Reviewer's report

Title: The importance of iron in long-term survival of maintenance hemodialysis patients treated with epoetin-alpha and intravenous iron: analysis of 9.5 years of prospectively collected data

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Reviewer: Michal Mysliwiec

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This is a retrospective study of prospectively computerized data of 1774 patients treated by maintenance hemodialysis in 3 dialysis units in the US from January 1998 to June, 2007. For survival analysis within average 9.5 years of this observational trial, univariate Kaplan-Meier analysis was followed by multivariate analysis with Cox’s regression, using as variables age, race, gender, major comorbid conditions, epoetin a or b weekly dose, intravenous iron monthly dose, and 15 laboratory tests. It has been found that a high Hb level (>120 g/L) and a high serum iron (>10.7 µmol/L), TSAT (>25%), and serum ferritin (>600 µg/L) were associated with the best survival, a relatively low Hb level (110 g/L) and low iron indices with the worst.

The influence of IV iron on survival was profound with the best survival observed in patients receiving 1-202 mg per month, the worst in patients receiving no IV iron at all, and in those receiving >455 mg per month. The influence of EPO on survival was very small, but the best survival was in patients receiving 12.1 x 103 units of EPO per week.

This valuable observational longitudinal study for 9.5 years provide data which are in conflict with data of several controlled clinical trials published recently. Results of Normal Hematocrit study (Besarab A.. NEJM 1998,339,584) and studies of Parfrey et al ( JASN 2005,16,21800) demonstrated increased cardiovascular risk of high hemoglobin level in hemodialysed patients, particularly in patients with heart failure. Recent data from the CHOIR RCT performed in pre-dialysis CKD patients showed increased deaths and cardiovascular complications (myocardial infarction, heart failure, and stroke) with no significant improvement in quality of life in the higher (12.6 g/dL vs 11.3 g/dL versus lower hemoglobin group. Similar were the CREATE study.

The Authors should better describe the clinical state of their patients, particularly some comorbidities like heart failure and infections which have been known to be associated with higher death rate in HD patients with high hemoglobin level. The same deals with LVH, did the Authors observe any changes in LVMI over the years of observations in dependence of hemoglobin level? Was quality of life of the patients studied
There are too much discussion on possible changes in cytokines and only superficial explanation of the results on real clinical grounds.

Recently published guidelines state that no patient should not be routinely maintained at greater than 13 g/dL of hemoglobin level, which is considered to be the upper threshold in ESA-treated patients. The FDA has recently issued a black box warning that recommended that HB in pts with kidney disease not rise beyond 12 g/dL (www.FDA.gov.cder/drug/advisory/RHE2007.htm). Both these warnings should be mentioned in the discussion section.