JPPT | Single-Center Retrospective Study

Clinical Experience of a Long-acting Pegylated Erythropoietin-Stimulating Agent in Pediatric Chronic Kidney Disease

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OBJECTIVE Management of anemia of chronic kidney disease (CKD) often includes subcutaneous or intravenous administration of erythropoietin-stimulating agents (ESAs). Mircera, a pegylated continuous erythropoietin receptor agonist, has a longer duration of action and requires less frequent administration than other ESAs. Pediatric experience with Mircera is limited. We retrospectively reviewed our long-term experience of Mircera in a national pediatric nephrology center.

METHODS Patients were identified via an electronic patient record database. Data collected included demographics (sex, age, etiology of CKD, CKD stage, dialysis modality), dosing information, and laboratory data—hemoglobin (Hb), parathormone (PTH), ferritin, hematinics prior to commencing Mircera and all subsequent values associated with dose adjustments.

RESULTS Seventy-seven patients aged 2 to 18 years, with CKD stages 2 to 5T had received at least 1 dose of Mircera, with 75 patients having sufficient data and a total of 1473 doses. No patients discontinued Mircera owing to adverse effects. One patient experienced a potential severe adverse drug reaction. Mircera was effective in improving or maintaining Hb ≥10.0 g/dL in most (58/75, 77.3%) patients. The median dose to achieve Hb ≥10.0 g/dL was 2.1 µg/kg/4 wk. Most doses (1039, 71.5%) were administered 4-weekly. The doses (161, 11.1%) that were administered 6-weekly remained efficacious. Thirty-two patients started Mircera with Hb <10.0 g/dL; 26 (81%) achieved Hb ≥10.0 g/dL within a median time of 4 months. Mircera was less effective if given every 8 weeks, or in the presence of hyperparathyroidism or hyperferritinemia.

CONCLUSION Mircera appears safe and effective in pediatric patients with CKD.

ABBREVIATIONS ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blockers; CKD, chronic kidney disease; DOLPHIN, Dose Finding Trial of Pediatrics on Hemodialysis in Nephrology; eGFR, estimated glomerular filtration rate; EPO, erythropoietin; ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; PTH, parathormone; TSAT, transferrin saturation

KEYWORDS anemia; dialysis; erythropoiesis-stimulating agent; hemoglobin; Mircera; renal insufficiency; chronic

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Introduction

Management of chronic kidney disease (CKD) includes prevention and treatment of anemia.[1] Anemia in CKD is multifactorial with a chief cause recognized to be absolute iron deficiency.[2] In children with CKD this can be due to limited enteral iron absorption, suboptimal iron intake, and frequent blood losses, associated with recurring venepuncture needs and hemodialysis circuit losses.[3] Functional iron deficiency, whereby iron stores are used in the erythropoiesis process by the bone marrow, and iron deficiency secondary to inflammation, whereby iron trafficking is reduced, may also contribute to anemia in CKD.[4] Insufficiency or dysregulation of erythropoietin (EPO) is another critical cause of anemia.[2] In health, renal EPO production is stimulated by reduced tissue oxygen saturation, promoting marrow hematopoiesis. In CKD, EPO production is impaired or the response blunted.[5] Further causes of anemia in CKD include overproduction of uremic toxins, which induce hemolysis, shortening the red blood cell lifespan; hyperparathyroidism; and nutritional deficiencies of vitamins B12 and C, folate, carnitine, and copper.[2,3]

Multiple guidelines highlight the importance of managing anemia of CKD.[5] Current UK guidance includes ensuring patients are iron-replete and alternative causes of anemia are excluded. Subsequent management

includes use of an erythropoiesis-stimulating agent (ESA), typically a recombinant human EPO.[1] The target hemoglobin (Hb) in UK guidance for children aged 2 to 18 years is 10.0 to 12.0 g/dL when receiving an ESA.[5] No specific recommendations are provided for initial dosing or formulation, instead suggesting these are tailored to individual patients.

ESA formulations include epoetin alfa and beta (short acting) requiring administration 2 to 3 times per week[6] or darbepoetin alfa (longer acting) requiring administration 1 to 2 weekly.[7] Formulations for pediatric use are limited. Subcutaneous administration is via prefilled syringes in a fixed range of doses,[6,7] which may not allow small dose increments by body weight. Subcutaneous administration is upsetting for many children, and alternatives to minimize dose frequency hold potential benefit.

Methoxypolyethylene glycol–epoetin beta, available commercially as Mircera (Roche Products Limited, Welwyn Garden City, England), is a continuous erythropoietin receptor activator, functioning as a long-acting ESA. The Mircera molecule is structurally similar to epoetin beta, with an added large water-soluble polyethylene glycol group.[8] Pegylation affects the pharmacokinetics of the conjugated protein. The polyethylene glycol moeity increases the molecular weight, reduces renal clearance, increases solubility, and impairs dissolution by antibodies and proteolytic enzymes.[9] For Mircera, the half-life is prolonged to approximately 130 hours after subcutaneous or intravenous administration, with a slower rate of receptor binding and enhanced erythropoietic activity.[10]

Mircera was licensed in Europe for the treatment of symptomatic anemia of CKD in adults in 2007. The recommended starting dose is 1.2 µg/kg/mo.[11] Safety and efficacy is confirmed in several series, including pre dialysis and post renal transplant.[12] A Cochrane systematic review in 2017 noted the paucity of pediatric data.[13] Case series in pediatric patients on peritoneal dialysis and post transplant were published prior to that review,[14,15] with only the DOLPHIN (Dose Finding Trial of Pediatrics on Hemodialysis in Nephrology) study in pediatric hemodialysis patients[16] subsequently. There are limited data available on the "real-world" use of Mircera in pediatric patients.

Table 1. Definitions Used to Determine Response to Mircera, Classified by Changes in Hemoglobin Concentration

Response	Hemoglobin Change
Over-response	Any Hb >13.0 g/dL
Response	Hb values ≥10.0 and ≤13.0 g/dL, when previous Hb value was <10.0 g/dL or >13.0 g/dL
Maintained response	2 consecutive Hb values between 10.0 and 13.0 g/dL with <10% decrease from 10.0 to 13.0 g/dL on the same dose
Poor response	2 consecutive Hb values between 10.0 and 13.0 g/dL with ≥10% decrease between values
No response	Hb was never ≥10.0 g/dL or was previously ≥10.0 g/dL and fell to <10.0 g/dL on treatment

Hb, hemoglobin

Our unit is the sole provider of pediatric dialysis and renal transplant in Scotland, serving a population of 5.45 million. All patients with significant CKD are reviewed by clinicians at this center. The commercial withdrawal of prefilled 1000-, 10,000-, and 20,000-unit multidose epoetin beta "pens" in 2010, plus encouraging early reports of Mircera use in children, prompted our institution to begin using Mircera for selected patients with CKD, on dialysis, and post transplant, starting in 2011. Our local guidance recommends a starting dose of 1.3 µg/kg/2 wk, based on the larger dosage reported in pediatric case series,[14,15] prior to establishing a 4-weekly maintenance regimen. We aimed to review our experience of Mircera use in our pediatric population, including adverse events leading to therapy discontinuation, and efficacy outside the context of a clinical trial.

Materials and Methods

An electronic patient database, Strathclyde Electronic Patient Record (SERPR, VitalPulse) captures all patients attending our center; this was used to identify patients prescribed and administered Mircera in the local renal clinic by qualified staff from January 1, 2011, to database lock on October 31, 2019. Additional clinical data were collected retrospectively using a second electronic database, Clinical Portal (V8, InterSystems). Demographic data included sex, CKD stage at first Mircera dose, CKD etiology (glomerular or non-glomerular), renal replacement modality (pre dialysis, hemodialysis, peritoneal dialysis, transplant), and previous ESA use. Laboratory data were collected prior to initiation of Mircera, nearest values corresponding to ongoing administration, and at therapy discontinuation; these were Hb, parathormone (PTH), estimated glomerular filtration rate (eGFR—using the bedside Schwartz equation),[17] ferritin, and iron status, and transferrin saturation (TSAT), serum iron. Rationale for discontinuation of therapy was collected. Missing data were annotated as not available and omitted from the analysis.

The primary outcome measure was efficacy of Mircera, defined as either resolution of anemia in patients with initial Hb <10.0 g/dL, or maintenance of adequate Hb in patients with initial Hb ≥10.0 g/dL. Table 1 provides the definitions of response used.

Secondary outcome measures included dose range, treatment duration, treatment discontinuation due to

adverse effects, and overtreatment—defined as no dose reduction occurring when Hb ≥ 13.0 g/dL.

Additional analyses included association of efficacy with hyperparathyroidism, defined as PTH ≥60 pmol/L[18] (9x the upper limit of normal on local reference ranges); eGFR (using the bedside Schwartz equation)[17]; etiology; hyperferritinemia; medication; renal replacement therapy; transplant status; and iron status. Hyperferritinemia was defined as ferritin >500 ng/mL and presumed to represent either an inflammatory state or reduced iron mobilization.[19] C-reactive protein and erythrocyte sedimentation rate were not routinely tested in these patients.

Iron status was assessed before Mircera onset, at every dose change, and at end of treatment, where data were available. Iron status was evaluated as serum iron ≥8 µmol/L, TSAT % ≥20%, ferritin ≥100 ng/mL.

If all 3 values were below the specified ranges, patients were classified as iron deplete; and if all 3 above, as iron replete. If 1 or 2 were low, they were classified as iron insufficient. If parameters were missing, patients were classified by using available data.

Analysis was performed with RStudio (2021). Continuous variables were reported as median and IQR. Categorical variables were described as counts and percentages. A Pearson chi-square test with Yates continuity correction was undertaken for comparison of ≥2 independent groups with categorical variables. A Wilcoxon rank sum test with continuity correction was performed for comparison of 2 independent groups with continuous and nonparametric variables. A Kruskal-Wallis test was performed for comparison of >2 independent groups with continuous and nonparametric variables, with a Dunn test with Bonferroni correction *post hoc* to allow for multiple comparisons. Kaplan-Meier curves were plotted to estimate time to event (Hb ≥10.0 g/dL). A p value <0.05 was considered significant.

Results

Seventy-seven patients were identified. Two patients were excluded with insufficient data, leaving 75 patients for analysis. The median age of the included patients was 12 years (2–18), with age following a bimodal distribution. Demographic data are summarized in Table 2. A total of 1473 doses of Mircera were administered, with 511 associated Hb values available—256 Hb values before, and 255 values after treatment and/or dose adjustment.

Thirty-two patients (43%) started Mircera for treatment of anemia with an initial Hb <10.0 g/dL. Twenty-two of 32 patients achieved Hb ≥10.0 g/dL (9/32 had at least 1 subsequent Hb ≥13.0 g/dL), with 8/22 requiring dose escalation. Six patients never achieved Hb ≥10.0 g/dL, and 4 patients did not maintain their initial response.

Forty-three patients (57%) had Hb ≥10.0 g/dL at onset and converted to Mircera as maintenance therapy. Thirty-four of 43 patients maintained their Hb at the initial dose, though 3 were classed as "poor response" with decrements in Hb >10%. Five patients required dose increases to maintain Hb ≥10.0 g/dL, which was effective. Mircera was discontinued for 4 patients when it failed to maintain Hb ≥10.0 g/dL. Of posttreatment doses with data available, 171/255 (67.1%) were associated with Hb ≥10.0 g/dL. Flowcharts of patient responses are shown in Figure 1 and the total number of Mircera doses administered for every patient in our cohort is presented in the Supplemental Figure (supplemental material, Supplemental Figure S1).

Reasons for Mircera discontinuation were transplant (18/75 [24%]), conversion to alternative ESA (21/75 [28%]), no longer required (23/75 [30.7%]), direct adverse events (nil), or death (nil). Thirteen patients were receiving Mircera at database lock. Fifty-eight of 75 (77.3%) had Hb ≥10.0 g/dL at treatment cessation. Of 17/75 patients with Hb <10.0 g/dL, 1 received a transplant, 11 patients were converted to an alternative ESA, and 3 were receiving Mircera at database lock.

One potential adverse drug reaction was noted—a patient developed flushing, drowsiness, and cyanosis upon intravenous bolus administration of the first dose of Mircera via a central venous catheter. The patient received high-flow oxygen and a 24-hour period of in-patient observation; no additional treatment was required. A second Mircera dose was administered subcutaneously 4 weeks later with no adverse effects. No other doses were administered intravenously in this cohort; all were subcutaneous.

Dosing. The initial dose administered was <1 µg/kg/4 wk in 5 patients (6.7%), 1 to 2 µg/kg/4 wk in 30 patients (40%), and >2 µg/kg/4 wk in 40 patients (53.3%). The median initial dose for all patients was 2.1 µg/kg/4 wk (1.5–2.5). The median dose to achieve Hb ≥10.0 g/dL was also 2.1 µg/kg/4 wk (1.3–3.3). Patients developing Hb ≥13.0 g/dL received a median dose of 2.5 µg/kg/4 wk (1.7–4.8).

The initial dose of Mircera for the ESA-converted cohort was calculated by using a conversion factor (supplemental material, Supplemental Table S1). Expectedly, the initial doses for ESA-converted patients were significantly larger than for ESA-naïve patients (p = 0.009), median doses being 2.3 µg/kg/4 wk (1.8–3.5) and 1.9 µg/kg/4 wk (1.3–2.2), respectively.

Similarly, the doses associated with Hb ≥10.0 g/dL were significantly different for ESA-naïve and ESA-converted patients (p = 0.012), with a median dose of 1.9 µg/kg/4 wk (1.2–2.9) versus 2.4 µg/kg/4 wk (1.5–4.1), respectively.

The median maintenance dose for all patients with Hb ≥10.0 g/dL was 1.8 µg/kg/4 wk (1.2–3.0). All administered doses with resulting Hb values are presented in Figure 2. To investigate the effect of Mircera on Hb change, the difference between Hb values before and after treatment was calculated for every documented

Table 2. Demographics of Included Patients

Total number of patients	**75**					
Male sex, n (%)	50 (66)					
Age at onset of Mircera, median (range), y	12 (2–18)					
Etiology of disease, n (%)	55 non-glomerular (73) 19 glomerular (25) 1 unknown (1)					
CKD stage*	2	3a	3b	4	5	5T
Mircera onset, n†	2	3	4	17	31	18‡
Mircera end, n†	/	3	5	7	24	36
RRT	No RRT		PD and/or HD		Transplant	
Mircera onset, n	26		32		17‡	
Mircera end, n	15		25		35	
Hb <10.0 g/dL at Mircera onset, n (%)	32/75 (42.3)					
Receiving alternative ESA at Mircera onset, n (%)	40/75 (53.3)					
Total patients achieving Hb ≥10.0 g/dL at treatment cessation, n (%)	58/75 (77.3)					
Changed to alternative ESA at Mircera end, n (%)	21/75 (28)					
Discontinuing owing to adverse events, n (%)	Nil					
Reported adverse events, n (%)	1/75 (1.3)					
Patients discontinuing owing to transplant, n (%)	18/75 (21.3)					

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ESA, erythropoietin-stimulating agent; Hb; hemoglobin; HD, hemodialysis; PD; peritoneal dialysis; RRT, renal replacement therapy

*CKD stages defined by using eGFR cutoffs as described.[17]
†CKD stage at Mircera onset and Mircera end was defined as the CKD stage of the patient at the start and end of Mircera treatment, respectively.
‡One transplant patient had graft failure and was undergoing PD, hence CKD5T having 18 patients, but "Transplant" having 17.

administered dose. Larger Mircera doses were found to correlate with greater positive changes in Hb, as illustrated by Figure 3. Further dosing information is presented in supplemental material, Supplemental Table S2.

At the time of therapy discontinuation, 7 patients (9.3%) were receiving <1 µg/kg/4 wk; 34 patients (45.3%), 1 to 2 µg/kg/4 wk; and 34 patients (45.3%), >2 µg/kg/4 wk. The median final dose was 1.9 µg/kg/4 wk (1.3–2.0).

Hemoglobin response groups were developed to associate individual dose responses, with results as follows:

Group 1: no improvement in Hb (median, −12%; −20 to −5.1) associated with a median dose of 1.8 µg/kg/4 wk (1.1–2.8);

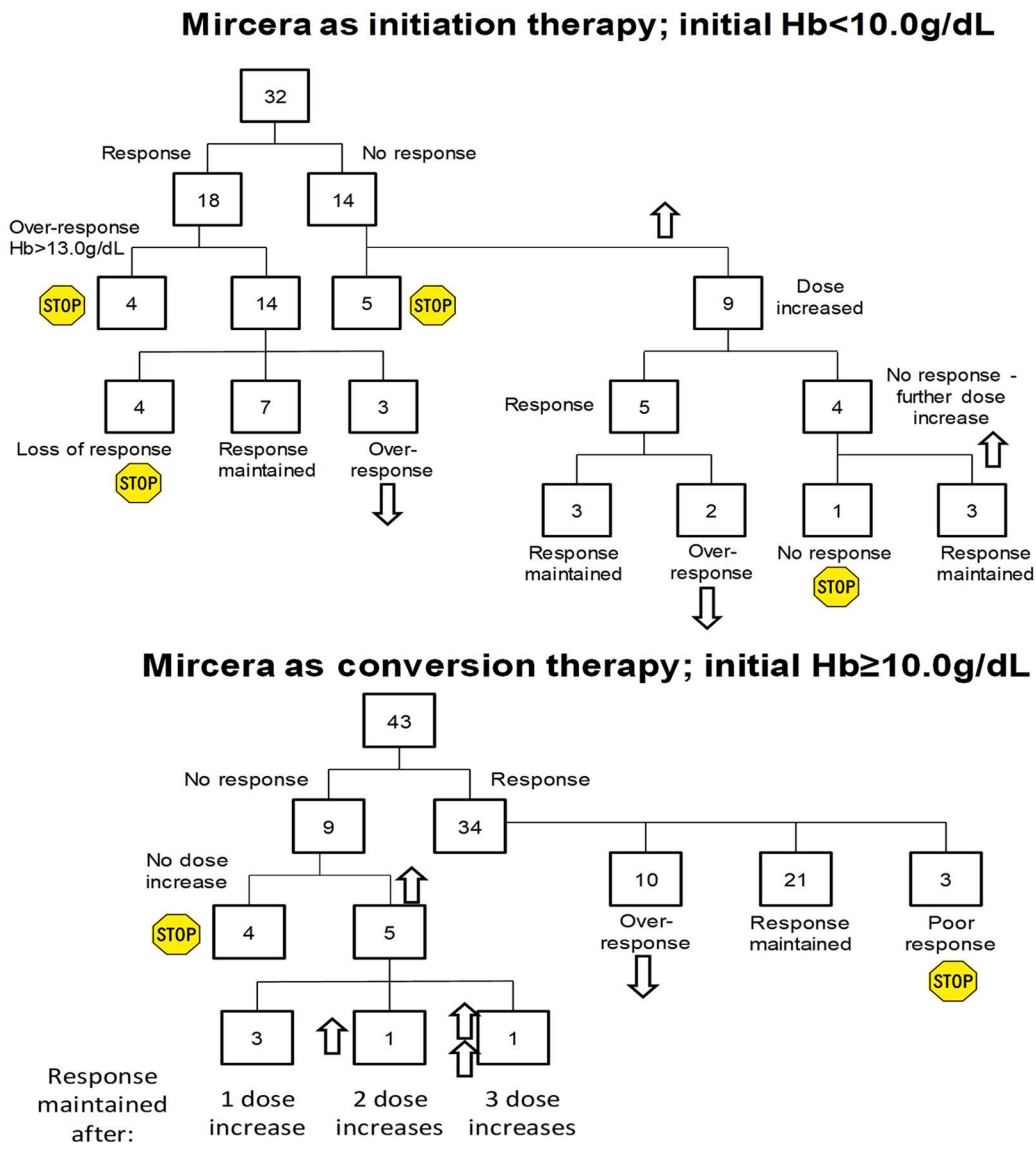
Group 2: >0% to 15% improvement in Hb (median Hb increase, 6.2%; 2–10.5) associated with a median dose of 2.2 µg/kg/4 wk (1.4–3.5);

Group 3: >15% improvement in Hb (median Hb increase, 31.1%; 21.9–42.8) associated with a median dose of 2.6 µg/kg/4 wk (1.7–3.8).

Of 1473 doses, 1453 had data available to classify a dose-frequency response; 988 doses (68%) were associated with Hb ≥10.0 g/dL. Dosing frequency ranged from 1 to 8 weeks, with 1039 doses (71.5%) administered 4-weekly; 180 doses (12.4%), every 1 to 2 weeks; 19 doses (1.3%), 3-weekly; 161 doses (11.1%), every 6 weeks; and 54 doses (5.0%), every 8 weeks. Hemoglobin was ≥10.0 g/dL post dose in 725 doses (69.8%) given 4-weekly, 105 doses (58.3%) given 1- to 2-weekly, 7 doses (36.8%) given 3-weekly, 137 doses (85.1%) given 6-weekly, and 14 doses (25.9%) given 8-weekly (supplemental material, Supplemental Table S3). No dose frequency was significantly associated with Hb ≥10.0 g/dL ($p = 0.360$), though a lower proportion of patients receiving Mircera 8-weekly had adequate Hb values.

Treatment Duration. The median treatment duration was 17 months (8.25–27.75), when patients who received only 1 to 2 doses were excluded and 13 months (6–25) when all patients were included in the analysis. The median time to achieve Hb ≥10.0 g/dL for the first time was 4 months (2–6), excluding patients who started Mircera with Hb ≥10.0 g/dL (n = 43) and those who never achieved Hb ≥10.0 g/dL (n = 6).

Figure 1. Diagrammatic response to Mircera treatment, according to initial Hb.



Hb, hemoglobin.

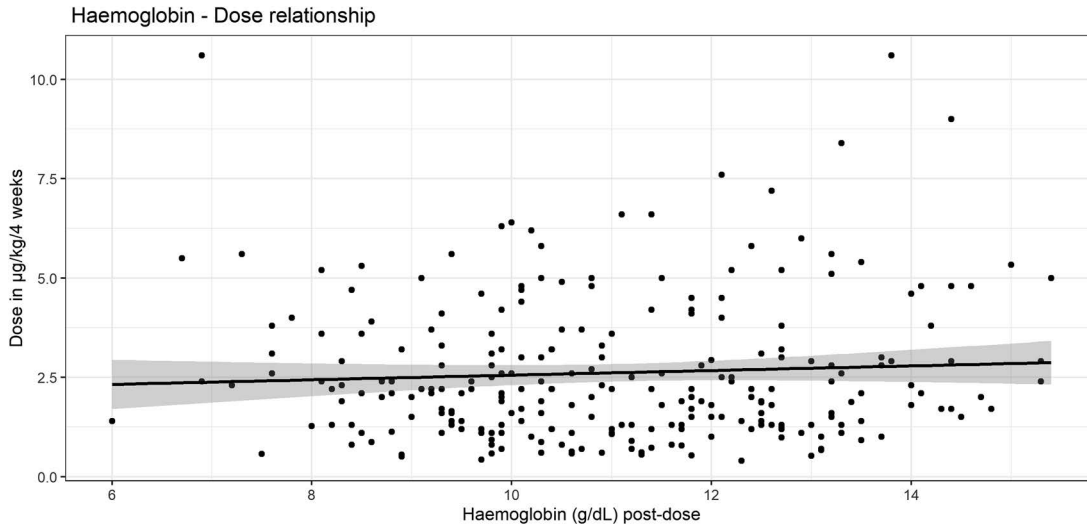
Longer treatment duration was associated with a reduction in the prevalence of anemia. Eighteen of 26 patients (69%) receiving Mircera for 1 to 8 months, 20/24 (83%) receiving Mircera for 9 to 21 months, and 20/25 (80%) receiving Mircera for >22 months achieved Hb ≥10.0 g/dL at the end of treatment.

The time to achieve the first Hb ≥10.0 g/dL per patient was analyzed by starting-dose group (Figure 4). No patients with a starting dose of ≤1 µg/kg/4 wk achieved Hb ≥10.0 g/dL without dose titrations. Patients receiving 1 to 1.9 and ≥3 µg/kg/4 wk required a median of 5 months, and patients receiving 2 to 2.9 µg/kg/4 wk required a median of 6 months to achieve Hb ≥10.0 g/dL.

Further analysis demonstrated that larger-dose groups (≥3 µg/kg/4 wk) achieved Hb ≥10.0 g/dL faster than smaller-dose groups (5 months versus 6, 8, and 11 months for 2–2.9, 1–1.9, and <1 µg/kg/4 wk, respectively).

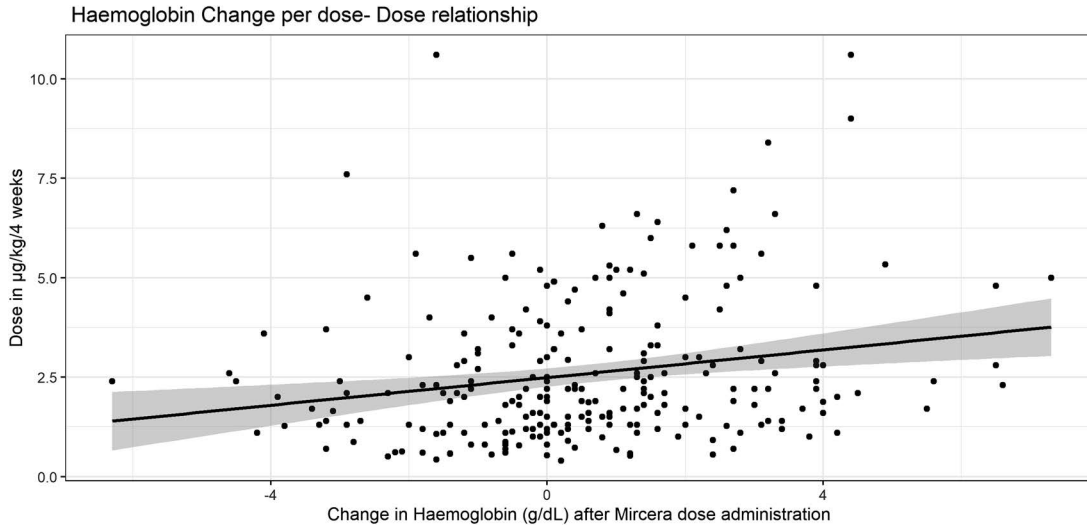
Patient Factors Affecting Response. The number of Mircera doses associated with Hb ≥10.0 g/dL were analyzed against sex, etiology, eGFR, dialysis, transplant status, iron status, PTH, ferritin, and use of angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) medications. Hyperparathyroidism ($p = 0.005$), "no transplant" status ($p = 0.03$), and hyperferritinemia ($p < 0.001$) were

Figure 2. All administered Mircera doses in µg/kg/4 wk with resulting Hb values. Linear trend-line and confidence region (default confidence level of 0.95) indicate variability in response to Mircera and the wide range of doses administered. Regression line equation: y = 2 + 0.0058x, R^2 = 0.0039, p = 0.32.



Hb, hemoglobin.

Figure 3. Effect of administered Mircera doses in µg/kg/4 wk on Hb change. The difference between the Hb value before and after treatment was calculated (Hb_{after} – Hb_{before} = Hb change) for every documented administered dose. Linear trend-line and confidence region (default confidence level of 0.95) indicate improved response to Mircera with increasing dose. Regression line equation: y = 2.5 + 0.017x, R^2 = 0.045, p = 0.0009.



Hb, hemoglobin.

associated with lower Hb values. Patients categorized as "iron deplete" had higher Hb values than the "iron replete" (p = 0.001) and "iron insufficient" (p = 0.009) groups. Further analysis showed that "iron deplete" patients overall received larger doses of Mircera than "iron replete" patients; however, this association was not statistically significant after Bonferroni adjustment ($p\ value_{unadj}$ = 0.021, $p\ value_{adj}$ = 0.065).

Patients not on dialysis (including patients who had undergone transplant) had a higher overall response rate than patients on dialysis, though only "hemodialysis" versus "no dialysis" reached significance (p = 0.003).

Patients with higher eGFR had a greater overall response rate, though only the comparison of CKD5 with CKD5T was significant (p = 0.029).

Comparison of ESA-Naïve and ESA-Converted Patients. Twenty-one patients converted from darbepoetin, and 19 patients converted from epoetin beta to Mircera. There was no difference (all p values not significant) between ESA-converted (n = 40) and ESA-naïve patients (n = 35) in etiology, dialysis status, eGFR, iron status, ferritin >500 ng/L, and PTH (supplemental material, Supplemental Table S4). Though median eGFR was similar for ESA-converted (22.4 mL/min/1.73 m^2) and ESA-naïve patients (18.3 mL/min/1.73 m^2), the range of function was narrower for the latter (9.2–59.9 mL/min/1.73 m^2 for ESA-converted versus 13.25 to 30.95 mL/min/1.73 m^2 for ESA-naïve). Only 1 ESA-naïve patient (1.3%) had ferritin ≥500 ng/mL in comparison to 6 ESA-converted patients (8%).

There was no difference in response between ESA-converted and ESA-naïve patients; ESA-converted patients had more values of Hb ≥13.0 g/dL (13/40) than ESA-naïve patients (3/35) (p = 0.012). There was no difference in Hb values between groups converted from darbepoetin compared with epoetin beta (p = 0.910).

Discussion

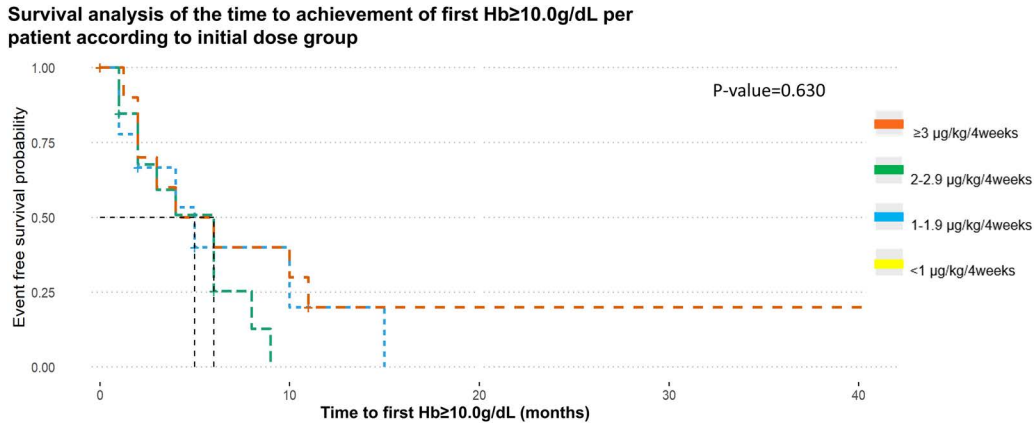
Mircera has been used with safety and efficacy in adult patients with CKD since 2007.[12] This cohort adds to the limited pediatric literature, describing the administration of over 1400 doses in children with CKD undergoing hemodialysis, peritoneal dialysis, or post renal transplant.

A German case series first reported use in pediatric patients, in 12 children aged 6 to 17 years, 3 to 9 years post renal transplant.[14] Five patients converted from darbepoetin, 7 were ESA-naive. Follow-up was at least 6 months per patient, over 18 months. Efficacy was seen more in ESA-naïve patients, with 1 ESA-converted patient requiring cessation of Mircera temporarily owing to high Hb. The median dose was 2.5 µg/kg/mo. No adverse effects were noted, in particular no hypertensive events.

A Chilean group reported on 16 pediatric patients aged 3 to 14 years receiving peritoneal dialysis[15] with administration of Mircera every 2 weeks at an initial dose of 0.5 µg/kg/2 wk. All patients were previously treated with recombinant human EPO. Eleven patients completed 6 months of treatment, with significantly improved Hb after 4 months. The mean final dose was 1.6 µg/kg/2 wk. No additional adverse effects, thrombotic events, or changes in blood pressure centiles were noted.

The DOLPHIN study[16] recruited 64 pediatric patients aged 5 to 17 years on maintenance hemodialysis from 28 centers in 10 countries. Eligible patients required Hb 10 to 12 g/dL and a stable ESA dose for 8 weeks preceding trial participation. Forty-seven patients completed a 20-week course of Mircera administered every 4 weeks, with 17 patients followed up until 73 weeks. Dose adjustments were made by Hb response. The final median dose was 2.3 µg/kg/4 wk. No novel adverse effects were seen. Forty-nine patients had at least 1 adverse effect, with 25 serious events in 16 patients, including hypertension, thrombosis, headache, and nasopharyngitis. One thrombotic episode required active treatment.

Figure 4. Time to achieve the first Hb ≥10.0 g/dL per patient according to starting-dose group. Patients starting with Hb ≥10.0 g/dL were not included in this graph because the event of interest (Hb ≥10.0 g/dL) has already happened (left censored). Patients who never achieved Hb ≥10.0 g/dL after treatment were annotated with a "+" sign on the graph (right censored). No patients with a starting dose of ≤1 µg/kg/4 wk achieved Hb ≥10.0 g/dL without dose adjustments. No dose group resulted in Hb ≥10.0 g/dL significantly faster (p = 0.630).



Hb, hemoglobin.

The SKIPPER study[20] (NH19708; NCT03552393), a phase II open-label, single-arm, multicenter study, recruited 40 participants aged 3 months to 17 years with a baseline Hb concentration of 10.0 to 12.0 g/dL. All participants had anemia due to CKD, 23 of whom were on dialysis, and all were switched from epoetin alfa or beta or darbepoetin to 4-weekly Mircera. Thirty-eight participants completed the 23-week core study period and 25 continued to the 24-week safety extension period. The mean change in Hb reported in this cohort was 0.48 g/dL, with 24/38 patients (63.2%) maintaining their Hb concentration within 10 to 12 g/dL, 19 (50%) maintaining their Hb within 1 g/dL from their baseline, and 18 (47.4%) maintaining their Hb within 10 to 12 g/dL and within 1 g/dL from their baseline. Notably, the starting doses administered in this study were larger than the final doses (median dose of 75 µg, week 1 versus 50 µg, week 17). No unexpected adverse drug reactions were observed.

Anemia of CKD is multifactorial; relative EPO resistance or EPO deficiency is compounded by other disease factors including secondary hyperparathyroidism and inflammatory states.[12] Our cohort demonstrated poorer response to Mircera in those patients with hyperparathyroidism, hyperferritinemia, and in more severe renal dysfunction. Though we noted an association between Mircera use and ACE inhibitor or ARB use, this was in a relatively small "real-world" cohort so there may have been other confounding clinical factors. Further work is required to ascertain whether this is a true association.

For the purposes of this study we evaluated iron status by using serum iron, ferritin, and TSAT, rather than only the serum ferritin and TSAT, as mentioned in the KDIGO 2012 guidelines.[21] TSAT is estimated by dividing serum iron by the total iron-binding capacity and as such iron availability may be overestimated if the total iron-binding capacity is reduced. Interestingly, a study reported that as CKD severity increases, the total iron-binding capacity decreases, overestimating the TSAT.[22] Indeed, a study demonstrated that patients with CKD and with normal TSAT and low serum iron are at risk of anemia.[23] Furthermore, serum iron is a useful clinical indicator because it can correlate with iron availability and usage in hemoglobin production.

Considerable patient-dose variation was seen in this cohort, not unusual in the '"real-world" setting. ESA-converted patients had a broader dose range than ESA-naïve patients, though in both patient groups the median initial dose, final dose, and doses required to achieve Hb ≥10.0 g/dL were larger than the product recommendation[11] but comparable to previous literature.[14–16] Specifically, our local guidance was developed by using dosage information reported in pediatric case series.[14,15] It recommends a starting dose of 1.3 µg/kg/2 wk, almost double the starting dose recommended by the product recommendation[11] (0.6 µg/kg/2 wk or 1.2 µg/kg/4 wk). Nonetheless, this product recommendation is only applicable to an adult population and states that Mircera is not recommended in children owing to lack of safety and efficacy data.[11]

Our local practice is to commence a larger dose to achieve efficacy, then wean to a maintenance dose—this mandates regular Hb monitoring to avoid overtreatment. We suggest an initial dose of 2 µg/kg/4 wk for ESA-naïve patients, then adjustment within the range of 1 to 2 µg/kg/4 wk maintenance dosing, according to Hb. ESA-converted patients may initially require a larger dose, determined by the conversion factor. If after ≥3 doses the Hb has failed to reach 10.0 g/dL, and a >15% Hb increase is desired, the dose can be escalated safely to 2.6 µg/kg/4 wk.

Dosing on both a 4-weekly and 6-weekly schedule was effective—the latter could be considered for stable patients as an alternative to dose reduction, because this was associated with a reduced incidence of overtreatment, fewer injections, and lower costs. However, an 8-weekly schedule was associated with a nonsignificant reduction in response, and this is not recommended. In our cohort, most doses were administered 4-weekly; however, the dosing frequency ranged from 1 to 8 weeks. This reflects not only the fortnightly starting regimen of our local guidance prior to establishing a 4-weekly maintenance regimen, but also the "real-world" practicalities of administered Mircera in the clinic, whereby availability of appointments is required to align with the availability of the carers and also the desired administration frequency.

The single adverse event in our cohort was associated with intravenous bolus administration of Mircera, which may have precipitated the event, that is, a vasovagal response to the sensation of intravenous delivery, rather than actual drug. Following this adverse event, our center elected not to administer any further doses intravenously, as the subcutaneous route appeared safe and effective. No treatment discontinuation occurred owing to safety concerns or intolerable adverse effects. This cohort does not identify any new concerns for Mircera use in children.

Limitations of this study include retrospective data collection over a decade of clinical practice, though there have not been significant changes in the management of anemia of CKD in children in our center over that time. Dose adjustments and administration frequencies were decided by practicing clinicians rather than by protocol, which partly explains the higher proportion of children with higher Hb values above target without dose reduction than in other reports. Ineffective doses may also not have been incremented as quickly as in clinical trials. Furthermore, biochemical markers such as C-reactive protein and serum calcium concentrations were not routinely recorded and thus interpreting data on inflammation and hyperparathyroidism is

limited. Ferritin was used as a surrogate for inflammation; however, a high ferritin status can also indicate iron overload. Moreover, the "poor response" definition used to classify response to treatment does not differentiate between intended therapeutic reductions in Hb (e.g., 13.0 g/dL–12.0 g/dL) and a true "poor response." Notably, in our center efforts were made to reduce the number of unnecessary venepunctures in children, thus even though 1473 Mircera doses were administered, there were only 511 Hb values available for analysis. These factors could cause an underestimation or overestimation of Mircera efficacy in this population. Finally, no child had a hypertensive crisis following administration of Mircera, but hypertension is a common finding at all stages of CKD, and a contributory element of Mircera cannot be excluded.

Conclusions

Mircera appears safe and effective in children aged 2 to 18 years. A starting dose of 2 µg/kg/4 wk is well tolerated, with dose adjustment to 1 to 2 µg/kg/4 wk for maintenance, according to Hb response. Our data demonstrated that a median treatment duration of 4 months was required for the most appropriate (resulting in Hb ≥10.0 g/dL) Mircera dose to be established. Therefore, we recommend Mircera to be continued for 4 months, while adjusting the dose to response as needed, before declaring treatment to be unsuccessful. Dose frequency should be initially 4-weekly but may be extended to 6-weekly in stable patients as an alternative to dose reduction without loss of efficacy. The adverse effect profile of Mircera in pediatric patients in a "real-world" setting remains encouraging.

Article Information

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References

1. National Institute for Health and Care Excellence. Chronic Kidney Disease: Assessment and Management. 2021. Accessed May 13, 2022. https://www.nice.org.uk/guidance/ng203/chapter/Recommendations
2. Atkinson MA, Warady BA. Anemia in chronic kidney disease. *Pediatr Nephrol*. 2018;33(2):227–238.
3. Greenbaum LA. Anemia in children with chronic kidney disease. *Adv Chronic Kidney Dis*. 2005;12(4):385–396.
4. Atkinson MA, Furth SL. Anemia in children with chronic kidney disease. *Nat Rev Nephrol*. 2011;7(11):635–641.
5. Mikhail A, Brown C, Williams JA, et al. Renal association clinical practice guideline on Anaemia of Chronic Kidney Disease. *BMC Nephrol*. 2017;18(1):345.
6. Martindale. Epoetins. 2022. Accessed May 13, 2022. https://www-medicinescomplete-com.knowledge.idm.oclc.org/#/content/martindale/16635-r?hspl=epoetins.
7. Martindale. Darbepoetin alfa. 2022. Accessed May 13, 2022. https://www-medicinescomplete-com.knowledge.idm.oclc.org/#/content/martindale/20270-f
8. European Medicines Agency. European public assessment report : MIRCERA (scientific discussion). 2007. Accessed May 3, 2022. https://www.ema.europa.eu/en/documents/scientific-discussion/mircera-epar-scientific-discussion_en.pdf
9. Biochempeg. PEGylation of therapeutic proteins: development and challenge. 2020. Accessed May 13, 2022. https://www.biochempeg.com/article/90.html
10. Macdougall IC, Robson R, Opatrna S, et al. Pharmacokinetics and pharmacodynamics of intravenous and subcutaneous continuous erythropoietin receptor activator (C.E.R.A.) in patients with chronic kidney disease. *Clin J Am Soc Nephrol*. 2006;1(6):1211–1215.
11. Roche. Mircera solution for injection in pre-filled syringe. 2021. Accessed May 13, 2022. https://www.medicines.org.uk/emc/medicine/19960
12. Frimat L, Mariat C, Landais P, et al. Anaemia management with C.E.R.A. in routine clinical practice: OCEANE (CohorteMircera patients non-dialysés), a national, multicenter, longitudinal, observational prospective study, in patients with chronic kidney disease not on dialysis. *BMJ Open*. 2013;3(3):e001888.
13. Saglimbene VM, Palmer SC, Ruospo M, et al. Continuous erythropoiesis receptor activator (CERA) for the anaemia of chronic kidney disease. *Cochrane Database Syst Rev*. 2017;8:CD009904.
14. Wedekin M, Ehrich JHH, Pape L. Effective treatment of anemia in pediatric kidney transplant recipients with

methoxy polyethylene glycol-epoetin beta. *Pediatr Transplant*. 2011;15(3):329–333.
15. Cano F, Alarcon C, Azocar M, et al. Continuous EPO receptor activator therapy of anemia in children under peritoneal dialysis. *Pediatr Nephrol*. 2011;26(8): 1303–1310.
16. Fischbach M, Wühl E, Reigner SCM, et al. Efficacy and long-term safety of C.E.R.A. maintenance in pediatric hemodialysis patients with anemia of CKD. *Clin J Am Soc Nephrol*. 2018;13(1):81–90.
17. Schwartz GJ, Work DF. Measurement and estimation of GFR in children and adolescents. *Clin J Am Soc Nephrol*. 2009;4(11):1832-1843.
18. Eknoyan G, Levin A, Levin NW. Bone metabolism and disease in chronic kidney disease. *Am J Kidney Dis*. 2003;42(Suppl3):1–201.
19. Peyrin-Biroulet L, Williet N, Cacoub P. Guidelines on the diagnosis and treatment of iron deficiency across indications: a systematic review. *Am J Clin Nutr*. 2015;102(6):1585–1594.
20. Warady B, Meyer Reigner S, Tirodkar C, et al. FC037: A study to ascertain the optimum starting dose of subcutaneous (SC) C.E.R.A. for maintenance treatment of anemia in pediatric patients with chronic kidney disease (CKD) on dialysis or not yet on dialysis. *Nephrol Dial Transplant*. 2022;37(Suppl3): i803–i806.
21. Kidney Disease Improving Global Outcomes. Kidney Disease Improving Global Outcomes Clinical Practice Guideline for Anemia in Chronic Kidney Disease. Kidney International Supplements. 2012. Accessed July 8, 2022. https://kdigo.org/wp-content/uploads/2016/10/KDIGO-2012-Anemia-Guideline-English.pdf
22. Besarab A, Drueke TB. The problem with transferrin saturation as an indicator of iron 'sufficiency' in chronic kidney disease. *Nephrol Dial Transplant*. 2021;36(8): 1377–1383.
23. Yu P-H, Lin M-Y, Chiu Y-W, et al. Low serum iron is associated with anemia in CKD stage 1–4 patients with normal transferrin saturations. *Sci Rep*. 2021;11(1):8343.