ANNALES
UNIVERSITATIS MARIAE CURIE-SKŁODOWSKA
LUBLIN – POLONIA
VOL. LIX, N 2, 128 SECTIO D 2004

Department of Neonatal Pathology, Infants, and Cardiology, Skubiszewski Medical University of Lublin

GRAŻYNA POLKOWSKA, ELŻBIETA WÓJCIK-SKIERUCHA,
WANDA FURMAGA-JABŁOŃSKA

The use of recombinant human erythropoietin in the treatment of anaemia of prematurity

Anaemia is the most common haematological disorder in premature newborns and it constitutes a serious clinical problem. Anaemia of prematurity (AOP) begins between 5th and 7th day of life and lasts for about 6–12 weeks since delivery (1). So far, numerous blood transfusions have been the only effective treatment of AOP. This treatment is jeopardized by many complications like overload of circulation, high risk of viral infections (HIV, HBV, CMV), or it may cause production of allo-antibodies (9). Therefore, safer methods of AOP treatment were searched.

The AOP is caused, in part, by a deficiency of erythropoietin (Epo), which is secreted by hepatocytes and peritubular nephrocytes in response to hypoxia. The Epo is glycoprotein hormone of 34,000 molecular weight, which is the main factor regulating the erythropoiesis both in intrauterine and post-fetal life. Epo stimulates differentiation and growth of erythroid progenitors (colony forming units – CFU) which evolve into mature functioning erythrocytes – normoblasts (6, 7). The Epo does not transfer through placenta, therefore, its fetal concentration measured in serum of the umbilical cord blood reflects its synthesis (10). Low concentrations of the hormone in preterm infants are caused by decreased metabolism, thus reduced oxygen consumption and different pharmacokinetics of the hormone. Importantly, synthesis of the Epo in fetal period takes place in the liver, and only after 30th week of pregnancy this function is taken over by kidneys, which are much more susceptible for hypoxia (6, 10). The amount of the Epo produced in response to the hypoxia by hepatocytes is 10 times smaller than the Epo amount produced in the same conditions by kidneys (10).

In 1985, the gene responsible for synthesis of the human recombinant erythropoietin (rHuEpo) was cloned, and thus industrial scale of the Epo production was initiated. This enabled detailed recognition of biological features of the hormone and its clinical application in the treatment of anaemia (15). In 1989, Halperin was the first to use the rHuEpo in the treatment of AOP (8,15). The first clinical trial evaluating the use of rHuEpo for the treatment of AOP was performed in the early 90's, following successful clinical trials using rHuEpo to treat adults with anaemia of end-stage renal disease. Nowadays rHuEpo is used to prevent and treat anaemia in preterm infants instead of blood transfusions (5, 11, 14). The use of rHuEpo in the treatment of AOP in children with low or very low body mass becomes more and more common, resulting in diminished use of supplementary blood transfusions in this group of patients. There is still lack of unequivocal indications to the treatment with rHuEpo, neither range of normal concentrations of the endogenous Epo has been defined, nor the opinion concerning total safety of the method has been settled down (15).

The aim of the study was to evaluate the influence of the rHuEpo treatment on parameters of the erythrocytic system in peripheral blood, iron concentration, and

unsaturated iron bind capacity (UIBC), as well as on erythrocyte transfusion requirements in preterm infants with AOP having no infection and not receiving oxygen support.

MATERIAL AND METHODS

Twenty-four children with AOP, that were hospitalized during one year, with no signs of infection and without any form of oxygen therapy, were investigated. Gestational age of the children was 27–29 weeks in 42%, 30–32 weeks in 33%, and 33–37 weeks in 42% of children. Birth weight of the children was 940–1500 g in 46%, 1501–2000g in 25%, and 2001–2500 g in 29% of children. Body weight of the children in the beginning of the rHuEpo treatment was 1300–2000 g in 25%, 2001–2500 g in 21%, and over 2500 g in 54% of patients.

The rHuEpo (Recormon, Boehringer Mannheim, Germany) was administered subcutaneously 700 U/kg/week, in two doses. Infants also received oral iron (6 mg/kg per day). Changes of haemoglobin (Hb), haematocrit (Ht), red blood cell count (RBC), reticulocytes, iron serum concentration, and UIBC following consecutive doses of rHuEpo were recorded. The rHuEpo therapy had been discontinued when Hb was above 10 g/dL and Ht above 30%. The percentage of children with AOP treated by supplementary transfusions was compared in two one-year periods, before and after the introduction of rHuEpo therapy.

RESULTS

Distribution of the rHuEpo doses in the group of investigated children is presented in Figure 1. In over 50% of children, satisfactory improvement of erythrocytic picture was achieved after administration of 4–7 doses of rHuEpo. Ht, Hb, RBC, the number of reticulocytes, serum iron concentration, and UIBC before and after each dose of the rHuEpo are depicted in Figures 2, 3, 4, 5, 6, and 7, respectively. In the year prior to introduction of rHuEpo therapy, 91% of children with AOP required supplementary red cells transfusions, while only 13% when rHuEpo was applied.

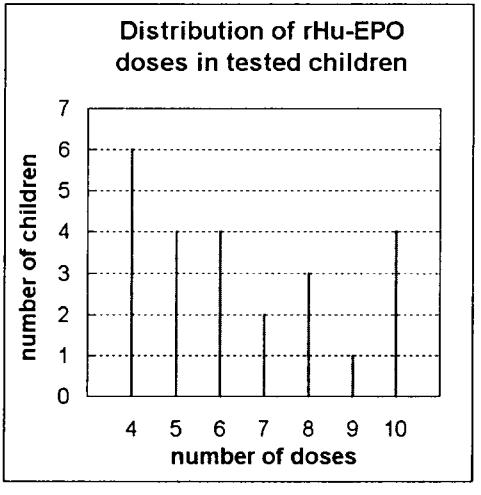

Fig. 1

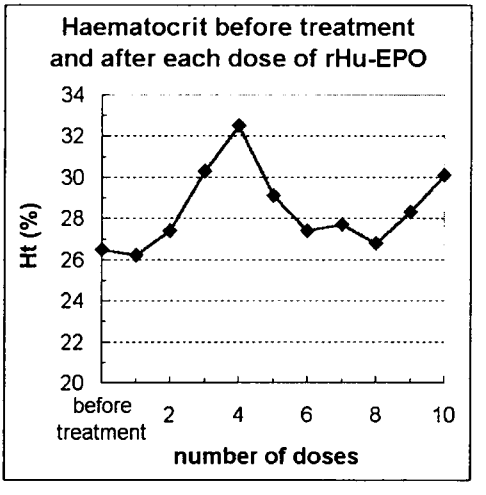

Fig. 2

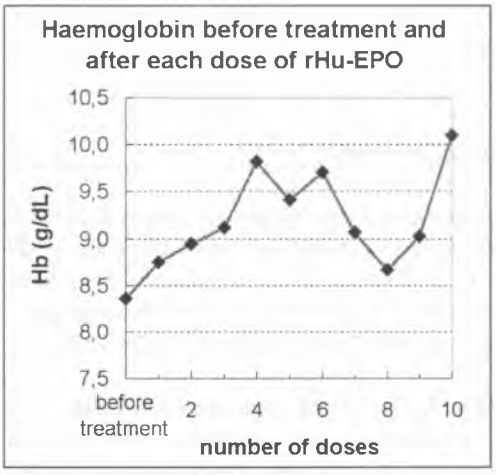

Fig. 3

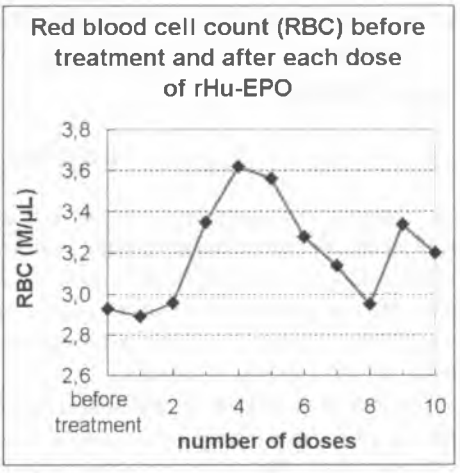

Fig. 4

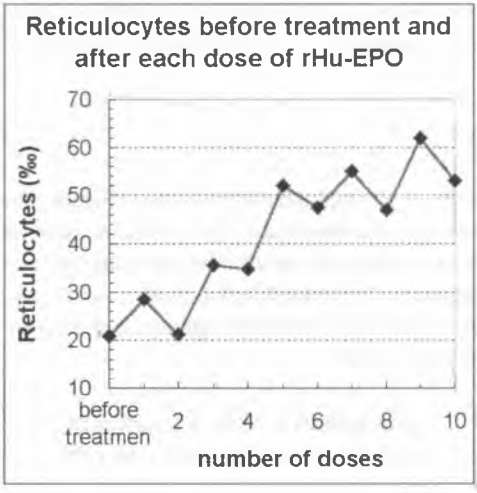

Fig. 5

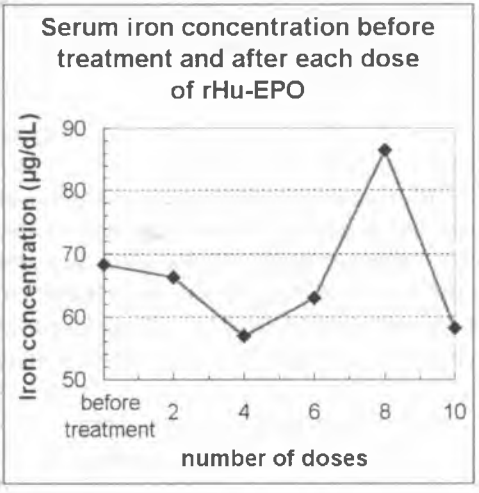

Fig. 6

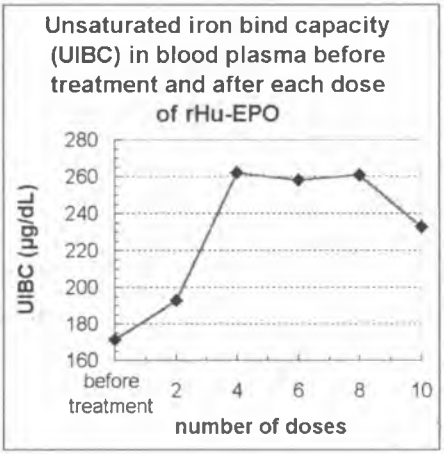

Fig. 7

DISCUSSION

Newborns delivered prematurely have low concentration of endogenous Epo, whereas the amount of erythroid progenitors (CFU) of the bone marrow is supposed to be sufficient for adequate haematopoiesis. The use of rHuEpo together with the iron supplementation and vitamins important for erythropoiesis, may prevent decrease of haemoglobin and reduce the number of blood transfusions (5, 6, 7, 10). Based on results of the present study, the use of the rHuEpo treatment caused decreased demand for the blood transfusions from 91% to 13% of patients. In the investigated group of patients between 7th and 8th dose of the rHuEpo, the gradual drops in haemoglobin, haematocrit, and red blood cells count (RBC) were observed followed by the gradual increase and stabilisation of these parameters. This is a favourable observation in comparison to children who do not receive the rHuEpo therapy, and in whom permanent decrease of the haematological parameters is observed (9, 14). The majority of authors report the significant increase of reticulocytosis in the course of the treatment (9, 12, 14). Results of the present study confirm this observation, although attention needs finding of increase of reticulocytosis from 4th dose of rHuEpo, and decrease after 10th dose. It may be speculated that this decrease is associated with the decline of the endogenous erythropoietin concentration in response to haemoglobin increase or with the reduced response to the rHuEpo because of the rHuEpo receptors depletion (9). In this situation, the increase of the dose and time interval between consecutive doses of the rHuEpo into 72 hours could be effective (9, 12). Frequently described iron deficiency in patients treated with erythropoietin may limit effectiveness of such treatment (3, 13). Low iron supply and limited iron absorption from breast or artificial feeding, as well as side-effects of oral iron intake, frequently do not allow to achieve adequate iron concentration in the situation of increased erythropoiesis (3, 13). In this study the decrease of serum iron concentration with associated increase of iron requirement (increase of latent iron binding capacity) were observed, which may account for high iron utilization for erythrocytes production (4). In order to avoid haemolysis in the course of high doses of iron administration, vitamin E with antioxidant effect should be administered concomitantly (2). Intravenous iron administration is not necessary, since oral route of intake is usually sufficient in the course of rHuEpo treatment (2). Based on our experience, no adverse or side-effects of erythropoietin were observed in the treatment of newborns.

CONCLUSIONS

1. The rHuEpo is the drug of choice in the treatment of anaemia of prematurity.
2. Therapeutic use of rHuEpo markedly diminished the quantity of supplementary transfusions in children with AOP.

REFERENCES

1. Bechensteen A. G. et al.: Erythropoietin (EPO), protein and iron supplementation and prevention of anemia of prematurity: effects on serum immunoreactive Epo, growth and protein and iron metabolis. Acta Paediatrica, 85, 490, 1996.
2. Frącka B. et al.: Ocena stosowania ludzkiej rekombinowanej erytropoetyny w leczeniu noworodków i młodych niemowląt. Przegl. Pediatr., 23, 63, 1993.
3. Halperin D. S. et al.: Effects of recombinant human erythropoietin in infants with the anemia of prematurity: a pilot study. J. Pediatr., 116, 779, 1990.
4. Jaworska A.: Dziesięć lat stosowania erytropoetyny w niedokrwistości wcześniaków. Post. Neonat., 1 III, 12, 2002.

5. Jaworska A., Szczapa J.: Ocena wstępnych wyników stosowania ludzkiej rekombinowanej erytropoetyny w niedokrwistości wcześniaków. Post. Neonat., 6, 43, 1995.
6. Kivivuori S. M. et al.: Oral iron sufficient for erythropoietin treatment of very low birthweight infants. Eur. J. Pediatr., 158, 147, 1999.
7. Kling P. L. et al.: Serum erthropoietin levels during infancy: Associations with erythropoiesis. J. Pediatr., 128, 791, 1996.
8. Kornacka M. K.: Erytropoetyna znana i nieznana. Post. Neonat., 1 III, 7, 2002.
9. Messer J. et al.: Early treatment of premature infants with recombinant human erythropoietin. Pediatrics, 92, 614, 1993.
10. Meyer M. P. et al.: Recombinant human erythropoitein in the treatment of the anemia of prematurity: results of a double-blind, placebo-controlled study. Pediatrics, 93, 918, 1994.
11. Nazir S. et al.: Comparison of 2 iron doses in infants receiving recombinant human erythropoietin therapy. Arch. Pediatr. Adolesc. Med., 156, 540, 2002.
12. Palis J., Segel G. B.: Developmental biology of erythropoiesis. Blood Rev., 12, 2, 106, 1998.
13. Rao R., Georgieff M. K.: Neonatal iron nutrition. Semin. Neonatol., 6, 425, 2001.
14. Schannon K. M. et al.: Circulating erythroid progenitors in the anemia of prematurity. N. Engl. J. Med., 317, 728, 1987.
15. Ziemba A. et al.: Zastosowanie rekombinowanej ludzkiej erytropoetyny w leczeniu niedokrwistości noworodków z bardzo małą urodzeniową masą ciała – wstępne doświadczenia własne. Post. Neonat., Supl. III, 141, 2003.

SUMMARY

Anaemia of prematurity (AOP) is caused by a deficiency of erythropoietin, which stimulates differentiation, and growth of erythroid progenitors. The previous standard of therapy of AOP was erythrocyte transfusions. Following successful clinical trials using recombinant human eryrthropoietin (rHuEpo) to treat adults, the rHuEpo has been used to prevent and treat anaemia in preterm infants. The aim of the study was to evaluate the influence of rHuEpo treatment on parameters of the erythrocytic system in peripheral blood, iron concentration, and unsaturated iron bind capacity (UIBC), as well as on erythrocyte transfusion requirements, in preterm infants with AOP, having no infection and not receiving oxygen support. Twenty-four children with AOP, that were hospitalized during one year, with no signs of infection and without any form of oxygen therapy, were investigated. The rHuEpo was administered subcutaneously 700 U/kg/week, in two doses. Infants also received oral iron. The percentage of children with AOP treated by supplementary transfusions was compared in two one-year periods, before and after the introduction of rHuEpo therapy. In over 50% of children, satisfactory improvement of erythrocytic picture was achieved after administration of 4–7 doses of rHuEpo. In the year prior to the introduction of rHuEpo therapy, 91% of children with AOP required supplementary red cells transfusions, while only 13% when rHuEpo was applied. Conclusions: The rHuEpo is the drug of choice in the treatment of anaemia of prematurity. Therapeutic use of rHuEpo markedly diminished quantity of supplementary transfusions in children with AOP.

Zastosowanie ludzkiej rekombinowanej erytropoetyny w leczeniu niedokrwistości wcześniaków

Jedną z przyczyn niedokrwistości wcześniaków jest niedobór erytropoetyny, która stymuluje proliferację i różnicowanie prekursorów układu czerwonokrwinkowego do normoblastów. Do niedawna jedynym skutecznym sposobem leczenia niedokrwistości wcześniaków były transfuzje krwinek czerwonych (KKCz). Przydatność ludzkiej rekombinowanej erytropoetyny (rHuEpo) w leczeniu i zapobieganiu niedokrwistości u dorosłych została potwierdzona w licznych badaniach randomizowanych. Obecnie od kilku lat stosowana jest ona w leczeniu niedokrwistości u wcześniaków. Celem pracy była próba oceny wpływu leczenia rHuEpo na parametry układu czerwonokrwinkowego, stężenie żelaza i utajoną zdolność wiązania żelaza w surowicy krwi oraz porównanie ilości transfuzji uzupełniających KKCz u wcześniaków z niedokrwistością leczonych i nieleczonych rHUEpo. Badaniami objęto 24 wcześniaki z niedokrwistością, bez cech infekcji oraz bez żadnej formy tlenoterapii, hospitalizowane przez okres jednego roku w naszej klinice. Dzieci te otrzymywały podskórnie rHuEpo w dawce 700 U/kg/tydzień w dwu podzielonych dawkach, oraz doustnie żelazo w dawce 6 mg/kg/dobę. Odsetek wykonanych transfuzji koncentratem krwinek czerwonych u wcześniaków leczonych rHuEpo porównano z ilością transfuzji KKCz wykonanych w takim samym okresie u wcześniaków nieleczonych rHuEpo.U 50% badanych dzieci uzyskano zadowalający wzrost wartości obrazu czerwonokrwinkowego po 4–7 dawkach leku. Ilość transfuzji KKCz u dzieci otrzymujących rHuEpo wynosiła 13%, podczas gdy w porównywanym okresie u dzieci nieotrzymujących preparatu erytropoetyny 91%. Wnioski: 1. RHuEpo jest lekiem z wyboru w leczeniu niedokrwistości wcześniaków. 2. Leczenie rHuEpo znacząco ograniczyło konieczność stosowania transfuzji uzupełniających KKCz u wcześniaków z niedokrwistością.