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OPTIMIZING THE ERYTHROPOIETIN USE IN CHRONIC RENAL FAILURE PATIENTS

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Summary. *Thirteen years have passed since the first patient with end stage renal disease received recombinant human erythropoietin (r-HuEPO). During this time many thousands of patients have been receiving r-HuEPO, and the knowledge of how to use EPO successfully and how to avoid adverse effects has been achieved. However, because of the costs of r-HuEPO, a great number of patients still lack beneficial effects of this treatment. The attempt to optimize the use of r-HuEPO in the treatment of chronic renal failure anemia could bring its benefits to a wider spectrum of patients. That is why we tried to summarize the answers to unresolved questions concerning r-HuEPO therapy that are already published. These are: when to start the treatment; what should be the target hemoglobin for patients receiving r-HuEPO, what route of administration should be used, what dosage will result in optimal response and what are the benefits expected. Identification and correction of reasons for failure of response to r-HuEPO therapy is important in ensuring the optimal use of EPO. The question is how common is iron deficiency, usually named as major cause for the hyporesponsiveness to EPO, and how should it be monitored and treated? What are the other causes of failure to respond to r-HuEPO and how could they be avoided. Finally, we are presenting brief listing of possibilities of adjuvant therapy and new EPO mimetic*.

Key words: *Erythropoietin, iron, anemia, chronic renal failure*

Many decades after discovery of erythropoietin passed. In Appendix milestones of results in erythropoietin studies that finally led to its clinical use are presented. Fourteen years have passed since the first patient received recombinant human erythropoietin (r-HuEPO) in Seattle, November 1985 (1,2). It quickly became evident that r-HuEPO is effective in reversing anemia of renal failure and all its diverse consequences. Still, many unresolved issues remain, particularly concerning the optimum use of erythropoietin. That is why in 1997 the National Kidney Foundation set evidence-based standards for treatment in the United States (3). Modifying this document, the Janssen-Cilag Advisory Board is preparing the guidelines to reflect European clinical practice and experience, that was not yet published. Here, data on the optimization of erythropoietin treatment are presented.

Patient selection. The high efficacy of r-HuEPO in therapy of anemia was first demonstrated in uremic patients on hemodialysis (1,2). In the meantime it became clear that all renal failure patients, including pre dialysis (4,5,6) and renal transplanted ones (7), regardless the way of dialysis and etiology of renal disease (8), benefit of r-HuEPO therapy.

Criteria for treatment. The essential criterion for starting r-HuEPO is hematocrit (Hct) value less than 30%, hemoglobin (Hb) less than 95 g/l, unless other conditions, such as angina pectoris, heart failure, overt symptoms of anemia or the need for regular blood transfusions are present (9). There is a strong argument for starting r-HuEPO on the basis of individual tolerance of anemia, rather than on rigid Hct or Hb values.

Routes of administration. Four possible routes of r-HuEPO administration exist.

Intravenous application was initially used in clinical trials with EPO, because it was easy access in patients on hemodialysis (HD). The high, but short lasting peak concentration of EPO (Fig. 1) results in correction of anemia (10). This is an inconvenient route for outpatients. The adverse effects (flu like syndrome, bone and muscle pain, headache) seem to occur more frequently than in s.c. administration.

The most convenient and cost-effective alternative and preferred route nowadays is *subcutaneous application*. Though bioavailability was disappointingly low compared with i.v. route, longer plasma half-life (Figure 1) and persistence of continuous stimulation is as effective as i.v. given r-HuEPO. The studies soon showed

that, compared with i.v., the s.c. route allowed a reduction in doses of approximately 30-40% with similar results (11,12). Recent prospective randomized cross-over studies show the same elevation of Hb level weather the r-HuEPO is given by i.v. or s.c. route (10). Another advantage is the possibility of self administration.

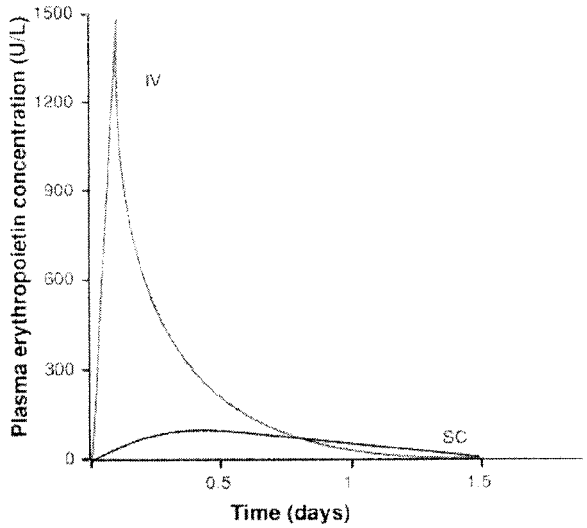

Fig 1. Plasma concentrations of erythropoietin after a single injection of r-HuEPO 80 U intravenously or subcutaneously

Intraperitoneal route is appropriate only for patients on peritoneal dialysis, who often do not even demand EPO treatment (13). Larger doses of r-HuEPO are required compared with intravenous (i.v.) or subcutaneous (s.c.) application because bioavailability of hormone is very low (14).

Preliminary results with *intradermal injection* of EPO suggest that it is at least as good as intravenous or subcutaneous administration (15).

For pre-dialysis and patients on continuous ambulatory peritoneal dialysis (CAPD) s.c. application is the only practicable one. Patients on hemodialysis do have the i.v. route, but s.c. option is thought to bee more economical and most patients receive EPO by this way (16).

Dosage of r-HuEPO. The safest starting dose is not defined. A "low and slow" dosing protocol, common in Europe, means 50–60 U/kg three times weakly (17). The side effects of treatment (hypertension, seizures, vascular access thrombosis) are more likely to occur if the Hb level increases rapidly. When the satisfactory Hb value is reached, the dose of EPO should be titrated down gradually. Individual differences to EPO should be considered (18).

Target hemoglobin and hematocrit. There is no agreement on target Hb and Hct, but Hct of 35% should be reached (19,20). Some data favor an almost normal Hb (21). Because of r-HuEPO cost, target Hct should be individually determined, with near normal levels in active, working patients, and those with heart disease. Sedentary, inactive and elderly patients without heart disease may have a lower target hematocrit.

A total absence of response to EPO is uncommon in uremic patients.

Hyporesponsiveness to r-HuEPO. Hyporesponsiveness to r-HuEPO may have many causes.

Iron deficiency is the most common one. Eschbach said that iron would be the Achilles heel of r-HuEPO therapy.

Iron is stored in reticuloendothelial system and in red blood cells (22). The connection between these two stores is transferrin iron pool, with only 0,1% of the body iron. An imbalance in this pool arises when erythropoiesis is stimulated or when the rate at which iron replenishes the pool is limited.

Before initiating the r-HuEPO therapy, iron status should be assessed in all the patients, and iron deficiency, if present, corrected. Serum ferritin value less than 100 µg/l suggests the insufficient iron stores, while transferrin saturation below 16% indicates that the iron supply will be inadequate (23, 24).

Table 1. Differentiation between absolute and functional iron deficiency

Absolute iron deficiency	Functional iron deficiency
ferritin < 50 ng/ml	ferritin normal or elevated
transferrin saturation < 20%	transferrin saturation < 16-20%
serum iron < 50 µg/dl	serum iron < 50 ug/dl
	hypochromic red cells > 5%
	mean erythrocyte indices unchanged

Table 2. Monitoring iron status in patients receiving r-HuEPO therapy

Assessment	Methods
Iron stores	Serum ferritin
	Bone marrow stainable iron
Circulating available iron	Serum iron (Fe)
	Percentage of hypochromic red cells
	Serum transferrin saturation (Fe/TIBCx100%)
Adequacy of iron	Serum transferrin receptor
supply to erythroid marrow	Erythrocyte ferritin
	Erythrocyte protoporfirin
Utilization of iron by	Erythrocyte indices (MCV, MCH)
erythroid marrow	Percentage of hypochromic red cells
	Hemoglobin concentration

Significant changes of iron metabolism occur with EPO administration. Large quantities of iron are consumed by the new red cells under r-HuEPO stimulation. In some patients the iron stores are inadequate to support the requirements of the marrow, and absolute iron deficiency develops (Table 1). In others stores are adequate, but the iron cannot be released or supplied to the marrow rapidly enough to satisfy the demands and functional iron deficiency occurs (17,25). The best clinical measurement for detecting absolute iron deficiency is serum ferritin level, and for functional iron deficiency is percentage of hypochromic red cell and transferrin saturation (Table 2), as they reflect the amount of iron actually getting into the red cells (26, 27).

That is why iron supplementation is almost always needed. The aim is to achieve and maintain serum ferritin level of 300–500 μg/l and transferrin saturation of 25–35%.

Intramuscular application is not recommended, because it is painful, iron absorption varies, a risk of bleeding into the muscle and increased incidence of sarcomas at the injection site exist.

Oral iron therapy should be reserved for hemodialysis patients intolerant of available i.v. iron preparations, CAPD patients with no evidence for functional iron deficiency and chronic renal failure patients not yet on dialysis (28).

Intravenous iron supplementation is frequently required. In a correction phase up to six doses of 100 mg of iron during the two weeks is advisable in patients with low serum ferritin. When the target Hb is reached the dose should be lowered to a 10-20 mg three times a week, no more than 100 mg per week, or the regimen could be 200 mg every second week (29). *To avoid iron toxicity, extreme caution is necessary in patients with serum ferritin near 1000 μg/l* (30).

Aluminum overload, less frequent in recent years, remains problem in patients on hemodialysis and in those receiving aluminum containing compounds. It may lead to hyporesponsiveness to EPO by several mechanisms: disturbances of iron uptake or utilization (31), suppression of enzyme activities involved in hem and globin synthesis. Diagnosis of overload includes monitoring of serum aluminum level and desferroxiamine test if serum aluminum is over 60μg/l (32).

Hyperparathyreoidism may induce or aggravate the anemia in uremic patients by a direct toxic effect of elevated PTH on EPO synthesis, red blood cell production and survival, and an indirect effect via the induction of marrow fibrosis interfering with erythropoiesis (33). Severe osteitis fibrosa is associated with a partial resistance to EPO. The surgical or medical correction of severe secondary hyperparathyroidism is often followed by an improvement in the response to the hormone.

The other cause of hyporesponsivness to EPO is the presence of **inflammatory disease, chronic disease and malignancy**. They all result in increased blood level of TNF alpha, interleukin 1, interferon gamma. They act through the inhibition of iron release, EPO synthesis and erythroid progenitor cell development primary in CFU-E stage (34).

Other, less common causes of hyporesponsiveness to EPO are endocrine disorders, severe metabolic acidosis, deficiency of vitamin B6, deficiency of vitamin B12, hemoglobinopathies, oxalosis, uremic toxins. Identification and correction of reasons for lack of response to r-HuEPO is important in ensuring the optimal usage of the drug.

Problem of *adjuvant therapy* in uremic patients treated with EPO is still unresolved (35). Vitamin B6 requirements are increased. Ascorbic acid can overcome r-HuEPO resistance in patients with functional iron deficiency. In secondary hyperparathyroidism patients receiving calcitriol or alfacalcidiol reduction of weekly r-HuEPO dose is reported. Androgens (36) and L-carnitine could be helpful. Insulin-like growth factor 1 improves carbohydrate and protein metabolism, glomerular filtration rate and renal plasma flow.

The efforts concerning r-HuEPO are continued with aim to develop new generation of oral erythropoietin mimetic, more convenient to administer and simpler to produce (Table 3). Gene transfer of erythropoietin could become a viable alternative to the injection of the purified recombinant protein, once reliable procedures for controlling transgene expression are available (37).

Table 3.

EPO	EPO mimetic peptide	Small-molecule EPO mimetic
- 34 kDa glycoprotein - 18 kDa polypeptide core - administered by injection - 3-D structureunknown	2.09 kDa peptide not orally available X-ray crystal structure available	orally available

EPO - erythropoietin

The beneficial effects of r-HuEPO treatment of uremic patients resulted in rise of erythroid progenitor cells in bone marrow (38), increased hematocrit value and exercise tolerance, improved cognitive function, reduction in the number of anginal episodes, reduced needs for blood transfusion, reduced risk of sensitization, prevention of iron overload, improved quality of life (39). The success obtained encourages the use of erythropoietin in conditions with different pathophysiology of anemia.

Conclusion

Erythropoietin is effective in reversing the anemia of renal failure and all its diverse consequences. Nevertheless, long-term effects have not yet been determined. Unfortunately, because of the price of r-HuEPO, the percentage of patients who receive it in different countries depends on the country's economic level. Optimal use of r-HuEPO should achieve the greatest benefits at the lowest cost. The challenge now is to optimize the r-HuEPO treatment and to allow a wider spectrum of patients to use it. Concerning up to date knowledge and experience with EPO, one can get best of r-HuEPO following recommendations:

- start EPO treatment at hematocrit of 30% or less, or on the basis of anemic symptoms;
- reach hematocrit of 35% or higher;
- use subcutaneous route, suitable for most patients, administration two to three times weekly;
- detect and correct iron deficiency obligatory;
- control blood pressure closely;
- search for the reasons of hyporesponsiveness.

Appendix:
History of erythropoietin and its clinical use

1836-40 Bright, Christison and Rayer - anemia of CRF

1878-90 Jourdanet, Bert, Viault - polycythemia of altitude

1893 Miescher - does hypoxia stimulate erythropoiesis

1906 Carnot and Deflandre - anemic rabbit serum promotes erythropoiesis?

1948 Bonsdorff and Jalavisto - "erythropoietin"

1950 Reissman - hypoxic blood promotes erythropoiesis in parabiotic animals

1953 Erslev - anemic rabbit serum promotes erythropoiesis

1957 Jacobson - kidney - the source of EPO (indirectly)

1960 Gallagher et al. - uremics deficient in erythropoietin

1961 Kuratowska, Fisher - kidney is the source of EPO (directly)

1965 Pavlović-Kentera - kidney is the source of EPO (directly)

1966 Cotes and Bangham - standardized preparation

1977 Miyake et al. - erythropoietin purified from urine

1985 Lin et al., Jacobson et al. - erythropoietin gene cloned

1986-7 Eschbach, Winearls - first patient given recombinant human EPO

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NAJBOLJI NAČIN PRIMENE ERITROPOETINA U LEČENJU OBOLELIH OD HRONIČNE INSUFICIJENCIJE BUBREGA

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Kratak sadržaj: *Prošlo je trinaest godina od kada je prvi bolesnik sa terminalnom hroničnom insuficijencijom bubrega dobio rekombinovani humani eritropoetin (r-HuEPO). Tokom proteklog perioda r-HuEPO je korišćen za lečenje hiljada bolesnika. Stečena su znanja o tome kako da se EPO primenjuje uspešno i kako da se izbegnu nepovoljna dejstva leka. Medjutim, zbog cene r-HuEPO, veliki broj obolelih još uvek ne može da koristi povoljne efekte lečenja ovim preparatom. Nalaženje najboljeg načina za primenu r-HuEPO u lečenju anemije u hroničnoj insuficijenciji bubrega omogućilo bi većem broju bolesnika da uživa pogodnosti delovanja ovog preparata. Zbog toga smo pokušali da sumiramo do sada objavljene odgovore na još nerazjašnjena pitanja u vezi sa upotrebom r-HuEPO. To su: kada započeti lečenje, koje vrednosti hemoglobina treba dostići u bolesnika koji dobijaju r-HuEPO, koji način davanja leka treba primeniti, koje doze će dovesti do optimalnog odgovora i koji se povoljni efekti očekuju. Da bi se osigurao najbolji način primene EPO važno je otkriti i ukloniti razloge koji su doveli do nedovoljnog odgovora na lečenje r-HuEPO. Pitanje je koliko je čest nedostatak gvoždja, obično smatran najvažnijim razlogom za nedovoljni odgovor na EPO, i kako ga treba pratiti i lečiti? Koji su drugi razlozi za neodgovarajući učinak r-HuEPO i kako se oni mogu izbeći. Na kraju prikazujemo kratku listu mogućnosti adjuvantne terapije i nove EPO oblike.*

Ključne reči: *Eritropoetin, gvoždje, anemija, hronična bubrežna insuficijencija*

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