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USE OF DARBEPOETIN ALFA (ARANESP®) FOR ANEMIA TREATMENT IN CHILDREN WITH CHRONIC KIDNEY DISEASE – CLINICAL EXPERIENCE OF BULGARIAN PEDIATRIC GROUP

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ABSTRACT

Darbepoetin alfa (DA) is indicated for treatment of symptomatic anemia related to chronic kidney disease (CKD) in adult and pediatric patients. In comparison with the recombinant human erythropoietin (rHuEpo), darbepoetin alfa has two additional carbohydrates containing sialic acid which prolong its half-life and enhance its biological activity *in vivo*. Herein, our clinical experience of using darbepoetin alfa (s.c.) for treatment of anemia in seven pediatric non-dialysis patients is presented. Subjects, aged 3-16 years were receiving (DA) for the period of 5 to 34 months to achieve and maintain hemoglobin levels between 100 and 120 g/l. Our secondary purpose was to establish whether the use of DA in children would reduce the frequency of painful injections, when administered subcutaneously, and improve the compliance of treatment. The early response of darbepoetin therapy was hemoglobin levels between 107 and 124 g/l. The subcutaneous administration of DA resulted in 2 dose corrections and showed that 86% of subjects achieved Hb level between 100 and 120 g/l.

Keywords: Darbepoetin alfa, Anemia, Chronic kidney disease, Pediatrics,

INTRODUCTION

Human erythropoietin (EPO) is an endogenous glycoprotein hormone that is the primary regulator of erythropoiesis through specific interaction with the erythropoietin receptor on the erythroid progenitor cells in the bone marrow. The production of erythropoietin primarily occurs in and is regulated by the kidney in response to changes in tissue oxygenation. Production of endogenous erythropoietin is impaired in patients with chronic renal failure and the primary cause of their anaemia is due to erythropoietin deficiency [1, 2]. During the past decade, the use of recombinant human EPO (r-HuEPO) has been shown to be a successful treatment of anemia in this patient population [2, 3, 4, 5, 6].

Darbepoetin alfa stimulates erythropoiesis by the same mechanism as the endogenous EPO. The chemical composition of darbepoetin alfa includes five N-linked carbohydrate chains whereas the endogenous hormone and r-HuEPOs have three. The additional sugar residues are molecularly indistinct from those on the endogenous hormone. Due to its increased carbohydrate content darbepoetin alfa has a longer terminal half-life than r-HuEPO and consequently a greater *in vivo* activity. Despite these molecular changes, darbepoetin alfa retains a very narrow specificity for the erythropoietin receptor [7, 8].

It is well established that anaemia symptoms and sequelae vary with age, gender, and overall burden of disease. Aranesp can be administered either subcutaneously or intravenously targeting haemoglobin level not greater than 12 g/dl (7.5 mmol/l). In order to avoid the puncture of peripheral veins, subcutaneous use is preferable in patients who are not receiving haemodialysis. Haemoglobin variability should be addressed through dose management, with consideration for the haemoglobin target range of 10 g/dl to 12 g/dl [7, 9].

There are no available data on the treatment of pediatric patients younger than 1 year of age. Following the prescribing information, in children e" 11 years, not on dialysis, an initial dose of 0.75 ìg/kg may be administered subcutaneously as a single injection once every two weeks. The change of hemoglobin level has to be closely monitored and dose modifications by approximately 25% should be considered. The haemoglobin should be measured every one or two weeks until establishment of a stable level.

Data from pharmacokinetic analyses confirm the prolonged half-life of darbepoetin compared with EPO in children [10, 11]. Therefore, it is expected that less frequent administration will be required for children prescribed darbepoetin alfa and better compliance will be achieved. Preliminary data from a small group of children on hemodialysis suggest that darbepoetin is efficacious [7, 8, 9].

The objective of this paper is to present the clinical experience of using darbepoetin alfa for anemia treatment in children with CKD in Bulgaria, in accordance with product label (SmPC) and individual patient characteristics.

PATIENTS AND METHODS

Seven children (4 male and 3 female, age range from 3 to 16 years) with chronic renal failure have been treated with darbepoetin alfa for a period of 5 to 34 months. All patients were clinically stable children with CKD and mean baseline hemoglobin levels below 125 g/l. Children with body weight below 25 kg were not treated with darbepoetin in order to ensure precise dosing using the smallest available unidose syringe containing 20ìg of darbepoetin. None of the patients was treated with hemodialysis or peritoneal dialysis before darbepoetin initiation. The dose of darbepoetin was increased by 25-50% according to the prescribing information, when the hemoglobin level was not as high as expected.

Patients with prior erythropoetin use had hemoglobin levels at entry 122 - 126 g/l. For recombinant human EPO (rHuEPO) naïve patients, the hemoglobin levels at start were between 78 and 129 g/l. Iron deficient patients were included with transferrin saturation under 20 at baseline. The starting dose was 0.9 µg/ kg/ 2 weeks (based on data provided by American Corp that this dose was an estimated equivalent to rHuEPO 100 U/kg/week). In Bulgaria, darbepoetin is supplied in prefilled syringes containing 20, 40, 60, and 80 µg. Adjustment of dosing interval was performed in order to provide the correct dose for patients of different weight. The primary outcome measure was hemoglobin response within a target range of 100-120 g/l.

RESULTS

Patient disposition

All seven patients (M:F 4:3) had chronic kidney disease, including kidney polycystosis, cystic kidney or nephritic syndrome. Treatment with darbepoetin alfa was initiated at a different disease stage for each patient. Two patients were previously treated with another ESA (Neo Recormon) in the dosage of 2000UI/week and currently converted to darbepoetin at the concentration of 1 × 40 µg/ month. These two patients represent the group of r-HuEPO-switched patients (Fig. 1 A, B) and the rest 5 patients compose the group of r-HuEPO-naïve patients (Fig. 2 A-E). The groups were not comparable since the patients from the r-HuEPO-switched group were younger and respectively had lower height and weight (Tabl. 1). All patients received subcutaneous injections of darbepoetin alfa.

Fig. 1. Hemoglobin changes in r-HuEPO-switched patients (n = 2) treated with Aranesp

fig 1A.

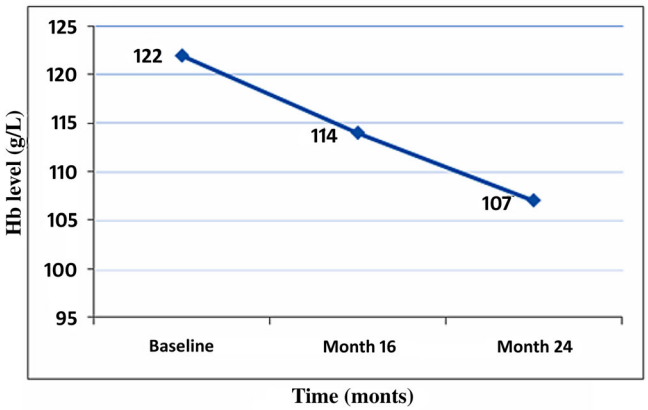
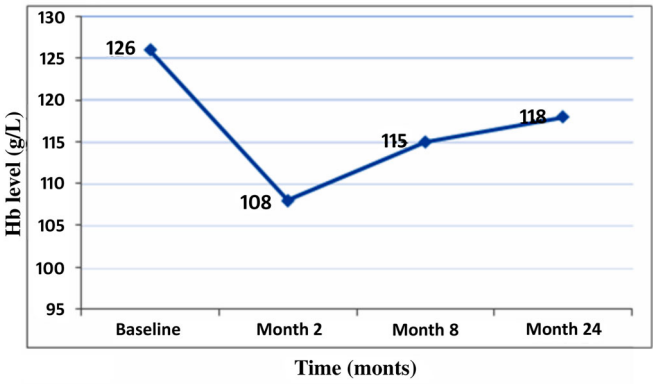


fig 1B.



Hemoglobin values are presented in g/l as measured at the respective time points of the treatment period. **A: patient 1.** Hemoglobin was measured at month 16 and month 24. Treatment dose of this patient is 1 × 40 µg/ month; **B: patient 2.** Hemoglobin was measured at month 2, 8 and 24. Aranesp dose at initiation was 1 × 40 µg/ month. The treatment dose was changed to 1 × 60 µg/ month at month 2.

Fig. 2. Hemoglobin changes in r-HuEPO-naïve patients (n = 5) treated with Aranesp

fig 2A.

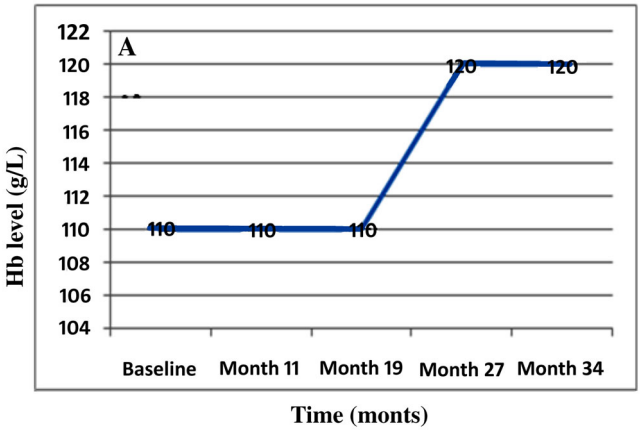


fig 2B.

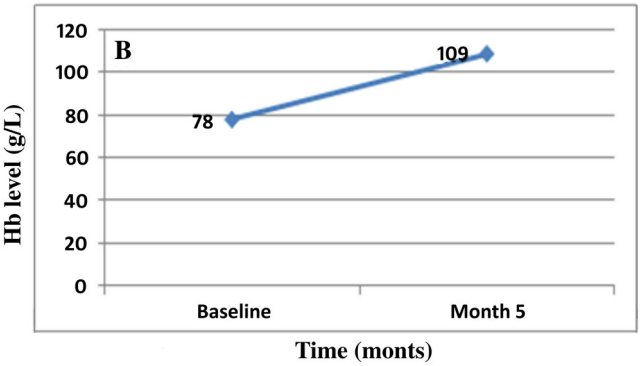


fig 2C.

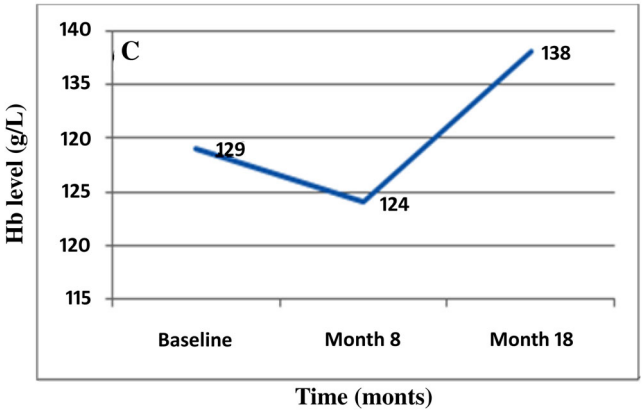


Fig 2D.

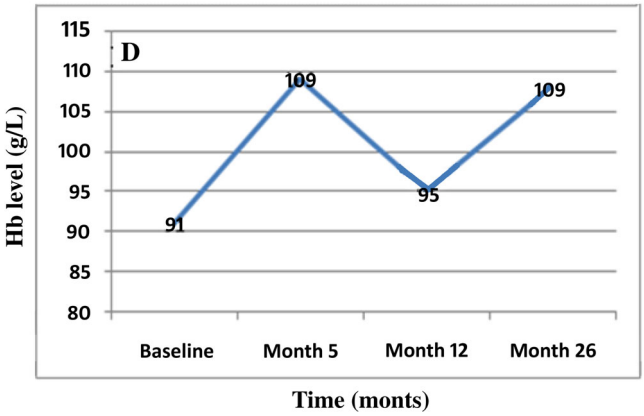
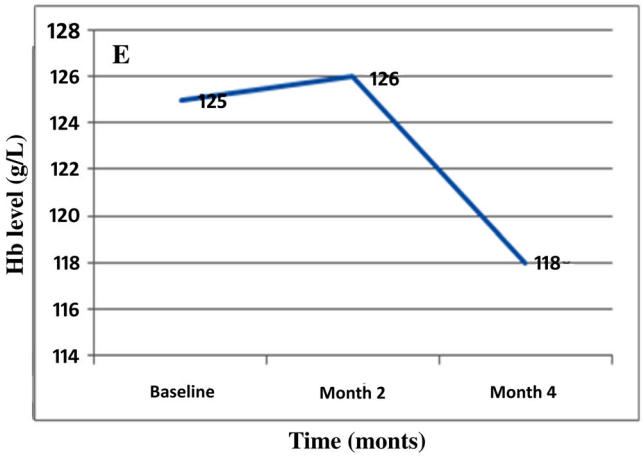


Fig 2E.



Hemoglobin values are presented in g/l as measured at the respective time points of the treatment period for each patient. **A: Patient 1**. Initial treatment dose was 1 × 60 µg/month and changed to 2 x 40 µg/month at month 19; **B: Patient 2**. Dose of 1 × 10 µg/10days was used for the whole analysed treatment period; **C: Patient 3**. Dose of 2 × 40 µg/month with no adjustments; **D: Patient 4**. Dose of 2 × 20 µg/month with no adjustments; **E: Patient 5**. Dose of 2 × 40 µg/month with no adjustments.

Table 1. Demographic and baseline characteristics of patients (n=7)

Characteristics	Naive (n = 5)	Switched (n = 2)	Total (n = 7)
Gender (male/female)	3/2	1/1	5/3
Age (years)	10.7 ± 4.3	5.8 ± 3.2	10.1 ± 5.0
Weight (kg)	36.5 ± 21.6	17.2 ± 4.5	31.7 ± 20.4
Height (cm)	134.3 ± 26.6	102.0 ± 11.3	126.3 ± 29.1
Dialysis, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)
Hemoglobin, *n*Hbd≤11 g/dl	4 (50)	0 (0.0)	4 (50%)
T-sat, mean ± SD	25.5 ± 16.5	16.4 ± 4.0	23.2 ± 15.9

Naive – patients not previously treated with r-HuEPO
Switched – patients previously treated with r-HuEPO (Neo Recormon)
Values expressed as mean ± standard deviation

Dosage of darbepoetin

Considering the weight of each individual patient, treatment doses were calculated accordingly. The mean dose of darbepoetin alfa that was used for treatment of all patients was 0.724 µg/kg/2 weeks or 1.45 µg/kg/month which is in accordance with the prescribing information of the product. The two patients assigned to the HuEPO-switched group started darbepoetin treatment at the dose of 1 × 40 µg/month. The mean baseline Hb level for that group is 124 g/L due to their previous ESA treatment. After darbepoetin initiation for patient 2, a rapid decrease in the Hb level at month 2 was observed and the treatment dose was thereafter increased to 1 × 60 µg/month (Fig. 1B). The same trend, although towards the end of the observation period (month 24), of Hb drop was observed for patient 1 from this group and the same dose increase was considered for correcting the Hb level. The mean baseline Hb level for the group of HuEPO-naïve patients was 107 g/L. Patient 1 from this group started darbepoetin treatment at the dose of 1 × 60 µg/month, which was changed to 2 × 40 µg/month at month 19 due to lack of response for the initial period. Patient 2 from that group was initiated at the dose of 1 × 10 µg/10 days whereas patients 3, 5 and patient 4 were treated with darbepoetin at doses of 2 × 40 µg/month and 2 × 20 µg/month, respectively with no dose adjustments (Fig. 2 A-E).

Dosing intervals

Depending on patients' availability for regular check-ups, the Hb levels of each patient has been monitored at different time intervals and different interim Hb measurements were performed. In this regard, the patients from r-HuEPO-switched group have been monitored for 24 months and the patients from HuEPO-naïve group – for 4 to 34 months, respectively (Figs 1, 2).

Treatment response to darbepoetin alfa

Among all treated patients, 86% achieved the targeted Hb level of higher or equal of 118 g/l. From the group of HuEPO-switched patients, patient 2 showed a clear trend of stabilization of Hb level above 115g/l, reaching 118 g/l at month 24 (Fig. 1B). Patient 1 from that group had a gradual Hb decrease ending with 107 g/l at month 24 (Fig. 1A). A slight dose increase of darbepoetin for that patient is to be considered. All the subjects assigned to the group of HuEPO-naïve patients also showed different responses to darbepoetin alfa treatment. The highest treatment effect was demonstrated in patient 1 from that group. The Hb levels of this patient increased from 110 g/l to 120 g/ll (with the dose increase to 2 × 40 μg/month) and were stabilized at that level for 15 months (Fig. 2A). Patient 2 had a very short time of treatment observation, 5 months. However, for that period there was a clear trend of increase of the Hb level as compared with the baseline measurement (Fig. 2B). There was a fluctuation in the Hb levels of patient 3 that led to a gradual increase up to 138 g/l at month 18 (Fig. 2C). No further measurements have been performed thereafter due to the lost of that patient for follow-up. A similar picture was observed for patient 4 – fluctuating Hb levels that reach 108 g/l at month 26. Still, it was noted that this patient was well responding to the treatment by increasing the Hb level after each darbepoetin administration (Fig. 2D). The last patient from this group was also monitored for a very short period of time (only 4 months). Despite this, after three drug applications the level of Hb was normalized to 118 g/l (Fig. 2E).

Safety

Darbepoetin alfa treatment was generally well accepted by all patients. No serious adverse event was recorded. Side effects as uncontrolled hypertension or asymptomatic thrombocytosis were not reported by the patients. Four of the children had mild hypertension as a part of the clinic of chronic renal failure. All side effects are in accordance with the described events in the summary of product characteristics of Aranesp [7].

DISCUSSION

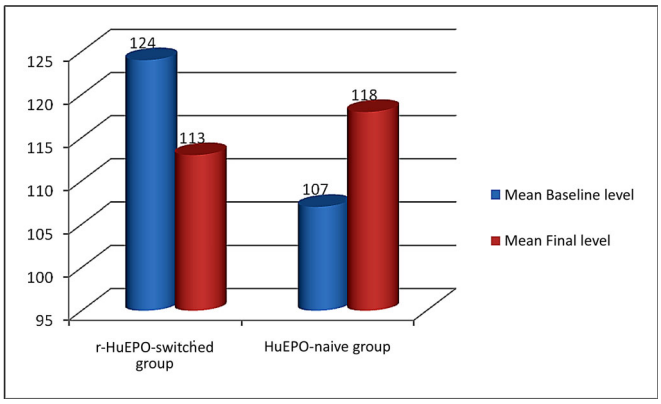
A limited number of published data on the clinical application of darbepoetin alfa in pediatric population is available. However, all the reported clinical data confirm that darbepoetin effectively treat anemia in children with CKD which may be related to the possibility of dose adjustments and decrease of dosing intervals [12-15]. The initial weekly paediatric dose of Aranesp (ìg/week) can be determined by dividing the total weekly dose of r-HuEPO (IU/week) by 240. The initial every other week dose of Aranesp (ìg/every other week) can be determined by dividing the total cumulative dose of r-HuEPO administered over a two-week period by 240. When substituting r-HuEPO with darbepoetin the haemoglobin should be monitored every one or two weeks and the same route of administration should be used [7]. Due to individual variability, titration to optimal therapeutic doses is expected for individual patients.

A recent study by De Palo et al reported that intravenous darbepoetin successfully controlled anemia in 7 children on hemodialysis [12]. Another paper by Geary et al. [16] confirmed and extended these results to children with chronic renal insufficiency and on peritoneal dialysis where the drug was administered subcutaneously. In addition, Andre J-L and colleagues [17] reported that darbepoetin effectively maintained the Hb levels in children, aged 11-18 years, with CRF at extended dosing intervals. In a multicenter prospective study in Japan, darbepoetin was investigated for treatment of anemia in children (1-18 years) undergoing peritoneal dialysis after switching from another ESA. Authors showed that the target Hb concentration (11- d" 13 g/dL) was achieved in 88% of the patients and 60% maintained the target value until study completion [18].

Our study adds additional data supporting these findings. Moreover, all patients were taking the medication less often than once every week which is another benefit of using this treatment. In adults, it has been shown that darbepoetin is effective if administered every 4 weeks [19]. In the present study, 2 children who received injections on a q 28 -day schedule seemed to respond as well as the rest, however, further study of this extended dosing interval in children is required.

Both treatment groups (r-HuEPO switched and naïve patients) responded well to the administration of darbepoetin alfa. In the group of switched patients, a dose adjustment has to be considered for patient 1 (Fig. 1A) as well as monitoring the Hb levels in closer intervals in order to achieve Hb level above 110 g/l. This is also relevant for some patients in the r-HuEPO naïve group, i.e. patients 2 and 3 (Fig. 2 B, C) where some dose changes may be considered as well as asking the parents to be more responsible for the treatment and to bring the children for more regular checking and follow-up. The final Hb levels were maintained within the target Hb value of 100-120 g/l for 86% of the patients (Fig. 3).

Fig. 3. Change of Hb levels after treatment with Aranesp in the two treatment groups



Both treatment groups (r-HuEPO switched and naïve patients) responded well to the administration of darbepoetin alfa. Hemoglobin levels are presented as mean values of the baseline and final point measurements for each group, respectively. Due to the low number of patients, statistical analysis and significance of the results could not be claimed. The final Hb levels were maintained within the target Hb value of 100-120 g/l.

Darbepoetin alfa was well tolerated by all treated patients. The only observed side effect was pain at the injected site, which was not exceeding the pain associated with the injection of other recombinant human EPOs. No adverse effects as worsening of hypertension were documented in our study.

Our clinical experience reveals that darbepoetin alfa can be effectively used for treatment of anemia associated with chronic renal failure in children. As expected, less frequent administration is required for children on darbepoetin therapy because of the prolonged half-life of the drug in the pediatric population. As a result, the frequency of painful injections for children is reduced and compliance is improved.

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