, due to the limited number of included studies and sample sizes, our results may have limited reliability. Second, the definition of a partial response differed among the included studies, which may have caused potential bias. For example, the definition of partial response in a randomised prospective multicentre trial by Goronkova et al., was an ANC $\geq 0.5 \times 10^9$/L, Hb levels $\geq$ 85 g/dL, and platelet counts $\geq 30 \times 10^9$/L, whereas the definition in a retrospective study by Jie et al., was an ANC $\geq 0.5 \times 10^9$/L, Hb levels $\geq$ 80 g/dL, and platelet counts $\geq 20 \times 10^9$/L. Third, some baseline characteristics of the included studies could not be determined, which may have led to bias. Fourth, there were three retrospective studies and three prospective studies among the six studies included; therefore, the mixed results of the different types of studies may have affected the conclusions. Fifth, the conclusion may be inaccurate due to the subgroup analysis of "children" and "children and adults" groups. Further studies should be performed to explore the reliability of the conclusions of our study and to identify whether there is a difference in the efficacy of EPAG between children and adults.

5 Conclusions

Our results showed that the addition of EPAG to IST resulted in a better haematologic response rate in patients with SAA than in those treated with IST alone. However, this conclusion is not reliable in children. Large-scale, high-quality RCTs are required to further investigate the efficacy of EPAG because of the limitations of our study.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40261-023-01266-7.

Acknowledgements Senlin Zhang especially appreciated Weisong Zhao (Department of Orthopaedics, Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine) for his help during the study conduction.

Declarations

Funding This study was supported by the Translational Research Grant of NCRCH, No. 2020ZKPB02, the Suzhou Health Talents Program, GSWS2020039, and the Suzhou Clinical Trial Institution Capacity Enhancement Program, SLT2021003.

Conflict of interest Senlin Zhang, Qingwei Wang, Kai Cui, Bingjie Cheng, Junjie Fan and Shaoyan Hu declare that they have no conflict of interest.

Ethics approval No ethical approval was required because this study synthesised and analysed data from previously published studies and did not involve any participants or patients.

Data availability All data sources are included in this published article and electronic supplementary materials.

Consent to participate Not applicable.

Consent for publication Not applicable.

Code availability Not applicable.

Author contributions Senlin Zhang and Qingwei Wang: literature search, statistical analysis, data extraction, interpretation of the data, and drafting of the manuscript. Kai Cui and Bingjie Cheng: Statistical analyses and data extraction. Shaoyan Hu and Junjie Fan: data interpretation, interim discussion, and manuscript revision.

References

1. Shin SH, Lee JW. The optimal immunosuppressive therapy for aplastic anemia. Int J Hematol. 2013;97(5):564–72.
2. Young NS. Aplastic anemia. N Engl J Med. 2018;379(17):1643–56.
3. Young NS, Calado RT, Scheinberg P. Current concepts in the pathophysiology and treatment of aplastic anemia. Blood. 2006;108(8):2509–19.
4. Bejanyan N, Kim S, Hebert KM, Kekre N, Abdel-Azim H, Ahmed I, et al. Choice of conditioning regimens for bone marrow transplantation in severe aplastic anemia. Blood Adv. 2019;3(20):3123–31.
5. Bacigalupo A, Socié G, Hamladji RM, Aljurf M, Maschan A, Kyrcz-Krzemien S, et al. Current outcome of HLA identical sibling versus unrelated donor transplants in severe aplastic anemia: an EBMT analysis. Haematologica. 2015;100(5):696.
6. Storb R, Thomas ED, Buckner CD, Clift RA, Deeg HJ, Fefer A, et al. Marrow transplantation in thirty" untransfused" patients with severe aplastic anemia. Ann Inter Med. 1980;92(1):30–6.
7. Scheinberg P, Young NS. How I treat acquired aplastic anemia. Blood J Am Soc Hematol. 2012;120(6):1185–96.
8. Dufour C, Pillon M, Sociè G, Rovò A, Carraro E, Bacigalupo A, 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. Br J Haematol. 2015;169(4):565–73.
9. Yoshida N, Kobayashi R, Yabe H, Kosaka Y, Yagasaki H, Watanabe K-I, et al. First-line treatment for severe aplastic anemia in children: bone marrow transplantation from a matched family donor versus immunosuppressive therapy. Haematologica. 2014;99(12):1784.
10. Scheinberg P. Novel therapeutic choices in immune aplastic anemia. F1000Research. 2020;2020:9.
11. Pierri F, Dufour C. Management of aplastic anemia after failure of frontline immunosuppression. Expert Rev Hematol. 2019;12(10):809–19.
12. Townsley DM, Scheinberg P, Winkler T, Desmond R, Dumitriu B, Rios O, et al. Eltrombopag added to standard immunosuppression for aplastic anemia. N Engl J Med. 2017;376(16):1540–50.
13. Winkler T, Fan X, Cooper J, Desmond R, Young DJ, Townsley DM, et al. Treatment optimization and genomic outcomes in refractory severe aplastic anemia treated with eltrombopag. Blood J Am Soc Hematol. 2019;133(24):2575–85.
14. Kaushansky K. Historical review: megakaryopoiesis and thrombopoiesis. Blood J Am Soc Hematol. 2008;111(3):981–6.
15. Alexander WS, Roberts AW, Nicola NA, Li R, Metcalf D. Deficiencies in progenitor cells of multiple hematopoietic lineages and defective megakaryocytopoiesis in mice lacking the thrombopoietic receptor c-Mpl. Cell Stem Cell. 1996;1:671–84.
16. Qian H, Buza-Vidas N, Hyland CD, Jensen CT, Antonchuk J, Månsson R, et al. Critical role of thrombopoietin in maintaining adult quiescent hematopoietic stem cells. Cell Stem Cell. 2007;1(6):671–84.
17. McCormack PL. Eltrombopag: a review of its use in patients with severe aplastic anaemia. Drugs. 2015;75(5):525–31.
18. Jinsong J, Jiang H, Huang XJ. Outcome of standard immunosuppressive therapy with or without eltrombopag for Chinese patients with severe aplastic anemia in the real world. Blood. 2019;134:5019.
19. Olnes MJ, Scheinberg P, Calvo KR, Desmond R, Tang Y, Dumitriu B, et al. Eltrombopag and improved hematopoiesis in refractory aplastic anemia. N Engl J Med. 2012;367(1):11–9.
20. Desmond R, Townsley DM, Dumitriu B, Olnes MJ, Scheinberg P, Bevans M, et al. Eltrombopag restores trilineage

hematopoiesis in refractory severe aplastic anemia that can be sustained on discontinuation of drug. Blood J Am Soc Hematol. 2014;123(12):1818–25.
21. Groarke EM, Patel BA, Diamond C, Gutierrez-Rodrigues F, Vicente A, Rios O, et al. Outcomes in pediatric patients with severe aplastic anemia treated with standard immunosuppression and eltrombopag. Blood. 2019;134:454.
22. Jie M, Fu L, Li S, He Y, Yao J, Cheng X, et al. Efficacy and safety of eltrombopag in the first-line therapy of severe aplastic anemia in children. Pediatr Hematol Oncol. 2021;38(7):647–57.
23. Peffault-de-Latour R, Kulasekararaj A, Iacobelli S, Terwel SR, Cook R, Griffin M, et al. Eltrombopag added to immunosuppression in severe aplastic anemia. N Engl J Med. 2022;386(1):11–23.
24. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. Int J Surg. 2021;88: 105906.
25. Patel BA, Groarke EM, Lotter J, Shalhoub R, Gutierrez-Rodrigues F, Rios O, et al. Long-term outcomes in patients with severe aplastic anemia treated with immunosuppression and eltrombopag: a phase 2 study. Blood. 2022;139(1):34–43.
26. Fang M, Song H, Zhang J, Li S, Shen D, Tang Y. Efficacy and safety of immunosuppressive therapy with or without eltrombopag in pediatric patients with acquired aplastic anemia: a Chinese retrospective study. Pediatr Hematol Oncol. 2021;38(7):633–46.
27. Lesmana H, Jacobs T, Boals M, Gray N, Lewis S, Ding J, et al. Eltrombopag in children with severe aplastic anemia. Pediatr Blood Cancer. 2021;68(8): e29066.
28. Goronkova O, Novichkova G, Salimova T, Kalinina I, Baidildina D, Petrova U, et al. Efficacy of combined immunosuppression with or without eltrombopag in children with newly diagnosed aplastic anemia. Blood Adv. 2023;7(6):953–62.
29. Groarke EM, Patel BA, Gutierrez-Rodrigues F, Rios O, Lotter J, Baldoni D, et al. Eltrombopag added to immunosuppression for children with treatment-naïve severe aplastic anaemia. Br J Haematol. 2021;192(3):605–14.
30. Zaimoku Y, Patel BA, Shalhoub R, Groarke EM, Feng X, Wu CO, et al. Predicting response of severe aplastic anemia to immunosuppression combined with eltrombopag. Haematologica. 2022;107(1):126.
31. Hong Y, Li X, Wan B, Li N, Chen Y. Efficacy and safety of eltrombopag for aplastic anemia: a systematic review and meta-analysis. Clin Drug Investig. 2019;39(2):141–56.
32. Winkler T, Fan X, Cooper J, Desmond R, Young DJ, Townsley DM, et al. Treatment optimization and genomic outcomes in refractory severe aplastic anemia treated with eltrombopag. Blood. 2019;133(24):2575–85.
33. Rosenfeld S, Follmann D, Nunez O, Young NS. Antithymocyte globulin and cyclosporine for severe aplastic anemia: association between hematologic response and long-term outcome. JAMA. 2003;289(9):1130–5.
34. Scheinberg P, Wu CO, Nunez O, Young NS. Predicting response to immunosuppressive therapy and survival in severe aplastic anaemia. Br J Haematol. 2009;144(2):206–16.
35. Sugimori C, Chuhjo T, Feng X, Yamazaki H, Takami A, Teramura M, et al. Minor population of CD55-CD59-blood cells predicts response to immunosuppressive therapy and prognosis in patients with aplastic anemia. Blood. 2006;107(4):1308–14.
36. Tichelli A, Socié G, Henry-Amar M, Marsh J, Passweg J, Schrezenmeier H, et al. Effectiveness of immunosuppressive therapy in older patients with aplastic anemia. Ann Intern Med. 1999;130(3):193–201.
37. Jang JH, Tomiyama Y, Miyazaki K, Nagafuji K, Usuki K, Uoshima N, et al. Efficacy and safety of romiplostim in refractory aplastic anaemia: a Phase II/III, multicentre, open-label study. Br J Haematol. 2021;192(1):190–9.
38. Zhao LP, Sicre-De-Fontbrune F, Contejean A, Abraham J, Terriou L, Chabrot C, et al. Nationwide survey in France on the use of romiplostim in patients with refractory severe aplastic anemia. Bone Marrow Transplant. 2019;54(7):1161–3.
39. Chi Y, Hu Q, Yang C, Chen M, Han B. Avatrombopag is effective in patients with chemoradiotherapy-induced aplastic anemia: a single-center, retrospective study. Exp Hematol. 2023;117:62–8.
40. Tu J, Pan H, Li R, Wang Z, Lian Y, Li W, et al. PNH Clones for aplastic anemia with immunosuppressive therapy: A systematic review and meta-analysis. Acta Haematol. 2021;144(1):34–43.