Immunosuppressive therapy for severe aplastic anemia in children under the age of 3 years yields a high response rate: a North American collaborative study

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Abstract

Distinguishing acquired (idiopathic/immune) severe aplastic anemia (SAA) from inherited bone marrow failure syndromes (IBMFS) is critical since only acquired cases respond to immunosuppressive therapy (IST), the standard treatment in cases without a matched sibling donor. Differentiating SAA from IBMFS is particularly challenging in children younger than 3 years, in whom inherited disorders are more prevalent. No age threshold exists to guide IST use in this population. Thus, we evaluated IST outcomes in children aged <3 years, diagnosed with acquired SAA across three registries: the North American Pediatric Aplastic Anemia Consortium, the Canadian Aplastic Anemia and Myelodysplasia Study, and the Canadian Inherited Marrow Failure Registry. Patients with suspected IBMFS based on clinical assessment, first-degree family history of marrow failure, or insufficient data were excluded. Among 30 patients aged 15.6-34.8 months at diagnosis, 93% received horse antithymocyte globulin and cyclosporine A; 80% ultimately achieved a complete response. The median duration of cyclosporine A use among responders was 20.4 months (range, 5.6-55). By 4, 6, and 12 months, 50%, 92%, and 100% of responders, respectively, were transfusion-independent. Once achieved, complete responses were durable, with no relaps-

es during a median 56-month follow-up after cyclosporine A cessation. Six patients (20%) did not respond: five underwent hematopoietic stem cell transplantation; one achieved a complete response to second IST after an initial partial response and transition to danazol. Complications included infections, bleeding, hypertension, gingival hypertrophy, and chronic kidney disease. No deaths occurred during follow-up (median, 73 months). In conclusion, these findings highlight, for the first time, strong IST efficacy in children aged 1.3-<3 years with acquired SAA.

Introduction

Acquired severe aplastic anemia (SAA) is a rare but serious hematologic disorder, with an incidence of approximately two cases per million children annually in North America and Europe, and two to three times higher in East Asia.[1,2] It is characterized by peripheral blood cytopenias and a hypocellular bone marrow, most often considered idiopathic and frequently presumed to be immune.[2,3]

The frequent overlap in clinical presentation between acquired SAA and inherited bone marrow failure syndromes (IBMFS) creates diagnostic and management challenges, particularly in infancy, as the disease mechanism and treatment strategies diverge substantially. Accurate differentiation is essential, as patients with IBMFS (e.g., Fanconi anemia, dyskeratosis congenita) do not respond to immunosuppressive therapy (IST) and require hematopoietic stem cell transplantation (HSCT) for curative therapy or alternative approaches, such as androgens (e.g., danazol and oxymetholone), tailored to the underlying genetic disorder.[4-7]

For patients with acquired SAA lacking a matched sibling donor (MSD), IST with horse antithymocyte globulin (ATG) and cyclosporine is the standard of care in North America.[8] In pediatric populations, IST achieves overall response rates of approximately 70-75%, with a substantial proportion attaining a complete response (CR).[10-12] Children generally respond more favorably to IST than adults, with higher CR rates, more robust trilineage recovery and lower rates of clonal evolution, provided that inherited etiologies, which are more prevalent among younger patients, are carefully excluded.[9,12]

There is a paucity of data specifically addressing outcomes of IST in children under 3 years of age with SAA, in whom inherited diseases are more prevalent. Most published pediatric studies have included children younger than 3 years within their reported response rates; however, very few toddlers were included in these studies and none has stratified outcomes to examine this age group separately.[13-17] As a result, it remains unclear whether these very young patients, when apparent inherited disorders are excluded based on clinical and currently available laboratory testing, respond to IST similarly to older children. Given this uncertainty, children presenting with SAA require prompt and comprehensive evaluation for IBMFS, and if no MSD is available and inherited causes are excluded, IST should be initiated without delay.[8]

In this study, we aimed to characterize and analyze the clinical and laboratory features and treatment outcomes of children diagnosed with SAA before 3 years of age who received IST, and to determine whether there is an age below which response to IST is unlikely, suggesting an underlying inherited cause of bone marrow failure.

Methods

Study design and participants

This retrospective cohort study included pediatric patients identified through three established multicenter data sources: the North American Pediatric Aplastic Anemia Consortium (NAPAAC), the Canadian Aplastic Anemia and Myelodysplastic Syndrome Study (CAMS), and the Canadian Inherited Marrow Failure Registry (CIMFR). All patients had SAA and were diagnosed and treated across North American institutions.

For this study, potentially eligible patients were identified through extraction of existing registry entries; no additional institution-level case finding was performed for this analysis. When overlap between data sources was identified, duplicate entries were reconciled and counted once.

Patients were included if they met criteria for SAA, were under 3 years of age at diagnosis, and received IST.

For inclusion, IST regimens combining horse ATG, corticosteroids and a calcineurin inhibitor (cyclosporine or tacrolimus) required a minimum of 3 months of calcineurin inhibitor therapy. Patients treated with cyclophosphamide monotherapy given as a single 4-day course were also eligible.[18]

Patients were excluded if they were ≥3 years at diagnosis, had suspected IBMFS based on clinical assessment (physical anomalies/family history; evaluation per local practice and test availability), received HSCT as first-line therapy, or had insufficient clinical data for analysis.

Definitions

SAA was defined by bone marrow cellularity <30% of the expected value for age, without significant fibrosis or malignant infiltration, based on biopsy. If unavailable or inconclusive, a markedly hypocellular marrow aspirate was accepted. Patients also had to meet two or more of the following peripheral blood criteria: absolute neutrophil count $<0.5\times10^9$/L, platelet count $<20\times10^9$/L, and/or absolute reticulocyte count $<20\times10^9$/L (or <1% corrected for hematocrit).[2,9,19,20]

Outcomes

The primary outcome was best hematologic response to IST, assessed using modified criteria adapted from Camitta *et al.*[21] Sustained response was defined as lasting ≥2 months. CR to treatment for SAA was defined by normalization of hemoglobin for age, absolute neutrophil count >1.5×10^9/L, and platelet count >150×10^9/L, without need for transfusions or growth factors. Partial response was defined as transfusion independence and no longer meeting criteria for severe disease, but not CR. Patients were classified as non-responders if they continued to meet criteria for severe disease.

Secondary outcomes included relapse (per NAPAAC protocol; ≥50% decline from peak absolute neutrophil count and/or platelet count and/or hemoglobin drop of ≥2 g/dL, or transfusion re-dependence), major IST-related toxicities or complications, 5-year overall survival (when applicable), and subsequent treatment regimens, including HSCT.

Statistical analysis

Descriptive statistics summarized patients' characteristics and outcomes. Response rates were calculated as proportions and compared to published pediatric response rates using a one-sample proportion z-test. Continuous variables were compared between groups using the Wilcoxon rank-sum test. $P<0.05$ was considered statistically significant. Analyses were conducted in R (V4.3.3).

Ethical considerations

CAMS and CIMFR were approved by the research ethics board at the Hospital for Sick Children and other participating centers. NAPAAC data collection was approved by Institutional Review Boards at each participating institution or through reliance on a central Institutional Review Board at Boston Children's Hospital.[9] All data were de-identified prior to analysis in accordance with institutional and national standards.

Results

Patients' characteristics

Data were extracted for patients diagnosed with SAA between 2001 and 2021 from CAMS and CIMFR, which included a total of 103 and 716 patients, respectively, at the 2021 data cutoff. Additional patients were identified through NAPAAC, using data from a previously conducted retrospective study of pediatric cases of SAA diagnosed between 2002 and 2014, which included 314 children aged 1-20 years treated with IST and followed for a minimum of 2 years;[9] patients meeting our inclusion criteria were selected from this cohort.

Across these sources, 36 children diagnosed with SAA before age of 3 years and considered for first-line IST were identified. Six were excluded prior to analysis: three due to missing data required for analysis (NAPAAC N=1, CAMS N=1, CIMFR N=1), one due to duplication across sources (a NAPAAC entry also captured in CIMFR), one patient with hepatitis-associated SAA following liver transplant already receiving tacrolimus, with very short telomere length (<1st percentile), in whom additional IST was not administered; and one patient who died in the pediatric intensive care unit, prior to initiation of IST.

A total of 30 patients under the age of 3 years who received IST as first-line treatment for SAA met our inclusion criteria and were included in the final analysis. The patients' characteristics are summarized in Table 1. The age range at diagnosis was 15.6-34.8 months. Seventeen patients (57%) were female, and ten (33%) had hepatitis-associated SAA. None of the patients had short stature below the third percentile for age. Mild congenital anomalies were identified in three patients (10%), including vesicoureteral reflux, patent ductus arteriosus, and mild hearing impairment. Family history data were unavailable for five patients (17%). Among those with available data, five patients (20%) had a family history of malignancy in second- or third-degree relatives; all malignancies occurred in middle-aged or older adults,

Table 1. Characteristics of children who were diagnosed with severe aplastic anemia before 3 years of age.

Characteristics	Values
Total patients, N (%)	30 (100)
Female/male, N (%)	17/13 (57/43)
Age at diagnosis, months, median (range)	26.8 (15.6-34.8)
Hepatitis-associated SAA, N (%)	10 (33)
Mild physical congenital anomalies, N (%)	3 (10)
Patent ductus arteriosus	1 (3)
Mild hearing impairment	1 (3)
Vesicoureteral reflux	1 (3)
Short stature below 3rd percentile	0 (0)
Family history findings,* N (%)	6 (20)
Malignancy in 2nd or 3rd degree relatives	5 (17)
Hematologic and solid	2 (7)
Solid only	3 (10)
Polycythemia vera (1st degree relative)	1 (3)
Hyper-eosinophilic syndrome (3rd degree relative)	1 (3)
Consanguinity (relationship unspecified)	1 (3)
Unknown or unavailable family history	5 (17)
IBMFS evaluation, N (%)	
Chromosomal breakage testing performed	28 (93)
Negative among tested	28 (100)
SBDS genetic testing performed	9 (30)
Negative among tested	8 (89)
Heterozygous carrier state	1 (11)
Telomere length testing performed	11 (37)
Normal among tested	9 (82)
Short (1st-10th percentile) among tested	2 (18)

*Family history items are not mutually exclusive (i.e. a patient may have >1 finding). IBMFS: inherited bone marrow failure syndrome; SAA: severe aplastic anemia; *SBDS*: Shwachman-Bodian-Diamond syndrome.

with none reported in childhood or adolescence. Reported cancers in these family members included hematologic malignancies (leukemia and lymphoma) and solid tumors (breast, ovarian, uterine, throat, skin, bone, and prostate). Of these five patients, one also had a first-degree relative with polycythemia vera, and another had parental consanguinity (exact relation undocumented). One additional patient had a cousin with hyper-eosinophilic syndrome.

Evaluation for IBMFS followed local practice and test availability over the study period. Chromosomal breakage testing for Fanconi anemia was negative in 28/30 patients (not performed in 2/30), Schwachman-Bodian-Diamond syndrome (*SBDS*) genetic testing was performed in 9/30 patients (negative in 8/9; one heterozygous carrier of a known pathogenic variant), and telomere length testing was performed in 11/30 patients (normal in 9/11; short, at 1st-10th percentile, in 2/11). In the included patients, bone marrow biopsy reports described marked hypocellularity meeting SAA criteria without reported dysplasia or increased blasts, and no clonal cytogenetic abnormalities were reported, supporting SAA rather than refractory cytopenia of childhood or hypocellular MDS. Paroxysmal nocturnal hemoglobinuria (PNH) clone testing at initial evaluation was available for 19/30 patients and was negative in all; repeat PNH testing after IST was not protocolized or consistently captured in the registries and remained negative in a small subset (N=5) who were re-tested.

The majority of patients (N=28, 93%) were treated with horse ATG and cyclosporine A (CSA). The median time from diagnosis to initiation of IST was 18 days (range, 0-182). Twenty-two of the 28 patients (79%) had documentation of concurrent treatment with corticosteroids; indication, dose and duration were not consistently captured in the registries. Information on corticosteroid treatment in the remaining six patients was unavailable. Two patients (7%) were treated with a single 4-day course of cyclophosphamide monotherapy (treated in 2003 and 2010), initiated 23 and 346 days from diagnosis, respectively. Reasons for the observed variation in timing of treatment initiation were not captured in the registry data.

Response to immunosuppressive therapy

A CR to IST was ultimately achieved in 24 of the 30 patients (80%; best hematologic response) (Figure 1). This included both patients treated with cyclophosphamide monotherapy, who each achieved CR. Excluding these two patients did not materially change the overall CR estimate (22/28 [79%] *vs*. 24/30 [80%])

Because complete blood count monitoring intervals and transfusion documentation varied across patients in the registries at the discretion of individual treating teams, response could not be consistently assessed at prespecified landmark timepoints. Accordingly, Figure 1 summarizes best achieved response categories rather than fixed-time response rates, as the timing of partial response could not be reliably determined from registry data. Transfusion independence is therefore reported as a complementary, clinically meaningful outcome (Figure 2); however, its recorded timing may also overestimate the true time to transfusion independence given the non-uniform capture of complete blood count and transfusion intervals. Transfusion independence was observed in ten patients (42%) by 3-4 months, in 22 patients (92%) by 6 months, and in all 24 responders (100%) by 1 year following the initiation of IST. At 3-4 months, six patients received packed red blood cell transfusions only, one patient received platelet transfusions only, and seven patients received both packed red blood cells and platelets. By 6 months, two patients who would eventually become responders remained transfusion-dependent: one receiving packed red blood cells only and one receiving both packed red blood cells and platelet transfusions. Among responders with a documented CSA stop date (N=17), CSA was discontinued at a median of 20.4 months (range, 5.6-55). CSA stop dates were unavailable for seven additional patients, precluding systematic assessment of long-term CSA dependence in the full cohort. No relapses were reported during long-term follow-up after CSA cessation (median 56 months; range, 12-178). Details of treatment and response outcomes are summarized in Table 2.

The observed complete response rate of 80% was not significantly different from published response rates in pediatric cohorts (70-75%),[10-12] based on one-sample proportion z-tests (P=0.232 *vs*. 70%; P=0.527 *vs*. 75%).

Six patients (20%) did not respond to first-line IST and received additional therapy. Of these six patients, four were treated with a second course of IST with rabbit ATG. Three of these four remained unresponsive and subsequently underwent HSCT, while the fourth patient achieved a partial response and was transitioned to danazol, ultimately attaining CR on the latter treatment. Two of the six non-responders proceeded directly to HSCT (without a second course of IST): one was transplanted after an unsuccessful course of danazol therapy (no response), and one was transplanted without interim medical therapy. Individual treatment timelines, stratified by response to treatment and organized by age at diagnosis, are depicted in Figure 3. Of note, the time from diagnosis to IST initiation did not differ between responders and non-responders (median 18 days in both groups; Wilcoxon rank-sum P=0.889).

Complications during immunosuppressive therapy

Table 3 summarizes the complications observed during the first year following IST. Nine patients (32%) developed serum sickness following ATG therapy; severity and management were not consistently captured (recorded as yes/no), and this designation likely included both mild, self-limited symptoms as well as more clinically significant cases.

Within the first 3 months after IST, infections included culture-proven bacteremia (N=6 episodes in 5 patients),

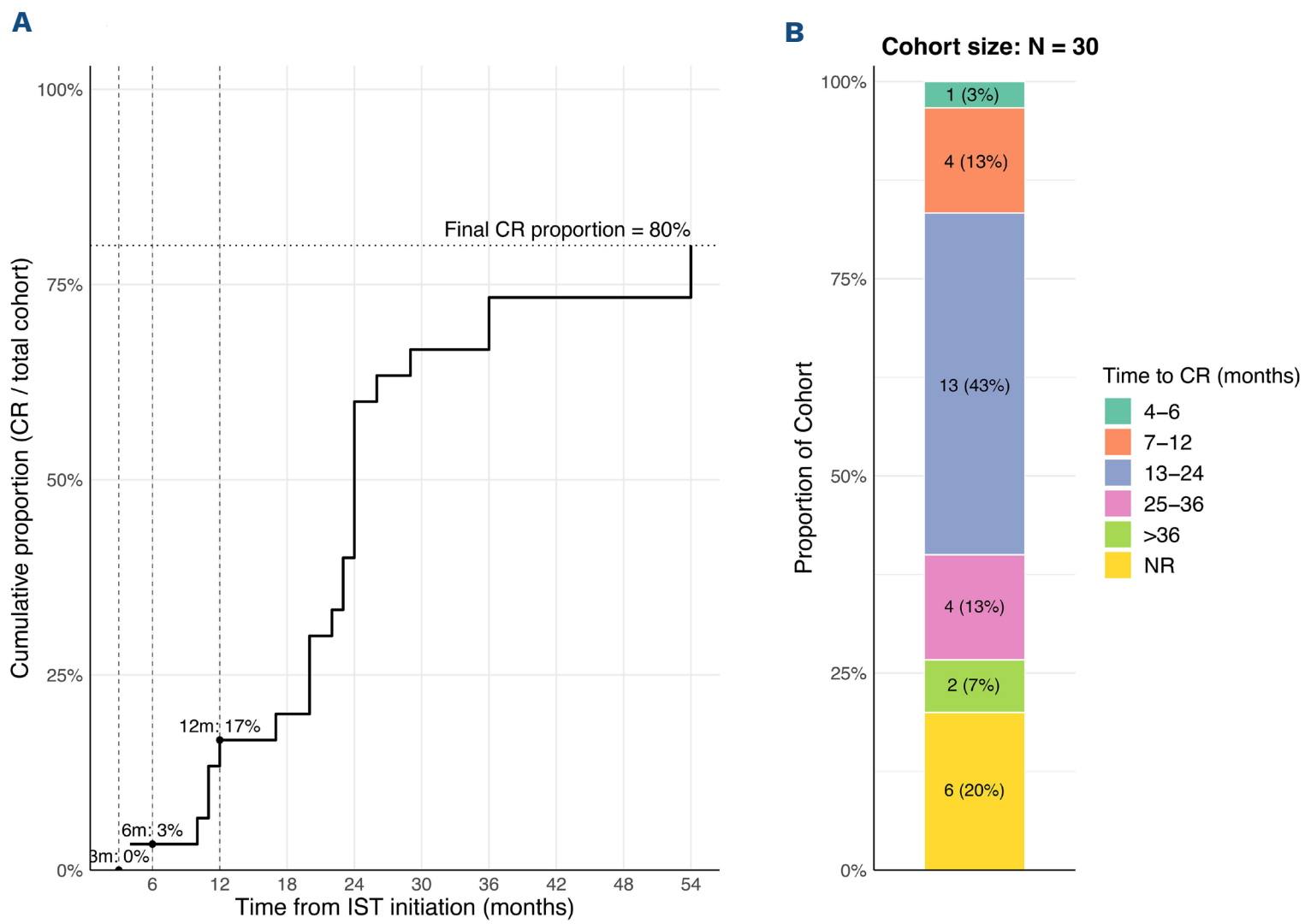

Figure 1. Best hematologic response to first-line immunosuppressive therapy in children under 3 years with severe aplastic anemia. (A) Cumulative proportion of patients ultimately achieving complete response (CR) over time, with non-responders remaining in the denominator. Best hematologic response was defined according to modified criteria adapted from Camitta *et al.*,[21] with timing based on the earliest available complete blood count meeting CR thresholds in the registry datasets. Vertical dashed lines mark 3, 6, and 12 months with point estimates. The dotted horizontal line indicates the final proportion of CR (80%), reached by 54 months and maintained thereafter. Of note, due to variability in complete blood count monitoring frequency, recorded times to CR may be an overestimate of the actual response. (B) Distribution of time to CR categories: 4-6, 7-12, 13-24, 25-36, and >36 months from initiation of immunosuppressive therapy. Bars represent the proportion of patients in each category who ultimately achieved CR or remained non-responders (yellow). IST: immunosuppressive therapy; m: months; NR: no response.

cellulitis (N=2), and viral gastroenteritis (N=1). Organisms associated with bacteremia included *Enterococcus faecalis*, *Serratia marcescens*, coagulase-negative *Staphylococcus* and *Enterobacter cloacae*; one patient experienced two distinct bacteremia episodes in this interval - *Streptococcus viridans* and, separately, coagulase-negative *Staphylococcus* with *Pseudomonas aeruginosa* with concurrent cellulitis. Bleeding within the first 3 months consisted of gross hematuria in two patients, occurring within 30 and 60 days of IST initiation. Additional early complications included hypertension (N=5) and gingival hyperplasia (n=1). One patient had transient acute kidney injury attributed to CSA (creatinine rise without specific intervention). Between 3 to 6 months after treatment, one patient had oral bleeding, and one patient developed bacteremia with blood cultures positive for *Acinetobacter lwoffi*, *Staphylococcus spp*., and *Cellulosimicrobium spp*. Between 6 to 12 months after treatment, one patient developed *Streptococcus viridans* bacteremia, two developed hypertension, and one was diagnosed with chronic kidney disease, attributed to CSA, which presented with echogenic kidneys on ultrasound, hypertension, mild creatinine elevation, and a mild decline in glomerular filtration rate. Hypertension was managed with antihypertensive therapy (amlodipine in most cases; enalapril in 1 case), and one patient required only as-needed nifedipine during IST initiation, attributed to corticosteroids and resolving after steroid tapering. All abnormalities resolved following CSA cessation in the responding patients. Because admission-level details (including specific antibiotic agents given) and Common Terminology Criteria for Adverse Events (CTCAE) grading were not uniformly captured in the registries, complications are reported using available clinical descriptors. Notably, no deaths occurred during the follow-up period (median time from diagnosis, 73 months; range, 12-234 months) and no posterior reversible encephalopathy syndrome was reported in this cohort of patients. No clonal evolution was reported during follow-up; however, repeat bone marrow examinations and cytogenetic surveillance were not routinely performed or uniformly captured across the registries.

Discussion

This study is the first to specifically evaluate the response to first-line IST in children diagnosed with acquired SAA under the age of 3 years. We observed a high success rate, with an 80% CR rate in children diagnosed between 15.6 to 34.8 months of age. These findings are consistent with outcomes reported in major older pediatric IST cohorts treated with horse ATG and cyclosporine, including the National Institutes of Health experience (Scheinberg *et al.*),[22] the North American Pediatric Aplastic Anemia Consortium study (Rogers *et al.*),[9] and long-term pediatric series comparing IST with matched sibling donor transplantation (Kojima *et al.*).[15] These studies collectively demonstrated strong response rates and excellent overall survival in children receiving IST, albeit with a subset requiring subsequent interventions due to non-response and/or relapse. However, these pivotal datasets included very few patients under 3 years of age, limiting toddler-specific inferences; our cohort directly addresses this evidence gap by characterizing outcomes and durability of IST in this very young age group.

While guidelines emphasize the importance of comprehensive genetic testing and detailed phenotypic assessment for all pediatric patients with aplastic anemia,[2,8,23,24] there remains no universally accepted age threshold below which the likelihood of an inherited disorder outweighs consideration of IST and no previous studies have determined outcomes after IST in this infant age group. Due to unavailability of data, it is possible that children under the age of 3 years may be presumed to have a higher likelihood of IBMFS and undergo HSCT rather than IST. Notably, no children younger than 15 months (1.3 years) met eligibility criteria, suggesting that patients under this age are less likely to present with acquired SAA and more commonly have an IBMFS, or are treated upfront with a non-MSD HSCT, rather than IST, due to the perceived higher likelihood of an inherited cause. This observation supports the clinical perception that acquired SAA is exceedingly rare in infancy and underscores the importance of comprehensive and timely evaluation before considering IST in this age group, including family history, physical examination, chromosomal breakage testing, telomere length analysis, and genetic panels. Our findings address this gap, demonstrating that very young children between 1.3 to <3 years with SAA achieve excellent outcomes with IST when appropriately screened for IBMFS with no greater toxicities than older children and adolescents. These data support the approach that in patients with critical pancytopenia without clear evidence of IBMFS, the initiation of IST should not be delayed when a MSD is unavailable.

We found that 92% of responders achieved transfusion independence within 6 months, with all responders transfusion-independent by 1 year, which is similar to previously reported outcomes in broader pediatric SAA populations.[15,25] Treatment was generally well tolerated, with complications that were mostly transient and are commonly seen in older pediatric patients who receive IST, and included infections, bleeding, gingival hyperplasia, hypertension, and chronic kidney disease. Infections and bleeding episodes predominantly occurred early after IST initiation, during the period of greatest cytopenia, and likely reflect vulnerability prior to hematologic recovery, rather than being strictly treatment-related. Notably, no relapses or deaths occurred during long-term follow-up. Relapse definitions vary across published pediatric SAA cohorts, ranging from reinstitution of IST[22] to return to SAA/moderate AA thresholds.[15] We used the prespecified NAPAAC protocol definition for consistency across participating centers. Together, these findings suggest that young age does not negatively impact the durability of response to IST, when inherited causes are appropriately excluded. More broadly, responses to IST appear more durable in pediatric cohorts than in adults in several published series, although the reasons are not fully defined.[9,12] Potential contributors include greater hematopoietic stem/progenitor reserve and regenerative capacity in children,[26,27] fewer age-related clonal hematopoiesis changes/genomic instability,[28] and differences in immune regulation with age,[1,24] along with a lower competing comorbidity burden and better treatment tolerance that may support durable recovery.[12,29]

The role of eltrombopag, a thrombopoietin receptor agonist, as an adjunct to IST in children with newly diagnosed SAA remains an area of active study. In the National Institutes of Health pediatric experience reported by

Table 2. First- and second-line treatments and response to immunosuppressive therapy

Treatments	Values
First-line treatment, N (%)	30 (100)
Horse ATG + CSA	28 (93)
Cyclophosphamide	2 (7)
Response to first-line IST	
CR, N (%)	24 (80)
NR, N (%)	6 (20)
Time on CSA, months, median (range)	24.1 (5.6-126.4)
CSA discontinued completely, N (%)	17 (71% of responders)
Follow-up after CSA cessation, months, median (range)	56.1 (11.7-178.2)
Second-line treatment among non-responders, N (%)	6 (20)
Rabbit ATG (NR) → HSCT, N (%)	3 (50)
Rabbit ATG (PR) → Danazol (CR), N (%)	1 (17)
Danazol (NR) → HSCT, N (%)	1 (17)
HSCT without interim therapy, N (%)	1 (17)
Age at diagnosis (NR group), months, median (range)	28.1 (23.4-34.0)
Time from 1st-line IST to 2nd-line therapy, months, median (range)	3.7 (3.5-12.9)

ATG: antithymocyte globulin; CR: complete response; CSA; cyclosporine A; HSCT: hematopoietic stem cell transplantation; IST: immunosuppressive therapy; NR: no response; PR: partial response.

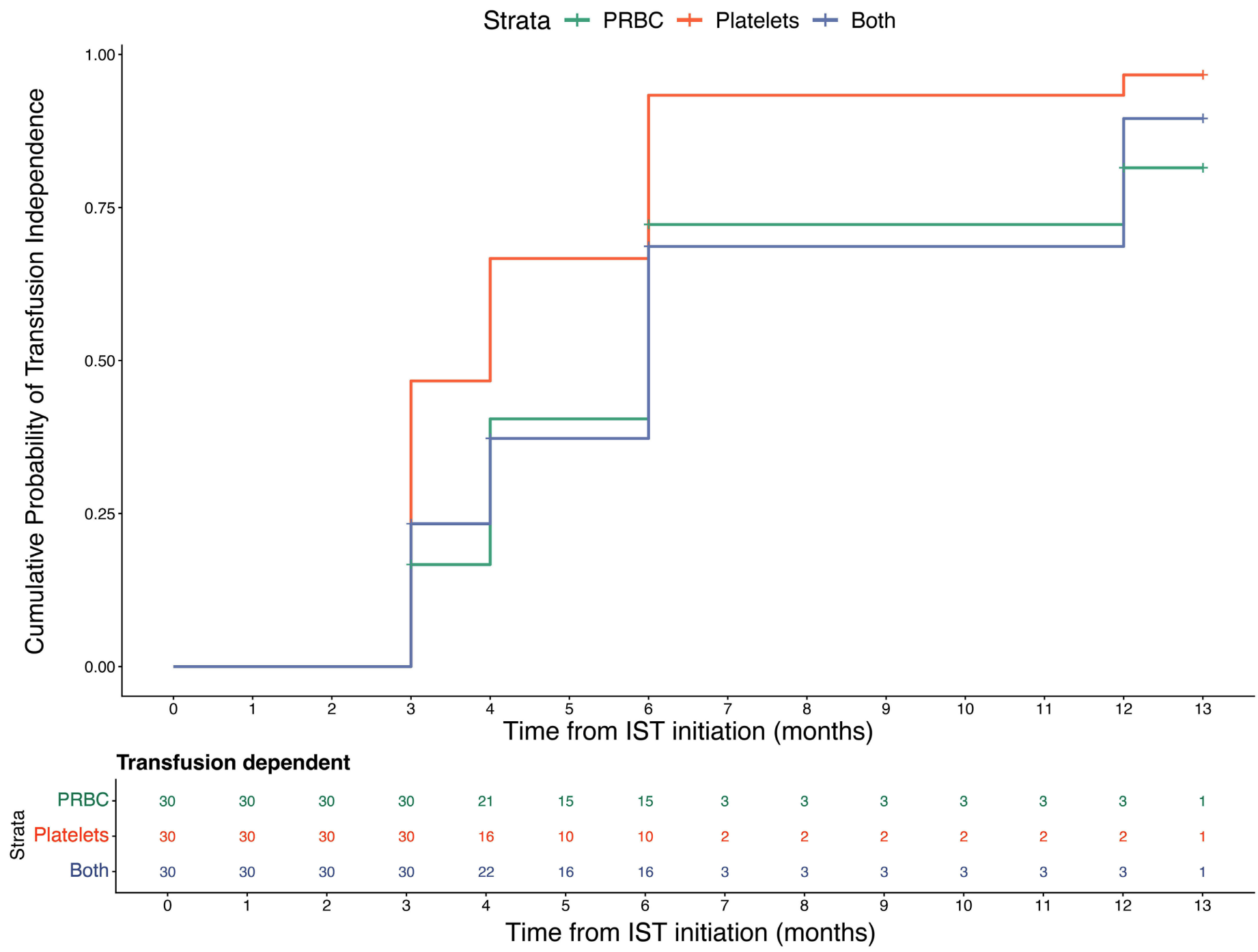

Figure 2. Time to transfusion independence following immunosuppressive therapy. Inverted Kaplan-Meier curves for independence from transfusion with packed red blood cells, platelets, or both. Patients proceeding to second-line therapy were censored. The "Transfusion dependent" table shows the number of patients still receiving the respective type of transfusion at each timepoint. Due to variability in the frequency of complete blood count monitoring, recorded times to transfusion independence may be an overestimate of the actual response. IST: immunosuppressive therapy; PRBC: packed red blood cells.

Groarke *et al.*,[30] the addition of eltrombopag to standard IST in treatment-naïve children did not improve outcomes compared with IST alone, with a trend toward higher relapse and significantly lower event-free survival, leading the authors to caution against automatically considering eltrombopag standard of care in pediatrics. Consistent with this, recent pediatric evidence-based recommendations do not support routine upfront eltrombopag addition for all children, and emphasize the need to better define subgroups most likely to benefit.[8] In our cohort, eltrombopag was not used; thus, the outcomes presented reflect ATG/calcineurin inhibitor-based IST alone and provide a benchmark for response and durability in very young children treated without eltrombopag.

HSCT in children with acquired SAA, particularly in those diagnosed at a very young age, carries distinct risks. In a recent multicenter series of 32 children with acquired SAA diagnosed between 3-69 months of life (median age 33 months), the day-100 transplant-related mortality was 9.4%, graft failure occurred in approximately 22% of patients, and long-term survivors experienced complications such as iron overload, endocrine-metabolic disorders, and growth impairment.[31] These differences highlight the favorable short- and long-term safety profile of IST in appropriately selected young children compared with HSCT, particularly when a MSD is unavailable.

Practice patterns for children without a MSD vary by region and have evolved over time. In Europe, guidelines, including those from the Pediatric Hemato-Oncology Italian Association (AIEOP)[2] and the British Society for Haematolo-

gy,[32] have increasingly incorporated the algorithm proposed by Dufour *et al.*[33] According to this algorithm, the authors recommend a rapid unrelated donor search after diagnosis, and consideration of upfront matched unrelated donor (MUD) HSCT when a suitably matched donor is likely to be available within 3-4 months, with the choice between upfront MUD HSCT and IST ideally made within the first 6-8 weeks to avoid delaying therapy. In Japan, guidelines recommend considering upfront MUD transplantation particularly for subgroups felt to have a lower likelihood of response to IST, specifically very severe or fulminant SAA.[24] In contrast, during the study era and across the North American centers represented in these registries, first-line therapy for pediatric patients without a MSD has generally been IST with horse ATG and cyclosporine, consistent with recent NAPAAC evidence-based recommendations,[8] with MUD transplantation more commonly reserved for non-response or relapse. Prospective comparative data are still needed to define the optimal first-line strategy for children lacking an MSD, and the ongoing NAPAAC randomized trial comparing upfront MUD HSCT with IST (TransiT; NCT05600426) is expected to help inform future standards of care.[34]

This study is limited by its retrospective design, small cohort size, and reliance on registry data. Case identification for the current analysis was based on existing registry entries rather than independent institution-level screening, thus, the completeness of capture of all eligible cases within participating catchment areas cannot be quantified, and selection bias is possible. In addition, evaluation for IBMFS was not uniform across the cohort, reflecting local practice and test availability over the study period. Treatment approaches spanned two decades, and included two patients treated with high-dose cyclophosphamide, a historical regimen, which is now widely discouraged in routine clinical practice, due to toxicity concerns;[35,36] we retained these cases to reflect real-world practice over the study period, and their exclusion did not alter the primary findings. As with many registry-based studies, variability in clinical follow-up schedules, and consequently in complete blood count monitoring intervals, determined by individual treating teams, may have led to overestimation of the recorded times to transfusion independence and, subsequently, to CR relative to the actual time to response. Complication ascertainment was limited by registry-level reporting, and severity could not be consistently graded: some complications were recorded only as binary variables (including serum sickness), while others were captured as event labels (e.g., gross hematuria) or bacteremia with specified pathogens, without standardized definitions, management details, or hospitalization/Intensive Care Unit data; documentation may also have varied across centers. CSA discontinuation dates were not available for 29% of responders, limiting assessment of prolonged CSA dependence. Additionally, although the duration of follow-up was sufficient to assess initial response and relapse, it may not provide full information about certain late complications such as clonal evolution or long-term toxicities associated with IST. Repeat bone marrow examinations and cytogenetic surveillance were not protocolized, were not routinely performed in patients with sustained count recovery and were not uniformly captured in registry records. However, all responders achieved sustained normalization of peripheral blood counts, making clinically overt clonal evolution during the study period unlikely in the absence of recurrent cytopenias. In published cohorts, most cases of clonal evolution occur within the first few years following IST,[9,27,29] and responders in our cohort (N=24) had a median follow-up of 79 months from IST initiation, with 17 patients followed for more than 5 years. Similarly, baseline PNH testing was not available for all patients and serial PNH screening was not protocolized; thus, absence of reported PNH evolution should be interpreted cautiously, as small emergent clones could have been missed without systematic follow-up testing. Despite these limitations, this study provides invaluable data to guide clinical decision-making in a patient population with previously limited evidence to support treatment strategies. Furthermore, the study highlights the importance of collaborative multicenter efforts and continued registry development to advance research and improve outcomes in rare pediatric diseases, such as SAA.

In conclusion, our findings demonstrate that IST is highly effective in children under 3 years of age diagnosed with acquired SAA, achieving CR rates comparable to those in older children. These results support the use of IST in this age group when a MSD is unavailable, provided comprehensive but prompt IBMFS evaluation is undertaken. Ongoing

Table 3. Complications following immunosuppressive therapy by time interval after treatment initiation.

Complications	Total, N (%)*		
	0-3 months	3-6 months	6-12 months
Total patients followed	30 (100)	27 (90)	25 (83)
Serum sickness	9 (30)	-	-
Infections	7 (23)	1 (4)	1 (4)
Bacteremia/sepsis	5 (17)**	1 (4)	1 (4)
Cellulitis	2 (7)	-	-
Viral gastroenteritis	1 (3)	-	-
Gross bleeding episode	2 (7)	1 (4)	-
Gingival hyperplasia	1 (3)	-	-
Hypertension	5 (17)	-	2 (8)
Hyperkalemia	-	1 (4)	-
Acute kidney injury	1 (3)	-	-
Chronic kidney disease	-	-	1 (4)

*Percentages for the 3- to 6-month and 6- to 12-month intervals correspond to patients actively followed during those intervals. **A single patient had two episodes of bacteremia within the same time period.

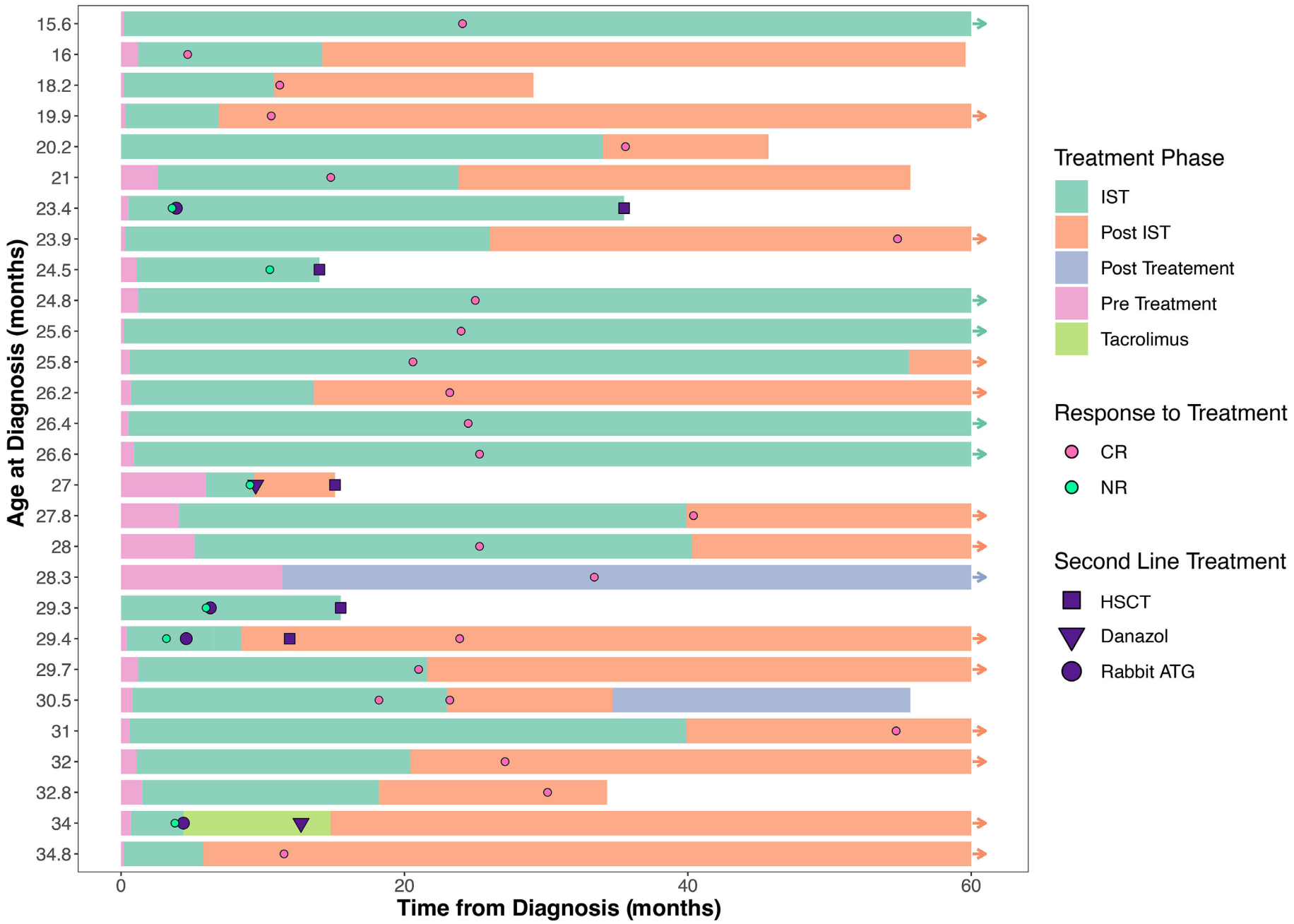

Figure 3. Longitudinal treatment and response overview. A swimmer plot depicting treatment, best hematologic response and outcomes, stratified by response to treatment and organized by age at diagnosis. IST refers to patients who received treatment with horse antithymocyte globulin and cyclosporine A (CSA) as first-line therapy. Post IST refers to follow-up after CSA cessation. Post IST refers to follow-up after CSA cessation. Post treatment refers to patients who received a single 4-day course of cyclophosphamide as first-line therapy. Due to variability in the frequency of complete blood count monitoring, recorded times to complete response may be an overestimate of the actual response. Of note, CSA stop date was not captured in the registry extract for seven patients; it is, therefore, unclear whether CSA had been discontinued by the time of data cutoff or whether the stop date was simply not recorded. ATG: antithymocyte globulin; CR: complete response; HSCT: hematopoietic stem cell transplantation; IST: immunosuppressive therapy; NR: no response.

prospective studies will further clarify the optimal first-line approach for children lacking an MSD. Future prospective studies incorporating uniform genetic screening, extended follow-up, standardized marrow/cytogenetic and PNH surveillance, and international collaboration are essential to refine treatment approaches and monitor for late effects in a very young population with this rare disease.

Disclosures

No conflicts of interest to disclose.

Contributions

TWD wrote the original draft, reviewed and edited the manuscript, and was responsible for visualization, data curation, investigation, formal analysis, and conceptualization of the study. LW reviewed and edited the manuscript, curated data, and was involved in the investigation, methodology, and conceptualization of the study. SDA, JB, MC, TDC, CC-B, CJG, AEG, BG, GMK, TAN, TSO, ZRR, AS, CT, AAT, and DAW reviewed and edited the manuscript and curated data. YD reviewed and edited the manuscript, supervised the study, curated data, and was responsible for investigation, validation, methodology, and conceptualization of the study.

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Artificial intelligence

During the preparation of this work the authors used ChatGPT for text editing in some sections of this manuscript, to refine the language and improve clarity. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Data-sharing statement

The data underlying this study are not publicly available due to privacy and ethical restrictions. De-identified data may be made available upon reasonable request to the corresponding author and with permission from the contributing registries.

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