Reviewer's report

Title: Evaluating the effectiveness of IV iron dosing for anemia management in common clinical practice: Results from the Dialysis Outcomes and Practice Patterns Study (DOPPS)

Version: 0 Date: 31 Mar 2017

Reviewer: Roberto Minutolo

Reviewer's report:

Robinson et al evaluated the effects of different iv iron dosing on the short-term Hgb changes in a wide sample of hemodialysis patients enrolled in DOPPS phase 4. The paper is rather difficult to read and data presentation should be improved. The finding that IV iron dosing was associated directly with Hgb, TSAT, and ferritin change, and inversely with ESA dose change was not new but the secondary analyses provide some original information.

Major comments

DOPPS, being an observational study, provides information on association and not causality. Therefore, study aim and some sentence in discussion should be changed accordingly (i.e. at beginning of discussion, sentences as "Our findings…… support the effectiveness of IV iron dosing ……" or "….iron dosing of less than 300 mg/month…… may be the most effective strategy…." seem more appropriate for a randomized trials rather than for an observational study). Similarly, in the study aim and in the abstract stating that objective is to compare effectiveness of IV iron doses is misleading.

The last sentence of introduction appears related to the study findings rather than to objective (utility) of the study (again, assessing "optimal IV iron management practices" requires an RCT and not a prospective observational study).

From a clinical perspective, the results, as reported, are of relatively limited interest because anemia correction recognized simultaneous assessment of laboratory parameters as well as contemporary evaluation of iron and ESA administration. Therefore, I would be more interested in looking sensitivity analysis such as Hgb by TSAT or ferritin in ESA-treated and untreated patients. Furthermore, Hgb changes in 3 months were strictly dependent on ESA dose changes that, however, were not considered as exposure variable. Indeed, the larger ESA dose reduction was detected in patients with Hgb <11 receiving iron probably as results of greater presence of iron deficiency in these groups. However, no data were provided to support this hypothesis. I think more informative for clinicians an additional (or alternative) analysis evaluating Hb changes (primary endpoint of the present study) associated with different IV iron doses in either iron deficient or iron replete patients stratified for tertiles of ESA dose or, better, for ESA dose
changes in the 3 months (assessed by slope of ESA dose). The corresponding figure will have three panels (stable, decreasing or increasing ESA dose) with Hgb strata on x-axis and with two marks (iron deficient and iron replete) for each Hb stratum. You may also consider three different figures (stable, decreasing or increasing ESA dose) each containing two panels (iron deficient and iron replete patients). In this way, readers could appreciate the role of different iron dosing on Hb changes according to iron status and ESA dose changes.

Results are rather difficult to read. I suggest moving data on the relative change of parameters from the bottom of figures to a new table by adding also the difference between 0 and >300 iron dosing. I recommend reporting n. of patients in each Hgb, TSAT or Ferritin category in figures 1-4.

Definition of "maintenance" and replacement" dosing is discrepant throughout the manuscript. Indeed, in the methods, you reported replacement dosing and maintenance dosing as >500 mg/mo and 300-500 mg/mo, respectively. In the discussion, you indicated as "maintenance IV iron dosing" a dose <300 mg/mo (discussion lines 216-218) and different cut-offs for figure S4 (discussion lines 259-260).

Discussion should be shortened and simplified (it reflects the complexity of results reported).

Minor comments

The sentence stating that IV iron dosing at <300 mg/month may, on average, limit the need for ESA dosing adjustments (Page 12 lines 272-273) is ambiguous and should be clarified. It seems, in fact, that Authors may want support the use of IV iron to limit the need of ESA dose adjustment while the objective of iron supplementation is correcting iron deficiency. The natural consequence of better availability of iron for erythropoiesis is the reduction of ESA dose.

In the Table 1, it would be of interest reporting type of iron administered even though, as correctly reported by Authors, it is not possible to fully analyze the effects of different IV iron formulations.
Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
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