Letters and Replies

Does dose matter?

Sir,

We read the recently published paper by Locatelli et al. [1] on the Dialysis Outcomes and Practice Patterns Study (DOPPS) with great interest. The researchers used a Cox regression analysis to evaluate the relationships between haemoglobin concentration at study entry and rates of mortality and hospitalization across five European countries. They concluded that lower haemoglobin concentrations were associated with higher morbidities and mortality among European haemodialysis patients treated with epoetin. We would like to point out that haemoglobin concentration has not been validated as a surrogate endpoint for mortality or morbidity in either CKD or ESRD, and therefore the observed association between anaemia and morbidity or mortality should not be accepted as evidence of a clinical benefit that can be achieved by increasing haemoglobin levels with epoetin treatment [2]. The validation of surrogate endpoints is complex and usually entails conducting interventional trials or a meta-analysis [3,4]. The most widely accepted validation criteria are those of Prentice, who stipulates that both of the following conditions must be satisfied: (i) the surrogate endpoint must be correlated with the true clinical outcome; and (ii) the surrogate endpoint must fully capture the net effect of the treatment on the clinical outcome [5].

With regard to the first criterion, which is usually easy to verify [3], results of DOPPS were consistent with previous studies [6,7] confirming that higher haemoglobin concentrations were associated with decreased relative risk for mortality and hospitalization. However, haemoglobin may fail as a surrogate endpoint by not satisfying the second, more stringent criterion. There are numerous examples in the medical literature of putative surrogates that have failed to adequately predict clinical endpoints [8–10]. In the case of DOPPS, although considerable resources were devoted to collecting and analysing data on epoetin dosing, this information was inexplicably not used as an explanatory or confounding variable in their multivariate analysis predicting mortality and hospitalization. Could the exclusion of epoetin be due to the variability across countries in the route of administration, thereby making it difficult to compare dosing? Or, did the authors assume that the haemoglobin information fully captures any additional information obtained from epoetin dosing because of the well established relationship between epoetin and haemoglobin?

In summary, failure to control for epoetin dose will lead to misinterpretation of the correlation between observed haemoglobin concentrations and morbidity or mortality. In doing so, Locatelli et al. have implicitly assumed that epoetin has no other mechanisms of action other than to increase haemoglobin and thus decrease hospitalization and mortality for all study participants. This ignores the important concern that epoetin, particularly in large doses, may exacerbate hypertension and cause other cardiovascular complications that may affect survival and hospitalization among ESRD patients [11,12]. The high mortality rates, particularly among the US haemodialysis patients, call for clarification of the role of epoetin treatment on morbidity and mortality. Had the DOPPS study controlled for epoetin dose, it would have made an important contribution in this regard.

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Reply

Sir,

Zhang et al. note that the associations in observational studies do not prove a causal relationship, a caveat already.