Author's response to reviews

Title: Heme Iron Polypeptide For The Treatment Of Iron Deficiency Anemia In Non-Dialysis Chronic Kidney Disease Patients: A Randomized Controlled Trial

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Author's response to reviews: see over
Dear Dr Henderson,

Thank-you for the opportunity to submit a revised version of our manuscript to BMC Nephrology. Please see our comments below for each of the reviewers and the editorial board.

Reviewer #1

The first reviewer has several concerns: 1) The comparator being intravenous iron instead of a non-heme iron – in our institution; due to the tremendous cost differential of oral versus intravenous iron - oral iron salts are typically used first in an attempt to correct iron deficiency and only if they are ineffective or poorly tolerated is intravenous iron (venofer) ordered. Similarly, heme iron polypeptide is prohibitively expensive to use for all patients…therefore our purpose was to determine if HIP was as effective as venofer as we did expect to realize cost savings if this was in fact the case; 2) The small sample size and duration of the study - we would argue that this first study was necessary in order to determine if the larger and longer study was justified. The sample size that is required to demonstrate this depends on what is considered a significant difference in the means of the two treatment groups. In a survey of our division, a minimal acceptable difference in mean Hb was 12.5% (range was 10-20%) which is actually a difference of 13.8g/L (in this study); that non-inferiority study would only require 16 patients. However, I think it is very unlikely that anyone would accept this as representing a non-inferior treatment. If I change the difference to 5g/L or 2g/L, I get a total 112 or 694 patients required for the study on anemia. We do not have numbers from which to determine cardiovascular endpoints but I expect we would need to repeat a study like SHARP but with iron as the intervention.

The p-values for the baseline Hgbs have been added to page 6 and to page 7 for the comparison of baseline to month 6.

Reviewer #2

The second reviewer also had several concerns: 1) Sample size – as for reviewer number one, we have included the power and non-inferiority number in the discussion. In order to definitively prove that HIP was non-inferior to intravenous iron sucrose would require a much larger study than we have done; 2) The typical iron sucrose of 1 gram over 3-10 settings has been established in hemodialysis patients who come to the centre 3x/week. The optimal dose and duration has not been established for patients with chronic kidney
disease. In our institution, we serve a very wide catchment area and many patients are reluctant to come more frequently than every 2-4 weeks for treatment. The protocol was written to reflect this practice. Importantly, we also wanted both groups to be iron replete over the same time frame. It is very unlikely that 1 gram of oral iron over 2-3 weeks would be tolerated; 3) The differences in age between the two groups may in fact bias the study against the HIP group. Older individuals are more likely to be inflamed such that the effectiveness of an oral product may be reduced (Guralnik JM, Eisenstaedt RS, Ferrucci L, Klein HG, Woodman RC. Prevalence of anemia in persons 65 years and older in the United States: evidence for a high rate of unexplained anemia. Blood. 2004 Oct 15;104(8):2263-68; Ferrucci L, Corsi A, Lauretani F, Bandinelli S, Bartali B, Taub DD, Guralnik JM, Longo DL. The origins of age-related proinflammatory state. Blood 105: 2294–2299, 2005).

Editorial Comments

We have added the full name of the ethics committee at our hospital and followed the appropriate journal formatting.

I hope that the revisions are considered satisfactory. Thank-you for your time

Yours truly,
Deborah Zimmerman MD, MSc