

## Brief report

# Fatal agranulocytosis after deferiprone therapy in a child with Diamond-Blackfan anemia

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**A 10-year-old girl with steroid-resistant Diamond-Blackfan anemia (DBA) developed agranulocytosis 9 weeks after chelation with deferiprone was initiated (45 mg/kg daily, 60% of recommended dose) in addition to her ordinary deferoxamine therapy. The blood counts, checked weekly, dropped markedly between weeks 8 and 9. She rapidly developed a septicemia and was admitted with high fever (40.9°C), white blood cell count  $0.4 \times 10^9$ /**

**L, absolute neutrophil count  $0.1 \times 10^9$ /L and platelets  $114 \times 10^9$ /L. She was administered broad spectrum antibiotics, G-CSF (10 microgram/kg daily) and corticosteroids but remained neutropenic and died 6 weeks after admission. Bone marrow examination day 23 revealed areas with low cellularity (around 30%), but also areas with infiltrates of T cells; granulopoiesis and erythropoiesis were scarce. We conclude that weekly neutrophil monitor-**

**ing is not sufficient to avoid fatal agranulocytosis. We suggest that deferiprone not be prescribed to DBA patients unless the clinical indications are particularly strong, and that the risk of agranulocytosis in thalassemia patients be carefully considered. (Blood. 2007;109:5157-5159)**

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## Introduction

In Diamond-Blackfan anemia (DBA), a pure red cell anemia with autosomal dominant inheritance with known linkage to chromosomes 19q13.2 (*DBA1*) and 8p23-22 (*DBA2*),<sup>1-5</sup> most patients respond to corticosteroids, but 15-20% are steroid-resistant already at diagnosis and this figure may increase over time<sup>1</sup>. For some steroid-resistant patients, hematopoietic stem cell transplant (HSCT) is a reasonable treatment, but for many patients regular erythrocyte transfusions are required.<sup>1</sup>

Secondary hemochromatosis is a major medical problem in transfusion-dependent patients.<sup>1,5</sup> In addition to the widely accepted chelation therapy with deferoxamine, oral chelating substances are now available, such as deferiprone and deferasirox, which are reported to be beneficial alone or in combination with deferoxamine.<sup>6-12</sup> These studies have been facilitated by the T2\* magnetic resonance imaging (MRI) technique.<sup>8,13</sup>

Most drugs have side effects, and it is important to be aware of them and their potential severity to properly weigh pros and cons. Deferiprone is effective in reducing myocardial iron, but its value has also been disputed.<sup>14,15</sup> Here we report a 10-year-old girl with DBA who died with agranulocytosis shortly after the introduction of deferiprone therapy.

## Results and discussion

### Case report

A 2-month-old girl born to healthy related parents was diagnosed with DBA (hemoglobin 27 g/L, white blood cell (WBC) count  $14.1 \times 10^9$ /L, platelets  $746 \times 10^9$ /L, reticulocytes 0.0% at admission). Bone marrow examination revealed an almost complete lack

of erythropoiesis, consistent with DBA. She had no external malformations; ultrasound of the kidneys and skeletal survey were normal. In addition to erythrocyte transfusions, she was administered prednisolone up to 4 mg/kg daily without any response. HSCT was considered, but she had no matched related donor and an unrelated donor transplant was at that time not recommended.<sup>16</sup> Up to the age of 10 she was on a regular transfusion-chelating program with good compliance and ferritin levels typically between 1000-2000 microgram/L. A third prednisolone trial was not successful, nor was an attempt with cyclosporin A.<sup>17</sup> Audiometry, normal at age 4, revealed a severe left side sensorineural hearing deficiency at age 6, the cause of which could not be fully explained.<sup>18,19</sup> HSCT was reconsidered several times, but not accepted.<sup>16</sup> Liver biopsies, performed at 3 and 6 years of age, revealed pronounced iron load and interstitial fibrosis but no cirrhosis.

The result of T2\* MRI, performed at 10 years, was 21.3-28.2 msec in the heart (reference 16-20 msec) and 4.0-7.6 msec in the liver, clearly abnormal and below the lower normal reference of 17-19 msec. Ferritin was 2208 microgram/L. Her regular treatment was erythrocyte transfusions (15 ml/kg) every second week and deferoxamine (750 mg) intravenously daily, corresponding to 34 mg/kg. Based on the abnormal T2\* results, the liver biopsy findings of fibrosis, and high ferritin values despite regular deferoxamine therapy, deferiprone (Ferriprox®) 500 mg twice daily was added, corresponding to 60% of the recommended dose, in an attempt to reduce side effects. Blood counts were meticulously monitored on a weekly basis (Table 1). A secondary aim was to improve her quality of life. The parents were informed of the risk of agranulocytosis, which was the reason for the weekly blood count monitoring, and gave their consent to the therapy. Initially the deferiprone

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**Table 1. Weekly blood counts from the introduction of deferiprone until the agranulocytosis had developed.**

	Weeks after therapy start									
	0§	1*	2	3*	4	5*	6*	7	8*	9#
Hemoglobin (g/L)	109	81	93	73	91	70	84	105	83	87
WBC ( $\times 10^9/L$ )	5.4	3.7	4.0	3.9	5.5	3.8	3.7	4.6	2.5	0.9
ANC ( $\times 10^9/L$ )	3.7	2.4	2.7	2.6	4.0	2.6	no data	3.0	1.4	<0.1
Platelets ( $\times 10^9/L$ )	273	234	227	263	222	170	278	208	151	164
Ferritin (microgram/L)		2027			1740	1986	1716		1491	

§Values prior to start of deferiprone therapy

\*Erythrocyte transfusions 15 ml/kg body weight

#Deferiprone therapy was stopped this day and the patient was admitted to hospital the following day with septicemia

treatment was entirely successful, but the 9th week after initiating deferiprone her blood counts dropped markedly to absolute neutrophil counts (ANC) less than  $0.1 \times 10^9/L$ , WBC  $0.9 \times 10^9/L$  and platelets  $164 \times 10^9/L$ ; deferiprone administration was stopped promptly (Table 1). However, by the following day she had developed a sore throat, moderate cough, and high fever ( $40.9^\circ C$ ) and was admitted with C-reactive protein (CRP) 37 mg/L, WBC  $0.4 \times 10^9/L$ , ANC  $0.1 \times 10^9/L$  and platelets  $114 \times 10^9/L$ .

Intravenous broad spectrum antibiotic therapy was initiated promptly, and the deferiprone manufacturer was informed within a few days (April 2006). Pulmonary computed tomography (CT) reported 10-15 rounded infiltrates consistent with septic emboli, and blood culture revealed *Staphylococcus aureus*. Repeated echocardiograms revealed no signs of endocarditis. Filgrastim, 5 microgram per kg daily subcutaneously, was initiated soon after admission; from day 5 onwards 10 microgram per kg daily was administered. Her platelet counts (nadir  $72 \times 10^9/L$  day 2) were normalized to more than  $150 \times 10^9/L$  on day 6, but they declined again her last week of life (nadir  $39 \times 10^9/L$ ). The WBC (nadir  $0.2 \times 10^9/L$  days 2 and 4) increased above  $10^9/L$  on day 11 but dropped below  $10^9/L$  day 23 and were never more than  $0.5 \times 10^9/L$  from day 30 onwards, except her last 2 days. Finally, her ANC remained at or below  $0.1 \times 10^9/L$  except for days 5, 19 and 20 (with  $0.4 \times 10^9/L$  at most; Figure 1).

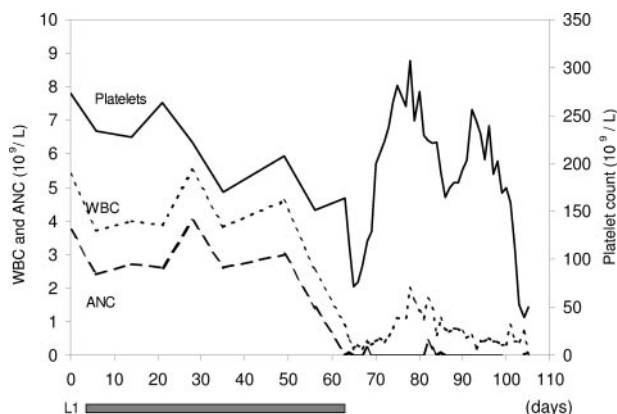
On day 33, high doses of corticosteroids were introduced and on day 36 she was referred to the HSCT unit, afebrile and with CRP 7 mg/L, WBC  $0.3 \times 10^9/L$ , ANC less than  $0.1 \times 10^9/L$  and platelets  $169 \times 10^9/L$ . Despite the corticosteroids there was a trend with declining platelet counts, so cyclosporin A was tried. At day 42, while at home for the first time in a long while, she experienced increasing dyspnea, upper abdominal pains, and shivers. Examination at readmission showed an axillary temperature of  $35.9^\circ C$ , pulse

144, respiration rate 46 per minute and blood pressure 73/46 mmHg. Physical examination of the lungs and abdomen were reported as normal. CRP was 11 mg/L. The child had vomits, developed decreasing saturation, and had a cardiac arrest. Resuscitation was initiated, but she died despite all efforts made at the ICU. The parents declined autopsy but approved postmortal CT, performed 13 hours after death. No conclusive cause of death could be obtained. Blood culture was negative.

Bone marrow examination on day 23 revealed variable cellularity with infiltrates of lymphocytes; between these infiltrates the cellularity was around 30% with signs of fibrosis. In areas with low cellularity, mostly macrophages and in particular megakaryocytes were found. Granulopoiesis and erythropoiesis was very scarce. The widely spread lymphoid infiltrates consisted mainly of a mixture of CD4+ and CD8+ T-cells; around the lymphoid infiltrates were a few polyclonal plasma cells. CD117 staining revealed a diffuse increase of mast cells. Bone marrow flow cytometry revealed that 72% of the cells were in the lymphocyte region: of these, 86% were T-cells with signs of activation and 57% stained for T-cell markers and HLADR. The CD4/CD8 ratio was 0.68. CD56+ cells were 21% and CD57+ cells 27%, the latter mostly CD8+CD28-. Furthermore, CD69+ T-cells were elevated (14%), indicating activation. CD34+ cells were 0.37% of all cells.

An updated review of PubMed (December 12, 2006) revealed one patient with DBA that developed agranulocytosis with deferiprone.<sup>20</sup> In the patient, a 28-year-old female, neutrophils reappeared after 17 days and normalized after 36 days. In addition, a 19-year-old male patient that developed neutropenia that was stable for one year but later progressed into a fatal aplastic anemia has been reported from Venezuela at a medical meeting.<sup>21</sup> Additional important information with respect to deferiprone and agranulocytosis was published December 20, 2006, on the Cooley's Anemia Foundation website (<http://www.cooleysanemia.org/bodies/body309.php>). The notice briefly describes 46 cases of deferiprone-associated agranulocytosis reported to the manufacturer since 1999. Importantly, 9 of these cases were fatal. The manufacturer (ApoPharma Inc) recently distributed a letter (available through the website above) that also mentions the risk of neurological disorders with the use of deferiprone. Other known hazards associated with deferiprone therapy include progression of fibrosis associated with an increase in iron overload or hepatitis C, arthropathy, liver function abnormalities, and gastrointestinal disturbances.

It has previously been reported that a large proportion of steroid-refractory DBA patients develop moderate to severe generalized bone marrow hypoplasia over time.<sup>22</sup> Moreover, reduced clonogenic cell output in long-term culture-initiating cell assays, quantifying multilineage primitive hematopoietic progenitors, also suggest that the underlying defect in steroid-refractory DBA is not limited to the erythroid lineage.<sup>22</sup> The bone marrow investigation in the present patient, with widely spread T-cell infiltrates consistent



**Figure 1: Blood counts in a patient with Diamond-Blackfan anemia that died with agranulocytosis after initiating deferiprone (L1) as a complement to ongoing deferiprone therapy.**

with signs of T-cell activation, suggests that immunological mechanisms may play a role in the development of the bone marrow hypoplasia in DBA. Thus, DBA patients may be more prone than thalassemia patients to developing deferiprone-associated agranulocytosis.

We conclude that since the agranulocytosis developed rapidly, weekly monitoring of blood counts during deferiprone therapy is not sufficient to avoid the development of persistent and potentially fatal agranulocytosis. Moreover, the rapid development of a prolonged agranulocytosis, despite administering only 60% of the recommended dose, suggests that this side effect may not be dose-dependent. Since the development of agranulocytosis is not predictable and possibly not dose-dependent, and since it is not avoidable despite meticulous blood count monitoring, we suggest that deferiprone not be prescribed to patients with DBA, or prescribed only if the clinical indications are particularly strong. Data on the risk of agranulocytosis in thalassemia was updated in 2003<sup>23</sup> and additional information on deferiprone-associated agranulocytosis, available through the manufacturer, has now been presented (available through the website reported above). It is

important that information regarding the risk of developing non-reversible agranulocytosis secondary to deferiprone, in particular in DBA patients, is widely distributed.

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## Authorship

Contribution: Both authors cared for the patient; JIH wrote the paper.

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