Delayed hemolytic transfusion reaction in children with sickle cell disease: first 5-year retrospective study in mainland France

Delayed hemolytic transfusion reaction (DHTR) is increasingly being reported as a serious complication of red blood cell (RBC) transfusion in patients with sickle cell disease (SCD).[1,2] Alloimmunization against RBC antigens has been identified as its leading underlying cause.[3,4]

DHTR remains a major challenge as it may be under-recognized, leading to patient receiving inappropriate further transfusion that may result in life-threatening exacerbation of hemolysis.[1,5] Moreover there is no consensus on its optimal management. Immunoglobulins (IVIG) and erythropoïetin (EPO) are considered beneficial, and eculizumab has recently emerged as a possible alternative treatment. It has been recommended that RBC transfusions be withheld during DHTR as this might aggravate hemolysis, whereas the use of corticosteroids (CS) is still controversial because of its suspected vaso-occlusive triggering effect.[6-9] However, in the setting of acute severe DHTR, the potential risks of steroids associated with RBC transfusion must be balanced against their potential life-saving effects. For patients requiring further transfusion away from the DHTR acute episode, rituximab is recommended to prevent the production of additional alloantibodies.[9] However, there is currently a lack of evidence to guide the best management of these “untransfusable” patients.

Our main objective was therefore to update the clinical description of DHTR, immuno-hematology findings, laboratory explorations and immediate management, at nationwide scale for children with SCD, over a 5-year period beginning in 2015, a period of improved awareness of DHTR. The secondary objective was to describe future patient management, when a subsequent RBC transfusion was required, later following the resolution of DHTR.

This study was based on a national survey performed through the French national SCD network in which all cases of DHTR in children (age <18 years) diagnosed with SCD, occurring between January 1, 2015 and December 31, 2020 and followed-up in mainland France were collected. Relevant patient data were retrospectively collected from medical files and anonymized. The data collected included clinical and laboratory data at the time of the triggering transfusion (TT) and during the DHTR episode (including evidence of the selective destruction of transfused cells over self-sickle RBC), management and clinical course. Transfusion and antibody history data from the French Blood Agency information system were also analyzed. Following national recommendations, all French centers deliver cross-matched, leukocyte-reduced, RBC units matched for ABO, RH and K. This study was performed in accordance with the Declaration of Helsinki.

DHTR was defined as the occurence at least 3 days after a transfusion, of signs indicating accelerated hemolysis together with a significant decrease in hemoglobin (Hb) (<30%), particularly HbA, indicating preferential hemolysis of the transfused RBC. Whenever possible, the previously published nomogram was applied to confirm the diagnosis.[10] Forty-one DHTR were reported by all but one center of the SCD network. Four were excluded due to alternative diagnoses of splenic sequestration in one case, and autoimmune hemolytic anemia in the other three. For these four cases, sequential determinations of hemoglobin A indicated that the increased hemolysis did not selectively target transfused donor RBC. We, thus, considered, 37 DHTR episodes in total, at 18 pediatric centers in mainland France, in 37 children including 35 with HbSS, one with HbSβ°, and one with HbSβ^{+} diseases. Median age at DHTR diagnosis was 9 years (range, 3-15). Twenty-two patients developed DHTR while on hydroxyurea therapy. For 34 children, the TT was delivered as an occasional transfusion episode, mostly during an inflammatory state (vaso-occlusive crisis [VOC], acute chest syndrom [ACS], infection, pre-operative setting). Three patients were on chronic transfusion programs, initiated 3 to 6 months before the DHTR episode.

Clinical symptoms and biological data collected during DHTR are detailed in Table 1. Pain mimicking VOC was the leading symptom followed by dark urine, indicating of hemoglobinuria. Half the patients developed fever during the DHTR episode. No death or stroke occurred in our series, but we observed posterior reversible leukoencephalopathy syndrome in one child, acute tubular necrosis in another, and ACS in 12 children. All complications occurred before further transfusion.

Post-TT determinations of Hb level and HbA% were monitored in only 20 and nine cases, respectively. During DHTR, Hb electrophoresis was performed for only 16 children, suggesting that the diagnosis of DHTR was initially overlooked for 21 of 37 children. Hb and HbA% were assessed both shortly after the TT and at the time of DHTR symptoms in only nine children. Using nomogram, there was a high risk of ongoing DHTR in these nine episodes.[10]

For other episodes, signs of accelerated hemolysis, in-

Table 1. Clinical and laboratory data during delayed hemolytic transfusion reaction and by treatment.

	Supportive care N=11		Immuno-suppression N=9		Additional transfusion N=17		*p**	Total N=37	
Days, median (range) from TT to DHTR diagnosis	N=11	10 (5-13)	N=9	12 (3-18)	N=17	7 (4-38)	0.81	N=37	10 (4-38)
Clinical symptoms at admission, N (%)									
Pain	N=11	9 (81)	N=9	7 (78)	N=17	15 (88)	0.78	N=37	31 (84)
Dark urine	N=11	6 (55)	N=9	5 (56)	N=17	9 (53)	0.99	N=37	20 (54)
Fever	N=11	4 (36)	N=9	5 (56)	N=17	12 (70)	0.21	N=37	21 (57)
Icterus	N=11	4 (36)	N=9	5 (56)	N=17	6 (35)	0.59	N=37	15 (40)
SCD complications, N(%)									
Acute chest syndrome (ACS)	N=11	4 (36)	N=9	1 (11)	N=17	7 (41)	0.29	N=37	12 (32)
Kidney failure	N=11	0	N=9	0	N=17	1 (6)	0.56	N=37	1 (3)
Neurological impairment	N=11	0	N=9	0	N=17	1 (6)	0.56	N=37	1 (3)
Outcomes, N (%)									
Clinical and biological improvement	N=11	7 (64)	N=9	8 (89)	N=17	8 (47)	0.11	N=37	23 (62)
Long-term consequences/death	N=11	0	N=9	0	N=17	0	-	N=37	0
Length of hospital stay in days, median (range)	N=11	8 (0-21)	N=9	9 (4-11)	N=17	15 (1-30)	**0.02**	N=37	9 (0-30)
Number of ICU admission	N=11	3 (27)	N=9	5 (55)	N=17	10 (59)	0.19	N=37	18 (49)
Biological parameters during TT, median (range)									
Pre-TT Hb, g/dL	N=10	7.4 (5.3-10.3)	N=6	6.7 (4.5-8.5)	N=16	6.7 (5.0-10.8)	0.19	N=34	6.7 (4.5-10.8)
Post-TT Hb, g/dL	N=9	9.3 (7.5-12.5)	N=5	9.6 (7.6-10.8)	N=13	9.5 (7.8-11.4)	0.7	N=20	9.5 (7.5-12.5)
Post-TT HbA, %	N=5	35 (20-55.4)	N=1	35	N=4	24 (21.9-31.8)	-	N=9	27 (20-55.4)
Biological parameters during TT, median (range)									
Hb nadir, g/dL	N=11	5.6 (3.7-7.1)	N=9	4.8 (3.1-5.7)	N=17	4.9 (2.9-11.1)	0.26	N=37	5.1 (2.9-11.1)
HbA nadir, %	N=8	11 (0-28)	N=3	5 (0-13)	N=5	18 (3-28)	-	N=16	10 (0-28)
Highest leukocyte count, $x10^9$/L	N=8	18.9 (9.8-31.8)	N=8	15.6 (12.9-27.1)	N=13	21.1 (14.1-36.4)	0.39	N=29	20 (9.8-36.4)
Lowest platelet count, $x10^9$/L	N=6	353 (194-519)	N=7	282 (113-395)	N=15	247 (126-847)	0.57	N=28	250 (113-847)
Lowest reticulocyte count, $x10^9$/L	N=8	339 (126-547)	N=6	223 (79-420)	N=14	147 (31-339)	**0.006**	N=28	220 (31-547)
LDH max, IU/L	N=9	1,156 (636-4,052)	N=7	1,045 (691-6,490)	N=12	1,460 (611-9,181)	0.35	N=28	1,224 (611-9,181)
CRP max, mg/L	N=9	132 (5.4-252)	N=7	192 (2.8-264)	N=10	149 (7-286)	0.75	N=26	125 (2.8-264)
Bilirubin max, mmol/L	N=7	86 (34-226)	N=8	54 (20-122)	N=14	75 (17-117)	0.25	N=28	76 (17-226)

DHTR: delayed hemolytic transfusion reaction; TT: triggering transfusion; Hb: hemoglobin; HbA: hemoglobin A; ICU: intensive care unit; SCD sickle cell disease; supportive care: erythropoietin, hydration, oxygenation and analgesic opioids; immunosuppression: immunoglobulins, corticosteroids, rituximab. *Analyses of multiple groups were performed by one-way ANOVA. A probability value $P<0.05$ was considered statistically significant. **Biological parameters before additional transfusion.

cluding an inappropriate marked drop in HbA levels after the TT were used to diagnose DHTR. Hyperhemolysis (HH) with Hb levels falling below pretransfusion values, occurred in 32 of 37 children. Reticulocyte counts were significantly lower in the subgroup of 17 children receiving an additional transfusion, suggesting that profound erythropoiesis impairment might have contributed to the decision to transfuse during DHTR. None of the other clinical or biological parameters differed significantly between the subgroups receiving only supportive care including EPO (n=11), immunosuppression without transfusion (CS, IVIG, and/or rituximab) (n=9) or further transfusion (n=17). In-

terestingly, HbA levels were unavailable for the eight children who received further transfusions without immunosuppression, suggesting that DHTR was undiagnosed at the time of retransfusion.

Patient management during DHTR is detailed in Table 2. Seventeen patients received an additional transfusion. When no immunosuppressive agent was associated with transfusion, it clearly and consistently worsened hemolysis and resulted in HH episodes. The addition of CS at 1 mg/kg, prescribed for two children was ineffective. When higher CS dose (2 mg/kg) were prescribed for seven children in addition to transfusion, post-transfusion Hb levels were effectively maintained. Interestingly, three of these children had previously experienced a DHTR recurrence when transfusion was attempted with 1 mg/kg of CS for one or without any CS cover for the two others. Eleven patients received IVIG, among which eight did not require further transfusion. For one child, IVIG was the only immunosuppression prescribed, precluding any conclusions on its efficacy to mitigate DHTR.

We were able to obtain previous transfusion records and antibody testing results for all but six children, these remaining children having received transfusion outside France (Table 3). Consistent with adult data showing a history of DHTR and/or alloimmunization to be associated with a higher risk of DHTR, 16 children in our cohort had a history of alloimmunization and/or DHTR.[11-13] The number of RBC units transfused before the TT was low (median 4) but seven children developed DHTR after receiving ≥ 12 RBC units. Nine of the 21 patients with no immunization history, therefore receiving RH/K-matched units, developed antibodies. Sixteen patients were already immunized, and were transfused with extended (FY, JK, Ss) matched RBC units. Six of these patients, developed new antibodies, which were anti-M in three cases (M compatibility was not taken into account). For five patients, antibodies were detected only during later tests (3 weeks to 3 months after DHTR).

Eleven children received subsequent transfusions, a median of 3 months (range, 10 days-3 years) after resolution of the DHTR episode (*Online Supplementary Figure S1*). All three alloimmunized children received rituximab

Table 2. Delayed hemolytic transfusion reaction management and outcome.

	Patients	EPO	IVIG g/kg	Rituximab mg/m²	Eculizumab	CS mg/kg	AT1	Initial outcome	EPO	IVIG g/kg	Rituximab mg/m²	CS mg/kg	AT2	Later outcome
Supportive care	3,4,5,7,17,18,27							CBR						
	12,16,21,22	X						CBR						
Immuno-suppression	10	X	0.8					CBR						
	13	X				2		CBR						
	14	X	2	375				CBR						
	28	X	3			2		CBR						
	29		1					CBR						
	30	X	0.8					CBR						
	32	X	1					CBR						
	36		1	375				CBR						
	37	X	1					CBR						
Additional transfusion	9		0.4			2	X	CBR						
	11,24,34					2	X	CBR						
	31	X	1	375	X		X	CBR						
	25	X		375	X		X	H	X					CBR
	6					1	X	H			375	2	X	CBR
	19					1	X	H	X			1		CBR
	35	X	1				X	HH	X	1	375			CBR
	1						X	HH				2	X	CBR
	8						X	HH		1				CBR
	2						X	HH			375	2	X	CBR
	15						X	HH	X	1	375			CBR
	20						X	HH	X					CBR
	23						X	HH						CBR
	26,33						X	HH					X	HH

Supportive care: erythropoietin (EPO), hydration, oxygenation and analgesic opioids; immunosuppression: immunoglobulins, corticosteroids, rituximab, eculizumab; CS: corticosteroids (the dose refers to the total dose prescribed the day transfusion is delivered. The initial dose is usually kept unchanged for 48 hours and then tapered. Overall, mean duration of steroids was 7 days in our study) ; IVIG: intravenous immunoglobulin (total dose); AT1: first additional transfusion; AT2: second additional transfusion; DHTR: delayed hemolytic transfusion reaction; HH: hyperhemolysis; H: hemolysis; CBR: clinical and biological recovery.

Table 3. Immunohematologic characteristics of the patients.

Patients	Transfusion history					DHTR		
	Number of previous TF		Previous known Ab		Previous DHTR	Screening test before TT	Screening test during DHTR	Post-DHTR screening test (3 weeks-3 months)
	TF episodes	RBC units	Auto-Ab	Allo-Ab				
Patients without alloimmunization history (N=21)								
2	1	1				-	-	-
3	na	na				-	-	-
4	6	12				-	-	-
5	17	39				-	-	-
11	1	1				-	-	anti-S
13	na	na				-	-	-
14	1	4				-	-	**anti-Mg**
17	3	3				-	-	-
20	3	4				-	-	-
21	1	1				-	-	-
22	2	2				-	-	-
23	2	2				-	**anti-Jkb**	**anti-Jkb**
25	4	5				-	-	-
26	1	1				-	**anti-M**	**anti-M**
27	na	na				-	-	-
29	13	18				-	**anti-e**	**anti-e**
30	27	30				-	-	-
32	3	6				-	-	**anti-S**
33	2	2				-	**anti-Jkb**	**anti-Jkb**
34	4	4				-	**anti-Jka**	**anti-Jka**
37	2	2				-	**anti-s, anti Fya, anti Fy3, anti-c**	**anti-s, anti Fya, anti Fy3, anti-c**
N=21	2.5 (1-27)°	3.5 (1-39)°				0	New Ab: 6 (29%)	New Ab: 9 (43%)
Patients with alloimunization or DHTR history (N=16)								
1	4	4	-	anti-M	X	-	-	nd
6	1	1	-	anti-Lua	-	anti-Lua	anti-Lua	anti-Lua
7	4	9	-	anti-Jka	-	anti-Jka	anti-Jka	**anti-M**, anti-Jka
8	14	16	-	anti-Jka, anti-S	X	anti-S	anti-S	anti-S
9	1	1	-	anti-M	-	-	-	-
10	2	2	-	anti-M	-	anti-M	anti-M	anti-M
12	na	na	na	na	X	-	**anti-Jka, anti-M**	**anti-Jka, anti-M**
15	4	7	anti-e	anti-S	-	-	**anti-Jkb**	**anti-Jkb**
16	4	4	anti-e	anti-M	-	-	-	auto
18	8	14	-	anti-KEL3	-	anti-KEL3	anti-KEL3	nd
19	5	7	-	0	X	-	-	-
24	11	13	anti-Jka	anti-D*, anti Lea	-	aspecific	**anti-M**	**anti-M**
28	1	1	-	anti-M	-	anti-M	anti-M	**anti-Fya**
31	3	4	-	anti-KEL3	-	-	-	non-specific Ab
35	na	na	non-specific Ab	anti-C⁂, anti-S	na	-	**anti-M**, anti-S	**anti-M**, anti-S
36	na	na	-	anti-c⁂, anti-M	na	anti-c, anti-M	anti-c, anti-M	nd
N=16	4 (1-14)°	5 (1-16)°	4 (25%)	14 (87%)	4 (25%)	8 (50%)	New Ab: 4 (25%)	New Ab: 6 (38%)
All patients (N=37)								
N=37	3.5 (1-27)°	4 (1-39)°	4 (11%)	14 (38%)	4 (11%)	8 (22%)	New Ab: 10 (27%)	New Ab: 15 (41%)

In bold: new alloantibodies detected after the DHTR episode; DHTR: delayed hemolytic transfusion reaction; TF: transfusion; TT: triggering transfusion; Ab: antibody; RBC: red blood cell; na: not available: number of RBC transfusions unknown due to previous transfusion episodes outside France (mostly in Africa); nd: not done. For patients with antibodies against expressed antigens, molecular analysis was performed to distinguish between allo-and autoantibodies. *Molecular analysis revealed partial D antigen; ⁂these patients were transfused in Africa, where prophylactic antigen matching for Rh antigens is not routinely performed; °median range.

for non-specific prevention, and RBC units compatible in FY, JK and MNS systems, DHTR recurred in one child. Among the eight children without alloimmunization history, four were managed with rituximab and extensively

matched RBC, with an uneventful course for all children. Without rituximab, three of the other four non-alloimmunized children experienced DHTR recurrence.

This analysis of 37 children presenting a DHTR episode during a recent 5-year period in mainland France shows, that DHTR complications are regularly encountered in the pediatric SCD population. Some milder cases almost certainly passed unnoticed, but we can confirm that DHTR morbidity is high in children, as in adults, with SCD-related severe complications occurring in 12 of 37 children.[2,11-14] Whenever possible, we used the diagnostic nomogram developed for adults[10] to assess the likelihood of DHTR. We recommend the systematic determination of Hb and HbA concentrations within 48 hours of every occasional transfusion, and repeatedly in case of any symptoms occurring in a context of a recent transfusion. Given the non-specific symptoms observed at DHTR presentation, this would facilitate the timely diagnosis of DHTR.

Once DHTR has been recognized, the timing of antibody testing is also of key importance: in our study, late screening allowed to capture five among the 15 newly identified alloantibodies, highlighting the need for sequential testing during follow-up.

Further transfusion should be avoided during the acute episode, as it can lead to HH, as observed in eight children in our study with apparently overlooked DHTR. However, the SCD-related complications, as well as life-threatening anemia and intravascular hemolysis reactions that can arise during DHTR are not without risks.[2,11-14] Timely transfusion, before irreversible multiorgan failure or stroke has occurred, should be considered, to improve oxygen delivery, together with the use of corticosteroids to reduce inflammation.[8,9] The efficacy of more recent therapeutic interventions such as eculizumab or tocilizumab needs to be confirmed by additionnal reports.[7,15] In the acute DHTR setting, as during future patient management in situations which subsequent RBC transfusion may be required, shared decision-making is crucial. We propose national multidisciplinary meetings, to facilitate close communication between SCD physicians and transfusion medicine specialists for the discussion of preventive strategies.[16]

Authors

Claire Falguière,[1] Slimane Allali,[2] Bassem Khazem,[1] Annie Kamdem,[1] Cécile Arnaud,[1] Marie Belloy,[3] Corinne Guitton,[4] Marie-Hélène Odièvre,[5] Sophie Pertuisel,[6] Cecile Dumesnil,[7] Cécile Guillaumat,[8] Nathalie Garrec,[9] Alexandra Gauthier,[10] Perrine Mahe,[11] Valerie Soussan-Banini,[12] Laure Le-Carrer,[13] Etienne Merlin,[14] Audrey David,[15] Beatrice Pellegrino,[16] Catherine Paillard,[17] Jean-Francois Brasme,[18] Marie Lagarde,[19] France Pirenne[20,21] and Corinne Pondarre[1,21]

[1]Pediatric Department, Sickle Cell Disease Referral Center, Creteil; [2]Pediatric Department, Sickle Cell Disease Referral Center, Necker Hospital, APHP, Paris; [3]Pediatric Department, Center for Sickle Cell Disease, Aulnay sous-bois; [4]Pediatric Department, Sickle Cell Disease Referral Center, APHP, Kremlin-Bicetre; [5]Pediatric Department, Center for Sickle Cell Disease, Trousseau Hospital, APHP, Sorbonne Universite, INSERM UMRS 1134, BIGR, Paris; [6]Department of Pediatric Hemato-oncology, University Hospital of Rennes, Rennes; [7]Department of Pediatric Hemato-oncology, Hopital Charles Nicolle, Rouen; [8]Pediatric Department, Center for Sickle Cell Disease, Corbeil-Essonnes; [9]Pediatric Department, Center for Sickle Cell Disease, Jossigny; [10]Department of Pediatric Hemato-oncology, Hospices Civils de Lyon, Lyon; [11]Pediatric Department, Sickle Cell Disease Referral Center, Montpellier; [12]Pediatric Department, Center for Sickle Cell Disease, Boulogne-Billancourt; [13]Pediatric Department, Center for Sickle Cell Disease, Orsay; [14]Pediatric Department, Center for Sickle Cell Disease, Clermont-Ferrand University Hospital, Clermont-Ferrand; [15]Department of Pediatric Hemato-oncology, University Hospital of Saint-etienne, Saint-etienne; [16]Pediatric Department, Center for Sickle Cell Disease, Poissy; [17]Department of Pediatric Hemato-oncology and Bone Marrow Transplantation Unit, Hopital de Hautepierre, Strasbourg; [18]Department of Pediatric Hemato-oncology, University Hospital of Angers, Angers; [19]Pediatric Department, Center for Sickle Cell Disease, Bordeaux; [20]Etablissement Francais du Sang, Creteil, and [21]Universite Paris Est Creteil INSERM U955, Creteil, France

Correspondence:
C. FALGUIÈRE - claire.falguiere@chicreteil.fr

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Contributions

CF and CoP cared for some patients, designed and initiated the study, collected and interpreted the data, carried out the statistical analysis, wrote the paper, and had final responsibility for the decision to submit for publication; FP was involved in the collection of transfusion data, interpretation of results, and writing of the manuscript; SA followed up patients, was involved in the interpretation of results, and writing of the manuscript; BK, CA, AK, MB, CoG, MHO, SPCD, CeG, NG, AG, PM, VSB, LL, EM, AD, BP, CaP, JFB and ML cared for the patients and contributed to the writing of

the paper. All authors reviewed the paper and approved the final manuscript.

Data-sharing statement

All data generated or analyzed during this study are included in this published article (and its *Online Supplementary Appendix*).

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