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Candidate biomarkers for erythropoietin response in end-stage renal disease

Anatole Besarab[1] and Jerry Yee[1]

Hyporesponsiveness to erythropoiesis-stimulating agents (ESAs) is important clinically and economically. Escalation of dose may produce harm. *Post hoc* analyses of clinical trials showed that responsiveness could be predicted by hemoglobin response to a fixed dose escalation. This maneuver requires weeks to months. The study by Merchant *et al.* offers promise that peptidomic analyses of patient sera and mass spectrometry can identify biomarkers of both responsiveness and resistance to ESAs.

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The paper by Merchant *et al.*[1] in this issue of *Kidney International* is an important approach to the issue of hyporesponsiveness to erythropoiesis-stimulating agents (ESAs) when obvious causes are not apparent. Their approach is identification of biomarkers of ESA response in hemodialysis patients, using peptidomic analyses of patient sera and mass spectrometry. The findings of these experiments are interesting and novel, marking the discovery of serum peptides originating from the oncostatin M receptor and cysteine/histidine-rich 1 proteins as candidate biomarkers of poor and good response to ESA therapy, respectively. Although the study was restricted to the use of the first-generation ESA epoetin alfa, the approach is likely to extend to similar-class biosimilar and longer-acting agents and may extend to newly developing hypoxia-inducible factor (HIF)-acting agents.

It must be stressed that introduction of ESAs produced substantial reductions in the blood transfusion requirements of patients suffering from chronic kidney disease (CKD). Thus, hyporesponsiveness to ESAs is an important issue in the successful management of anemia in patients with CKD, and hyporesponsiveness may be transient or persistent. The two most common reasons why patients become relatively unresponsive to ESA therapy are the development of true iron deficiency (which occurs less frequently now as a result of aggressive iron supplementation) and the onset of an inflammatory state that impairs the response to ESAs.[2] These elements are not unique to patients with CKD, but patients with CKD, especially those on hemodialysis, may be at an increased risk due to inflammation and may have previously been subject to decreases in hemoglobin (Hb) and hematocrit and consequent increased ESA dose requirements. Importantly, the bone marrow progenitor cells that are the most sensitive to the various cytokines produced during inflammation are the erythroid colony-forming units, as opposed to the more primitive erythroid burst-forming units. The effects of some cytokines, such as tumor necrosis factor-α, are not overcome by a simple increase in the ESA concentrations.

Intercurrent infection is almost certainly the most common reason why patients become temporarily (and reversibly) ESA-resistant. ESA responsiveness improves when iron deficiency (or another substrate deficiency) or an underlying inflammatory condition is treated. Response to iron repletion is relatively rapid, and very high Hb levels may obtain when ESA doses are not down-titrated rapidly. After therapy and control of the inflammatory state, it may take weeks to realize full responsiveness and several months to attain the desired Hb level. Reduction in cytokines, through prompt treatment of the underlying disorder, invariably engenders a much lower ESA dose to achieve the target Hb level.

Entities that induce chronic ESA hyporesponsiveness that can be partially overcome by escalating ESA doses include myelofibrosis, malignancy, thalassemia, sickle-cell disease, and untreated HIV/AIDS. The presence of these is usually known at the time of anemia treatment and ESA dose escalation. More recently described is pure red-cell aplasia, which results from antibodies directed against endogenous and exogenous epoetins. Until recently, the only available therapies were immunosuppression and/or red blood cell transfusions, but now administration of an erythromimetic peptide without homology to erythropoietin has been salutary.

It has been recognized since the initial introduction of the first ESA, epoetin alfa, in 1986–1987 that individual dialysis-dependent CKD patients vary significantly in the dose of ESA required to correct their anemia. Many studies have shown that the target mean Hb achieved is proportional to the dose given, at the population level. Data from the Clinical Performance Measures Project of the Centers for Medicare and Medicaid Services clearly demonstrate parallel increases of Hb levels and epoetin doses from 1995 to 2004. As the dose increased from 175 U/kg to 275 U/kg weekly, the mean Hb increased from 10.5 to 11.7 g/dl, while the ESA dose of people who achieved an Hb level of 11–13 g/dl varied more than 50-fold. The pressure to attain higher Hb levels from 1997 to 2006 evolved in part from perceived improvements in quality of life and persistent observational findings of lower mortality and hospitalization

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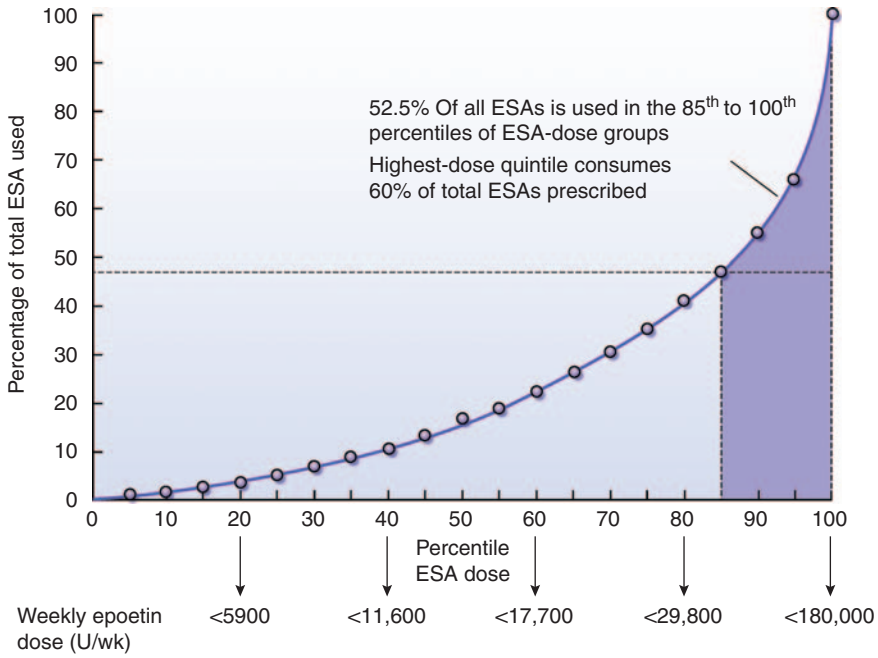

Figure 1 | Data on epoetin alfa usage in the last quarter of 2005 in the United States, based on a sample of 7400 patients. The percentage of total epoetin used according to percentile of dose range is an exponential curve. Hyporesponsive patients (> 150 U/kg of epoetin three times weekly) are in the highest quintile of doses (> 30,000 U/wk). Not surprisingly, they consume more than half of all the epoetin used, yet their hemoglobin levels are never greater than those of the patients in the lower quintiles. ESA, erythropoiesis-stimulating agent.

at higher as compared with lower achieved Hb values in hemodialysis patients.

This upward trend in Hb levels ended abruptly in 2006 with the publication of the Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta (CREATE) and Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) trials in non-dialysis CKD patients, and a meta-analysis in dialysis-dependent and non-dialysis CKD patients that targeted an entire population to a Hb level of at least 13 g/dl produced harm rather than further benefit,[3] confirming the original observation of the Normal Hematocrit Trial (NHCT).[4] These recent clinical trials included dialysis-dependent[5] and non-dialysis CKD patients[6] treated with ESAs to Hb targets greater than the range labeled by the US Food and Drug Administration, 10–12 g/dl, and raised safety concerns. Product labeling was subsequently revised to include a black-box warning, which, in the United States, led to a reduction from 60% to 46% in the proportion of non-dialysis CKD patients receiving an ESA, a 25% reduction in ESA dose and a decrease from 11.5 g/dl to 10.6 g/dl in mean Hb achieved.[7] Notably, this trend had begun before publication of the CHOIR trial in 2007 and accelerated thereafter. US Renal Data System data depict a similar, less dramatic decrease in mean Hb (of 0.5 g/dl) and in ESA dose in dialysis-dependent CKD patients (A.J. Collins, personal communication).

The paradox of observational trials demonstrating benefit and randomized controlled trials revealing harm at higher achieved Hb levels may arise from the administration of futile higher ESA doses to relatively ESA-resistant CKD patients. In an analysis of data from 7400 randomly selected patients representing the US hemodialysis population in 2005 (the Clinical Performance Measures Project), we found that 15% of hyporesponsive patients (defined as > 150 U/kg of epoetin alfa administered three times weekly) consumed 52.5% of the total ESAs prescribed (Figure 1). In many, ESA dose escalations did not alter Hb over a 3-month period. Consequently, we proposed a hypothesis based on *post hoc* analyses of the NHCT[8] and the CHOIR trial:[9] failure to achieve high Hb levels, rather than the level itself, may have been responsible for the poor outcomes. Similarly, the Trial to Reduce Cardiovascular Events With Aranesp Therapy (TREAT) *post hoc* analysis by Solomon and colleagues[10] correlated an initial suboptimal response with enhanced risk for a cardiovascular composite event (hazard ratio 1.31) and for all-cause death (hazard ratio 1.41). The poor outcomes may have resulted from toxicities related to high-dose ESAs, patient-level factors underpinning ESA hyporesponsiveness, or a combination of both. The CREATE trial did not demonstrate any harm from the greater targeted Hb, but the median epoetin doses were considerably lower (5000 IU/wk and 2000 IU/wk in the normal and subnormal Hb groups, respectively) than those in the NHCT and CHOIR studies, suggesting that a high Hb target *per se* may not have been directly responsible for worse outcomes when high doses of ESAs were avoided.

Currently, there is reasonable evidence to indicate possibly more harm than benefit from targeting higher Hb levels with ESA therapy, especially in hyporesponsive people. Clinical trials to date have focused primarily on Hb targets and have neglected ESA dosing and other patient-related factors, including concurrent illness, inflammation, and iron therapy. We contend that a two-by-two factorial trial of the hyporesponsive patient should be conducted. Eligible patients would be randomized to a higher or lower ESA dose and a higher or lower Hb target within the currently recommended range, 10–12 g/dl.

Unfortunately, until the study by Merchant *et al.*,[1] there has been disagreement on a uniform definition of hyporesponsiveness. Assigning responsiveness from a snapshot of data over 1 or 2 months could easily produce misclassification, particularly in ESA-naive patients. Transient cycling within a 6-month period is well established, and during the cycle, Hb may vary by 2–4 g/dl while ESA doses are varied monthly (or more frequently) in an attempt to avoid Hb levels outside the range, usually with a pronounced lag phase between the ESA change and the resulting Hb level.

A major strength of the study by Merchant *et al.*[1] is that an observation period of 6 months was used to determine

patients' ESA response index and the division of responses into quintiles. This avoided inclusion of transiently hyporesponsive patients based on conditions not immediately apparent to the clinician. Our own experience suggests that a period of 6 months is needed to detect hyporesponsiveness in about 15% of the hemodialysis population, who remain hyporesponsive for that duration. Their dose of ESA is markedly higher than that of sensitive patients, but because of the constraints of the 'target' range, the same mean Hb is attained. The importance of detecting this subset resides in the economic cost of ESA therapy (Figure 1) and in opportunities to avoid harm from "excessive" ESA dosing to reach the desired Hb target.

As important as economics is, the issue of risk versus benefit when higher Hb levels are targeted may be more important. If the findings of an association between the relative abundance of oncostatin M fragments and poor response, and between cysteine/histidine-rich 1 and good response, can be confirmed in larger cohorts of patients, it may allow us to actually conduct the randomized controlled trials necessary to find the best strategy for managing such poorly responsive patients. Certainly, this strategy cannot be to increase the ESA dose until the same Hb level is reached in poor as in better responders—that is, equivalent Hb attainment in all quartiles or quintiles of dose. The ability to periodically determine the responsiveness of the patient can only help refine the use and prevent the misuse of ESAs.

DISCLOSURE
The authors declared no competing interests.

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Prevention of vascular calcification: is pyrophosphate therapy a solution?

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Pyrophosphate, a ubiquitous small-molecule inhibitor of mineralization abundantly present in the extracellular environment, binds to calcium and mineral surfaces to inhibit crystal growth. O'Neill and colleagues show in uremic rats that systemic administration of pyrophosphate prevents or reduces uremia-related vascular calcification, without overt negative consequences for bone and without calcium pyrophosphate deposition disease. These findings prompt further research into the potential of pyrophosphate as treatment for vascular calcification in chronic kidney disease patients.

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Chronic kidney disease (CKD) strongly increases patient risk for cardiovascular morbidity and mortality. This striking difference in cardiovascular risk between CKD patients and the general population is not attributable only to increased exposure to the traditional Framingham Study risk factors but in addition depends on a number of so-called 'novel,' uremia-related risk factors, among which mineralization of blood vessels (vascular calcification, an ectopic mineralization) takes a prominent position.[1]

Numerous epidemiologic studies have found that vascular calcification in CKD patients contributes to the increased cardiovascular risk in this population, and that hyperphosphatemia and hypercalcemic episodes are associated with the development of uremia-related vascular calcification. The intimate link between disturbances of mineral metabolism inherent to impaired renal function and the development of both renal osteodystrophy and vascular calcification is now broadly captured under the term 'chronic kidney disease–mineral and bone disorder.'[2]

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