Combination erythropoietin-hydroxyurea therapy in sickle cell disease: experience from the National Institutes of Health and a literature review

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Erythropoietin is being used more widely in the management of sickle cell disease (SCD, inclusive of homozygous sickle beta, SS, and compound heterozygous sickle beta thalassemia, $S\beta^0$ thal), often in conjunction with hydroxyurea (HU). Herein, we summarize the published experience with erythropoietin use in SCD, in 39 patients (SS, n=30; $S\beta^0$ thal, n=9) who were treated between 1990 and 1996; and in 13 patients with sickle syndromes (SS, n=12, compound heterozygous SC disease, n=1) who were treated with erythropoietin or darbepoietin at the National Institutes of Health (NIH) since 2002. The dose range of erythropoietin for SCD in the published series, at a median of >200 U/Kg/dose, is higher than that used in end-stage renal disease. The median duration of erythropoietin therapy was ≥3 months, with minimal reported side-effects. At the NIH, the median age of sickle syndrome patients who received erythropoietin or darbepoietin (both referred to as EPO in the NIH series) was 51 (24 to 70) years; 12/13 patients had sickle-associated pulmonary hypertension. Eleven out of the 13 patients were treated with both HU and EPO for > 4 months (median of 11 months on EPO) without complication. Of the 13 patients, five (all SS) with pulmonary hypertension were given EPO for reticulocytopenia (<100,000/μL) on HU; 5/13 patients (all SS), with pulmonary hypertension, were given EPO and HU concurrently, in the light of an estimated glomerular filtration rate of <80 mL/minute. Three of the 13 patients (2 SS, 1 SC) were treated with EPO for miscellaneous reasons. Hematologic responses, detailed herein, suggest that EPO therapy may allow more aggressive HU dosing in high-risk SCD patients and in the setting of mild renal insufficiency, common to the aging sickle cell population. Furthermore EPO appears to be safe in SCD, particularly when used in conjunction with HU. We outline our current therapeutic strategy for EPO use in SCD.

Key words: sickle cell disease, erythropoietin, hydroxyurea, pulmonary hypertension.

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Sickle cell disease is a hemoglobinopathy arising from a single nucleotide substitution in codon 6 of the beta (β) globin gene[1] which, when homozygous, results in an abnormal sickle hemoglobin (HbS) that polymerizes in deoxygenated red cells. Accumulated polymer within red blood cells ultimately causes an irreversibly altered red cell morphology. Red cells that contain substantial amounts of polymerized HbS are not deformable and are prone to hemolysis. These sickled cells can lodge in end-arterioles and capillaries, causing tissue infarction, clinical vaso-occlusive crises and cumulative damage to the cerebral, pulmonary, splenic, and renal vasculature; clinical sequelae may include cerebrovascular accidents, pulmonary hypertension, splenic infarction, and renal injury. The clinical manifestations of homozygous sickle cell (SS) and compound heterozygous $S\beta^0$ thalassemia ($S\beta^0$ thal) are similar; these populations, both designated for simplicity as having sickle cell disease (SCD), account for the majority of patients discussed here. Compound heteroxygous HbSC disease, seen in one patient treated at the National Institutes of Health (NIH), is clinically milder and characterized by less anemia than that occurring in SCD.[2]

Erythropoietin, the major regulator of erythropoiesis, is a cytokine that is secreted by the kidneys constitutively and in response to anemia. Serum erythropoietin levels are often elevated in chronic anemic states such as SCD.[3] Erythropoietin's physiological regulation, and its role in any given patient, are complicated by the abnormal oxygen affinity of polymerized HbS and by the abnormal renal function that accompanies sickle cell disease.

Red cells that contain polymerized HbS often have a *right-shifted* oxygen dissociation curve (lower affinity),[4] in which more oxygen is released to tissues relative to that released from red cells that contain normal adult hemoglobin, HbA. Thus, the hypoxia-driven erythropoietin response to anemia may be diminished in SCD.[5] The level of fetal hemoglobin (HbF) may further modu-

late erythropoietin expression, as red cells containing HbF, with a *left-shifted* oxygen dissociation curve (higher affinity), release less oxygen at a given oxygen tension[6,7] than do red cells containing HbA or HbS. At very high HbF levels, serum erythropoietin levels can be elevated relative to normal.[8] In addition, hydroxyurea (HU) therapy, which can increase HbF in SCD patients, may directly or indirectly increase erythropoietin levels.[9,10]

Erythropoietin is produced primarily in the kidneys. In the general population, mild-to-moderate renal disease is associated with a decrease in total hemoglobin concentration. In a single, large, non-SCD, adult population-based study,[11] a corrected estimated glomerular filtration rate (GFR[12]) of 60 mL/min, which is approximately one-half of mean maximal GFR in childhood,[13] was associated with anemia (total Hb <12 g/dL, males, and <11 g/dL, females), in 1.3 to 1.8% of the general population; an esimated GFR between 59 and 30 or ≤29 mL/min was associated with anemia in 5.1% and 44.1%, respectively, of the general population. The impact of renal impairment in SCD on endogenous erythropoietin production and erythroid mass has not been well defined. An analysis of 31 SCD patients suggested an association between diminished creatinine clearance and relatively diminished erythropoietin and hemoglobin levels.[14]

The kidneys in SCD are sensitive to ischemia-reperfusion injury, owing to high oxygen extraction in the renal medulla, with deoxygenation of HbS and resultant polymerization. Many patients with SCD develop renal dysfunction that is characterized pathologically by both glomerular and tubular damage, and clinically by impaired urinary concentrating ability, proteinuria (in approximately a quarter of patients), and chronic renal insufficiency (in 4.6-6.7% of patients).[15-17]

Importantly, the recognition of diminished renal function in SCD is complicated by the cardiac-output related supranormal GFR measurements early in the course of SCD. In one study of renal function in SCD, mean GFR was 169 mL/min in children (4-11 years old) and 95 mL/min in adults (32-37 years old);[18] therefore, an estimated GFR of 80 mL/min in adults with SCD can reflect a 50% decrease in renal function from a childhood baseline.[11,19] In contrast, mean GFR in children (2-12 years old) without SCD was 133 mL/min, and in adults (30-39 years old) was 116 mL/min,[13] or a less than 15% decrease from a childhood baseline. In addition, careful evaluation of renal tubular function has revealed subtle impairments in SCD, relative to non-SCD controls, despite higher GFR measurements in patients with SCD.[20] Thus, functional renal impairment, and perhaps relative erythropoietin insufficiency, may occur in SCD at GFR measurements that are well within the normal range for patients without sickle cell disease.

Therapeutically, pharmacologic doses of erythropoietin, at 80-120 U/Kg/ per week, divided into three doses, have been used for many years in patients with chronic kidney disease, in order to reverse the erythropoietin-deficient anemia associated with end-stage renal disease. Published studies[21] of erythropoietin in small numbers of SCD patients with renal failure have suggested that higher doses, ranging from 150-250 U/Kg/dose, may be necessary, and are well tolerated, in these patients.[22-24]

There has also been interest in erythropoietin as a pharmacological agent to augment HbF response, with or without concomitant HU therapy, in SCD. *In vitro* studies and animal experiments have suggested that erythropoietin alone,[25-27] or in concert with other cytokines (reviewed 2005),[28] can raise HbF levels. Indeed, many of the previously published clinical trials of erythropoietin in SCD, summarized here, were instituted with the hope of augmenting HbF.[21,29-32]

The stimulation of HbF synthesis in patients with SCD reduces the clinical severity of the disease, presumably because HbF is excluded from the HbS polymer.[33] Most, but not all, natural history studies that predate widespread initiation of HU therapy in SCD found an inverse correlation between HbF and clinical course/mortality.[34-37] In addition, strategies to increase HbF, notably the large *Multicenter Study of Hydroxyurea* (MSH) trial, have shown that pharmacologic manipulations which achieve HbF levels of 5-10% of total hemoglobin can mitigate vaso-occlusive crises and, likely, reduce mortality in SCD.[38,39]

Efforts to optimize standard care have gained more momentum, as high-risk subsets of SCD have been better characterized (for example, Powars 2005).[40] Pulmonary hypertension, almost ubiquitous in the highly selected population followed at the NIH but present in approximately one-third of unselected adult patients with SCD, carries a 10.1-fold rate ratio for mortality at 30 months follow-up after diagnosis.[41] Pulmonary hypertension is characterized as an elevated pulmonary artery pressure, defined by baseline non-crisis tricuspid regurgitant jet velocities on echogardiogram of ≥2.5 m/s.

Anecdotally, the use of erythropoietin, concomitant with HU, has become more widespread in the management of SCD. Therefore, we have summarized data on erythropoietin use in SCD, with an emphasis on the toxicity and efficacy of this combination from published clinical reports and from our own experience at the NIH.

Methods

The electronic Pub Med database, from 1966 to the present, was cross-referenced for clinical reports on erythropoietin and SCD, including homozygous HbS and compound heterozygous HbS β^0 thal. One hundred and forty-four references were retrieved, of which ten ger-

mane references, describing 39 patients with SCD who were treated with erythropoietin, were examined in detail.

Adult patients with sickle syndromes [both homozygous HbS (SCD) and compound heterozygous (HbSC)] who had been treated with erythropoietin or long-acting darbepoietin in the Vascular Medicine Branch of the National Heart, Lung, and Blood Institute (NHLBI) at the NIH were identified Those patients with concomitant pulmonary hypertension were designated as *high-risk*. *Relative renal insufficiency* in the NIH population was defined as an estimated GFR, estimated by the four-value MDRD equation,[42] of <80 mL/min which represents a >50% decrement in GFR from published reports of mean GFR in childhood in SCD.[18] Both erythropoietin and darbepoietin therapy are considered together, and are referred to here as *EPO* therapy. All patients at the NIH provided written informed consent for a natural history protocol for the management of SCD. Outpatient charts for these patients were examined in detail.

HbF analyses were performed in the clinical laboratory of the National Institutes of Health on a VARIANT™ (BIO-RAD) automated high performance liquid chromatograph in which hemoglobin, from 5 μL of whole blood in EDTA that had been lysed in 1 mL of deionized water, was injected on to a cation exchange column. Retention times through 6.5 minutes, at 415 and 690 (background) nm, were analyzed; HbF was quantified automatically against calibrated standards.

For F-cell analyses, 2.5×10^7 red blood cells from whole blood in EDTA were fixed in 0.05% glutaraldehyde and permeabilized with 0.1% Triton X-100 for 5 min. After washing, the cells were stained with anti HbF monoclonal antibody (Caltag Laboratories Burlingame, CA, USA), washed twice, and the pellet resuspended in thiazole orange (1:10000) (Molecular Probes, Eugene, OR, USA). For each specimen tube, a total of 50,000 events were collected using a BD FACScan flow cytometer and analyzed using the CellQuest software package (BD Bioscence, Ca., USA.

Results and Discussion

Published reports on erythropoietin use in sickle cell disease

Ten reports have been published since 1990 in which 39 patients with SCD (SS n=30, or $S\beta^0$ thal n=9) were treated with erythropoietin, with or without HU and/or iron supplementation.[21-24,29-32,43,44] Doses of erythropoietin in these studies ranged between 100 and 3000 U/Kg per dose; 33 of 39 patients received ≥200U/Kg per dose of erythropoietin. Dosing frequency was daily for 3-4 months in five pregnant patients,[21] and was at least twice per week in 25 of the 34 remaining patients. Response of HbF to erythropoietin in these studies was inconsistent and inconsistently reported. In the largest evaluable study, erythropoietin without HU was administered to nine patients with SCD, reported in 1993.[30] The erythropoietin dose ranged between 400 and 1500 U/Kg twice per week, and was given for 3 months. HbF-containing reticulocyte counts (F-retics ulocytes) doubled in four patients who, unlike non-responders, were iron-replete (characterized by baseline iron overload or by iron supplementation). A contemporaneous less-detailed study of seven SCD patients treated with moderately high doses of erythropoietin (400 U/Kg intravenously (IV) once-a-week), plus standard doses of hydroxyurea, found an increase in HbF in three patients.[32,45] Another study published in 1993 reported on four SCD patients who were treated with consolidated (over 4 days) HU, supplemental iron, and high dose erythropoietin (1,000-3,000 U/Kg IV three times a week).[31] These patients had a significant rise in HbF with the addition of erythropoietin, relative to HU alone, with a mean 61.4%±30.3% increase from baseline in total HbF at 5 weeks. Dose and timing of therapy, and/or the addition of iron supplementation, may have been critical to the success of this strategy, as an earlier report of five SCD patients treated with daily HU, and up to 1500 U/Kg of erythropoietin twice weekly, but without iron supplementation, showed no change in HbF.[29]

Side effects from erythropoietin in these 39 patients, where reported, included bone pain (n=1) and an increased frequency of vaso-occlusive crises (n=2). No uncontrolled hypertension, thrombosis, active retinopathy or evidence of pure red cell aplasia was reported. Of note, three patients treated with moderately high dose erythropoietin, but not with HU, required phlebotomy for a too-rapid rise in hematocrit.[30]

Recent NIH experience with HU and EPO in sickle cell disease

Patients' characteristics

Since 2002, 13 patients with sickle syndromes (unique patient numbers, UPN, 1-13, n=12 SS; n=1 SC) whose data are summarized in Table 1), have been treated with recombinant erythropoietin or long-acting erythropoietin (darbepoietin), *EPO*, at the SCD and Vascular Therapeutics Clinic at the NIH. This group comprised seven males and six females, with a median age of 51 (24 to 60) years. Twelve of the 13 patients (11 SS, 1 SC) had sickle cell-associated pulmonary hypertension, with baseline triscupid regurgitant jet velocities on echogardiography of ≥2.5 m/s. The median estimated GFR at presentation in all patients treated with EPO was 69 (0-128) mL/min.

Table 1. NIH Experience since 2002.

Group	Unique Patient Number (gender & genotype)	Age (yrs)	eGFR+ (mL/min)	TR Jet,° pre-EPO (m/s)	Reticulocyte count, pre-EPO ($\times 10^3/\mu L$)	EPO Preparation† Maximum dose, route & frequency,	EPO* (Units/Kg/week)	Duration of EPO† (months, to 4/06))	Hb, pre-EPO (g/dL)	Hb, on EPO (g/dL), [change,%]
					A. *High-risk SCD & HU-intolerant*					
	UPN 1 (M/SS)	31	128	2.8	55, on HU	Epo/70,000 U SQ 3/week, at maximum	2718	24	5.5	Variable
	UPN 2 (M/SS)	51	69	2.6	69, on HU	Darbo/260 µg SQ/wk	≥327*	12+	6.5	7.2 [+10.8]
	UPN 3 (M/SS)	56	62	2.6	87, on HU	Epo/40,000 U SQ 3/wk	963	21+	7.7	8.7 [+13]
	UPN 4 (M/SS)	56	73	3.7	77, on HU	Darbo/250 mcg SQ/wk X 4 mos, now Epo 60,000 U SQ/wk	≥386*	11+	6.4	11.4 [+78]
	UPN 5 (F/SS)	54	113	2.9	167, on Epo and HU	Epo/40,000 U SQ 3/wk	1650	33+	8.6	9.9 [+31]
	Median:	*54*	*73*	*2.8*	*73 (UPN1-4)*		*?963*	*21+ mos.*	*6.5*	*9.3 [+22]*
					B. *High-risk SCD & estimated GFR <80 mL/min*					
	UPN 6 (F/SS)	46	45	3	103, pre HU	Epo/40,000 U SQ/wk	703	14+	6.2	11.5 [+85.5]
	UPN 7 (F/SS)	56	66	3.9	214, pre-HU	Epo/40,000 U SQ/wk	734	18+	6.1	8.2 [+34.4]
	UPN 8 (F/SS)	45	78	2.7	306, pre-HU	Darbo/260 µg SQ/wk	≥475*	34+	6.7	7.7 [+15]
	UPN 9 (M/SS)	60	61	3.3	240, pre-HU	Darbo/200 µg SQ/wk	≥455*	13+	4.7	6.7 [+42]
	UPN 10 (M/SS)	50	0, ESRD	3.5	N/A	Epo/13,000 U IV 3/wk	107	4	9.3-6.3¶	Variable
	Median:	*50*	*61*	*3.3*	*227*		*≥475*	*13.5+*	*6.2 (UPN 6-9)*	*8.0 [+34]*
					*Group **A** & **B** Median*					
					***C**:* Misc.					
		52.5	67.5	2.95	103		589	16+	6.4	8.5 [+32.7]
	UPN 11 (F/SC)	70	48	2.7	N/A	Epo/20,000 U SQ 2/wk	573	13+	7.0	10.5 [+50]
	UPN 12 (F/SS)	49	115	2.1	85, h/o HU intolerance, on transfusions	Darbo/100 mcg SQ/wk	≥521*	28+	9.2, on transfusions	8.5, off transfusions
	UPN 13 (M/SS)	24	213	2.5	51.3 (nadir)	Epo 40-60,000 U IV per day x 11 doses	N/A	<0.35	3.7 DHTR§	N/A

+eGFR: (mL/min/1.73 m²) = 186×(Scr)$^{-1.154}$×(Age)$^{-0.203}$×(0.742 if female)×(1.210 if African American) (conventional units).[42] *°TR Jet: triscupid regurgitant jet; †Total patient-years of experience: 18 years 9 months; ¶not included in median because of insufficient data; §delayed hemolytic transfusion reaction.*

Erythropoietin units/week	*Darbo µg/ dose*	*Erythropoietin units/ week*	*Darbo µg/ dose*
<2,500	6.25	18,000-33,999	60
2,500-4,999	12.5	34,000-89,999	100
5,000-10,999	25	≥90,000	200
11,000-17,999	40		

*†Erythropoietin (Epo): Darbepoietin (Darbo) *Equivalence Conversion.*[46]

Treatment groups

Eight patients were treated with erythropoietin, four patients were treated with darbepoietin, and one patient, UPN 5, was treated sequentially with both agents. Our patients can be devided into three groups on the basis of their treatment (Table 1).

Group A: high-risk SCD with HU-intolerance (n=5). EPO was begun in 5 SCD patients, (UPN 1 -5) because of HU-associated reticulocytopenia (<100,000 reticulocytes/µL), in the absence of other HU-limiting toxicities. UPN 5 was referred to us on both HU and EPO, after a local diagnosis of HU-intolerance.

Group B: high-risk SCD with relative renal insufficiency (n=5). EPO was begun concurrently to HU in four SCD patients, (UPN 6 -9), who had pulmonary hypertension and an estimated GFR of < 80 mL/min at pres-

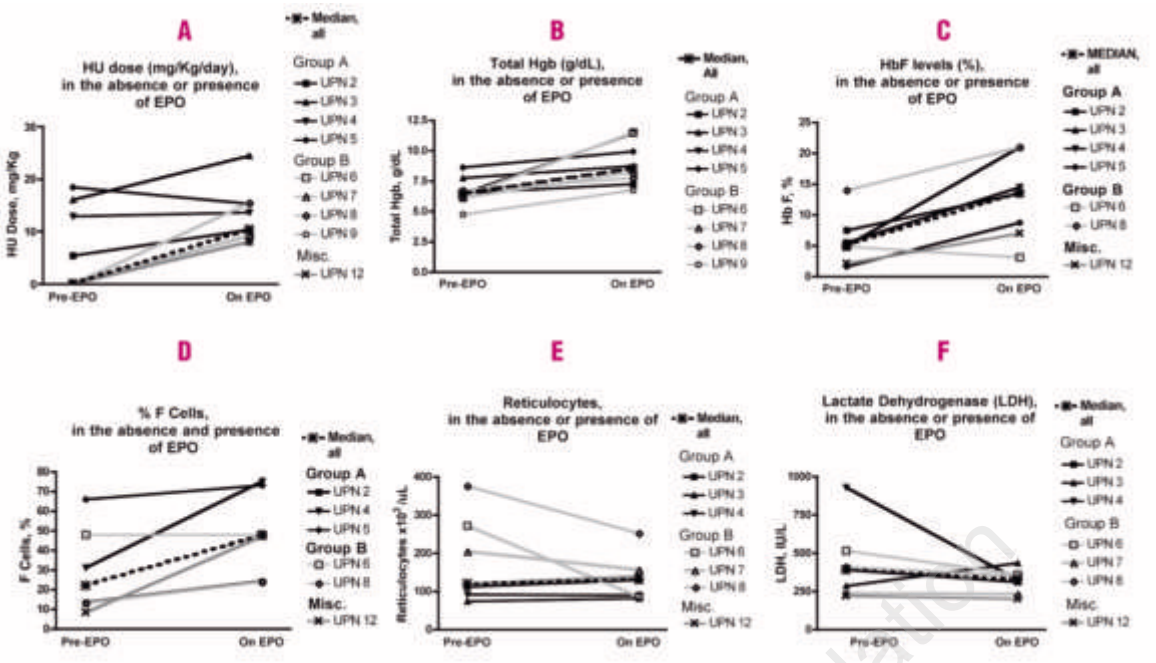

Figure 1. Data from evaluable patients in group A (high-risk, HU-intolerant, Black-) group B (high-risk, relative renal insufficiency, gray-), and UPN 12 (miscellaneous, dark grey); median values for all patients are shown (dotted black). A. HU dose, mg/Kg, B. total Hb, g/dL, C. % HbF, D. % F-cells, E. Reticulocytes, x10^3/μL, and F. lactate dehydrogenase IU/L, pre-EPO and after at least 11 months on EPO.

entation, due to concerns about delayed HU-dose advancement in these high-risk patients. EPO alone was begun in UPN 10, who developed end-stage renal disease after an orthotopic liver transplant for hepatitis C and liver failure; he received EPO replacement therapy while on dialysis.

Group C: miscellaneous. UPN 11 had HbSC disease and chronic kidney disease, attributed to both HbSC and systemic hypertension, with progressive symptomatic anemia, for which she received EPO and low-dose HU. UPN 12 was on transfusions with a history of poor erythroid tolerance to HU, and was begun on HU and EPO as she switched from transfusions. UPN 13 received 11 days of intravenous EPO therapy without HU when *in extremis* from severe anemia, (total Hb 3.9 g/dL), following a presumed delayed hemolytic transfusion reaction.

Treatment dose and duration

The median dose of erythropoietin, corrected for the patient's size, frequency of dose, and equivalence between erythropoietin and darbepoietin,[46] was ≥963 (≥327 to 2718) U/Kg/week in group A (high-risk, HU-intolerant) patients, and ≥589 (>107 to 734) U/Kg/week in group B (high-risk, relative renal insufficiency) patients. All patients were treated subcutaneously, except patients 10 and 13, who were treated intravenously.

The median duration of therapy, in the ten patients who are still on EPO, is 16 (11+ to 34+) months. Three patients are no longer on EPO. UPN 1 was switched to chronic exchange transfusions after 2 years of poor compliance with, and responsiveness to, EPO and HU therapy. UPN 10 was treated with EPO for 4 months, in the absence of HU, with complications as described below. UPN 13 was treated only briefly with EPO for a life-threatening delayed hemolytic transfusion reaction.

NIH results

The sub-groups of patients with sickle syndromes who were treated with EPO, whom we defined above, are small, heterogeneously treated, and retrospectively defined, which limits definitive conclusions. However, we can describe the laboratory and pharmacologic results of EPO therapy and we can comment on toxicity from EPO in SCD; we will also review our current clinical strategy for EPO use in SCD.

Hematologic and pharmacologic

The dose of HU rose in most patients treated with EPO, from a median dose of 0 (0-18.5) mg/Kg to 10.4 (7.9 to 24.5) mg/Kg in 9/13 evaluable patients (Figure 1A); as described, some patients were started on EPO subsequent to HU (group A) and some concurrent with HU (group B). Of note, only one of four patients from group A, UPN 3, was tolerating a dose of HU>15 mg/Kg/day prior to EPO; Furthermore, UPN 5, receiving a 16 mg/Kg/dose of HU, was on EPO and HU at referral. Only one of four patients from group B, UPN 8, achieved a dose of HU >15 mg/Kg/day when given EPO

and HU concurrently.

In eight evaluable patients from groups A and B (and UPN 12), total Hb concentration rose from a median of 6.4 (4.7 to 8.6) g/dL to 8.5 (6.7 to 11.5) g/dL (Figure 1B). HbF in these patients (Figure 1C) rose from a median of 5 (1.6-14)% to 13.5 (3.1-21)%, while F-cells increased from a median of 22 (13-66)% to 47.5 (24-75)% (Figure 1D). Among evaluable patients, reticulocyte counts, reflecting either SCD-associated hemolysis or HU toxicity, were stable in group A patients who were given EPO for HU-intolerance, and decreased in group B patients who were started on HU and EPO concurrently due to renal insufficiency (Figure 1E); the median lactate dehydrogenase concentration, also a reflection of hemolysis and disease activity, tended to decrease, from 388 (222-929) to 327 (202-433) IU/L during follow-up (Figure 1F).

Potential risks from erythropoietin in SCD

Theoretic concerns about erythropoietin use in SCD, especially in the absence of concurrent HU, include increasing the HbS concentration, the number of HbS-containing reticulocytes, and the hematocrit, thereby risking hypertension and hyperviscosity.[47-49] Erythropoietin has been associated with an increased risk of thrombosis in non-SCD patients who have an underlying procoagulant condition, such as malignancy;[50] however, a number of modest-sized randomized trials of erythropoietin in non-SCD dialysis patients have found no difference in thrombosis rates *in vivo* between erythropoietin-treated or non-treated patients.[51,52] SCD is, of itself, associated with numerous hemostatic perturbations,[53] and there are no data yet available about clinical risks for thrombosis in SCD patients who are taking erythropoietin.

Erythropoietin, especially but not exclusively, when marketed as Eprex® in an albumin-free formulation in Europe, was associated with pure red cell aplasia. Pure red cell aplasia is a life-threatening complication attributed to cross-reacting anti-erythropoietin antibodies;[54] the incidence of pure red cell aplasia from conventional or long-acting erythropoietin preparations is low, being estimated at 0.2 per 100,000 patient-years in end-stage renal disease.[55,56] Endogenous elevations in erythropoietin have been associated with proliferative retinopathy in diabetes;[57] the risk of this, if any, in SCD is not known.

Toxicity from EPO therapy at the NIH

Thirteen sickle syndrome patients were treated with EPO, cumulatively, for 18 years and 8 months. Twelve of the 13 patients treated with EPO did not experience worsening of symptomatic SCD, changes in ophthalmologic symptoms, or clinical thromboses while on HU and EPO. There was no evidence for pure red cell aplasia or systemic hypertension.

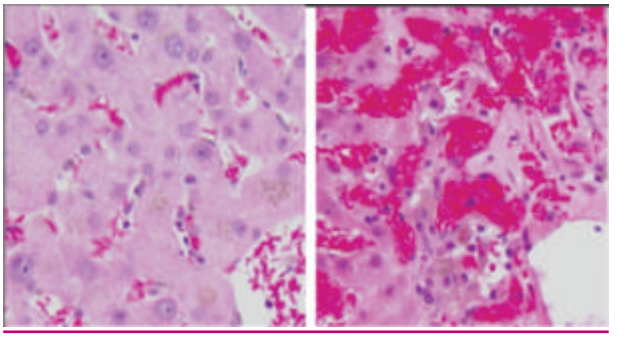

Figure 2. Hematoxylin and eosin (H&E) stain of a liver biopsy (50X) from UPN 10: A. 5 months and B. 9 months following an orthotopic liver transplant; during this interval the patient was treated thrice-weekly with erythropoietin.

Table 2. Erythropoietin use in SCD.

Consider in
• High-risk disease (end-organ damage such as pulmonary hypertension or a history of cerebrovascular disease) AND
• Hb <8 g/dL AND
• relative renal insufficiency (estimated GFR <100 mL/min) AND
• HU doses ≤15mg/Kg limited by reticulocytes <100,000/μL
Dose
• Erythropoietin subcutaneously 100U/Kg twice a week, increase by 100 U/Kg/dose every 4-6 weeks, until Hb rises.
• Hold EPO if Hb >10.5 g/dL or if rate-of-rise is >1.5 g/dL over 4 weeks
• Continue HU, increase as tolerated by neutrophil and platelet counts
Monitor on therapy
• Complete blood count, with reticulocytes (weekly after EPO dose change)
• Blood pressure (weekly after EPO dose change)
• For symptoms of thrombosis or new visual changes

UPN 10 experienced an exacerbation of sickle liver disease while receiving 180 U/Kg IV erythropoietin 3 times a week, without HU, in an attempt to minimize transfusion-associated iron overload. In the summer of 2004, UPN 10 had developed both liver failure caused by hepatitis C virus infection, for which he received an orthotopic liver transplant, and end-stage renal disease, for which he started dialysis. A routine liver biopsy 5 months after his transplant, coincident with the start of EPO therapy, showed mild intrahepatic sickling (Figure 2A) and possible mild reactive hepatitis C. During a 4-month interval on EPO, the median reticulocyte count rose from 90,000/μL to 149,000/μL, median transaminase, lactate dehydrogenase and total bilirubin levels more than doubled, and median packed cell volume dropped from 35% to 25.5%, on fewer transfusions; HbA was maintained at a median of 63% (47-77.5%). Nine months after transplant, a second liver biopsy showed widespread intrahepatic sickling (Figure 2B), hepatic necrosis and fibrosis, and extramedullry hematopoiesis, and was consistent with the possibility that EPO could have contributed to intrahepatic sickling and resultant hepatic necrosis. Erythropoietin was

stopped and blood transfusions were increased; HbA levels were subsequently maintained above 75% and reticulocytes below 40,000/μL. Lactate dehydrogenase and liver transaminase values normalized with this intervention.

Conclusions

In this report, we summarize published data on erythropoietin use in 39 patients with SCD, and on erythropoietin or darbopoeitin use in 13 patients with sickle syndromes treated since 2002 at the NIH. The ability of EPO to increase HbF indirectly, through enhanced HU dosing in SCD patients with relative renal insufficiency, is suggested by our experience at the NIH. In addition, both historical and current clinical reports suggest limited toxicity from EPO in SCD, especially when given with HU. Although causal associations are lacking, a single patient at the NIH experienced worsened sickle hepatopathy coincident with EPO therapy in the absence of HU. Our experience has led us to avoid EPO use in patients who are unable to take HU. We conclude that EPO therapy may be useful in patients with SCD and renal insufficiency who are not tolerating, or likely to tolerate, HU at a dose of 15 mg/Kg (Table 2). The addition of EPO may allow more aggressive HU dosing, and subsequent higher HbF levels. We, and others, have used doses of EPO in patients with sickle cell disease that are higher than those used conventionally for end stage renal disease, without apparent untoward effect.

Clarification of the role, dose, and toxicity of exogenous EPO therapy in patients with SCD who are at high-risk and have mild-to-moderate renal insufficiency awaits further study. However, in the interim, EPO may be considered as an adjunct to HU therapy in patients with high-risk SCD, anemia, low reticulocyte counts, and deteriorating renal function, particularly when HU therapy is limited by the erythroid reserve.

JAL: patient care, data evaluation, manuscript preparation; VMG: data evaluation; GK: patient care, data evaluation, manuscript preparation; KP: data evaluation; JF: patient care, manuscript preparation; IM: data evaluation; SM: data evaluation; JT VI, patient care; RM: patient care; TH: patient care, manuscript preparation; OC: patient care, manuscript preparation; MTG: patient care, data evaluation, manuscript preparation. The authors also declare that they have no potential conflicts of interest. Supported by intramural research program of the NHLBI and NIDDK. Manuscript received March 6, 2006. Accepted June 28, 2006.

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