

CORRESPONDENCE



Epoetin Alfa in Critically Ill Patients

TO THE EDITOR: Corwin et al. (Sept. 6 issue)¹ report that the use of epoetin alfa in critically ill patients does not reduce the incidence of red-cell transfusion but may reduce mortality among patients with trauma. However, the drug was given subcutaneously. It is well known that skin perfusion is impaired in patients with critical illness. Did the investigators conduct a pharmacokinetic evaluation in a subgroup to ensure adequate erythropoietin absorption? In addition, a relatively large erythropoietin dose was used in the study. Such a large dose could be associated with endothelial dysfunction, a proinflammatory state,² and increased thrombogenicity by inducing the expression of tissue factor.³ Giving smaller doses of erythropoietin at more frequent intervals in patients undergoing dialysis often improves responsiveness to the drug and decreases the total erythropoietin requirement. Designing similar studies with the use of smaller doses of erythropoietin, administered at more frequent intervals intravenously, might address these points.

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Dr. Mikhail reports having received honoraria from Roche, Amgen, and Astellas. No other potential conflict of interest relevant to this letter was reported.

1. Corwin HL, Gettinger A, Fabian TC, et al. Efficacy and safety of epoetin alfa in critically ill patients. *N Engl J Med* 2007;357:965-76.
2. Tobu M, Iqbal O, Fareed D, et al. Erythropoietin-induced thrombosis as a result of increased inflammation and thrombin activatable fibrinolytic inhibitor. *Clin Appl Thromb Hemost* 2004;10:225-32.
3. Fusté B, Serradell M, Escolar G, et al. Erythropoietin triggers a signaling pathway in endothelial cells and increases the thrombogenicity of their extracellular matrices in vitro. *Thromb Haemost* 2002;88:678-85.

TO THE EDITOR: Corwin et al. report both desired and unwanted effects of erythropoietin in their trial involving patients in the intensive care unit. Paradoxical effects of erythropoietin have been reported in other groups of patients and conditions, and the dose of erythropoietin may be important in this respect.

The statement that erythropoietin failed to decrease red-cell transfusions between days 1 and 29, however, may be based on a false premise, since it is generally accepted that in the first 14 days of its administration, this agent does not increase hemoglobin and thus should not influence the need for transfusion.¹

We are concerned about whether iron treatment in the participating patients was adequate and similar in the two groups. Among patients with chemotherapy-related anemia who receive similar amounts of epoetin, intravenous, but not oral, iron supplementation improves the response to epoetin.² In addition, oral iron supplements fail to maintain adequate iron stores in epoetin-treated patients undergoing hemodialysis.³ Therefore, it is possible that in the study by Corwin et al., patients in the epoetin alfa group received

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more parenteral iron than patients in the placebo group. Parenteral iron, as well as the high dose of erythropoietin, might have played a role in the observed, undesired effects of erythropoietin.

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Drs. van der Putten, Braam, and Gaillard report serving as investigators in the EPOCARES study (ClinicalTrials.gov number, NCT 00356733), which is funded by the Dutch Heart Foundation and Roche. No other potential conflict of interest relevant to this letter was reported.

1. van Iperen CE, Gaillard CA, Kraaijenhagen RJ, Braam BG, Marx JJ, van de Wiel A. Response of erythropoiesis and iron metabolism to recombinant human erythropoietin in intensive care unit patients. *Crit Care Med* 2000;28:2773-8.
2. Auerbach M, Ballard H, Trout JR, et al. Intravenous iron optimizes the response to recombinant human erythropoietin in cancer patients with chemotherapy-related anemia: a multicenter, open-label, randomized trial. *J Clin Oncol* 2004;22:1301-7.
3. Macdougall IC, Tucker B, Thompson J, Tomson CR, Baker LR, Raine AE. A randomized controlled study of iron supplementation in patients treated with erythropoietin. *Kidney Int* 1996; 50:1694-9.

TO THE EDITOR: Corwin et al. state in their article, "The most important finding in the current trial is the reduction in mortality among patients who received epoetin alfa as compared with those who received placebo, which was most apparent in the trauma patients." I believe that the most important finding concerns the prespecified primary end point of the trial: epoetin alfa had no significant benefit with respect to the percentage of patients receiving any red-cell transfusion between days 1 and 29. The next most important findings were the lack of any significant benefit of epoetin alfa with respect to the prespecified secondary end points, which were the number of red-cell units transfused, mortality at day 29 and at day 140, and the change in the hemoglobin concentration from baseline to day 29. The subgroup analysis showing decreased mortality among patients with trauma may be an artifact of multiple comparisons or the play of chance. At most, this finding might be considered hypothesis-generat-

ing for a future study of epoetin alfa in a population of patients with trauma.

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TO THE EDITOR: Survival is not the same as mortality. Corwin et al. state, "Mortality at day 29 . . . was significantly lower in the epoetin alfa group than in the placebo group (8.5% vs. 11.4%, $P=0.02$)." However, they report no statistical testing of this hypothesis. A Cox analysis, which tests hazard ratios, showed no significant difference. The significant P value reported is based on the Greenwood formula (which does not compare the total survival experience of the two groups) instead of on the log-rank test, because of concern about censoring of data. We are not aware of this limitation of the log-rank test.¹ We would submit that the appropriate test to compare the 8.5% and 11.4% mortality is Fisher's exact test, which yields a P value of 0.066 ($P=0.051$ for the subgroup of patients with trauma). Unfortunately, critical care clinical trials frequently confuse survival time and mortality by reporting the percentage of patients who die at a specific time with P values from a survival analysis that tests an entirely different hypothesis.²⁻⁴ Although we may place too much emphasis on arbitrary thresholds, the reported reduction in mortality at day 29 that was attributed to epoetin alfa was not statistically significant in the overall population or in the trauma subgroup.

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1. Leung KM, Elashoff RM, Afifi AA. Censoring issues in survival analysis. *Annu Rev Public Health* 1997;18:83-104.
2. Amato MBP, Barbas CSV, Medeiros DM, et al. Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. *N Engl J Med* 1998;338:347-54.
3. Annane D, Sébille V, Charpentier C, et al. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. *JAMA* 2002;288:862-71.
4. Schoenfeld D. Survival methods, including those using competing risk analysis, are not appropriate for intensive care unit outcome studies. *Crit Care* 2006;10:103.

THE AUTHOR REPLIES: Both Mikhail and van der Putten et al. raise issues regarding epoetin alfa

dosing and response. My colleagues and I believe that the absence of a reduction in the transfusion rate reflects transfusion practice, not a lack of hematopoietic effect. The hemoglobin concentration increased significantly, suggesting a hematopoietic effect with epoetin alfa. In our prior study,¹ epoetin alfa administered in a similar manner resulted in a reduction in the transfusion rate at day 29. The hemoglobin response was identical in our prior and current studies; the data for the epoetin alfa and placebo groups began to separate by day 7. Parenteral iron use was not increased with epoetin alfa. A recent study² of the pharmacokinetics and pharmacodynamics of the subcutaneous administration of an identical epoetin alfa dose in critically ill patients showed increased erythropoietin levels and a hematopoietic effect. Whether a different dose, dosing schedule, or route of administration would alter the clinical outcome is unknown.

We disagree with Eisen's characterization of the trauma subgroup. The outcome in this subgroup replicates the results of our prior trial.¹ In the current trial, randomization was stratified according to the admission group (trauma, medicine, or surgery) to ensure that the treatment groups were comparable within each subgroup. Thus, we have now demonstrated a mortality reduction among patients with trauma in two randomized trials. The analysis of the trauma subgroup was an appropriate subgroup analysis.^{3,4}

We agree with Cooke and Rubinfeld's statement that survival is not the same as mortality. Although the raw mortality rates are reported in our article, the P value (0.02) for the overall population was based on the comparison of Kaplan–Meier estimates within each stratum (trauma,

surgical, and medical) and the estimate of the standard deviation with the use of the Greenwood formula. Mortality rates based on the Kaplan–Meier method account for censoring before day 29. For the overall population, stratified analysis is more appropriate to preserve the randomization within each stratum. This is accommodated by the use of a stratified Kaplan–Meier approach. The very same approach was used for the comparison within the trauma subgroup, except that the stratified test was not applicable, since the analysis involved a single stratum. The difference in mortality rates was more pronounced in the trauma subgroup, but the P value was slightly higher (0.039) because of the smaller sample as compared with the overall population. Although the above analyses were the most appropriate, we performed several sensitivity analyses to assess the robustness of the findings. For the overall population, the log-rank P value was 0.049, the stratified log-rank P value was 0.056, and the Cochran–Mantel–Haenszel P value was 0.053. For the trauma subgroup, the log-rank P value was 0.039.

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1. Corwin HL, Gettinger A, Pearl RG, et al. Efficacy of recombinant human erythropoietin in critically ill patients: a randomized controlled trial. *JAMA* 2002;288:2827-35.
2. Vincent JL, Spapen HD, Creteur J, et al. Pharmacokinetics and pharmacodynamics of once-weekly subcutaneous epoetin alfa in critically ill patients: results of a randomized, double blind, placebo-controlled trial. *Crit Care Med* 2006;34:1661-7.
3. Oxman AD, Guyatt G. When to believe a subgroup analysis. In: Guyatte G, Rennie D, eds. *Users' guides to the medical literature: a manual for evidence based clinical practice*. Chicago: American Medical Association, 2002:553-65.
4. Corwin HL. Erythropoietin use in critically ill patients: forest and trees. *CMAJ* 2007;177:747-9.

Rheumatoid Arthritis, Systemic Lupus Erythematosus, and *STAT4*

TO THE EDITOR: Remmers and colleagues (Sept. 6 issue)¹ show that a variant allele of *STAT4* confers an increased risk of both rheumatoid arthritis and systemic lupus erythematosus and thus suggest a shared pathway for these diseases. If two diseases share a common pathogenic pathway, the expected prevalence of their concurrence should

exceed the chance probability of having both diseases. The clinical coexistence of rheumatoid arthritis and systemic lupus erythematosus is rare.²⁻⁵ In the largest reported cohort of patients with this condition, the observed prevalence of concurrent rheumatoid arthritis and systemic lupus erythematosus was 0.09% among patients