Pediatric Use of Recombinant Human Erythropoietin
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Recombinant human erythropoietin (rHuEPO), also referred to as epoetin alfa, has Food and Drug Administration (FDA) approval for the treatment of anemia in pediatric patients with chronic renal failure (CRF) requiring dialysis. Literature is also available supporting its use in children with anemia associated with cancer chemotherapy, prematurity, or chronic illness. Recombinant human erythropoietin is generally well tolerated and may offer the benefit of reducing the need for blood transfusions in these pediatric populations. This article will review the use of rHuEPO in infants and children.

Mechanism of Action
Erythropoietin is a glycoprotein which is essential in the production of red blood cells. It is produced in the kidney and stimulates the division and differentiation of erythroid progenitors in the bone marrow. Hypoxia and anemia increase the production of erythropoietin. Since rHuEPO is recombinant human erythropoietin, it has the same biological effects as endogenous erythropoietin.1-3

Use in Chronic Renal Failure
There are many clinical studies describing the efficacy of rHuEPO in adult patients with anemia pre-dialysis, during hemodialysis (HD) or peritoneal dialysis (PD), and after transplant. The body of literature in pediatrics is smaller, but supportive. In 1994, Jabs and colleagues reported the results of a randomized, placebo-controlled, multicenter trial of rHuEPO in 113 HD (42%) and PD (58%) patients between 5 and 17 years of age.4 The initial rHuEPO dose was 50 units/kg three times weekly, intravenously (IV) for HD patients or subcutaneously (SC) for PD patients. At 12 weeks, the mean Hct had increased in the rHuEPO group (HD: 21% to 28%, PD: 23% to 34%) and remained unchanged in the placebo group. There were no significant differences between groups in adverse effects. Following the initial 12-week trial, all patients were given rHuEPO. After 24 weeks of rHuEPO, mean Hct was 31% in HD and PD patients. However, the average dose required in HD patients was significantly higher compared to PD patients (155 units/kg/week versus 91 units/kg/week). The dose in PD patients was significantly higher in children < 5 years old than in those 5-17 years old. Systolic and diastolic blood pressures significantly increased in HD patients, while only the diastolic blood pressure increased in PD patients. In addition, iron deficiency worsened during treatment.

A prospective, randomized study in 1999 by Brandt and colleagues evaluated the use of rHuEPO in 44 children (4 months to 21 years of age) with chronic renal disease.5 There were 25 pre-dialysis patients, 10 PD, and 9 HD patients. The children were randomized to either low-dose rHuEPO (150 units/kg/week) or high-dose (450 units/kg/week) divided three times weekly for 12 weeks or until an age-determined target hemoglobin (Hgb) was reached. Dose was then titrated to a normal Hgb. Hemodialysis patients received IV rHuEPO and children on PD or who were pre-dialysis received SC rHuEPO.

Eighty-two percent of patients achieved target Hgb at a mean of 7.9 weeks; 95% of patients in the high-dose group and 66% in the low-dose group reached target within 12 weeks. The overall median dose of rHuEPO required to maintain a normal Hgb was 150 units/kg per week. Although, there were no significant differences, HD patients tended to have higher dosage requirements (median 250 units/kg/week). The increase in Hgb was significant for all groups except the low-dose PD group. Transfusion requirements and panel-reactive antibody levels decreased during the 12 weeks, although there were no significant differences between groups. Hypertension occurred in 30% of patients and was significantly more common in HD patients (66%) than in PD (33%) or pre-dialysis (16%) patients. Iron deficiency was found in 30% of patients.
Use in Anemia Associated with Cancer
There are a limited number of clinical studies evaluating the use of rHuEPO in pediatric cancer patients. However, two placebo-controlled, double-blind studies in the US and an open-label, randomized European study are underway and should provide additional data to clarify the appropriate use of rHuEPO in this population.

In a randomized, controlled study conducted by Bennetts and colleagues, 37 children with newly diagnosed acute lymphocytic leukemia (ALL) received rHuEPO 150 units/kg three times weekly IV or SC, or no treatment during three chemotherapy courses. The patients ranged in age from 1 to 7 years, with a median of 3.5 years. No significant difference in efficacy was seen in the number or amount of packed red blood cell (PRBC) transfusions. However, among the subset of children diagnosed with low-risk ALL, there was a significantly lower volume of PRBC transfused in the rHuEPO group versus the control group. No adverse effects were reported with rHuEPO; however, iron deficiency developed in patients in both groups.

In 1999, Varan and colleagues reported the results of a randomized trial evaluating the use of rHuEPO in 34 pediatric patients (6 months-18 years of age) undergoing chemotherapy. A dose of 150 units/kg was given 3 times a week for 8 weeks to 17 patients; 17 control patients received standard of care. A significant increase in the mean Hgb from 8.5 to 10.21 g/dL was seen after 4 weeks of treatment in the rHuEPO group. This effect continued throughout the study. Mean Hgb levels did not change significantly in the control group. Significantly fewer patients in the rHuEPO group required transfusions compared to the control group (5.9% versus 47%, respectively). One patient receiving rHuEPO developed hypertension requiring discontinuation of treatment; however, treatment was restarted after 1 week without further complications.

Use in Anemia of Prematurity
The majority of premature neonates require multiple blood transfusions. Anemia during the first 2 weeks of life is primarily a result of blood loss due to blood sampling. Anemia of prematurity is typically noted after the second week and has been attributed to erythropoietin deficiency. Use of rHuEPO during the first 2 weeks of life remains controversial. Although much information is available about the clinical use of rHuEPO in preterm infants, many questions, including appropriate administration timing and dosing regimen, remain unanswered. A multicenter, randomized, controlled trial conducted by Ohls and colleagues in 2001 evaluated the hypothesis that early rHuEPO and iron therapy would decrease transfusion requirements in preterm neonates whose birthweight was below 1,250 grams. A total of 290 patients were randomized to rHuEPO 400 units/kg three times weekly or placebo. Therapy was started by the fourth day of life and continued through the 35th postmenstrual week. All infants received supplemental iron. Infants in both groups had similar transfusion requirements. However, reticulocyte counts and Hct were higher in the infants who received rHuEPO.

Shannon and colleagues reported the results of a randomized, double-blind, placebo-controlled clinical trial evaluating the effect of rHuEPO on transfusion requirements in 157 preterm infants. Patients were randomized to rHuEPO 100 units/kg/day, 5 days per week, or placebo for 6 weeks. All patients received oral iron, (3 to 6 mg/kg/day elemental iron) and were managed according to conservative uniform transfusion guidelines. Infants in the rHuEPO group required significantly fewer transfusions (1.1 versus 1.6 per infant) and less volume per transfusion compared to those given placebo. However, similar percentages of infants in both groups were transfusion-free (43% versus 31% for placebo). Reticulocyte counts and Hct were significantly higher in the rHuEPO group.

Other Uses in Children
The use of rHuEPO in several other types of anemia has also been described. Zuccotti and colleagues demonstrated the efficacy of rHuEPO in treating three children with anemia associated with human immunodeficiency virus (HIV) infection. A dose of 50 units/kg twice weekly produced an increase in Hgb levels and eliminated the need for blood transfusions in all three children over a 4-month period.

A case report by Fridge and colleagues in 1998 described the use of rHuEPO and IV iron in 5 children with epidermolysis bullosa and severe refractory anemia. Iron dextran 10-20 mg/kg was given monthly, and rHuEPO was given in increasing doses of 150-350 units/kg three times per week. At the time of follow-up, the mean duration of treatment was 1.2 years. All patients responded with significant increases in mean Hgb from 6.8 to 10.0 g/dL and in mean Hct from 23.8% to 33.1%. Four of the five patients became transfusion-independent. In addition, an improved quality of life, accelerated wound healing, and improvement in weight-for-height percentile were reported.

Markham and Bryson evaluated the use of rHuEPO in 13 children with juvenile rheumatoid arthritis. The mean maintenance dose was 289 units/kg/week for 4 to 13 months. Significant increases in Hgb were observed as well as improved muscle strength, growth rate, and quality of life.
In 1994, Akingbola and colleagues successfully used rHuEPO to reverse severe anemia after a renal transplant in a 12 year old Jehovah’s Witness patient (Hgb 2.1 g/dL and Hct 6%). Recombinant human erythropoietin 10,000 units was given SC twice daily with IV iron and continued until discharge 17 days later. Hemoglobin increased to 7 g/dL and Hct to 22% by day 7 and to 8.6 g/dL and 26.6% at discharge.

A retrospective review by Roye of 178 pediatric patients undergoing surgery to correct scoliosis described the use of rHuEPO in 78 (44%) of these patients. Recombinant human erythropoietin 10,000 U was administered once per week for 3 weeks prior to surgery with oral iron. The patients who received rHuEPO required significantly fewer transfusions and had significantly higher Hct levels.

Pharmacokinetics
Recombinant human erythropoietin is available only for injection. The onset of response has been reported to occur as early as 7 days; however, some patients may require as long as 6 weeks of treatment to achieve optimal effect. Peak serum levels occur within 5 to 24 hours after SC administration and decrease slowly. Measurable plasma levels of rHuEPO are sustained for at least 24 hours. Recombinant human erythropoietin is extracted from plasma by erythroid precursors. It is eliminated via first-order kinetics with a circulating half-life of 4 to 13 hours after IV administration in patients with CRF. The half-life in healthy adults is 20% shorter than in CRF patients. Subcutaneous administration results in a prolonged half-life of approximately 27 hours. There is no apparent difference in half-life between patients with CRF not on dialysis and those maintained on dialysis.

The pharmacokinetics of rHuEPO in children and adolescents appear similar to those of adults. Pharmacokinetic data in neonates is limited. In children on continuous ambulatory peritoneal dialysis (CAPD), rHuEPO is sometimes administered by the intraperitoneal route in order to avoid the psychological distress associated with SC administration. A study by Kausz and colleagues evaluated the efficacy and pharmacokinetics of intraperitoneal rHuEPO in eight children. A single dose of 100 units/kg in 50 mL of dialysate was administered into a dry peritoneal cavity after nighttime dialysis. Relative bioavailability was similar to SC dosing. Patients maintained a normal Hct with an intraperitoneal rHuEPO dose that was similar to their previous SC dosage.

Drug Interactions
Although no significant drug interactions with rHuEPO were observed in the course of clinical trials, there have been post-marketing reports of interactions in the literature. A study by Matsumura and colleagues found that HD patients taking angiotensin converting enzyme inhibitors and rHuEPO concurrently required higher rHuEPO doses to maintain the target Hct. The clinical implications for this interaction are not yet clear, as a subsequent study failed to replicate these results.

Recombinant human erythropoietin may also alter heparin dosing. In a 1987 study by Casati and colleagues, 13 of 14 CRF patients required significantly increased mean heparin doses from 1,071 units/hour (pretreatment) to 1,558 units/hour (at full correction) after initiation of rHuEPO.

Adverse Effects
The most commonly reported adverse effects associated with rHuEPO in adults with CRF are hypertension (24% of patients), headache (16%), arthralgia (11%), nausea (11%), edema (9%), fatigue (9%), and diarrhea (9%). The adverse effect profile in pediatric patients with CRF on dialysis was similar to seen in adults. Additional adverse effects reported during the double-blind phase in greater than 10% of pediatric patients in either treatment group were: abdominal pain, dialysis access complications including infections and peritonitis in those receiving peritoneal dialysis, fever, upper respiratory infection, cough, pharyngitis, and constipation.

Seizures have been reported in 47 of 1,010 adult patients on dialysis for a rate of approximately 0.048 events per patient-year. However, there appeared to be a higher rate of seizures during the first 90 days of therapy (occurring in approximately 2.5% of patients).

Product Availability
Recombinant human erythropoietin is available as the brand name products Epogen® (Amgen) and Procrit® (Ortho Biotech). Both products are available as 2 mL multidose formulations. Each of these concentration is available in 1 mL vials. The 10,000 units/mL concentration is also available as 2 mL multidose vials. The multidose vials contain benzyl alcohol and should not be used in premature infants.

Dosing Recommendations
The recommended initial dose of rHuEPO for pediatric patients with CRF, cancer, or HIV infection is 50 to 150 units/kg IV or SC three times weekly. Clinical experience suggests that, with adequate iron supplementation, the SC and IV routes are equally efficacious; however, dosing requirements with chronic IV administration may be 30%-50% greater than...
with SC administration because of a more rapid decline in serum concentrations.\textsuperscript{17,24}

Dose adjustments should not be made more frequently than once a month, unless clinically indicated. Hct should be evaluated twice weekly for at least 2 to 6 weeks after any dose adjustment. The suggested Hct target range is 30 to 36%. The dose should be reduced as the Hct approaches 36% or increases by more than 4 units in any 2 week period. The dose should be increased if the Hct does not increase by 5 to 6 units after 8 weeks of therapy or is below the suggested target range. Iron stores should be assessed and supplementation provided to optimize patient response.\textsuperscript{1,3}

A number of alternative rHuEPO dosing strategies for children have also been reported. Once weekly regimens have been used in children with CRF, using a single dose equivalent to their previous total weekly dose. For infants with anemia of prematurity, several regimens have been studied, including giving 25 to 100 units/kg on the traditional three times weekly schedule, as well as 100 units/kg five times weekly or 200 units/kg every other day for up to 10 doses.\textsuperscript{1,2}

Summary
The use of rHuEPO in adults has been well described in a variety of clinical situations. Although it is currently approved only for children with CRF, its use in other pediatric patient populations continues to increase. Publication of additional data on its use in children is needed to determine efficacy, define appropriate dosing regimens, and evaluate cost-effectiveness.

References
2. Procrit\textsuperscript{®} product information. Ortho Biotech Products. December 2000. Available at \url{www.procrit.com/general/general_03_03.htm}

Formulary Update
The new Outpatient Pharmacy Formulary was reviewed by the Pharmacy and Therapeutics Committee at their meeting on 10/25/02.