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GUIDELINES FOR THE USE OF RECOMBINANT HUMAN ERYTHROPOIETIN

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Recombinant human erythropoietin (rHuEpo) is increasingly being used for the treatment of anemia. In view of the unpredictibility of response in most anemic states outside renal failure, the high economic cost, and the high expectation patients and physicians pose in its effect, its clinical use requires expertise and committment.

This article was prepared by five experts: four on behalf of the Editorial Board of this Journal and one on behalf of the Dompé Biotec Company which sells rHuEpo in Italy. The Editorial Board of Haematologica and Dompe' Biotec agreed that minimal guidelines for the clinical use of rHuEpo would be useful for a safe, rational and cost-effective use of the drug, both for the approved indications of rHuEpo in Italy as well as the main anemic conditions potentially treatable with rHuEpo. This co-operation between a medical Journal and a pharmaceutical company is based on the common aim of achieving an optimal use of new drugs in medical practice.

The method used for preparing these guidelines was an informal consensus development. The experts examined a list of problems concerning pre-treatment patient evaluation, dosing and monitoring therapy and cost-effectiveness evaluation. They discussed the single points in order to achieve an agreement on different judgments. This method for implementing guidelines is efficient in permitting the evaluation of a large number of clinical scenarios in a brief time, and the use of an expert panel improves the credibility of the recommendations produced. However, the panel is aware that this approach lacks both a formal meaning for the rating scale of the judgments and a formal mechanism for reconciling differences between panelists1.

Settings of rHuEpo use

rHuEpo is today employed in different settings. For certain indications, national scientific societies, local ad hoc committees, hospital departments staff have the role of leaders in the implementation of policy for the use of rHuEpo aimed at blood transfusions and their relative risks avoidance. According with this policy, Institutions implement planning and monitoring protocols for patient's management and audit the safety and the efficacy of treatment. We define this as Institutional setting. The treatment of anemia of patients with renal failure under dialysis, the management of anemia in surgical patients, the support of preoperative autologous blood donation, and the correction of anemia of prematurity are the major indications for this use.

More frequently, however, the individual physician working in a hematologic or internal medicine specialty faces with the possible use of rHuEpo in an individual anemic patient. He has to decide the opportunity, the dose and how to evaluate the response. We define this as a clinical practice setting.

Finally, rHuEpo may be also employed within phase I-II clinical trials in order to evaluate its safety and efficacy in the treatment of conditions where the use of the drug is under investigation. A number of collaborative protocols are under scrutiny in all the world and in this investigational setting, patients enter in the treatment only according an approval of the study.

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A) Institutional setting

Defective endogenous Epo production is the major cause of anemia of renal failure. Severe anemia is present in more than 90% of patients on chronic dialysis and most of these subjects have a regular need for blood transfusions2. Over 200,000 dialysis patients in the world are now receiving rHuEpo: it has been clearly shown that almost 100% of hemodialysis patients who are treated with rHuEpo have a positive response if adequate doses of hormone are given3. Consensus among scientific societies exists that the starting dose should be from 50 to 100 U per kg body weight three times a week.

Anemia of prematurity is characterized by inadequate Epo response, for which many very-low-birth-weight infants receive multiple transfusions4. A controlled, blinded trial has shown that these infants have less need of transfusions if given rHuEpo (250 U/kg three times weekly subcutaneously) during the first six weeks of life5. The indications of treatment and the dose of the drug is protocol-driven and decided by the hospital administrative and medical institutions according with the available resources and the confidence with the results of clinical trials.

In surgical patients, rHuEpo treatment is used to diminish or prevent the development of anemia of autolgous blood donors and reduce subsequent allogeneic blood need. The preoperative autologous blood donation is effective in open heart and

orthopedic surgery. Different trials from different Institutions adopted different rHuEpo doses. The best result in cardiac surgery has been reported by the subcutaneous administration of rHuEpo at 24,000 IU once a week for three weeks6. This dose is effective in permitting the deposition of 800 g of autologous blood. The risk of precipitating pulmonary infarction should be kept in mind, and patients with ab Hb level above 15 g/dL during preoperative period seem to be at higher risk6. Optimal result in orthopedic patients has been btained with 200 U/kg... (Mercurualki)7,8. A clear demonstration has been given that supplemental intravenous iron administration is necessary6,7,8.

B) Clinical practice setting

Although the literature reports occasional patient with adequate levels of s-Epo that have responded to the rHuEpo treatment, a strict relationship between responsiveness to rHuEpo and inadequate Epo production is convincingly demonstrated9. This relationship provides useful information about the likelihood that an individual patient might benefit from treatment with rHuEpo. Several anemic states are associated with blunted endogenous Epo production and are potentially responsive to rHuEpo10 (Table 1).

About 75-80% of patients with anemia of rheumatoid arthritis respond to erythropoietin treatment with steady increases in Hb level11. The doses of rHuEpo required to improve anemia are higher than those required for treatment of anemia of renal failure. It should be noted that only a small fraction of patients with rheumatoid arthritis have Hb values lower than 8-9 g/dL, and only occasional subjects have a need for transfusion.

Defective endogenous Epo production has been found in more then 50% of patients with anemia associated with multiple myeloma. rHuEpo is variably effective in ameliorating this anemia12,13: response may range from 50 to 75%, patients with less advanced disease and less heavily treated being those more likely to respond to rHuEpo. An inadequate andogenous Epo production has been found a predictor of response, whereas the degree of marrow impairement influences the effective dose of rHuEpo. These considerations are true also for the anemia associated with malignant lymphoma13.

Anemia is a frequent finding in patients with

Table 1. Anemias associated with blunted endogenous Epo production and potentially responsive to r-Hu-Epo

Anemia	Response rate (%)
Anemia of renal failure	100
Anemia of rheumatoid arthritis	75-80
Anemia of multiple myeloma	50-75
Anemia of solid tumors/lymphomas	50
Anemia of AIDS	
Anemia of myelodysplasias	16

cancer and may be due to different causes. In untreated subjects, the most common type is anemia of chronic disease. In addition, chemotherapy may cause or worsen anemia. In a large study, Miller et al.14 have found that most of 81 anemic patients with solid tumor had s-Epo levels inappropriately low for the degree of anemia, and that such levels were further decreased in subjects receiving chemotherapy. A number of clinical trials indicate that r-Hu-Epo has a role in palliating anemia, which may be responsible for significant morbidity in patients with advanced cancer15-17. Although response rate is influenced by the above mentioned variables, it may be estimated that about 50-60% of patients with anemia of cancer respond to rHuEpo. The s-Epo was the only baseline variable that discriminate significantly between future responsers and non responders18. The anemia associated with chemotherapy of non-myeloid malignancies is an approved indication for rHuEpo treatment in the USA.

Anemia is a frequent adverse effect of treatment of the acquired immunodeficiency syndrome (AIDS) with zidovudine. An overview of four clinical trials19 has shown that therapy with rHuEpo can increase the Hb level and decrease the mean transfusion requirement in anemic patients with AIDS who are receiving zidovudine and have low endogenous Epo levels (< 500 mU/ml). The proportion of patients responding to rHuEpo may be estimated as 30%.

Several studies were carried out to evaluate the efficacy of rHuEpo in the anemia of myelodysplastic syndromes (MDS). Review of these studies indicates that the overall response was 15%20. The low efficacy of rHuEpo in MDS is likely due to the low responsiveness of myelodysplastic progenitor cells to Epo. Patients showing low s-Epo levels are more likely to respond.

Patients with aplastic anemia or Fanconi anemia are also unlikely to respond to rHuEpo, and cautions for the use of growth factors are reported21.

Only few data are available on the use of rHuEpo in the treatment of anemia in idiopathic myelofibrosis13,22. The drug appears to be poorly effective in these patients (response rate of about 10 to 20%). In addition, it may produce symptomatic spleen enlargement, likely due to stimulation of extramedullary erythropoiesis13.

Delayed erythroid recovery is common after bone marrow transplantation (BMT), with some patients continuing to require red blood cell transfusion support. Inadequate s-Epo levels are found in the late phase of the post-transplant period. This happens in allogeneic but not in autologous BMT patients23-25. Both acute graft-versus-host disease (GVHD) and cyclosporin A (Cs-A) for GVHD prophylaxis produce a more marked suppression of the Epo response to anemia. Allogeneic BMT patients may benefit from rHuEpo treatment.

C) Investigational setting

The use of r-Hu-Epo outside the purpose of correcting an Epo deficiency anemia is emerged in the last few years. In these cases rHuEpo would allow extreme expansion of erythropoiesis with more subtle biological mechanisms. A study in sickle cell disease suggests that intravenous rHuEpo alternating with hydroxyurea can elevate fetal hemoglobin more than hydroxyurea alone26. This might be useful not only for treatment of sickle cell disease, but also for that of some patients with beta thalassemia27. However, it should be noted that the doses of rHuEpo required to obtain an increase in fetal hemoglobin synthesis were extremely high (1000 to 3000 U/kg).

Guidelines for the use of rHuEpo in the setting of clinical practice

A) Indications of use.

Facing a patient with anemia, clinicians must evaluate the opportunity of using rHuEpo according to the agenda of considerations summarized in Table 2.

a) Judging the severity of anemia. Clinicians must first decide at which Hb level treatment should be considered. There is no question that all anemic patients having a regular need for

Tab. 2. Guidelines for rHuEpo therapy in clinical practice

1. Never use rHuEpo without establishing the cause of the anemia.
2. Consider rHuEpo use only in red blood cell disorders where data from clinical trials have provided clear evidence that response may occurr.
3. Limit the use of rHuEpo to patients who are transfusion dependent or are canditates for blood transfusion
4. Rule out that beside the primary cause of anemia other accompanying situations are present that may be corrected, such as iron, B12 or folate deficiency.
5. Consider rHuEpo use only after an unadequate Epo production has been documented.

blood transfusion should be electively considered candidate for rHuEpo treatment. Among patients who are not transfusion-dependent, arbitrary Hb thresholds can be defined. In patients with Hb levels steadily below 8 g/dL blood transfusion is anticipated and they are candidates to treatment with rHuEpo. Patients with Hb levels greater than 10 g/dL can usually have a normal physical activity and do not need this specific treatment. Clinical decision is more difficult in patients whose Hb level is in the range from 8 to 10 g/dL: since oxygen transport depends also on factors other than Hb, decision to treat should be individualized.

b) Scrutiny of correctable causes of anemia. Before using rHuEpo, other causes of anemia should be recognized and remedied. Iron deficiency often complicates other anemic states: its correction may make the use of rHuEpo useless13. Serum iron, total iron binding capacitiy and serum ferritin are therefore required to recognize iron deficiency before a possible treatment with rHuEpo. Folate or vitamin B12 deficiency should also be excluded.

Tab.3. Recommendations for the assessment of s-Epo adequateness to the level of anemia in the single patient

1. Produce a home-made reference curve of the relationship between Hb and s-Epo using iron deficiency anemia patients
2. Use the same immunoassay for measuring s-Epo in the patient and in the reference anemic population
3. Calculate the observed/predicted (O/P) ratio of log s-Epo for evalating the adequateness of s-Epo.
4. Consider adequate an O/P greater than 0.9.

c) Evaluation of s-Epo level adequateness. The defintion of "inadequate Epo response to anemia" relies primarily on documentation of a down-regulated dependence of s-Epo on Hb, with respect to the same dependence in reference patients. Accordingly, the definiton is mainly mathematical, resulting from a comparison between the patient's s-Epo value and the reference s-Epo threshold values for that degree of anemia. Table 3 summarizes the recommendations for the assessment of s-Epo adequcy.

The first claim for the definition of inadequate Epo response to anemia is that every laboratory have a home made reference population of anemic subjects. The patients gathered to calculate a reference regression equation between s-Epo and Hb should have an anemia with a single simple mechanism. Chronic iron deficiency anemia patients due to non neoplastic and non inflammatory chronic blood loss have the advantages of being easily found, unequivocably defined and homogenous in nature. They could become the universal reference population.

Recently developed and commercially available Epo immunoassays should be used for the s-Epo assay. They are simple, reproducible and sensible (2-4 mU/ml). However, they are not precise. Recommendations is that the reference and test sera should be assayed for s-Epo with the same immunologic method. A dose/response curve in anemic iron deficient patients provided by the manufacturer would be widley accepted.

Finally, the observed s-Epo value to be evaluated for adequateness should be matched with the expected s-Epo value derived from reference regression at that particular Hb level. The O/P ratio allows categorization of each individual patient and has the advantage of providing a measure of the magnitude of inadequateness (see Appendix A). O/P values lower than 0.80 have to be considered inadequate Epo respose to anemia and values lower than 0.5 have to be considered severe hypoerythropoietinemias.

B) Dosing and monitoring rHuEpo

In the anemia of renal failure, guidelines deliverd by Scientific Societies converge toward

a recommended initial dose of rHuEpo of 50 to 100 Units per kg of body weight three times a week. 100-200 U/kg thrice weekly have been used in the majority of studies on the use of rHuEpo in patients with solid tumors, hematological malignancies, AIDS and rheumatoid arthritis. Neverthless, for subcutaneous administration, a dose as low as 50 U/kg three times per week has also been reported to be effective28. This may be considered the standard dose of rHuEpo in humans when the purpose is to correct an absolute or relative Epo deficiency. Therefore we suggest that a dose of 50-75 U/kg of rHuEpo subcutaneously three times per week should be initially given.

The available studies on the use of rHuEpo in anemia of diseases other than chronic renal failure, particularly in anemia of cancer, myeloma and MDS indicate that the time for an increase in Hb varied widely, but a response was achieved by 2 to 4 weeks29-31 with the initial dose, and that the final response is observed in a range of time between 5 and 12 weeks. Therefore we suggest that the dose should be escalated up to 100-150 U/kg if a response is not obtained within a month and therapy should be continued for 3 months before defining a patient as unresponsive. Beyond this time it is unlikely that an increase in hemoglobin value occurs (Table 4.).

In view of the high cost of the therapy it is mandatory the choice of a dose that allow the optimal utilization of each single vial in order not to waste the product. In almost all patients, rHuEpo can be given subcutaneously: after s.c. injection a peak is reached much later (approximately after 19 hours) than after i.v. administration, but a lower maintenance dose than after i.v. injection is effective, and patients can self-administrate the drug.

Complete blood count, reticulocyte count and iron status parameters should be serially monitored in order to evaluate the response of bone marrow to the therapy, and to prevent functional iron deficiency. These measurement must be done every four weeks after beginning of treatment.

In anemia of chronic renal failure, a substantial increase of Hb is always reached and the Hb is generally kept at levels not higher than 10-11 gr/dl to avoid side effects such as hypertension, seizure and thrombotic events. The response rate to rHuEpo is not as high in patients with other types of anemia, and even a partial response such as a significant reduction of trasfusion need is an acceptable result. Thus the criteria for evaluating the efficacy of therapy are less straightforward than in chronic renal failure.

Although the treatment should aim at reaching an Hb level equal to or greater than 10 gr/dl, in many patients the pretreatment values are very low (below 8 gr/dl) and in such instances a rise of 1 gr/dl indicates a valuable biological response, can reduce or abolish the need for blood transfusion, and substantially ameliorate the quality of life.

When an automatic, flow cytometry reticulocyte counter is available, a reticulocye count increase of at least 25x109/l over the basal level suggests a response to rHuEpo. The reponse is further confirmed by the increase in the number of the youngest retyculocytes (high fluorescence class).

Serum determination of soluble transferrin receptor (TfR) has been reported to represent a valuable index of response to therapy. As a matter of fact, TfR is found augmented if total marrow erythropoietic activity is increased. Enzyme linked immunassays are commercialy available for an easy evaluation of this parameter, but its use is not widespread in the clinical practice.

D) Assessing functional iron deficiency and indi-

Table 4. Recommended protocol for r-Hu-Epo therapy in the clinical practice

1. Start with a dose of 50-75 U/kg (according to the vial closer dose adjustement) three times a week subcutaneously
2. Evaluate the response at every four week of treatment.
3. If a response, as defined by an Hb increase greater than 1 g/dl, or reticulocyte count increase greater than 25x109/l, or every decrease of transfusional need, is not obtained within 1 month, double the dose (100-150 U/kg)
4. Stop the therapy if at the end of the third month of therapy a response has not been achieved.

cations to iron supplementation

A management issue frequently associated with rHuEpo treatment is functional iron deficiency32,33. This term is employed to define a situation in which body iron stores are normal (or even increased) but iron supply to the erythroid marrow is inadequate for the red cell precursor demand. Serum iron and transferrin saturation are low, whereas serum ferritin is normal to high: presumably, the amount of ready exchangeable iron in the reticuloendothelial cells is insufficient and iron procurement by transferrin is inadequate. An impaired iron supply to the erythroid marrow can blunt the erythropoietic response to rHuEpo and lead to defining as unresponsive, patients who would respond after correction of functional iron deficiency34.

Functional iron deficiency definition implies a serum iron level lower than 60 ug/dl and a percent transferrin saturation lower than 20%. Under these circumstances iron supplementation should be given by administering oral iron (100 to 200 mg of iron sulphate daily) or intravenous iron (iron saccharate, 100 mg by intravenous infusion, 2-3 times weekly). This latter route is to be preferred in those patients who show concomitant inflammation.

Using an automated blood count analyzer, it is possible to evaluate routinely the percentage of hypochromic red cells (Hb concentration < 28 g/dl): in normal subjects the percentage of hypochromic red cells is lower than 2.5%. An increase to over 10% during rHuEpo would indicate functional iron deficiency and the need for iron supplementation33. This test has the advantage of being performed on the same sample as the full blood count, and the result is immediate

e) Side effects.

All the available studies on the use of rHEpo in non-renal anemia do not report significant side effects, and in particular hypertension has not been observed as a consequence of the treatment. However, it appears prudent to monitor blood pressure initially, particularly in those patients with preexisting hypertension17.

Erythropoietin may produce symptomatic spleen enlargement in patients with myeloproliferative disorders. Spleen palpation should become a routine manoevre almost in the first few weeks after treatment.

The issue of rHuEpo use cost-effectiveness

RHuEpo is an expensive drug. Since cost containement is a major issue in health care policy today, health care providers, physicians included, have also to question whether its use represents good value for money. Determine whether a new technology represents a cost-effective use of resources is not a simple decision and it is difficult to capture all the benefits of a potentially blood conservative intervention like as rHuEpo.

RHuEpo primarely offers an alternative to blood transfusion. On the surface, blood transfusion appears to be cheaper. It cost about 200.000 Lit. per unit (approx 129 $), whereas rHuEpo costs approximately 70.000 Lit per 4000 units that means 9.500.00 Lit.(6,300 $) (hospital cost) for a year's treatment at a standard dose, i.e. 50 U/kg three times a week for a 70 kg body weight man. Only to the extent that it is successfull in eliminating 4 units of blood transfused per month, rHuEpo affects the direct cost of transfusions. Blood transfusion, however, also carries the indirect costs of inconvenience, acute reactions, hepatitis, and possibly further immunosupression. Moreover, rHuEpo offers additional benefits to patients in term of general well-being, and may improve income productivity.

The correct perspective is that health care governmental organizations would consider the total incremental cost of a rHuEpo management program for patients with a certain disease by using pharmacoeconomic techniques and compare it with the cost obtained for other health care interventions. A number of cost analysis of the drug have been performed both in patients with ESRD and in patients with anemia of AIDS. Based on these results and on that obtained with trials aimed at evaluating the effectiveness of the drug in different kinds of anemia, governmental officials established various types of restrictions on the use of rhuEpo.

However, a duty of the physician is to follow governement rules but also to be able to move from the public policy perspective concerned with average costs and implemented for average patients to one of the individual patient's needs perspective. The above presented guide-lines have been implemented on the basis of a evidence-based and in principle cost-effective use of the drug. As a matter of fact, the request of a preliminary documentation of unadequate Epo production, the recommended use of the drug only in patients with a transfusion-dependent anemia or candidate to trasfusional therapy, the criteria given for a rigorous evaluation of the response and the suggestion to stop early the drug administration when no response has been ascertained, all make highly probable the response and reduce resource wastage.

These guidelines should encourage physicians to endeavour so that officials responsible for drug delivery could provide the drug for individual patients that may benefit by it.

Appendix A: How to calculated the Epo O/P ratio in the single patient.

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