To the editor:

Optimizing chronic transfusion therapy for survivors of hemoglobin Barts hydrops fetalis

Ali Amid,[1] Shiyi Chen,[2] William Brien,[3] Melanie Kirby-Allen,[1,*] and Isaac Odame[1*]

[1]Division of Haematology/Oncology, Department of Paediatrics, [2]Department of Biostatistics, and [3]Department of Laboratory Medicine and Pathobiology, The Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada

Hemoglobin Barts hydrops fetalis (homozygous α^0-thalassemia) results from deletion of all 4 α-globin genes.[1] It was previously considered a universally fatal condition; however, with recent advances in prenatal care and the availability of intrauterine blood transfusions, an increasing number of patients are now surviving into adulthood.[2] Similar to patients with transfusion-dependent thalassemia due to β-thalassemia (TDT-β), these patients require lifelong and regular transfusions, as the option of curative stem cell transplant may not be available for the majority of these patients. Although the Thalassemia International Federation guidelines recommend a transfusion strategy similar to TDT-β for these patients,[3] no report exists on the optimal transfusion management of patients with homozygous α^0-thalassemia, which could be referred to as transfusion-dependent thalassemia due to α-thalassemia (TDT-α). In TDT-β, initiation of transfusions results in improvement of anemia and suppression of ineffective erythropoiesis, the main underlying pathophysiologic processes.

In early 2014, we critically reviewed the treatment strategy for four patients with homozygous α^0-thalassemia at our institution who were previously on regular blood transfusions to keep their hemoglobin levels >100 g/L. Research was approved by the institutional review board, and patients gave consent in accordance with the Declaration of Helsinki. All patients had significant splenomegaly, progressive peripheral blood reticulocytosis, and biochemical markers of hemolysis (high lactate dehydrogenase [LDH], aspartate aminotransferase, indirect bilirubin), erythropoiesis (elevated soluble transferrin receptor [STR]), and tissue hypoxia (high serum erythropoietin). In addition, 3 of the 4 showed brain magnetic resonance imaging changes in keeping with "silent" ischemic infarcts (Table 1; Figure 1).

On further investigation, hemoglobin analysis (by high-performance liquid chromatography and capillary zone electrophoresis) showed hemoglobin H (Hb H) percentage ranging from 24% to 64% in our patients, with older patients having higher Hb H. Hb H, a tetramer of 4 β-globin chains, has extremely high oxygen affinity and poor tissue oxygen delivery, making it essentially nonfunctional.[4-6] With the high Hb H levels observed in our chronically transfused patients with homozygous α^0-thalassemia, we estimated the patients' "functional"

Table 1. Patient characteristics

Patient	Patient 1	Patient 2	Patient 3	Patient 4
Age at the time of implementation of new transfusion strategy (years)	6	16	15	14
Sex	Male	Female	Male	Male
α Globin gene deletion	--SEA/--SEA	--SEA/--SEA	--SEA/--SEA	--SEA/--SEA
Proportion of Hb H before implementation of new transfusion strategy (%)*	24	64	49	44
Calculated functional hemoglobin before new transfusion strategy (g/L)	79.0	42.7	52.0	59.3
Endocrine abnormalities	None	Diabetes mellitus Delayed puberty Hypothyroidism	Hypogonadism Hypothyroidism Growth hormone deficiency	Hypogonadism Growth hormone deficiency
Bone disease (lumbar Z-score <2.0)	Yes	Yes	Yes	Yes
Short stature (height Z-score <2.0)	Yes	Yes	Yes	Yes
MRI changes compatible with silent ischemic infarct	Yes	No	Yes	Yes
Other complications	None identified	Gout Systemic lupus erythematosus Bleeding tendency	None identified	Gall stones
Spleen size (cm)†				
Before intervention	12.0	19.1	16.0	16.7
One year after intervention	10.2 (normal for age)	17.8	14.1	15.2
Serum erythropoetin level (mU/mL)				
Before intervention	252.0	421.0	709.0	68.5
One year after intervention	46.3	93.4	31.4	19.6

Characteristics of 4 homozygous α^0-thalassemia patients who are being followed in our institution. All patients provided consent for publication of this report. One patient (data not shown) was born after the implementation of new transfusion strategy and has been transfused based on the new regimen since birth.

MRI, magnetic resonance imaging.

*Patients' hemoglobin analysis was performed via high-performance liquid chromatography and confirmed using capillary zone electrophoresis.

†Spleen size was measured on ultrasonography.

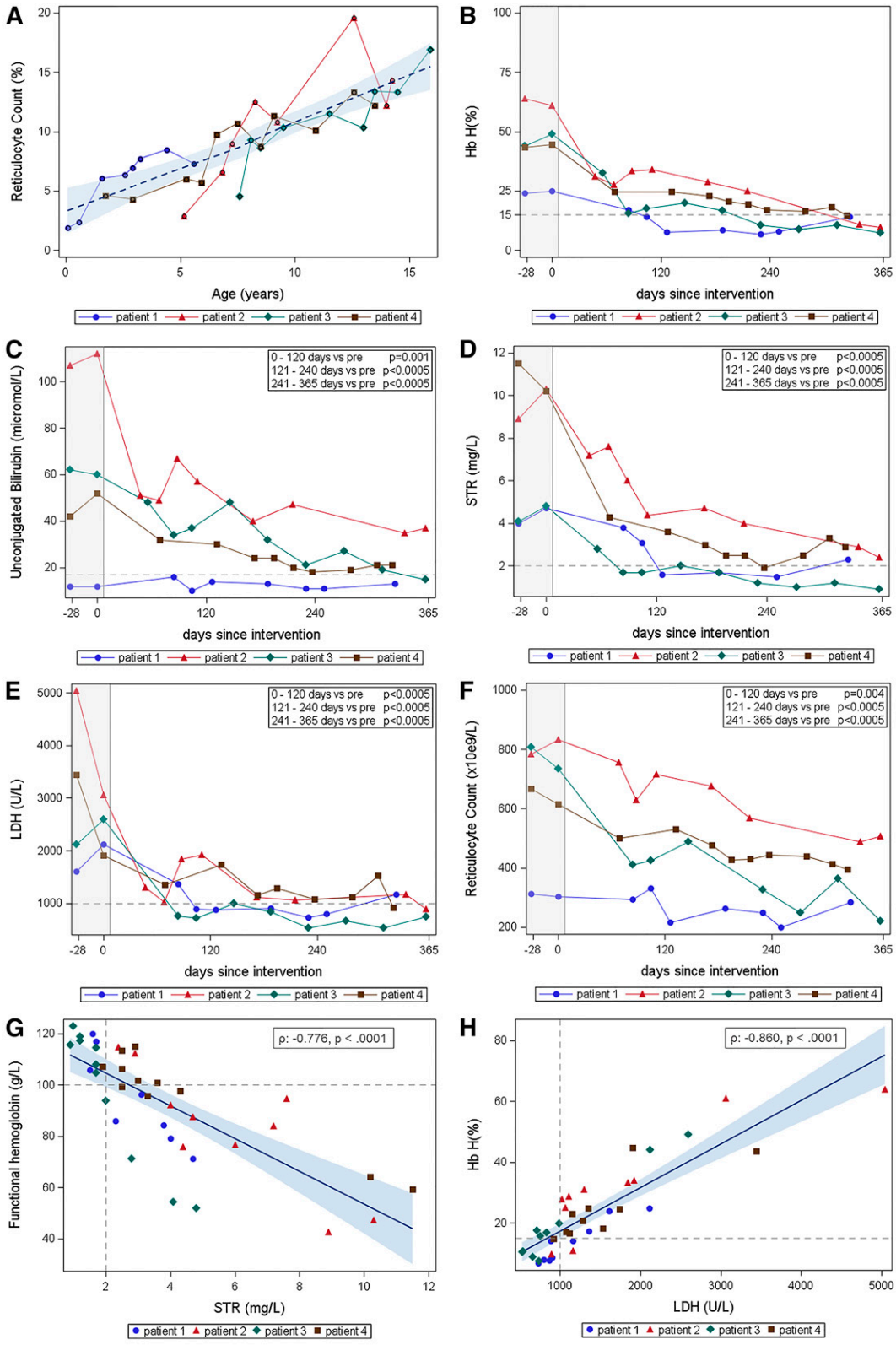

Figure 1. Effects of optimized transfusion therapy on hematologic and biochemical profiles of patients. (A) The trend in the pretransfusion reticulocyte count (%) in 4 patients with homozygous α^0-thalassemia on standard transfusion therapy before commencement of new transfusion regimen. The dashed line represents LOESS fit line with 95% confidence bands. (B) The trend in the pretransfusion Hb H level in peripheral blood. The dotted line represents the 15% target. (C-F) The trends in pretransfusion unconjugated bilirubin, STR, LDH, and reticulocyte count. Shaded areas indicate laboratory results before the implementation of new transfusion regimen (day 0). The dotted lines represent upper boundaries of normal values. We used repeated-measure analysis of variance to examine the association between intervention and biochemical or hematologic outcomes. Overall, intervention effect was significant for all laboratory outcomes. Moreover, the effects of intervention on improvement of outcomes remained persistent for each of the postintervention time brackets (0-120, 121-240, and 241-365 days). Eight to 12 months after the intervention, the average lactate dehydrogenase (964.37 [standard deviation [SD]: 239.85] vs 2736.75 [SD: 242.44]), indirect bilirubin (22.03 [SD: 5.53] vs 57.38 [SD: 10.45]), soluble transferrin receptor (2.15 [SD: 0.58] vs 7.31 [SD: 0.91]), and reticulocyte count (354.22 [SD: 36.42] vs 631.87 [SD: 82.54]) were all significantly lower compared with preintervention. (G-H) Associations of "functional" hemoglobin with STR and Hb H level with LDH. Dotted lines represent target values for functional hemoglobin and Hb H%, as well as the upper boundaries of normal values for LDH and STR. (See supplemental Materials available on the *Blood* Web site for the details of statistical analysis).

hemoglobin as total hemoglobin × (1 – Hb H%/100), which ranged from 42.7 to 79.0 g/L.

To improve tissue oxygenation and suppress hemolysis, we elected to modify our transfusion strategy by aggressively suppressing endogenous erythropoiesis with a goal to reduce Hb H percentage to <15% and to keep the functional hemoglobin >100 g/L in our patients. These targets were chosen to correspond to the average Hb H levels observed in patients with Hb H disease and the recommended pretransfusion hemoglobin level in TDT-β patients. To achieve these targets, 3 patients with Hb H levels of >25% also required 1 to 4 exchange transfusions (one received 1 exchange, another received 3, and the third patient received 4 exchange transfusions). One year following the implementation of the new transfusion regimen, we observed a significant and persistent improvement in all hematologic and biochemical markers of hemolysis and decreased spleen size in all patients (Table 1; Figure 1). Over the course of 1 year, the new transfusion strategy required a higher total volume of transfusion compared with the standard approach (286 [SD: 21] vs 208 mL/kg per year [SD: 14]). However, over the latest 4 months of the year-long intensive transfusion approach, the volume of transfusion decreased to 258 mL/kg per year (SD: 22) when the new steady-state targets for the total pretransfusion functional hemoglobin (>100 g/L) and Hb H level (<15%) had been achieved.

A fifth patient, male and homozygous for common Southeast Asian deletion ($--^{SEA}/--^{SEA}$), was born after the implementation of the new transfusion strategy and has been transfused accordingly since birth. Fourteen months into this new regular transfusion regimen, this patient has normal serum LDH, aspartate aminotransferase, unconjugated bilirubin, and STR levels but continues to have peripheral blood reticulocytosis. The patient has normal growth parameters (age- and sex-adjusted height: 58 percentile, z-score = 0.20), achieved normal developmental milestones, and, at the last follow-up, had no splenomegaly. Total volume of transfused packed red blood cell in this patient has been 251 mL/kg per year.

Despite adequate transfusion intensity based on the TDT-β approach, the homozygous α^0-thalassemia patients showed high Hb H levels in peripheral blood and profound reticulocytosis, suggesting that these patients maintained relatively more effective erythropoiesis (in contrast to ineffective erythropoiesis in their TDT-β counterparts) that was not adequately suppressed by transfusions. This suggests that homozygous α^0-thalassemia is a predominantly hemolytic disease with a robust erythropoietic response. This is likely due to the fact that Hb H aggregates preferentially in older red blood cells in the peripheral blood, whereas in TDT-β, unpaired α-globin chains form molecular aggregates that lead to apoptosis of erythroblasts early in the process of erythropoiesis in the bone marrow.[7] Our patients with homozygous α^0-thalassemia who were transfused using the TDT-β regimen had preserved erythropoiesis, leading, over time, to increased Hb H levels associated with increased peripheral hemolysis. With the high Hb H percentage, the proportion of functional hemoglobin decreased, and tissue hypoxia worsened (despite stable total hemoglobin), further inducing erythropoiesis.

Suboptimal transfusions (with associated anemia and hypoxia) and severe hemolysis have been shown to be associated with a variety of significant clinical sequelae in β-thalassemia patients and in other disorders.[8-10] Here we demonstrate that in patients with homozygous α^0-thalassemia (TDT-α), a transfusion strategy similar to those of TDT-β patients does not adequately ameliorate the underlying hemolytic process and the poor tissue oxygen delivery over time, making this approach suboptimal for the management of these patients. Although we are yet to demonstrate any long-term clinical benefits to these patients (which would require a longer duration of regular transfusions), a more intensive transfusion regimen targeted at reducing Hb H levels resulting in an increased functional hemoglobin, reduced tissue hypoxia, and hemolysis seems more appropriate for patients with homozygous α^0-thalassemia. Splenectomy has been associated with reduced transfusion requirements in TDT-β and improvement in hemoglobin level in Hb H disease patients with significant splenomegaly.[11] However, in patients with homozygous α^0-thalassemia, splenectomy, although prolonging survival of transfused Hb A-containing erythrocytes, would likely also prolong the lifespan of endogenous erythrocytes that almost exclusively carry nonfunctional Hb H. We considered these pathophysiologic differences, in addition to the known long-term complications of splenectomy, to inform our decision not to splenectomize our patients. Recently, an international registry of surviving patients with homozygous α^0-thalassemia has been established (Douglas R. Higgs, Oxford University, personal communication, January 10, 2014). Clinical data gathered from this registry will be invaluable in shedding light on the long-term clinical benefit of our proposed transfusion strategy compared with standard TDT-β strategy, helping to define optimal care for patients with homozygous α^0-thalassemia.

The intensive transfusion strategy comes with a price: increased transfusional iron burden that requires escalation of iron chelation therapy, posing significant challenges with treatment costs and patient adherence. Whether these drawbacks can be offset by better longer-term clinical outcomes of patients with homozygous α^0-thalassemia remains to be proven.

*M.K.-A. and I.O. contributed equally to this work.

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Correspondence: Ali Amid, Division of Haematology/Oncology, Hospital for Sick Children, 555 University Ave, Toronto, ON, Canada M5G 1X8; e-mail: ali.amid@sickkids.ca.

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