Response to “Data confusion” and “New data on the safety of IV iron -- but why the discrepancy with FIND-CKD?”: Should we REVOKE the initial use of IV iron or FIND CKD to spare ESA

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To answer the question posed by Professors MacDougall and Roger [1], I have compared the two trials in the Table.

| FIND-CKD funded by the makers of Ferinject | REVOKE funded by the National Institutes of Health, USA |
|-------------------------------------------|-------------------------------------------------------|
| **Acronym** | Ferinject® assessment in patients with Iron deficiency anaemia and Non-Dialysis-dependent Chronic Kidney Disease | Randomized trial to evaluate intravenous and oral iron in chronic kidney disease |
| **Intention** | To examine ESA sparing effect of intravenous iron | To examine whether IV iron accelerates the decline in measured GFR |
| **Design** | Open-Label, multicenter, 626 randomized, 193 sites, 3.2 participant/site, 56 weeks | Open-Label, single center, 137 randomized, 1 site, 137 participant/site, 104 weeks |
| **Intervention** | Ferric carboxymaltose targeting ferritin to high level (400 – 600 mcg/mL), lower level (100–200 mcg/L) or oral iron in randomization ratio of 1:1:2 | IV iron sucrose 1000 mg given over 5 visits 2 weeks apart or oral iron in randomization ratio 1:1 |
| **Oral iron dose used** | Ferrous sulfate 200 mg per day | Ferrous sulfate 325 mg three times daily |
| **Primary end point** | Time to initiation of other anaemia management (ESA, other iron therapy or blood transfusion) or haemoglobin (Hb) trigger of two consecutive values <10 g/dL during Weeks 8–52 | Rate of fall in measured GFR (iothalamate clearance measured over 5 hours using 13 blood samples on 5 occasions). |
| **Adverse event reporting** | Adverse events and serious adverse events are reported up to the point at which another anaemia therapy was initiated and/or the randomized study medication was discontinued | AE and SAE reported by intention to treat over the entire two year of the study. |
| **SAE reporting** | Serious adverse events are listed if they occurred in ≥4% of patients in any study group. | All SAEs reported regardless of frequency. AE and SAE were reported separately. |
| **SAE rate** | Serious adverse events were reported in 25.3, 24.0 and 18.9% of patients in the high-ferritin FCM, low-ferritin FCM and oral iron groups, respectively | SAEs in 40/69 (58 %) in oral iron group and 37/67 (55 %) in the IV iron group. Rates are nearly twice as many (for a study twice as long). |
Whereas FIND-CKD was designed to show benefit of IV iron REVOKE [2] was to assess safety. The dose of oral iron used in FIND-CKD was small. REVOKE used 975 mg of oral ferrous sulfate (in line with KDOQI guidelines) where FIND-CKD used 200 mg oral ferrous sulfate. FIND-CKD only found a benefit of high dose IV iron replacement with respect to the primary end point; no difference was found in the low-dose IV iron replacement vs oral iron. One could argue that even this might have been not possible had they given enough oral iron. The mean number of participants per site was 3.2 which suggests that heterogeneity in practice patterns, adherence to protocol or other factors may have influenced results. The follow up was half as long as REVOKE but the number of patients was nearly 5 times as much. Then why was a safety signal not observed in FIND-CKD?

Examining table 3 of the FIND-CKD report reveals in the footnotes that “Adverse events and serious adverse events are reported up to the point at which another anaemia therapy was initiated and/or the randomized study medication was discontinued”. This seriously violates the principle of intention-to-treat. As an example, if ESA was initiated in the IV iron group, the study stopped reporting adverse events. Furthermore, the reporting of adverse events and serious adverse events were not separated. This is important because constipation should not be counted the same as heart failure or pneumonia. If SAEs occurred in <1% of the patients they were not reported at all in FIND-CKD. Even so, the investigators report “serious adverse events were reported in 25.3, 24.0 and 18.9% of patients in the high-ferritin FCM, low-ferritin FCM and oral iron groups, respectively”. Thus, compared to oral iron group, IV iron SAE was between 27% and 34% higher.

Multiple events within patients were not reported. Specifically, Table 3 of FIND-CKD only reports the number of participants who had the event, not the number of events. In other words, multiple CHF events in one patient would only be reported once. REVOKE counted each event as a separate SAE.

MacDougall and Roger imply that single-center, single-investigator adjudicating all SAEs may be less appropriate than a worldwide trial. I will address the issue of adjudications of SAEs first and single-center next.

SAEs are rarely adjudicated, primary end points are. For example, in a cardiovascular trial, the primary end-point may be a composite of myocardial infarction, hospitalization for congestive heart failure, stroke and cardiovascular deaths. These events are adjudicated to establish efficacy of a drug. In such a study if the investigator reports pneumonia, fracture, or leukemia the SAEs are recorded as such. They are not adjudicated. The SAEs are what the investigators report and this provides information on the safety of a drug.
Next, we have to ask ourselves the question whether small, single-center trials are invalid if multicenter trials do not show a signal. Having chaired committees to adjudicate end points in several multicenter trials (BEACON, CREDENCE and SONAR as examples) I believe that I can accurately report SAEs in a clinical trial in which all participants come from my own hospitals. I have full access to their hospitalizations and have to report SAEs in real time as the principal investigator. Simply to state that the trial was done at a single-center by a single-investigator and therefore may not be as valid does not hold much water.

Finally, the reason why the infection-related SAE p values change so dramatically in the adjusted models is because we account for the background history. A person with a past history of pneumonia is much more likely to get another bout of pneumonia. However, the question we are interested in is whether IV iron use provokes infection-related hospitalizations. After accounting for the background history, the answer was an unequivocal yes; enough to compel an independent data safety monitoring board to halt the trial. Whether the SAE data should be adjusted in a randomized trial can be debated but we have reported the SAE data transparently, adjusted and unadjusted. We have even pointed out in the abstract that the SAE rates are adjusted results.

Bhandari [3] et al point out that 40 patients in the oral iron arm and 37 in the IV iron arm had SAEs. At face value it would go against the conclusions of REVOICE that IV iron increases risks of SAEs. What they should consider is not just the number of patients who had SAEs, but the frequency of events among patients who had these events. There were 176 SAEs in the oral iron treatment group and 201 SAEs in the intravenous iron group (adjusted incidence rate ratio (IRR) 1.60 (95% confidence interval (CI) 1.28–2.00, p<0.0001).

Bhandari et al propose that IV iron increasing infections by increasing labile iron is a hypothetical concern. While we did not measure labile iron, this concern for an increased risk of infections is no longer hypothetical. There were 27 hospitalized infectious events among 11 participants assigned to the oral iron treatment group and 37 events among 19 participants of the intravenous iron treatment group (adjusted incidence rate ratio (IRR) 2.12 (95% CI 1.24–3.64, p=0.006). This is not very different from what was seen when iron and folic acid were supplemented in a year-long randomized trial in preschool children in Tanzania [4]. With 25524 years of follow up, an increased risk of severe illness and death were noted with iron and the differences in event rates did not emerge till after 90 days after being on drug. So the contention of Bhandari et al that iron exposure should increase infection rates “within days or weeks” is also not borne out by another large trial which also reported multiple events.

Bhandari et al note that IV iron benefited patients with heart failure, then why the discrepant results in REVOICE. We cannot directly compare our results to the heart failure trials because we did not specifically recruit patients with heart failure. Nonetheless, CKD increases the risk of morbidity and mortality and in REVOICE hospitalizations for heart failure (adjusted IRR 2.08, p=0.038) were increased in intravenous iron group. Whereas 9 patients in each group experienced CHF hospitalization in each group, the frequency of CHF
events was more (15 oral, 28 IV). Thus REVOKE reveals the importance of reporting multiple SAEs within the same patient.

Since FIND-CKD did not report multiple events per patient as was done in REVOKE, I agree with Bhandari et al that the data become confusing. To remove this confusion, let us perform a large definitive trial with reporting of multiple events per patient to assert safety. In fact, I suggest that such a trial be mandated for reasons discussed below.

For approval of drugs used to treat a high risk population such as diabetes, the FDA requires establishing cardiovascular safety [5]. The FDA guidance states, "if the premarketing application contains clinical data that show that the upper bound of the two-sided 95 percent confidence interval for the estimated increased risk (i.e., risk ratio) is between 1.3 and 1.8, and the overall risk-benefit analysis supports approval, a postmarketing trial generally will be necessary to definitively show that the upper bound of the two-sided 95 percent confidence interval for the estimated risk ratio is less than 1.3" [5]. IV iron is liberally used in patients with CKD, a population that has a cardiovascular risk that is even higher than diabetes. Given that IV iron SAE was between 27% and 34% higher even in the FIND-CKD trial (and much higher in REVOKE), should the FDA not mandate a safety trial in this population?

Till such trials are completed, it is now up to the practitioner to decide whether they would REVOKE the initial use of IV iron in preference to oral iron or continue to FIND-CKD patients to use IV iron in the hopes of sparing ESA.

References

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