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Eltrombopag added to immunosuppression for children with treatment-naïve severe aplastic anaemia

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Summary

Acquired severe aplastic anaemia (SAA) has an immune pathogenesis, and immunosuppressive therapy (IST) with anti-thymocyte globulin and cyclosporine is effective therapy. Eltrombopag (EPAG) added to standard IST was associated with higher overall and complete response rates in patients with treatment-naïve SAA compared to a historical IST cohort. We performed a paediatric subgroup analysis of this trial including all patients aged <18 years who received EPAG plus standard IST ($n = 40$ patients) compared to a historical cohort ($n = 87$) who received IST alone. Response, relapse, clonal evolution, event-free survival (EFS), and overall survival were assessed. There was no significant difference in either the overall response rate (ORR) or complete response rate at 6 months (ORR 70% in EPAG group, 72% in historical group, $P = 0{\cdot}78$). Adults (≥18 years) had a significantly improved ORR of 82% with EPAG compared to 58% historically ($P < 0{\cdot}001$). Younger children had lower response rates than did adolescents. The trend towards relapse was

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Author contributions

Emma M. Groarke performed research, analysed results, provided clinical care, and wrote the paper; Bhavisha A. Patel performed research, analysed results, provided clinical care, and edited the paper; Fernanda Gutierrez-Rodrigues analysed results and edited the paper; Olga Rios and Jennifer Lotter provided clinical care; Daniela Baldoni and Annie St. Pierre analysed and contributed PK data; Ruba Shalhoub and Colin O. Wu analysed results, created figures, and edited the paper; Danielle M. Townsley designed research and provided clinical care; Neal S. Young designed and performed research, analysed results, provided clinical care and wrote the paper.

Conflict of interest

Neal S. Young has a cooperative research and development agreement (CRADA) with Novartis that provides research funding. Subsequent to her involvement with this research, Danielle M. Townsley became an employee of AstraZeneca but had no competing financial interests while at NIH. Daniela Baldoni and Annie St. Pierre are employees of Novartis. Novartis provided PK data for this manuscript and reviewed the manuscript prior to submission. All other authors have no conflicts of interest to declare.

Data sharing

De-identified patient data will be shared indefinitely with other researchers upon reasonable request to the corresponding author (emma.groarke@nih.gov) or last author (youngns@nhlbi.nih.gov). This will require a proposal to the study investigators and a data transfer agreement. The research protocol and patient consent will be made freely available to other researchers upon request to the corresponding author.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

higher and EFS significantly lower in children who received EPAG compared to IST alone. Addition of EPAG added to standard IST did not improve outcomes in children with treatment-naïve SAA. EPAG in the paediatric population should not automatically be considered standard of care. Registration: clinicaltrials.gov (NCT01623167).

Keywords

aplastic anaemia; marrow failure; paediatric aplastic anaemia; paediatric haematology

Introduction

Severe aplastic anaemia (SAA) is characterised by marked pancytopenia with serious clinical sequelae, and disproportionately affects children and young adults. Its aetiology is broadly characterised as either ‘constitutional’ or ‘acquired’. Acquired or immune AA is the most common and due to cytotoxic T-cell destruction of haematopoietic cells.[1]

Treatment for immune AA is either haematopoietic stem cell transplant (HSCT)[2] or immunosuppressive therapy (IST). In children and adults aged <40 years without a fully matched human leucocyte antigen (HLA) sibling donor, IST remains the standard-of-care. Haematological responses to IST in children are favourable,[3–5] with an overall response rate (ORR) of 70% and complete response (CR) rate of 23–60%. Overall survival (OS) rates are also high at 80–93%; however, long-term complications such as relapse and clonal evolution result in a long-term event-free survival (EFS) of only 56–62%.

Eltrombopag (EPAG) is an oral thrombopoietin-receptor agonist that is effective in both refractory and treatment-naïve SAA.[6–8] Currently, EPAG in combination with IST is approved by the United States Food and Drug Administration (FDA) for children aged ≥2 years as front-line treatment for SAA. Approval followed a National Institutes of Health (NIH) investigator-initiated study showing a significant improvement in both ORR and CR rate compared to a historical IST cohort. Complete response to IST has been previously associated with improved long-term outcomes.[9] A total of 19 children included in this initial publication were not reported as a subgroup and a further 21 children have subsequently been enrolled.

Patients and methods

A subgroup analysis was performed of children (aged <18 years) in our ongoing prospective non-randomised Phase I–II study of EPAG added to standard IST for treatment-naïve SAA (clinicaltrials.gov number: NCT01623167).[7] A historical paediatric treatment group using standard IST was used for comparison, as were adult patients who received EPAG and IST. Patients in both the EPAG and historical cohorts met clinical criteria for SAA (Table S3). All patients were assessed for: ORR at 3 and 6 months, CR rate, relapse, clonal evolution, EFS, and OS.

This study was approved by the Institutional Review Board of the National Heart, Lung, and Blood Institute (NHLBI). All patients or guardians provided written informed consent.

Paediatric EPAG group

All included patients were treated on protocol before November 2019, aged <18 years when enrolled, and had either reached primary end-point evaluation (6 months) or met off-study criteria prior. Off-study criteria were: protocol completion (5 years), initiation of IST other than cyclosporine (CSA) or steroids (including HSCT), intolerance to EPAG or horse anti-thymocyte globulin (hATG), high-risk clonal evolution (chromosome 7 abnormality, complex cytogenetics or overt myeloid malignancy), pregnancy, and subject choice. Primary end-points were safety and CR rate at 6 months. Patients were evaluated for baseline visits and mandated time-points: 3 and 6 months, 1 year, and yearly thereafter until 5 years. Standard clinical follow-up occurred once off-study. Bone marrow examination with cytogenetics was performed at baseline, all time-points, and as clinically indicated to exclude clonal evolution. All paediatric patients had a diepoxybutane clastogenic stress assay and were screened for germline variants with an inherited bone marrow failure panel (Table S1). Germline variants were further classified for pathogenicity using the Sherloc criteria, which incorporate the American College of Medical Genetics and Genomics (ACMG) criteria.[10] Patients were also screened for somatic variants in myeloid cancer genes using a targeted panel at baseline, 6 months, and 2 years. Plasma samples for pharmacokinetic (PK) studies were collected over a 24-h period after a minimum of 7 days of consecutive EPAG for measurement of concentrations at steady-state using a validated liquid chromatography with tandem mass spectrometry method and PK parameters derived by non-compartmental analysis (Phoenix version 6; Certara USA, Inc., Princeton, NJ, USA).

Horse ATG and CSA were administered at standard dosing; hATG at a dose of 40 mg/kg over 4 consecutive days and full-dose CSA at 3 mg/kg twice daily (trough level of 200–400 ng/ml) for 6 months. Due to high relapse rates, the protocol was amended so that responders would continue CSA at a reduced dose (2 mg/kg daily) from 6 months to 2 years; the majority of the patients in the paediatric EPAG group were enrolled after this amendment (n = 33, 83%) to receive CSA for 2 years. EPAG was dosed at 150 mg daily for patients aged ≥12 years, 75 mg for those aged 6–11 years and 2·5 mg/kg for those aged 2–5 years, with standard dosing adjustments made for patients of East Asian and Southeast Asian ancestry based on PK data in immune thrombocytopenic purpura.[11] The duration of EPAG administration was either 3 or 6 months, depending on assigned cohorts enrolled consecutively (Figure S1). Responders who relapsed were restarted on CSA and/or EPAG with a duration based on clinical response (Fig 1).[9]

Paediatric IST group

A historical cohort of 87 children treated at the NIH Clinical Center from 1989 to 2010 was used as a comparison arm (Figure S2). All those aged <18 years with treatment-naïve SAA treated with hATG-based IST were included (Table S3). Patients treated with rabbit ATG,[12] alemtuzumab[13] or cyclophosphamide[14] as front-line treatment were excluded due to study results demonstrating drug inferiority or toxicity. Data from four clinical trials were included: NCT00061360, NCT00001964, NCT00260689 and hATG/CSA (no NCT number).[9,14–16] All received hATG at 40 mg/kg over 4 consecutive days and CSA (target 200–400 ng/ml). CSA duration varied slightly among protocols (Table S4), but most patients were enrolled on studies that discontinued CSA at 6 months (n = 63, 72%) and the

remainder (n = 24, 28%) on studies with a further CSA taper over 18 months. In two studies, a third investigational immunosuppressive drug was added to standard IST: mycophenolate mofetil (MMF)[16] for 18 months (n = 21) or sirolimus[15] for 6 months (n = 10). Responses by specific clinical trial included in the historical group are shown in Table S5. Follow-up occurred at 3 months, 6 months, and yearly thereafter until study completion after which they were seen as clinically indicated (Fig 1).

Adult EPAG and adult IST groups

The adult EPAG comparator group comprised adults (aged ≥18 years) at the time of enrolment (n = 131) who received EPAG with IST on protocol (NCT01623167). The adult IST comparator arm comprised adults (aged ≥18 years) at the time of enrolment (n = 286) on the same four protocols as the paediatric IST group. All patients who had either reached primary end-point at 6 months or met off-study criteria prior were included. No age or sex matching was performed.

Response criteria

Response criteria were consistent across all protocols. Overall response was defined as blood counts no longer meeting Camitta criteria for SAA[17] with two out of three present: absolute reticulocyte count (ARC) ≥60 × 10^9/l, platelet count ≥20 × 10^9/l, or absolute neutrophil count (ANC) ≥0·5 × 10^9/l. Overall response was further categorised as CR or partial response (PR). Complete responders met the following criteria: haemoglobin (Hb) ≥100 g/l, platelet count ≥100 × 10^9/l, and ANC ≥1 × 10^9/l. Additionally, patients had to be transfusion and growth factor independent. Non-responders (NR) failed to achieve a response by 6 months.

Statistics

Analysis was performed on an intention-to-treat (ITT) basis. Summary statistics were used to describe baseline characteristics, response, and laboratory parameters. P values were computed using Student's t-test for continuous variables and Pearson's chi-squared test for categorical variables. Kaplan–Meier curves and the Cox proportional-hazards models were used to compare OS, EFS, relapse, and clonal evolution among the paediatric subgroups, and the likelihood ratio test was performed to assess statistical significance between curves. Analysis was performed using competing risk methods for clonal evolution, HSCT and death (Figure S6). As this was an ITT analysis, all patients who were taken off study prior to 6 months were deemed NR. Relapse was defined as a decrease in blood counts requiring AA-specific treatment including the re-initiation of full dose CSA or EPAG, additional IST or HSCT. For EFS, only patients who were responders at 6 months and experienced no events between the start of treatment and the 6-month end-point were included. We defined an event as relapse, clonal evolution, HSCT, or death. The data were analysed using R version 3.5.0 (R Foundation for Statistical Computing, Vienna, Austria) and the Statistical Analysis System (SAS) version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Patient characteristics

There were 40 patients in the paediatric EPAG group and 87 in the historical paediatric IST group. There were no significant differences in age or sex, or in baseline ARC, ANC or platelets (Table I). Baseline haemoglobin was significantly lower in the IST group. The median follow-up was 1432·5 days in the EPAG group and 2409 days in the IST group. Adolescents (aged ≥12 years) composed 60% (n = 24) of the EPAG group and 48% (n = 42) of the IST group, with younger children (aged <12 years) at 40% (n = 16) and 52% (n = 45) respectively.

Haematological response

In the EPAG group, the ORR was 68% at 3 months and 70% at 6 months compared to 63% at 3 months and 72% at 6 months in the IST group (6-month ORR P = 0·78). Complete responders totalled 23% at 3 months and 30% at 6 months in the EPAG group compared to the IST group at 14% and 23% respectively, again without statistical significance (6-month ORR P = 0·42; Table II). In contrast, in adults (aged ≥18 years) there was a significant difference in ORR at 6 months: 58% with IST alone compared with 82% with EPAG ($P \leq$ 0·001; Table S9). Response rates at 1 year were not significantly different between the EPAG and IST groups; however, patients who failed to achieve a response at 6 months were taken off protocol and not routinely followed, so late responses to treatment may not be captured.

Younger children had lower response rates than adolescents with the addition of EPAG, having an ORR of 63% compared with 78% for IST (P = 0·29) and a CR rate of just 6% compared to 24% with IST (P = 0·049), but patient numbers were low in this group. In contrast, adolescents achieved a CR rate of 46% with EPAG compared to 21% with IST (P = 0·052), and overall responses of 75% *versus* 67% (P = 0·48) respectively (Table III).

A higher proportion of patients went off study at or before 6 months in the EPAG group than in the IST group (6%, n = 5 in IST vs. 20%, n = 8 in EPAG) (Table S7). In the EPAG group, all patients pursued HSCT; two had clonal evolution (monosomy 7), four pursued HSCT due to urgent clinical necessity related to severe neutropenia and two underwent elective HSCT due to lack of response at 3 months. In the IST group, four died prior to 6 months and one pursued urgent HSCT.

Relapse and EFS

Of a total of 28 responders in the paediatric EPAG group, 43% relapsed (n = 12) compared to 27% (17 of 63 responders) in the paediatric IST group (P = 0·0661, Fig 2A). The median time to relapse was 349 days in the EPAG group and 585 days in the IST group. Relapses in the EPAG group peaked after 6 months and again at 2 years. Relapse in the EPAG group was initially treated with the re-initiation of full-dose CSA and/or EPAG; five of 11 (46%) patients recovered bloods counts and did not ultimately require further IST or HSCT, and one was lost to follow-up. Five children deemed 6-month responders received a 3-month course of sirolimus starting at the 2-year time-point on a separate clinical protocol (NCT02979873) investigating the use of sirolimus for relapse prevention in patients with

stable blood counts and on low-dose CSA; two remain in CR, one PR, and two had relapsed prior to enrolment. Children who received EPAG had a similar rate of relapse (43%) as adults who received EPAG (41%) (likelihood ratio $P = 0{\cdot}56$; Fig 2B). The EFS at 1432·5 days (the median follow-up time in the EPAG group), in 6-month responders, was significantly lower in the EPAG group (57%) compared with the IST group (69%, likelihood ratio $P = 0{\cdot}0499$; Fig 2C). All events prior to 6 months were excluded in the main EFS analysis; EFS for all patients (including non-responders) from time 0 can be seen in Figure S3.

Clonal evolution

Clonal evolution was not significantly different (13% in the paediatric EPAG group vs. 9% with IST, likelihood ratio $P = 0{\cdot}215$). High-risk clonal evolution was defined as a chromosome 7 abnormality, complex karyotype, or overt myeloid malignancy, with all other isolated chromosomal abnormalities considered low risk. Five children (13%) evolved in the EPAG group; three were high risk (all monosomy 7) and two low risk (one del 5q and one translocation 5;12). Two patients who developed monosomy 7 did so rapidly at 3 months. One high-risk patient was off protocol at the time of evolution; a non-responder who received further IST (alemtuzumab) and was on long-term CSA and EPAG when found to have acute myeloid leukaemia (AML) with monosomy 7. All those with high-risk evolution ultimately proceeded to transplant. In the IST group, 9% of children (eight of 87) had clonal evolution with four at high risk and four at low risk (Table IV).

Genomics

No patients had a pathogenic or likely pathogenic germline variant in genes related to inherited bone marrow failure. Although some patients were found with variants of unknown significance in genes associated with telomere diseases (EPAG9, 15, 20, and 27) or in sterile alpha motif domain containing 9/-like (SAMD9/L) (EPAG14 and 11), most evidence marks these variants as not contributing to disease; normal telomere length, lack of clinical manifestations or relevant family history, *in silico* predictions, and lack of bone marrow dysplasia or development of monosomy 7 in SAMD9/L patients (Table S2). Although unlikely, we cannot definitively exclude a modulating effect in these patients' disease.

All children who received EPAG were screened for somatic variants in myeloid cancer genes at different time-points. Clonal haematopoiesis is prevalent in SAA; variants in phosphatidylinositol glycan anchor biosynthesis class A (*PIGA*), BCL-6 co-repressor (*BCOR*) and BCL-6 co-repressor-like protein 1 (*BCORL1*) are associated with an improved response to IST, and unfavourable mutations as a group including in DNA methyltransferase 3α (*DNMT3A*) and additional sex combs like-1 (*ASXL1*) genes have been correlated with a poorer prognosis.[18]

At baseline, only one patient had a somatic variant, in *ASXL1* [variant allele fraction (VAF) of 6·2%]. Five patients developed somatic mutations having had none at baseline; four at the 6-month time-point [two with alpha thalassaemia/mental retardation syndrome X-linked (*ATRX*) variants at VAF 3·5% and 13%, and two with *ASXL1* variants at VAF 9% and 24%] as well as one with a Runt-related transcription factor 1 (*RUNX1*) variant (VAF 7%) at 21

months (Figure S4). None had morphological dysplasia or abnormal cytogenetics at the time of detection. Of patients with *ASXL1* variants, all were deemed 6-month NR; one (with baseline mutation) underwent HSCT for non-response, one responded to EPAG monotherapy restarted off protocol, and one developed clonal evolution off protocol (AML with monosomy 7). Two patients with *ATRX* variants remained in a CR and PR when last seen, and the patient with a *RUNX1* variant was lost to follow-up.

Survival

The OS at 1432·5 days was not significantly different between the paediatric EPAG group and paediatric IST group at 94% and 84% respectively (likelihood ratio $P = 0{\cdot}092$; Figure S6).

Pharmacokinetics

Pharmacokinetic parameters of EPAG at steady state were available in 11 paediatric patients with SAA (Table S4). Peak concentrations (C_{max}) in plasma were achieved between 4 and 6 h (T_{max}) after the morning dose and the overall variability of parameters was moderate, consistent with previous clinical studies. The C_{max}, area under the plasma concentration–time curve from, time zero to time of last measurable concentration (AUC_{last}), and trough plasma concentration (C_{trough}) normalised to the starting dose of 75 mg in patients aged 6–11 years were 39·5 μg/ml, 640 μg × h/ml, and 19·2 μg/ml respectively; these were similar (C_{max} and AUC) or slightly lower (C_{trough}, −25%) than in older (aged ≥12 years) patients receiving 150 mg as the initial dose. PK data in adolescents and adults were similar, the C_{max}, AUC_{last} and C_{trough} were 41·6 μg/ml, 767 μg × h/ml and 25·6 μg/ml respectively in the group aged 12–17 years, and 40·3 μg/ml, 785 μg × h/ml and 27·1 μg/ml in the group aged ≥18 years.

Safety

Safety data have been published.[7] There were three severe adverse events (SAEs) in the paediatric EPAG group that required cessation of study drug; two cutaneous eruptions (Grade 2 and 3), and one Grade 3 hyperbilirubinaemia. In all, 10 patients had reversible liver function abnormalities possibly attributable to EPAG that was reported as an AE (Grades 2–3 rise in bilirubin, aspartate aminotransferase and alanine transaminase).

No deaths occurred in the EPAG group while enrolled on protocol. Two patients later died of infection after HSCT.

Discussion

Optimal first-line treatment for children with SAA who lack a matched-sibling donor is not settled. For those treated with IST, responses are good but relapse and clonal evolution remain concerns, particularly in children who have the most benefit to gain over time. Improvements in transplant-related morbidity and mortality have made matched unrelated donor (MUD)[19,20] and alternative donor transplant[21–23] attractive options. In adults, the addition of EPAG has offered significant improvements in response rates to >80%, but this result was not replicated in children.

The explanation for our present results showing lower efficacy of EPAG in children is unclear. Children historically have had better response rates to IST than adults and they tolerate more intensive IST regimens.[3,24] The difference in response between younger children and adolescents may hint at an underlying biological difference. PKs do not appear to be responsible, as comparable EPAG exposures were achieved across age groups, although the number tested was low in the younger age group (more data will be acquired in an ongoing clinical trial, NCT03025698). There was no clear relationship between exposure and haematological response at the tested dose in each group. Inherited marrow failure disorders were excluded as much as was feasible in the EPAG arm with no definite pathogenic variants found, as unknown germline dispositions[25] would affect response to either regimen.

Relapse was higher and EFS significantly lower in the EPAG group. A peak in relapse at 6 months and 2 years, when drug modifications occur (EPAG discontinued and CSA dose stopped or reduced), was obvious. Haematological responses may in some patients be dependent on either marrow stimulation or ongoing IST. One series of 11 children showed longer-term administration of EPAG may be efficacious.[26]

There was a trend towards longer survival in the paediatric EPAG group, but this is likely related to disparate time-periods (1989–2010 for the IST group, 2012–2019 for the EPAG group) as survival in SAA has increased over time due to supportive care.[27] Transplant has become more widely utilised due to decreased transplant-related morbidity and mortality, and wider availability of alternative donors; more patients went off study in the EPAG group to pursue HSCT. Additionally, a paediatric subgroup analysis was not part of the initial trial design.

The safety profile of EPAG is good; no patients died or had serious morbidity as a result of EPAG. We noted that clonal evolution was more frequent in children who received EPAG, although the difference from the IST group was not statistically significant. EPAG is expensive and significantly increases the cost of IST for SAA,[28,29] a burden both to patients and to healthcare systems.

The data presented in this non-randomised subgroup analysis do not support the addition of EPAG to IST for treatment-naïve SAA in children, although this regimen has been FDA approved in patients aged ≥2 years. Results from randomised trials in progress and accumulated experience at paediatric haematology centres will be important in definitively addressing the role of thrombopoietin mimetics in children.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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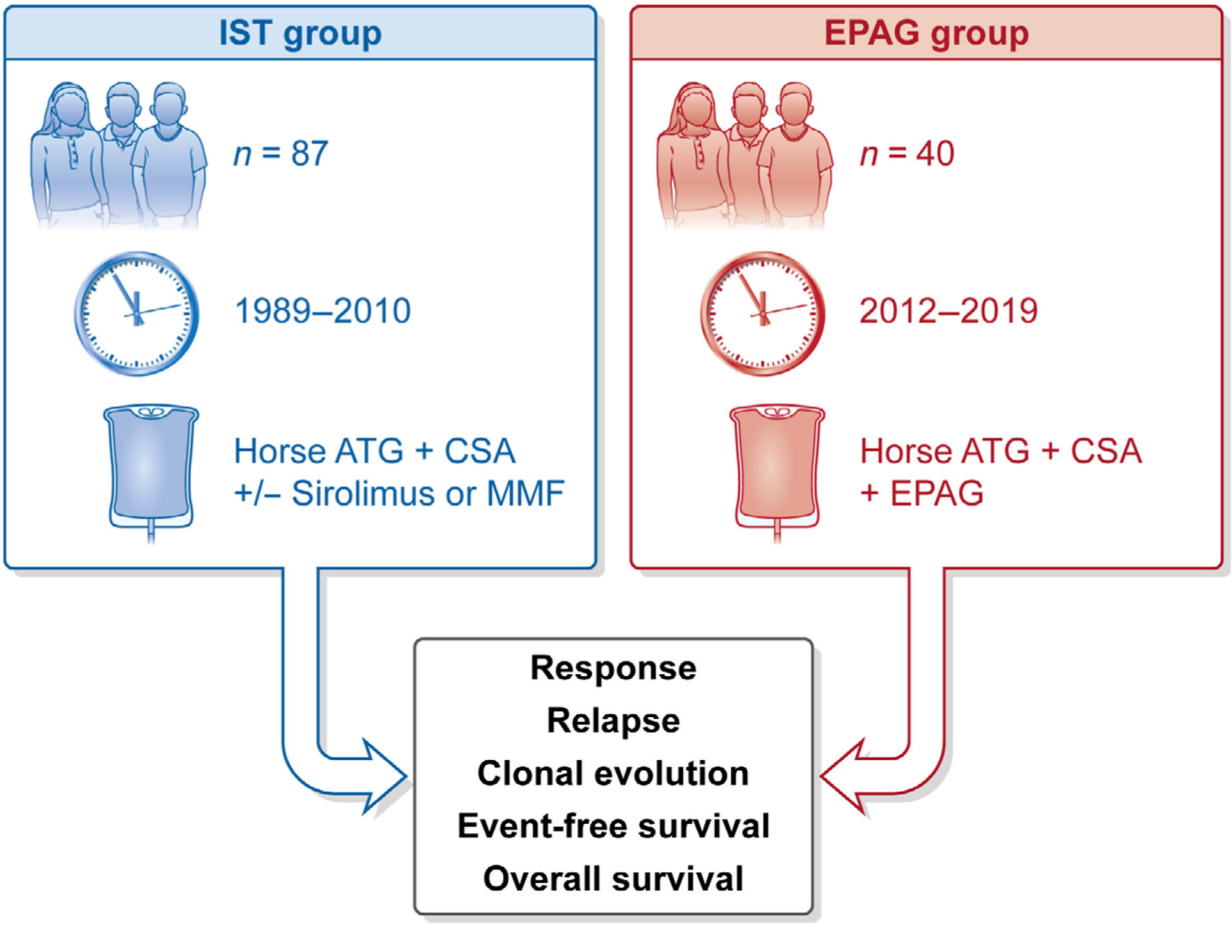

Fig 1.

Study design. The study compared two groups: the paediatric EPAG group and the historical paediatric IST group. The paediatric IST group consisted of 87 paediatric patients (aged <18 years) on four different clinical trials (NCT00061360, NCT00001964, NCT00260689 and (no NCT number available: Rosenfeld*et al.*, 2003[9]) taking place at the NIH from 1989 to 2010. The paediatric EPAG group consisted of 40 patients (aged <18 years) enrolled on NCT01623167 from 2012 to 2019; data of 19 patients were previously published.[7]Analysis was performed using intention to treat. Measured outcomes included: haematological response, relapse, clonal evolution, event-free survival, and overall survival. ATG, anti-thymocyte globulin; CSA, cyclosporine; EPAG, eltrombopag; IST, immunosuppressive therapy; NCT, national clinical trial; NIH, National Institutes of Health; MMF, mycophenolate mofetil.

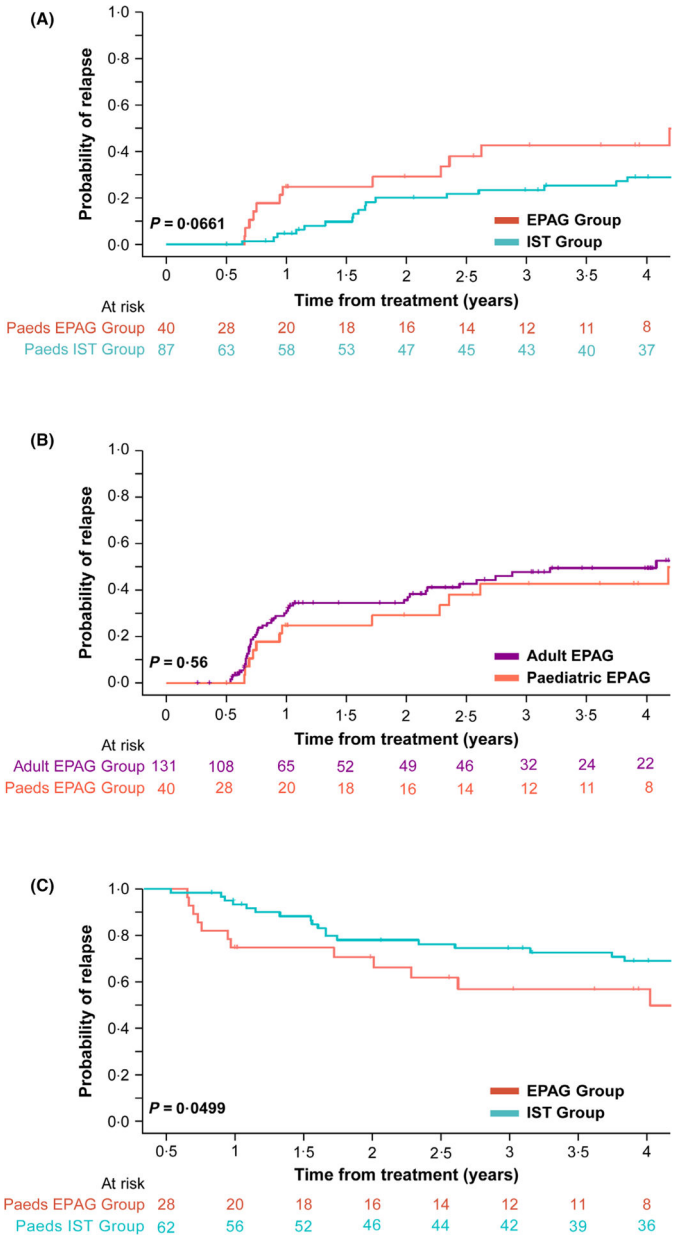

Fig 2.

Relapse and event-free survival (A) Kaplan–Meier curve comparing relapse in all paediatric responders; the paediatric IST *versus* paediatric EPAG group. The median time to relapse was 349 days in the EPAG group and 585 days in the IST group. Relapse was 43% in the EPAG group and 27% in the IST group. This difference was not significant (likelihood ratio $P = 0{\cdot}0661$). (B) Kaplan–Meier curve comparing relapse between children and adults who received EPAG. The median time to relapse was 349 days in children and 277 in adults. There was no significant difference in relapse seen with 41% of adults relapsing compared with 43% of children (likelihood ratio $P = 0{\cdot}56$). (C) Kaplan–Meier curve comparing EFS in paediatric responders in the IST *versus* EPAG group. At 1432·5 days (median follow-up time in the EPAG group) EFS was significantly lower in the EPAG group (57%) compared with

the IST group (69%) (likelihood ratio $P = 0{\cdot}0499$). The median follow-up time was 2409 days (6·6 years) in the paediatric IST group and 1432·5 days (3·9 years) in the paediatric EPAG group. EFS, event-free survival; EPAG, eltrombopag; IST, immunosuppressive therapy.

Table I.

Patients' baseline characteristics.

Baseline characteristic	IST (*n* = 87)	EPAG (*n* = 40)	*P*
Age at first IST, years, median (range)	11 (2–17)	13 (3–17)	0·42
Sex, *n* (%)			
Female	36 (41)	17 (43)	0·91
Male	51 (59)	23 (58)	
Age distribution, *n* (%)			
<12 years	45 (52)	16 (40)	0·22
≥12 years	42 (48)	24 (60)	
Laboratory values, median			
Haemoglobin, g/1			
All <18 years	73	84	<0·01
<12 years	72	81	
Absolute reticulocyte count, × 10^9/l			
All <18 years	12·1	12·9	0·63
<12 years	12·2	12·7	
Absolute neutrophil count, × 10^9/l			
All <18 years	0·22	0·16	0·36
<12 years	0·21	0·13	
Platelet count, × 10^9/l			
All <18 years	9	9	0·45
<12 years	10	8	
PNH clone >1% GPI deficient neutrophils, *n* (%)			
Yes	14 (29)	11 (31)	0·82
No	34 (71)	24 (69)	
Unknown	*n* = 39	*n* = 5	

Baseline data for the paediatric IST group are shown on the left and paediatric EPAG group on the right. EPAG, eltrombopag; IST, immunosuppressive therapy; PNH, paroxysmal nocturnal haemoglobinuria; GPI, glycosylphosphatidylinositol.

Table II.

Haematological response in paediatric IST group *versus* EPAG group.

	IST group (*n* = 87)	EPAG group (*n* = 40)	*P*
3-month response			
Response, *n* (%)			
Overall response	55 (63)	27 (68)	0·64
CR	12 (14)	9 (23)	0·26
PR	43 (49)	18 (45)	
NR	29 (33)	9 (23)	
Off study	3 (3)	4 (10)	
6-month response			
Response, *n* (%)			
Overall response	63 (72)	28 (70)	0·78
CR	20 (23)	12 (30)	0·42
PR	43 (49)	16 (40)	
NR	19 (22)	4 (10)	
Off study	5 (6)	8 (20)	
1-year response			
Response, *n* (%)			
Overall response	52 (60)	20 (50)	0·38
CR	31 (36)	16 (40)	0·57
PR	21 (24)	4 (10)	
NR	0 (0)	0 (0)	
Relapsed	5 (6)	7 (18)	
Off study	30 (34)	12 (30)	
Not reached	0 (0)	1 (3	

Rates of haematological response are shown for the paediatric IST group on the left and paediatric EPAG group on the right. Overall response is further broken down into CR or PR. Patients who were off study at 1 year were for many different reasons including: NR at 6 months, alternate treatment such as repeat IST or HSCT, death, or were lost to follow-up. Patients who were deemed non-responders at 6 months were not routinely monitored for late response beyond 6 months as they were taken off study. CR, complete response; EPAG, eltrombopag; IST, immunosuppressive therapy; NR, no response; PR, partial response.

Table III.

Haematological response at 6 months in younger children *versus* adolescents.

	IST group	EPAG group	*P*
Younger children aged <12 years			
Response, *n* (%)	*n* = 45	*n* = 16	
Overall response	35 (78)	10 (63)	0·29
CR	11 (24)	1 (6)	0·049 *
PR	24 (53)	9 (56)	
NR	9 (20)	2 (13)	
Off study	1 (2)	4 (25)	
Adolescents aged >12 years			
Response, *n* (%)	*n* = 42	*n* = 24	
Overall response	28 (67)	18 (75)	0·48
CR	9 (21)	11 (46)	0·052
PR	19 (45)	7 (29)	
NR	10 (24)	2 (8)	
Off study	4 (10)	4 (17)	

Rates of haematological response are shown for the paediatric IST group on the left and paediatric EPAG group on the right. Younger children (aged <12 years) are shown on the top and adolescents on the bottom. Overall response is further broken down into CR or PR. CR, complete response; EPAG, eltrombopag; IST, immunosuppressive therapy; NR, no response; PR, partial response.

* Note, significance uncertain given low patient numbers.

Table IV.

Clonal evolution in paediatric patients.

Patient	Time to clonal evolution, days	Clonal evolution	Karyotype	Risk category	*SAMD9/SAMD9L*
Paediatric EPAG group					
EPAG2	1470	Del 5q	46,XX,del(5)(q15q31)[2]/46,XX[19]	Low	Not assessed
EPAG9	733	Translocation (5;12)	46,XY,t(5;12)(p10;p10)[2]/46,XY[18]	Low	Not assessed
EPAG15	88	Monosomy 7	45,XY,−7[6]/46,XY[14]	High	Not assessed
EPAG28	1049	AML with Monosomy 7	45,XX,−7[7]/46,XX[13]	High	No
EPAG40	97	Monosomy 7	45,XY,−7[12]/46,XY[8]	High	No
Paediatric IST group					
IST46	2528	AML	46,XY[20]	High	
IST57	990	13q del	46,XX,del(13)(q12q14)[5]	Low	
IST20	185	Trisomy 8	47,XX,+8[2]/46,XX[19]	Low	
IST29	2715	MDS-MLD	Unavailable	High	
IST78	193	13q del	46,XY,del(13)(q12q14)[3]/46,XY[1]	Low	
IST92	955	Translocation (6;14)	46,XY,t(6;14)(q24;q24)[3] 46,XY[17]	Low	
IST97	359	Monosomy 7	45,XY,−7[4/20]	High	
			45,XY,−7,inv(12)(q15q24.1)[1/20]		
			46,XY,inv (12)(q15q24.1)[2/20]		
			46,XY[13/20]		
IST135	1853	Monosomy 7	Unavailable	High	

All patients in the paediatric IST and paediatric EPAG group who underwent clonal evolution are listed. Included is the type of clonal evolution, the karyotyping results, and whether it was deemed high or low risk. High risk was defined as a chromosome 7 abnormality, complex karyotype, or morphologically overt myelodysplastic syndrome or other myeloid malignancy with all other types of clonal evolution being deemed low risk. Assessment for variants in *SAMD9/SAMD9L* was performed only in EPAG 28 and 40. Germline mutations were not assessed in the IST group. AML, acute myeloid leukaemia; EPAG, eltrombopag; IST, immunosuppressive therapy; MDS-MLD, myelodysplastic syndrome with multilineage dysplasia; SAMD9/L, sterile alpha motif domain containing 9 like.