

## Erythropoietin therapy: need for rationality and active surveillance

Recombinant human erythropoietin (rHuEpo or epoetin) is a general term used to define erythropoietin molecules that are produced through molecular genetic technology. Epoetin alfa, epoetin beta and darbepoetin alfa are currently employed as therapeutic agents. Epoetin beta (NeoRecormon®) and darbepoetin alfa (Aranesp®) are available in just one formulation each although different brands are present in different countries. Epoetin alfa is available in different formulations and in different brands. Epogen® and Procrit® are identical formulations of epoetin alfa distributed only within the United States, while Eprex® is a different formulation of epoetin alfa distributed only outside the United States. There are tremendous financial interests in this field, as the total annual sales of rHu-Epo in the world might be in excess of six billion US dollars.

As a clinical investigator who has contributed to the development of erythropoietin therapy, I feel that the time has come to reconsider erythropoietin therapy in order to maximize its benefits for anemic patients, to minimize its adverse effects, and to avoid its misuse or abuse.

*A fundamental pathophysiologic notion that cannot be ignored by physicians: erythropoietin is a true hormone and, as such, is primarily effective in hormone deficiency*

Erythropoietin is essentially made by a single organ, the kidney, outside the bone marrow and participates in a classic negative feedback control system (Figure 1).<sup>1</sup> Erythropoietin-producing cells in the kidney are peritubular fibroblast-like interstitial cells, and hypoxia is the fundamental physiologic stimulus that causes a rapid increase in renal production of the hormone (up to 1,000-fold) through an exponential increase in the number of these cells. The central mediator of this response is a DNA binding complex termed hypoxia inducible factor 1 (HIF-1), which plays a key role in the regulation by oxygen of several genes besides the erythropoietin one.<sup>2</sup> The HIF-1 complex is formed in hypoxia and modulates gene expression through hypoxia response elements, while its oxygen-regulated destruction requires the von Hippel Lindau tumor suppressor protein (pVHL).

With respect to its molecular action, erythropoietin is primarily a survival factor for CFU-Es and proerythroblasts.<sup>3</sup> These erythroid progenitors require continual presence of the hormone in order

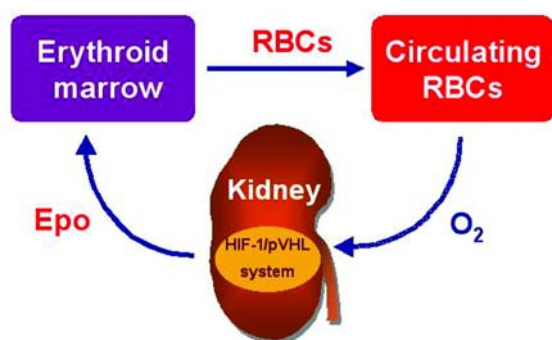
to survive although their sensitivity to erythropoietin varies widely. According to this model of erythropoiesis, based on erythropoietin prevention of programmed cell death, red cell production can be substantially and steadily expanded only through pre-amplification of erythropoietin-dependent progenitors. This notion is central to the clinical use of rHuEpo.<sup>4</sup> When erythropoietin levels are inappropriately low, administration of rHuEpo can have the effect of allowing more CFU-Es to survive and generating erythroid precursors that subsequently mature to red cells. By contrast, when endogenous erythropoietin is present in adequate amounts and nearly all available CFU-Es are already surviving, it is very unlikely that pharmacologic doses of rHu-Epo can further expand erythropoiesis. Clearly, there is room for using erythropoietin in non-anemic subjects in order to expand red cell production and prevent anemia, e.g., for potentiating autologous blood donation<sup>4</sup> or allowing regular phlebotomies.<sup>5</sup>

Ignoring this fundamental pathophysiologic notion may lead to irrational uses of rHuEpo. In particular, from both a medical and a community perspective, it does not make any sense to use this expensive drug in anemic patients with adequate endogenous erythropoietin production, in whom other factors are probably responsible for the erythroid failure.

*Treatment of renal anemia: the gold standard of the use of rHuEpo*

The use of rHuEpo for treatment of renal anemia can be regarded as the gold standard of erythropoietin therapy for several reasons. First, renal anemia is the prototype of an erythropoietin-deficient state, and administering the defective hormone is clearly appropriate. Second, although co-existing conditions may decrease the effectiveness of rHuEpo, nearly all renal patients treated with rHuEpo have a positive response if adequate doses are given and/or co-existing inhibitory factors are removed.<sup>6</sup> Third, the commonly used weekly maintenance dose of about 100 IU/kg body weight is cost-effective compared with a regular transfusion requirement of 2-3 units of blood per month. Fourth, quality of life improves remarkably in dialysis patients whose hemoglobin concentration increases from 6-7 to 9-10 g/dL, and is then steadily maintained around or just above this level.<sup>7</sup> Finally, findings of epidemiological studies suggest reductions in mortality and morbidity in renal patients receiving rHuEpo.<sup>8</sup>

Therefore, from all perspectives using rHuEpo in the treatment of renal anemia represents a rational use of this drug.



**Figure 1. Transcriptional feedback regulation of erythropoietin production.**

*Clinical trials have shown that defective endogenous erythropoietin production is a consistent predictor of response to rHuEpo also outside the setting of uremia*

Despite considerable differences in their designs, four European trials on the use of rHuEpo in patients with multiple myeloma or non-Hodgkin's lymphoma have shown that defective endogenous erythropoietin production is the only consistent baseline predictor of response to treatment.<sup>9-12</sup> This notion has been substantiated by recent reports in this journal.<sup>13,14</sup> Most of the evidence derives from studies on patients with hematologic malignancies, essentially because studies on patients with solid tumors have not specifically addressed this point.

In an individual patient, the adequacy of endogenous erythropoietin production can be easily assessed through the observed/predicted log(serum erythropoietin) ratio (O/P ratio).<sup>4</sup> Every laboratory should routinely provide this ratio together with the serum erythropoietin concentration. The O/P ratio is below 1 if the observed value is lower than the predicted one, and values lower than 0.9 indicate inadequate erythropoietin response to anemia. If the O/P ratio is not available, a serum erythropoietin level <100 mU/mL in an anemic patient can be taken as a reliable indicator of blunted erythropoietin production.<sup>11</sup>

Using rHuEpo in anemic patients with malignancy and defective endogenous erythropoietin production is a rational use of this expensive drug. Most anemic patients with multiple myeloma have low serum erythropoietin levels and greatly benefit from rHuEpo administration.<sup>11</sup> This is true also for many patients with non-Hodgkin's lymphoma and for a portion of patients with solid tumor. Preventing or correcting anemia in cancer patients receiving platinum derivatives is another example of a rational use of rhuEpo.

*Cancer anemia can result from factors other than defective endogenous erythropoietin production and there is a need for better prediction of response to rHuEpo in this setting*

Erythropoietin therapy is medically effective in only a portion of anemic cancer patients since the pathogenesis of cancer-related anemia is multifactorial and rHuEpo is not a magic wand that cures any anemia.<sup>4</sup> Anemic patients with elevated serum erythropoietin levels likely have other factors responsible for erythroid hypoproliferation: it is very unlikely that pharmacological doses of erythropoietin can correct this abnormality if the already increased endogenous hormone cannot.

Little information is currently available concerning prediction of response to rHuEpo in patients with solid tumors receiving chemotherapy. Consequently, as underlined in this journal,<sup>15</sup> physicians must treat 100 patients on chemotherapy with epoetin to reduce the number of transfusions in 11 of them. By better tailoring rHuEpo administration to patients with a high probability of response, i.e. improving the prediction of response, erythropoietin therapy would become more rational and also cost-effective.<sup>15</sup> In order to improve prediction of response we need clinical trials that are designed to reach this end-point, and not simply to show an overall efficacy of the drug in a heterogeneous population of cancer patients.

*The new issue of epoetin-induced autoimmune pure red cell aplasia (PRCA) in renal patients*

For years erythropoietin therapy has been considered remarkably safe. In 2002 Casadevall and her colleagues<sup>16</sup> reported a series of cases of epoetin-induced PRCA in renal patients. Thus, the scientific community became aware of the fact that neutralizing anti-erythropoietin antibodies and pure red cell aplasia can develop in patients with anemia of chronic renal failure during treatment with rHuEpo. Of the 22 renal patients reported by the French authors, 21 had been treated with epoetin alfa (the product distributed outside the United States) and one with epoetin beta.

A few months later the Food and Drug Administration reported data suggesting important differences between formulations of epoetin with regard to epoetin-induced PRCA.<sup>17</sup> For the period from July 1997 through December 2001, 82 cases were reported to the FDA. Four patients had received Epogen®, none had received Procrit®, and 78 had received Eprex® (these included the patients reported by Casadevall *et al.*<sup>16</sup>). The number of patients who received Eprex® increased sharply throughout this period, but the amount of drug distributed did not account for differences between the brands in the number of cases of PRCA reported.

On March 24, 2003, Johnson & Johnson released a summary of PRCA case reports as of December 31,

**Table 1. Cases of epoetin-induced autoimmune pure red cell aplasia in renal patients reported as of December 31, 2002. Since reliable estimates of numbers of patients at risk were not available to this journal, comparative incidences (number of cases per 100,000 patient-years) could not be calculated.**

Type of epoetin (which patients were exposed)	No. of cases	Source
Epoetin alfa (Eprex®) exclusively	142	Johnson & Johnson Summary of PRCA case reports. New Brunswick, NJ (March 24, 2003)* <sup>18</sup>
Epoetin alfa (Eprex®) and another epoetin	21	Johnson & Johnson Summary of PRCA case reports. New Brunswick, NJ (March 24, 2003)* <sup>18</sup>
Epoetin beta (NeoRecormon®) exclusively	8°	Hoffmann-La Roche quoted by Eckardt & Casadevall <sup>19</sup>
Epoetin alfa (Epoegen®) exclusively	4	Amgen quoted by Eckardt & Casadevall <sup>19</sup>

\*[http://www.jnj.com/news/jnj\\_news/1021024\\_095632.htm](http://www.jnj.com/news/jnj_news/1021024_095632.htm). The Company has changed Eprex® labeling to require intravenous (IV) administration of the HSA-free formulation in renal patients. In Europe, this resulted in the contraindication of subcutaneous administration in renal patients. So far no association between IV administration of Eprex® and PRCA has been reported.

°Three of these 8 are uncertain cases, in which an association between the use of epoetin beta and the development of PRCA cannot be excluded.

2002.<sup>18</sup> This summary contains 163 cases of antibody-positive PRCA: 142 had been exposed exclusively to Eprex®, and 21 to another epoetin and Eprex®. Interestingly, 157 out of the 161 cases occurred after 1997, when the drug formulation was modified (removal of human serum albumin to comply with new regulations from the European regulatory authorities) and administration modalities changed outside US (shift from IV to SC administration).

Combining the above-mentioned report from Johnson & Johnson with additional information from Eckardt and Casadevall<sup>19,20</sup> a tentative summary of cases of epoetin-induced autoimmune PRCA can be made as shown in Table 1. Despite recent increases the overall incidence of epoetin-induced autoimmune PRCA remains low, likely well below 50 per 100,000 patient-years, and rHuEpo continues to be a remarkably effective drug for renal patients. From an epidemiological point of view, this represents a rare adverse effect. Nonetheless, patients and physicians are increasingly worried about this complication. In particular, patients are not reassured at all by the fact that this complication is rare, and want that everything possible be done to avoid it. For detailed information the reader is referred to the excellent editorial by Eckardt and Casadevall.<sup>19</sup>

*Active surveillance: how to monitor patients receiving erythropoietin therapy in order to recognize PRCA early*

The main hematologic features of epoetin-induced autoimmune PRCA are as follows:<sup>19</sup>

- severe anemia with heavy transfusion requirement;
- reticulocyte count < 10×10<sup>9</sup>/L, close to zero in many instances;
- marked reduction of immature red cells in the bone marrow (< 5%) with block of maturation (nearly all residual immature red cells are proerythroblasts or basophilic erythroblasts);
- undetectable or low serum erythropoietin (a peculiar feature of this type of PRCA, since the remaining types typically have very elevated levels in the order of > 1000 mU/mL);
- presence of anti-erythropoietin antibodies and evidence for their neutralizing capacity.

Patients under epoetin therapy have normal to increased reticulocyte counts and normal to increased serum erythropoietin. The speed of onset of pure red-cell aplasia as a result of the development of neutralizing erythropoietin antibodies is not known.<sup>19</sup> However, changes in the hemoglobin concentration will definitely be preceded by changes in red-cell production, and these can be reliably assessed by automated reticulocyte counts. I, therefore, agree with Cavill and Williams<sup>21</sup> that monitoring the reticulocyte count should now be an integral part of recombinant human erythropoietin therapy. Any sharp fall in reticulocyte count should alert the physician to the possibility of PRCA: assaying serum erythropoietin and/or examining a bone marrow aspirate would be mandatory in this case. These patients should then be studied by reference laboratories for the possible presence of neutralizing anti-erythropoietin antibodies.

*Does epoetin-induced autoimmune PRCA occur outside the setting of uremia? The case of myelodysplastic syndromes*

Although there is no report in Medline® so far, at least two cases of epoetin-induced autoimmune PRCA have been observed in patients with myelodysplastic syndrome (MDS) receiving rHuEpo: one patient was treated with epoetin alfa, the other with epoetin beta.<sup>22</sup> This suggests that the risk of epoetin-induced pure red cell aplasia should now be taken into account in any treatment lasting more than 1-2 months in patients who are not being given concomitant immunosuppressive therapy. The finding of 2 cases in MDS patients should not be considered as a negligible observation. In fact, the number of MDS patients receiving rHuEpo is much lower than the number of renal patients, so the incidence may be comparable to that in renal anemia. Moreover, PRCA is more likely to be misdiagnosed in

MDS patients, in whom worsening of anemia and development of heavy transfusion requirement may also be compatible with the natural evolution of the basic disease.

Most MDS patients have evidence of adequate endogenous erythropoietin production and their anemia is due to primary hematopoietic cell abnormalities.<sup>23</sup> Epoetin may slightly and transiently increase red cell production in MDS patients with early disease and residual normal erythropoiesis.<sup>24</sup> However, the drug shows no consistent long-lasting effect in MDS patients with severe anemia and transfusion dependency, i.e., in those individuals who would most benefit from this treatment if it were effective.<sup>25</sup> Combining rHuEpo with granulocyte-colony stimulating factor might provide more benefits,<sup>26</sup> but this remains a strictly experimental treatment that should be given within the context of prospective clinical trials.

Routine erythropoietin treatment of MDS patients does not appear to be a rational use of rHuEpo, from either a medical or a community perspective. Tailoring treatment to MDS patients with defective endogenous erythropoietin production might be rational,<sup>27</sup> but no well-designed clinical trial is currently available that supports the long-term efficacy of this strategy, and provides information about its cost-effectiveness (some trials involve administration of doses greater than 1,000 IU/kg body weight per week). In addition, the risk of PRCA should now be considered, and rHuEpo should be used in MDS patients only following approval of the local institutional committee on human experimentation and within a prospective clinical trial.<sup>28,29</sup> In a journal with a Latin name, I use the same eternal language to remind readers that our primary duty is *primum non nocere*.

#### *The endless plague of blood doping with rHuEpo and the new risk of epoetin-induced autoimmune PRCA in healthy individuals*

Unfortunately rHuEpo is intricately intertwined with the endless plague of blood doping in endurance sports.<sup>30-34</sup> The available information (rumors) indicates that its use is reaching epidemic proportions. Epoetin-induced PRCA represents a further matter of concern.<sup>35</sup> Athletes are clearly procuring rHuEpo illegally, so non-optimal conservation of the drug is more likely. Should this be a factor in inducing drug antigenicity and antibody formation, the risk of PRCA would be higher in rHuEpo abusers.

It is unlikely that the objective of deterring blood doping will be achieved if only a few good Samaritans pursue it. We would like to see authorities and pharmaceutical companies themselves more committed to this task.

#### Conclusions

The pharmaceutical industry plays an essential

role in developing new therapeutic tools that improve quality of life and prolong survival of patients, as has been the case with rHuEpo in renal anemia so far. Clinical investigators and scientific societies, however, should play a more active role in defining clinical uses of drugs and monitoring their adverse effects. For instance, rHuEpo can be effective in several conditions outside uremia and cancer anemia, and physicians should actively promote studies to evaluate new clinical uses. The anemia of chronic heart failure is a notable example.<sup>36,37</sup> Correction of anemia after stem cell transplantation certainly involves fewer patients but represents another potential use of erythropoietin, as shown by Baron *et al.*<sup>38</sup> in this issue of *Haematologica*.

As practicing physicians our primary objective is the individual patient's interest. We also believe that, in the long term, maximizing benefits for patients, minimizing adverse effects, and avoiding misuses or abuses of any drug is in the interest of pharmaceutical companies themselves.

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#### Disclosures

The author of this note has participated and is participating in clinical trials on the use of epoetin beta in hematology and oncology. These trials are supported by F. Hoffmann-La Roche Ltd, Basel, Switzerland. The author has no significant financial relationship with this pharmaceutical company (according to: Drazen JM, Curfman GD. Financial associations of authors. *N Engl J Med* 2002;346:1901-2) and no financial interest (ownership of any equity or options, patent royalties, etc.) in any other companies selling epoetin or related drugs. More generally, he has no financial interest in any pharmaceutical, biomedical or biotechnology company.

#### When the bullet hits the target

Over the last few years the possibility of curing myocardial infarction by taking advantage of hematopoietic stem cells has become closer to reality and hopes have been fostered by quite a large body of studies suggesting that hematopoietic stem cells are not limited to differentiating into mature blood cells but can also mature into hepatic, intestinal, neural, skeletal and cardiac cells. In a questionable jargon expression this phenomenon is usually referred to as *stem cell plasticity*. However, it should be remembered that although many reports support the idea that hematopoietic stem cells can *transdifferentiate* into other cell types, the issue of hematopoietic stem cell plasticity is still matter of debate, and in some cases its existence has been challenged.<sup>1,2</sup>

Investigations suggesting the capacity of hemato-