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ORIGINAL ARTICLE

Continuous EPO receptor activator therapy of anemia in children under peritoneal dialysis

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Abstract The short half-life of erythropoietin (rHuEPO) leads to repeated fluctuations in hemoglobin levels and the need for frequent administration. Continuous erythropoietin receptor activator (CERA) therapy has been approved for once or twice a month in adult dialysis patients. To evaluate the efficacy and safety of CERA therapy in the management of anemia in pediatric peritoneal dialysis (PD) stable PD children under twice-a-week EPO were converted to a subcutaneous CERA, scheduled every 2 weeks. The follow-up was 6 months. The primary efficacy parameter was hemoglobin >11 g/dL. The exclusion criteria were ferritin <100 ng/ml and Hb saturation <20%. Sixteen children, aged 9.75±3.6 years, including 11 boys, participated in the study. Mean Hb level at month 0 was 10.8±1.9 g/dL. A decrease in hemoglobin to 10.38±1 g/dL at month 2 was observed. The CERA dose was increased from 0.86±0.33 to 1.67±0.4 μg/kg at month 3. The target Hb level was reached by the 3rd month. The Hb level and CERA dose were 12.2±1.2 and 1.6±0.67 μg/kg respectively at the end of the study. No adverse events were observed during the protocol. CERA is an effective and safe therapy for maintaining hemoglobin levels when administered twice, up to once a month, in PD children. Doses required to reach target Hb were higher than published experiences in adult populations.

Keywords Erythropoietin · EPO · CERA · Anemia · Children · Peritoneal dialysis

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Introduction

Anemia is a severe complication of chronic kidney disease, especially in dialysis patients. Although many mechanisms are involved in the pathogenesis of anemia in chronic renal failure (CRF), the primary cause is inadequate production of erythropoietin (EPO) [1]. Anemia starves the body of oxygen and has been associated with a decreased exercise capacity, cognitive impairment, and diminished quality of life. In adult and pediatric dialysis patients, it has also been associated with congestive heart failure, left ventricular hypertrophy, and mortality [2, 3].

No effective therapy for the treatment of anemia was available before the mid-1980s. Dialysis patients were managed primarily by blood transfusions, increasing the risk for infections and the likelihood of developing sensitivity to major histocompatibility antigens, affecting successful kidney transplantation.

The erythropoietin gene was identified in 1983, and clinical trials were initiated in 1985 in order to evaluate the

efficacy and safety of recombinant human erythropoietin. Recombinant human erythropoietin (rHuEPO, epoetin) for the treatment of anemia associated with chronic renal failure was available by 1990 [4].

In dialysis patients, epoetin is administered by subcutaneous or intravenous injection most often 1 to 2 times weekly. It is highly effective at stimulating erythropoiesis and produces a sustained increase in hemoglobin levels. However, the overall efficiency of epoetin is primarily limited by the need for its frequent administration [5, 6]. The short half-life of epoetin may contribute to repeated fluctuations in hemoglobin levels beyond target KDOQI ranges, which is often seen in patients treated with this agent [7, 8]. Lacson et al. [9] showed in 65,000 dialysis patients that only approximately 38% had hemoglobin levels within the range of 11 to 12 g/dl. Despite a mean hemoglobin level of 11.5 g/dl, patients showed a 1.4 g/dl fluctuation in hemoglobin levels during 1 year of follow-up. The US Renal Data System (USRDS) and other trials have also suggested that many patients who receive erythropoiesis-stimulating agents (ESA) experience fluctuations in hemoglobin over time, showing a high degree of variability below and above the target range [7–10]. In the USRDS study, patients were categorized into one of three cohorts of hemoglobin, less than 11.0 g/dl, 11.0 to 12.5 g/dl, and more than 12.5 g/dl, finding a significant movement between and within hemoglobin groups during a 3-month follow-up. Gilbertson et al. [11] evaluated 151,000 USRDS hemodialysis patients, finding the lowest mortality in the group of patients who maintained hemoglobin levels within the KDOQI range, 11.0 to 12.5 g/dl, suggesting that hemoglobin variability could be associated with mortality risk in the dialysis population.

Research into the biological properties of native human EPO and rHuEPO has revealed the critical role of sialic acid carbohydrate content in its in vivo activity, as well as the affinity for receptor binding capacity. rHuEPO contains three carbohydrate chains, and its activity varies inversely with this specific carbohydrate content. In the late 1990s, a hyperglycosylated rHuEPO analog with five N-linked carbohydrate chains, darbepoetin alfa, was introduced for clinical use [12].

Long-acting EPOs like darbepoetin have been used in recent years in CRF patients. Experiences at varying doses, routes, and frequency of administration in predialysis, peritoneal dialysis, and hemodialysis patients have been communicated [13–17].

Other epoetin that has recently become available is the continuous erythropoietin receptor activator (CERA), which integrates a large methoxy-polyethylene glycol polymer chain into the EPO molecule. The mass of the polymer chain is approximately 30 kD, doubling the molecular weight of CERA to approximately 60 kD, compared with epoietin (30.4 kD). Therefore, the half-life of circulating CERA is considerably prolonged compared with classic epoetin, until 130 h, allowing less frequent dosing regimens of once every 2 weeks and once every month [18].

To date, a number of multicentric phase III trials have confirmed the efficacy of CERA in the correction of anemia in CKD adult patients. The AMICUS Study (CER**A** ad**M**inistered **I**ntravenously for anemia **C**orrection and s**US**tained maintenance in dialysis) was a multicenter, randomized trial to determine whether CERA administered once every 2 weeks was as effective and well tolerated as epoetin (alfa or beta) administered three times weekly for the correction of anemia in 181 hemodialysis or peritoneal dialysis patients not receiving epoietin previously [19]. Another large-scale multicenter randomized trial, the RUBRA Study (Ta**R**getting s**U**stained haemoglo**B**in in dialysis with IV and SC CE**R**A **A**dministration) confirmed the efficacy, tolerability, and safety of subcutaneous or intravenous CERA given once every 2 weeks in hemo- and peritoneal dialysis patients (n=123) converted directly from patients under epoetin therapy (n=133). This study proved that patients can be directly converted to Q2W CERA from more frequent administration of epoetin [20].

In children under chronic peritoneal dialysis, EPO therapy requires 1–3 subcutaneous doses per week according 2008 NAPRTCS data. Given the results obtained with CERA in adult uremic patients, it is expected that the efficacy and safety of the drug will also be confirmed in pediatric patients, allowing less frequent administration, which would reduce the frequency of painful injections, improving compliance and quality of life in these children. The objective of this study was to evaluate the efficacy and safety of CERA in children under chronic peritoneal dialysis, and to determine an effective starting dose in CKD pediatric patients.

Patients and methods

Study participants

A prospective, pre-post design protocol was applied. Pediatric patients under chronic peritoneal dialysis at the Division of Pediatric Nephrology, Luis Calvo Mackenna Childrens Hospital, were included. The follow-up period was 6 months.

Inclusion criteria

Eligible patients must have had stable hemoglobin concentrations, defined as a maximum variation of 1 g/dL during a 4-week screening/baseline period. An Hb value more than

10 g/dL 1 month before starting the protocol was considered adequate for enrollment. Patients must have received daily peritoneal dialysis for 12 weeks before screening and during the 4-week screening/baseline period. They must have undergone maintenance weekly (one, two or three doses per week) subcutaneous epoetin alfa therapy for 12 weeks before screening and during the screening/baseline period. Patients also had to show adequate iron status, defined as serum ferritin >100 μg/L and a transferrin saturation >20%.

Patients were excluded if they had received RBC in the previous 12 weeks of the study, or had a nonrenal cause of anemia, such as hemolysis, hemoglobinopathy, and others. Maximum Hb level was not considered an exclusion criteria. Other exclusion criteria were C-reactive protein level greater than 30 mg/L, hypertension (BP>90th percentile), gastrointestinal bleeding; parathyroid hormone level >700 pg/mL; active systemic infection; a peritonitis episode within 30 days of signing the consent/assent, and previous poor compliance. Patients were retired from the study if poor compliance or two missing Hb values were confirmed. Compliance was defined as the extent to which the patient's or their parent's behavior, in terms of taking medications, following diets, or executing lifestyle changes, coincided with medical and nursing advice.

The design was approved by the Ethics Committee of the Faculty of Medicine, University of Chile, Luis Calvo Mackenna Children's Hospital. All participants gave prior written informed consent/assent, as requested by the Committee.

Procedures

Eligible patients were switched to methoxy polyethylene glycol epoetin beta starting at a mean dose of 0.5 μg/kg every 2 weeks, according to published experiences in adults with CKD [18–20].

Patients were assessed every 2 weeks for the first 3 months, and later monthly during the 6-month follow-up period. Hemoglobin, hematocrit, electrolytes, blood gases, plasma albumin, creatinine, and BUN were measured at each assessment visit. Reticulocyte index (reticulocyte count × (HCT/normal HCT)) was calculated at each visit. Parathormone, ferritin, transferrin saturation, biochemical profile and dialysis dose (Kt/V) were measured every 2 months until the final visit (week 24). All patients had a peritoneal equilibrium test (PET) prior to and after the protocol. A clinical evaluation including weight standard deviation scores (SDS), height SDS, and blood pressure was performed at each visit. Patients received i.v. iron 2 mg/kg/week for four doses to reach and maintain adequate iron status (Ferrous Sacarate, Cheltin®, Pharma Investi Labs) [21, 22].

Adverse events (AEs) were recorded throughout the treatment period, including blood pressure and any patient complaints, whether related to CERA therapy or not.

Study outcomes

The primary efficacy parameter was hemoglobin level >11 g/dL (>110 g/L) without RBC transfusion during the 24 weeks after the first dose. The secondary endpoint was dose change over time.

CERA dosing

Mircera® (F. Hoffmann-La Roche, Basel, Switzerland) was supplied as a solution in vials containing 1 mL of 50 and 100 μg.

The starting dose of Mircera was 0.5 μg/kg each 2 weeks, according published experience in adult patients [18–20]. Later on, doses were adjusted to achieve individual Hb levels of 11 g/dL or greater. Doses were increased by 25% if any increase in Hb level versus baseline was observed. Doses were increased by 50% if Hb level decreased to less than the baseline value. Doses were decreased by 25% if the Hb level increased by greater than 1 g/dL, and 50% if the Hb level increased by greater than 2 g/dL versus baseline. Treatment was switched to once a month if the Hb level was greater than 13.0 g/dL.

Sterile doses of Mircera were prepared at the Mixing Center, Pharmacy Service, at the Luis Calvo Mackenna Children's Hospital. The mixing center consists of three areas: parenteral nutrition, oncology, and antibiotics and high-cost, very low-dose medications. Each area has its own acclimatization system, with controlled air pressure, and maximum level of particles, as prescribed by the International Standards in the preparation of sterile products. A laminal flow chamber is also available depending on the product.

Mircera was prepared in the injectable medications area, from original 50- and 100-mg syringes. All preparations were made by the same pharmacist, in a TELSTAR vertical laminal flow chamber, model PV-30/70, class 100. The maximum number of particles allowed in this area is 100 particles of 0.5 μΩ in size per cubic foot.

The same pediatric nephrologist prescribed each individual dose per patient, which was prepared on the same day of administration to ensure chemical stability. One-millimeter syringes were used, with 0.01 ml markings to secure the exact dosage. The individually prepared syringe was wrapped in a sterile bag, and labeled with patient information, dose, date and time of preparation, and the name of the person who prepared it. Once preparation was completed, the Nephrology Nurse was notified for immediate pick-up and administration of the medication.

Results

Sixteen patients were included, 13 boys, mean age 9.7±3.9 years, all of them on automatized peritoneal dialysis (APD). Four children were excluded because poor compliance or peritonitis episodes were confirmed. Mean time on PD at the beginning of the protocol was 10.6±5.1 months. Reflux nephropathy (n=4), obstructive uropathy (n=4), and renal dysplasia (n=5) were the main causes of CRF in selected patients. Alport (n=1) and D(+) hemolytic uremic syndrome (n=2) were other etiologies. The overall data, including Hb values and CERA doses at months 0 and 6, are presented in Table 1. Eleven patients completed 6 months of treatment, 14 patients completed 5 months of treatment, and 2 patients were switched to hemodialysis at month 3 of the protocol. The mean EPO dose before starting the protocol was 3,500± 894 IU weekly, 120 IU/kg/week.

Mean Hb level at month 0 was 10.8±1.9 g/dL (median value 11.05, range 8.6–14.8). Four patients showed an initial hemoglobin level less than the cut-off value, but all of them had Hb>10 g/dL 1 month before entering the study. During the first 2 months of treatment, a decrease in the hemoglobin level to a minimum value of 10.38±1 g/dL at the end of the first month of treatment was observed. The initial CERA dose was increased from 0.86±0.33 (median value 0.77, range 0.5–1.5) to 1.67±0.4 (median value 1.6, range 1.2–2.4) at month 3 of the protocol. The steady state was reached by the 3rd month, with a mean Hb concentration of 11.29±1.4 g/dl. These results persisted at the 6-month follow-up, with a maximum CERA dose of 1.9±0.78 at month 4 and 1.6±0.67 (median value 1.5, range 1–2.7) at the end of the treatment. A repeated-measures linear model showed a statistically significant change in hemoglobin levels between month 0 and 6 (F= 2,757; GL=12; p=0.002, Fig. 1). A dichotomic analysis dividing the patients into two groups, those with Hb levels> 11 g/dL vs Hb levels<11 g/dL, showed 50% of patients in each group at the start of the study, changing to 90.9% vs 9.1% at the end of the protocol (inter-subject effect test, p< 0.001, Fig. 2). The relationship between CERA doses and Hb evolution is shown in Fig. 3. Two patients were switched to once-a-month treatment because Hb levels increased >13 g/dL, returning to the target range in the next control. Five patients showed an hemoglobin level >13 g/dL at the end of their treatment, patients number 2 and 7 were switched to HD and transplanted respectively, the other 3 patients returned to regular EPO when hemoglobin levels decreased to less than 13 g/dL. Six patients received iv iron during the protocol (patients 3, 9, 12, 13, 14, and 16) as detailed before. All patients showed a final ferritin level >100 ng/ml, and TSAT >20% at the end of the study (Table 1). The

Table 1 Characteristics of children treated with continuous erythropoietin receptor activator (CERA) during a 6-month follow-up protocol

Patient	Age (years)	Weight (SDS)	Height (SDS)	TSAT (end; %)	Ferritin (ng/ml; end)	Hb g/dL (before)	Hb g/dL (end)	CERA initial dose (μg/kg)	CERA final dose (μg/kg)	Blood pressure percentile (end)	Months of treatment	Final status (end)
Mean	9.7	−1.4	−1.99	28.7	375	11.12	12.2	0.86	1.6	57	5.4	
SDS	3.9	1.7	1.4	4.9	295	0.82	1.2	0.34	0.67	19	1	
1	14	−2.07	−2.4	25	190	10.3	10.2	0.8	1.5	75	3	HD month 3
2	10	−3.09	−3.93	24	180	10.1	13.7	0.7	1.4	50	3	HD month 3
3	14	−3	−3.29	32	862	10.4	11.7	1.1	2.4	75	5	HD month 5
4	10	1.98	0.62	29	143	10.7	13.6	1.0	1.0	75	6	End
5	11	−2.33	−2.45	25	159	13.0	13.0	0.6	0.8	75	6	End
6	3	−5	−4.8	24	213	11.0	11.4	0.6	2.9	25	6	End
7	14	−2.2	−2.1	25	146	11.6	13.5	0.9	1.4	50	5	Transplant month 5
8	11	0.68	−1.7	27	195	11.5	12.1	1.5	1.2	50	5	Transplant month 5
9	2	−2.8	−2.1	33	609	11.8	11.9	0.5	1.6	50	6	End
10	10	−0.6	−3.2	24	149	10.6	11.3	0.7	2.6	25	6	End
11	6	−2.1	−1.7	27	190	12.2	13.8	0.6	1.5	50	6	End
12	6	−0.27	−1.3	38	955	11.6	12	0.5	2.2	25	6	End
13	14	−1.27	−2.05	36	582	11.4	9.9	1.2	1.2	75	6	End
14	6	−0.6	0.6	34	798	10.1	12.4	1.3	1.6	75	6	End
15	13	−0.9	−1.7	23	114	11.2	11.6	1.3	1.3	75	6	End
16	12	0.6	−0.4	33	521	10.5	13.5	0.5	1	75	6	End

SDS = standard deviation scores; TSAT = transferrin saturation; HD = hemodialysis

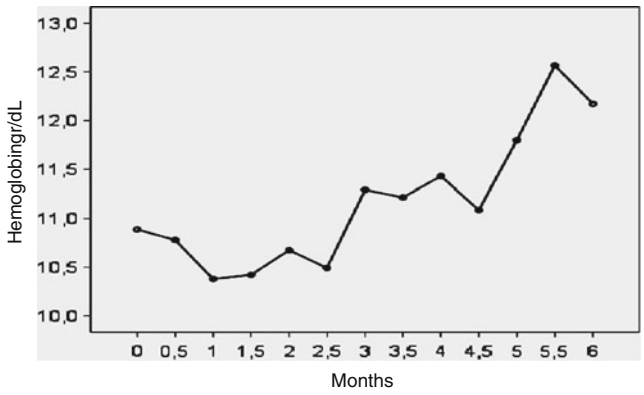

Fig. 1 Hemoglobin evolution during the 6-month follow-up

reticulocyte index was 2.3 and 1.65 at the beginning and at the end of the protocol respectively. Hypertension was not observed during the follow-up. The BP percentile for each patient was between p25 and p75 at the end of the treatment, with a mean percentile value of 57±19 (Table 1). No other adverse events were registered during the protocol.

Discussion

The most important clinical limitation of EPO treatment is the short half-life of the molecule, with the need for several administrations per week, which represents a disadvantage in pediatric patients under peritoneal dialysis.

During the last few years, research has been focused on producing longer-acting EPO analogs that retain the biological properties of endogenous EPO, but require less frequent dosing. Some pediatric trials have communicated the efficacy of darbepoetin in the correction of anemia at varying doses, routes, and frequencies of administration in peritoneal and hemodialysis patients. Darbepoetin alfa is a second-generation erythropoiesis-stimulating agent that contains two amino acid substitutions, providing greater metabolic stability and increasing the elimination half-life

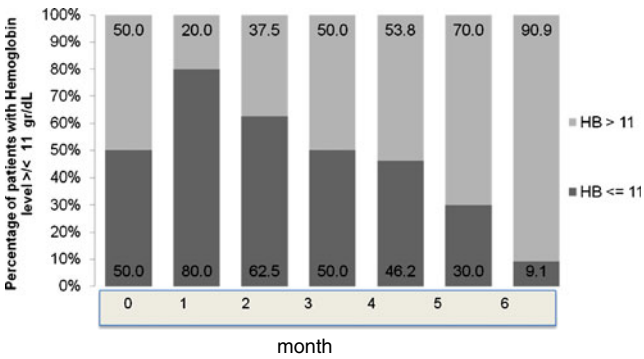

Fig. 2 Hemoglobin evolution: a dichotomic analysis with a cut-off level=11 g/dL

(25 h) compared with intravenous epoetin alfa (8.5 h). Studies have shown that darbepoetin alfa can be administered once weekly or once every other week. Warady and Ho evaluated the pharmacokinetic profile of darbepoetin in 120 pediatric patients with CKD stages 4 and 5; patients under hemodialysis or peritoneal dialysis therapy, or not yet receiving dialysis, were included. The mean half-life of subcutaneous darbepoetin alfa dose was 42.8 h, and 22.1 h after IV administration, approximately two- to four-fold longer than the half-life of epoetin allowing for less frequent dosing of darbepoetin in a clinical setting [3]. Some authors have proposed a "conversion index" (CI) to calculate darbepoetin dose according to the previous EPO dose [16]. The conversion index was defined by DePalo et al. as an epoietin weekly dose/200=NESP weekly dose. This CI derives from the knowledge that 200 IU of r-HuEPO contain the same peptide mass as 1 mg of NESP [16].

Despite the successful results of epoetin alfa and darbepoetin alfa, the management of anemia in dialysis patients is poised for further clinical advancement. The most recently introduced agent is the third-generation erythropoiesis-stimulating agent continuous erythropoiesis receptor activator, CERA. CERA's long duration of action is attributed to the addition of a large polymer chain into the EPO molecule, which confers to the molecule a longer elimination half-life of approximately 130 h.

The AMICUS Study [19] randomly assigned 181 adult dialysis patients to receive intravenous CERA once every 2 weeks vs epoetin three times weekly. An increase in Hb level>1 g/dL versus baseline, and Hb level >11 g/dL without blood transfusion during the 24-week follow-up period were the target variables. CERA initial dose was 0.40 μg/kg every 2 weeks. Both CERA and epoetin showed similar Hb response rates, 93.3% with CERA and 91.3% with epoetin. Mean change in Hb levels from baseline to the end of the correction period was 2.70 ±1.45 g/dL with CERA and 2.56 ±1.31 g/dL with epoetin. The authors did not find any difference in adverse events associated with both therapies, concluding that intravenous CERA was as safe and effective as epoetin for treating anemia in dialysis patients.

In the PROTOS Study [23], 572 adult dialysis patients were randomly assigned to receive regular epoetin, or subcutaneous CERA once monthly or twice monthly for 52 weeks. The starting CERA dose was based on the epoetin dosage received during the week preceding randomization. Mean Hb levels during the evaluation period for patients treated with CERA were within recommended ranges, 11.46 g/dL for once-monthly treatment and 11.70 for twice-monthly CERA. The results of this phase III study showed that switching directly from EPO to CERA once or twice a month was effective for maintaining Hb levels within the target range in this patient population.

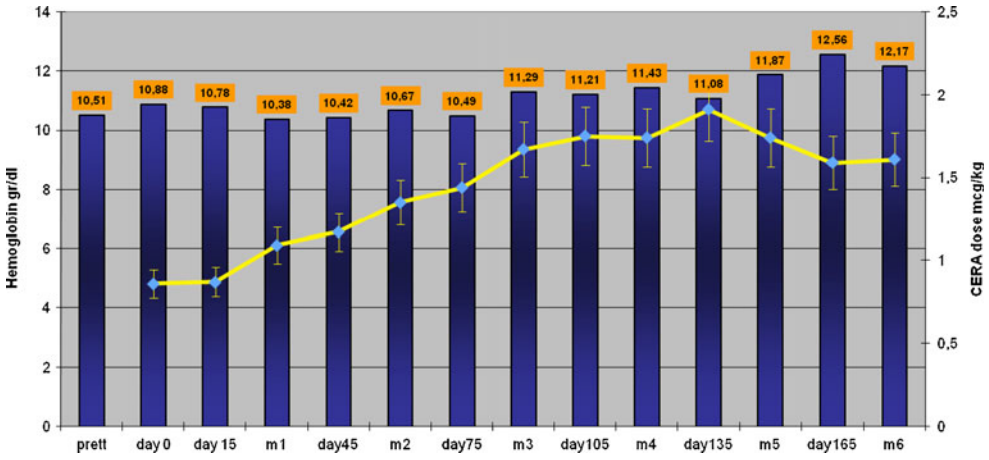

Fig. 3 Mircera dose vs hemoglobin levels in children under peritoneal dialysis

To date, no pediatric experiences have been communicated. In our study, the mean change in Hb levels from baseline to the end of the correction period was 1.32±0.76 (10.88±1.9 to 12.2±1.14 g/dL), reaching the primary endpoint at month 3 of treatment, with a statistically significant difference in Hb levels by month 4 of the treatment. Mircera was shown to be effective even in 4 patients who started the protocol with Hb<10 g/dL; those patients were included because they showed Hb values >10 g/dL 1 month before entering the study. Geary et al. [17], in a clinical study with darbepoetin, did not consider a minimum hemoglobin cut-off value as an inclusion criterion. As we did in this protocol, children who had at entry hemoglobin values from 8.1 g/dL were accepted for darbepoetin treatment.

Initial CERA dose was given according recommendations in adults [18–20], and subsequent adjustments were made according to pediatric experience with darbepoetin [17], because there are no available references regarding Mircera in children. However, hemoglobin levels slightly decreased to 10.49±1.28 g/dL during the first 2 months of the protocol, requiring an increase in CERA dose in order to reach target Hb levels. The same initial decrease in hemoglobin level was found by Carrera et al. in the PATRONUS Study [24]. The PATRONUS Study (com**P**Arator s**T**udy of CERA and darbep**O**etin alfa in patie**N**ts **U**ndergoing dialy**S**is) prospectively confirmed the efficacy and safety of monthly intravenous CERA vs darbepoetin alfa for the maintenance of hemoglobin concentrations in 490 adult hemodialysis patients. The dose was adjusted for an individual hemoglobin target of 11–13 g/dL, following KDOQI recommendation, as in our protocol. During the first weeks of treatment, the authors observed a decline in the median hemoglobin values in the two EPO groups, with a nadir of the median hemoglobin at 11.1 g/dL at week 14 for CERA, and 11.2 g/dL for darbepoetin alfa at week 16. In our patients, the mean hemoglobin value was 10.8 g/dL at baseline, decreasing to 10.4 g/dL at week 6 of therapy. After doses were adjusted, a smooth and sustained increase in hemoglobin levels was observed after the 3 month of treatment, reaching Hb levels between 11 and 12.5 g/dL during the follow-up period. According to this observation, the last 7 patients were started at higher doses, between 0.8 and 1.3 μg/kg, and a good response was observed without the initial hemoglobin decrease observed in the first patients. Mircera doses were prepared at the Mixing Center of the Pharmacy Service, and doses (syringes) were adjusted to round numbers, 10 μg, 20 μg, 30 μg, etc. That is a reason why initial doses were not always exactly the same. In another experiment, Geary et al. [17] treated their patients with an initial darbepoetin dose of 0.45 μg/kg/week, but darbepoetin was supplied in prefilled syringes containing 10, 20, 30, 40, 50, and 60 μg; therefore, the authors chose to adjust the dosing interval instead of the darbepoetin dose, in order to treat patients of different sizes. In the present protocol, we chose to modify the EPO dose instead the dosing interval.

In two CERA studies, the median time to response was 57 days in hemodialysis patients [19] compared with 31 days in epoetin alfa recipients, and 43 days in CKD patients not on dialysis [25] compared with 29 days in darbepoetin alfa recipients. In our children the time to response was longer, almost 90 days; however, we can hypothesize that it could be shorter if future studies consider starting CERA therapy at higher doses than we did in this protocol. Of note, the Hb level was higher than 13 g/dL in 5 out of 16 patients at the end of the treatment period, a value that has been shown in many studies in adults to represent a cardiovascular risk factor [26, 27]. The KDOQI recommendation for children clearly states that the desired hemoglobin level in pediatric dialysis and non-dialysis patients with CKD receiving ESA therapy should be within the range 11.0 to 12.0 g/dL, and should not be greater than 13.0 g/dL [5]. The high Hb levels observed in these patients suggest that Mircera could be scheduled once a month in some PD children.

At the beginning of the study the Mircera dosage was 0.86±0.33 μg/kg, reaching a dosage of 1.67±0.44 μg/kg at month 3 of the protocol. In a pediatric study with darbepoetin, the dosage was 0.45 μg/kg/week [17], while in another experiment in 7 hemodialyzed children, the authors concluded that the darbepoetin dose should be 0.25–0.75 mg/kg per week, following a conversion index as follows: epoetin alfa weekly dose/200=darbepoetin weekly dose [16]. Mircera phase III studies have been communicated by the Laboratory of origin. Four maintenance studies (BA 16739, BA 16740, BA 17283, and BA 17284) were performed on patients on dialysis receiving ESA [28]. Dose adjustments were based on phase II data and other ESA experiments. After 36 weeks of treatment (a 28-week dose titration period and an 8-week evaluation period), the authors concluded that for patients with a previous dose of EPO of less than 8,000 IU/week, the Mircera dose should be 60 μg every 2 weeks. These results can hardly be extrapolated to children on dialysis, because no recommendations have been made based on peptide mass, and all the data have been collected from adult studies. Our results show that, starting from a mean EPO dosage of 120 IU/kg/week, a final dosage of Mircera of 1.6 μg/kg/2 weeks was used. Therefore, 1.3 μg/kg/2 weeks (0.65 μg/kg/week) of Mircera corresponds to 100 IU/kg/week of EPO in this study.

Results should be interpreted with the assumption that this is a prospective study with a number of patients dropping out. There were 5 drop-outs before month 6, and 11 patients completed 6 months of treatment. Geary et al. [17] performed a protocol in 33 children (15 with chronic renal insufficiency, and 9 with HD, 9 with PD) to evaluate the efficacy and safety of darbepoetin. They had 10 drop-outs, 3 before 12 weeks and 7 after 12 weeks of follow-up. In that study, data were presented for a total of 30 patients at 12 weeks, and 23 children at 20 to 28 weeks. Both protocols experienced 30% drop-outs, which should be taken into account when analyzing the data presented.

With regard to adverse events, hypertension has often been associated with erythropoietic agents, and should be closely monitored when treating CRF children with ESA. Hypertension was observed by De Palo et al. [16] in 2 of the 7 children treated with darbepoetin when hemoglobin values were above 13.0 g/dL. They also reported thrombocytosis in 1 patient. In another pediatric study, Geary et al. [17] reported only 1 out of 13 serious adverse events (hypertension) possibly related to darbepoetin, while thrombocytosis was observed in 3 children. The AMICUS Study [19] showed a similar incidence of treatment-related adverse events in both treatment groups, CERA 14% vs epoetin 15%. Hypertension was observed in 19% of CERA-treated patients, vs 24% in the EPO group. In our study, we did not find any difference in adverse events associated with Mircera vs previous EPO therapy. Blood pressure percentiles between 25 and 75 were observed during the entire study, and no change in antihypertensive therapy was necessary. Thrombocytosis and thrombosis were not observed in this protocol and nor were any other adverse events. Although no quantitative measurement of pain associated with Mircera subcutaneous injection was performed, we did not observe any difference between EPO and Mircera with regard to discomfort according to patients' complaints.

Conclusion

To our knowledge, this is the first report on the administration of CERA to pediatric patients with CKD under peritoneal dialysis. Results suggest that Mircera® is an effective and safe therapy in maintaining hemoglobin levels after switching from classical EPO therapy when administered s.c. twice up to once-a-month in PD children. Doses required to reach target Hb levels were higher than published experiences in adult populations.

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