Author's response to reviews

Title: Optimal and continuous anaemia control in a cohort of dialysis patients in Switzerland

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Author's response to reviews: see over
Point-by-point answers to reviewer 4

Re: BMC Nephrology
Optimal and continuous anaemia control in a cohort of dialysis patients in Switzerland

We would like to thank reviewer 4 for her thoughtful comments. The different points raised by this reviewer have been treated as follows:

1. “The analysis does not appear to allow for clustering Hb values in individual patients over time and for clustering of patients within in centres. The joint analysis of haemoglobin levels and erythropoietin ignores their correlation within an individual and over time. All this leads to incorrect standard errors, confidence intervals and p-values”

We are uncertain whether the design of our study has been properly understood. This is a multi-centre cohort study lasting 12 months for each patient, although these patients did not start the study simultaneously. Each patient underwent 12 blood analysis for Hb, from month 1 (M1) to month 12 (M12), unless the patients was lost to follow-up (11.7%, see below). The use of the mean ± SEM values for Hb from M1 to M12 is to us an appropriate analysis of the control of anaemia. The same analysis has been performed for Epo dose.

We are well aware of the a link between Hb levels and the dose of Epo as reported in the manuscript. This was taken into account in the analysis of the relationship between the 2 parameters which was done on individual values, not on means.

2. “The authors state following aim: To assess "A) if the management of anaemia has improved since previous assessments in dialysed patients in Switzerland". There arise following questions for clarification: What are the control data that inform on whether the current data on Hb management are better or worse than before? Are these only the ESAM data from the surveys? If so, are these surveys comparable given the entirely different study designs with regards to follow up? Were patients in the cited comparison surveys treated with the same doses/agents”

Yes, we agree with the reviewer. We have changed “aim A” in the background on page 3. We also have added “aim D”.

Regarding the comparison between this study and previous assessments of anaemia control, we agree with the reviewer that there are important methodological differences between the Swiss data of ESAM 1998 and 2003 and the current cohort study. In ESAM 1998, patients were selected at random, they were followed during 6 months and mean Hb and other parameters were reported. ESAM 2003 was a one day assessment of Hb, Epo and other values in patients selected by randomisation as well. In both ESAM studies Epo alpha and Epo beta have been used. In contrast, our study has enrolled as many patients as possible on Epo beta only and the patients have been followed during 12 months. However, we would like to emphasize that, to our knowledge, there is no evidence of significant differences between Epo alpha and beta regarding the control of anaemia and Epo doses.

The proportion of patients from Switzerland reaching Hb > 11 g/dL was 65.1 % in ESAM 1998, 78.9% in ESAM 2003 and 85% in our study. In ESAM 1998, Hb values for patients in
Switzerland was 11.7 g/dL, Hb mean value was not reported for Switzerland in ESAM 2003 and it was 11.9 g/dL in our study. Looking at these numbers, we suggest that there is an improvement in the control of anaemia in Switzerland. However, we agree that the comparison between data of different studies requires a cautious interpretation. The 2\textsuperscript{nd} revision has been modified accordingly (page 11, 2\textsuperscript{nd} paragraph).

3. The authors write "Exclusion criteria were the following: unstable angina pectoris, untreated uncontrolled hypertension, haemoglobinopathy, haemolysis, gastrointestinal bleeding, acute infection or unstable systemic inflammatory disease, epilepsy, pregnancy, lactation, deficiency of vitamin B12 (&lt;200 ng/L), deficiency of acid folic (&lt;2?g/L), planned surgery during the survey period (except fistula surgery), known hypersensitivity to EPO beta". This text suggests selection to a relatively healthy prevalent group of patients. Are all the other comparison cohorts cited by the authors selected towards a healthy population in the same way? Based on the massive differences in prevalence of peripheral vascular disease when compared to ESAM 2003 this appears not to be the case. Has the historical comparison with the present data been adjusted for changes in case-mix occurring over time?

The discussion regarding the concern of a possible selection bias in our study has been treated during the first revision. Additional comments are provided:

The relatively high number of exclusion criteria was not aimed to select healthy patients. It was explained by our intention to enrol stable patients at entry. This does not mean that these patients remain stable during the year. Indeed, dialysed patients always have many complications during such a long follow-up, as stated by the mortality rate of about 10%, which is comparable to other studies in this population.

Some of the exclusion criteria, for instance unstable angina, have been chosen to prevent the selection of hospitalized patients who were equally excluded in both ESAM studies. The same can be said for active gastrointestinal bleeding.

Other exclusion criteria, for instance epilepsy and uncontrolled hypertension, may contraindicate the use of Epo and thus these patients have been excluded; however these conditions are not associated with a low Hb in this population.

The reviewer stresses the “massive difference in peripheral arteriopathy between ESAM 2003 and our study”. However, the absolute numbers are relatively low. The definition of peripheral arteriopathy may differ considerably from one study to another. Finally, to our knowledge, peripheral arteriopathy is not associated with a lower Hb in patients treated by haemodialysis.

Taken together, the assumption that the exclusion criteria used in this study may have significantly affected the message of our study, i.e. that HD patients treated in Switzerland have a good control of anaemia, cannot be supported.

4. The authors write "Participating centres were asked to include as many patients as possible, on a voluntary basis, meeting the inclusion/exclusion criteria. Ten dialysis centres included more than 80% of all their patients treated with epoetin beta, and 15 centres in total included more than 60% of their patients receiving epoetin beta, contributing to 71% of the patients included in this survey." Who are the other 29% of patients who are included in this survey?
The remaining 29% of patients came from the remaining 12 small dialysis centres.

5. The authors state as second aim: To assess "B) if the control of anaemia and its treatment parameters could be maintained over a long period of time ". In the methods they state: "...reasons for the incomplete data were the following: death (33), transplantation (7), unknown reason (1).". ""Missing values of patients (Hb, body weight, EPO dose, administration frequency, route of administration), who received at least one survey medication, were replaced by using the last observation carried forward method (LOCF). " This implies dead patients were assumed to have a haemoglobin or treatment dose value despite being dead. Similarly, for transplant patients, who are per definition not on dialysis the dialysis haemoglobin was assumed. This is not a realistic data analysis. Of course, with these assumptions it may be possible for dead people to maintain their haemoglobin. Because all analyses did not take account of clustering of Hb values within patients this may have an effect on the results, depending on the numbers of these partially missing data. The authors' claim that LOCF is a standard method - it is well known to be an approach to missing data that may be associated with severely biased results[1], [2], and the authors should at least make the effort to investigate whether this approach would have led to biased results or not buy conducting sensitivity analyses with another statistical approach.

We agree that the definition of LOCF we have not correctly used in the manuscript. We should have used LOCF only for patients in which some intermediate values were missing, not for patients who were lost to follow up. In the latter cases (11.7% of patients, death n=33, renal transplantation n=7, unknown reason n=1), the data were collected and analysed until the interruption of the follow-up, i.e. the last observation. In very rare cases, one intermediate value was missing in the follow-up and, thus, the LOCF method was used in these cases. We have now corrected the text accordingly.

Having said that, we are confident that the data presented in this study are not biased by missing data.