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Dialysis Adequacy and Response to Erythropoiesis-Stimulating Agents: What Is the Evidence Base?

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Despite an increase in the use and average dose of erythropoiesis-stimulating agents (ESA) over the past 15 years, a substantial percentage of patients still do not achieve hemoglobin targets recommended by international guidelines. A clear relationship among hemoglobin or hematocrit levels, ESA dose, and increase in dialysis dose has been pointed out by a number of prospective or retrospective studies. This is particularly true in patients receiving inadequate dialysis. Increasing attention also has been paid to the relationship between dialysis, increased inflammatory stimulus, and ESA response because dialysate contamination and low-compatible treatments may increase cytokine production and consequently inhibit erythropoiesis. The biocompatibility of dialysis membranes and flux are other important factors. However, in highly selected, adequately dialyzed patients without iron or vitamin depletion, the effect of these treatment modalities on anemia seems to be smaller than expected. The role of on-line treatments still is controversial given that it is still difficult to discriminate between the effect of on-line hemodiafiltration per se from that of an increased dialysis dose. Very preliminary results obtained with short or long nocturnal daily hemodialysis on anemia correction are encouraging.
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Anemia is a very frequent condition that affects patients with chronic kidney disease (CKD); many factors contribute toward causing it. The most important trigger is a reduction in erythropoiesis caused by reduced renal production of erythropoietin (EPO) and by resistance of bone marrow cells to this hormone; in addition, shortened survival of red blood cells often is present. Although iron deficiency is probably the most important factor affecting the response to erythropoiesis-stimulating agents (ESA) in most patients, occult blood loss, infection, and inflammation also are important. Adequate dialysis can contribute to anemia correction by removing small and possibly medium/large molecules that may inhibit erythropoiesis. However, the role of dialysis dose per se on the response to ESA treatment largely has been underestimated in the past. Only recently has more interest been focused on this matter.

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Uremic Toxins and Anemia

A possible causal role of putative uremic toxins in the development of anemia in CKD patients is certainly not a new issue. Already in 1966, toxic substances inhibiting erythropoiesis were found in serum of uremic nephrectomized rabbits.[1] A number of metabolites have been implicated as potential EPO toxins, including various polyamines, such as spermine, spermidine, putrescine, and cadaverine, and parathyroid hormone. However, these substances have been found to be general bone marrow toxins and not specific suppressors of erythropoiesis.[2] More recently, polymeric polyamine-protein conjugates have been shown to have a selective inhibitory effect on colony-forming units-erythroid proliferation without any appreciable effect on burst-forming units-erythroid.[3] Another possible mechanism causing anemia in CKD patients could be the inhibition of EPO synthesis. Quinolinic acid, which is the product of tryptophan oxidation that increases after enzymatic changes in the kynurenine pathway, accumulates in the presence of renal failure and is an endogenous, specific *N*-methyl-D-aspartate receptor agonist, which on activation may direct disturbances in cellular metabolic processes promoting apoptosis. Results of in vivo

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and in vitro studies have shown that this substance had a dose-dependent inhibitory effect on hypoxia- and cobalt-induced EPO gene expression without any cell toxicity.[4,5]

In recent years, evidence accumulated for the role of inflammatory cytokines in the inhibition of erythropoiesis in the anemia of CKD. About 35% to 65% of CKD patients receiving hemodialysis show signs of inflammation. Several factors, such as impaired clearance of cytokines, accumulation of advanced glycation end-products, atherosclerosis, and other inflammatory diseases and unrecognized persistent infections have been implicated. In addition, the dialysis procedure has been linked to an increased risk of inflammation. Indeed, the prevalence of increased serum levels of C-reactive protein (CRP) is higher after the start of dialysis.[6]

The most important mechanism for cytokine-induced anemia is the suppression of bone-marrow erythropoiesis, but the extent to which increased cytokine levels and acute-phase response may contribute to resistance to ESA treatment still is not clear. In 1997, Barany et al[7] first described a clear relationship between CRP levels and ESA dose in 30 hemodialysis patients. In particular, in patients with CRP levels of 20 mg/L or more, the weekly ESA dose was 80% higher than those showing lower CRP values. This observation was confirmed by Gunnell et al[8] in a cross-sectional study of 92 patients on hemodialysis and 36 on peritoneal dialysis. The investigators described a clear positive association between CRP levels (expressed in the logarithmic scale) and the EPO/hematocrit ratio ($r = .337$; $P = .0010$).[8] This ratio, also known as the *EPO responsiveness index*, was proposed to normalize the amount of required EPO for the degree of anemia severity.[8] Besides low serum albumin level, which was the most significant predictor of EPO resistance in this population, CRP was found as an important independent factor predicting the EPO/hematocrit ratio at the regression analysis in both hemodialysis and peritoneal dialysis patients.[8] More recently, Locatelli et al[9] published the results of a cross-sectional study performed on 670 hemodialysis patients who were recruited from 5 Italian centers. The median CRP level was significantly higher in the patients of the hyporesponsive group (last decile of EPO dose; median, 262.9 IU/kg/wk; range, 240-319.2 IU/kg/wk) compared with the other 3 groups receiving lower ESA doses or no therapy (CRP of 1.9 versus. 0.8 mg/dL, respectively; $P = .004$). In the multiple linear regression analysis with the natural logarithm of the weekly ESA dose as the dependent variable, CRP levels were related directly with the weekly ESA dose (positive B coefficient, 0.051; $P = .004$), whereas serum albumin level, body mass index, hemoglobin level, and serum iron level were associated inversely. Similar findings were obtained by logistic regression analysis, using the hyporesponsive group as cases and the patients in the other groups as controls.

In CKD patients, increased levels of CRP have been found to correlate positively with other inflammatory cytokines, such as interleukin-6 (IL-6).[10] This is a pro-inflammatory cytokine that is 8- to 10-fold higher in hemodialysis patients and has been related to their poor outcome.[11] Even if available data are not univocal,[12] IL-6 has been found to antagonize EPO effect on bone-marrow proliferation.[13] Furthermore, IL-6 levels were related directly to ESA dose in hemodialysis patients.[14] Interestingly enough, the levels of this cytokine can differ according to the dialysis membrane used: IL-6 levels were significantly higher in patients treated with less-compatible membranes.[14] Recently, Kalantar-Zadeh et al[15] performed a cross-sectional analysis of 339 hemodialysis patients enrolled in an ongoing prospective study with the aim of evaluating the possible association between the prescribed ESA dose and several laboratory baseline values known to be related to inflammation and/or nutrition. The investigators confirmed a strong correlation between IL-6 concentration and weekly EPO dose.[15] In addition, they found a strong correlation between the levels of this cytokine and the EPO responsiveness index.[15]

Allen et al[16] investigated the effect of sera from patients with ESRD with and without infection or inflammatory disease on colony-forming units-erythroid colony formation in vitro. Colony formation was suppressed by soluble factors in the sera of uremic patients with or without inflammation stimulating the production of interferon-γ; and tumor necrosis factor-α, thus further inhibiting erythropoiesis. Interestingly enough, tumor necrosis factor-α was a significant individual predictor of ESA requirements in 34 hemodialysis patients.[17] On the contrary, the patients needing more ESA had lower levels of interferon-γ; and IL-12.[17]

The Role of Dialysate Fluid Contamination

Patients receiving hemodialysis come into blood contact with a huge quantity of water on every dialysis session. For this reason, chronic exposure to even low concentrations of toxic substances can produce a number of complications and, among these, the development or the worsening of anemia. Some contaminants are present in the water at the source, others are added as part of a treatment process for the production of safe drinking water or leached from the water piping system. The introduction of reverse osmosis treatment, which satisfactorily removes aluminum and many other substances from water, and of activated carbon filters, which remove chloramines, partially have solved these problems. Dialysis fluid could contain detectable levels of bacteria or endotoxin higher than the accepted standards even after adequate treatment.[18] These organisms can multiply in dialysis fluids to achieve a level of contamination sufficient to cause bacteremia or pyrogenic reactions. This inflammatory stimulus, often subclinical, can contribute to monocyte activation, cytokine production, and consequent inhibition of erythropoiesis. Given the importance of dialysate quality and purity, not only in anemia correction but also in reducing patient morbidity, stringent controls of the function of each component of the water treatment system and of both the chemical and microbial purity of water and final dialysis fluid are mandatory.