Title: r.hu-Erythropoietin (EPO) treatment of pre-ESRD patients slows the rate of progression of renal decline

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Version: 1 Date: 17 Feb 2003

Reviewer: Marek Brabec

Level of interest: A paper whose findings are important to those with closely related research interests

Advice on publication: Unable to decide on acceptance or rejection until the authors have responded to the compulsory revisions

General comments:
It was interesting to read the paper. It concentrates on possible beneficial effect that the EPO treatment might have upon renal function. This effect might(if proven sufficiently) be of considerable practical value. In this context, it is certainly interesting to see observations of this study, which are based on real-world data from routine patient monitoring. On the other hand, such findings are obviously somewhat less strong, compared to results from a fully controlled and carefully designed study. This could be reflected in the conclusions. They probably should be less authoritative. Also, treatment of certain technical details and wording used in the paper could be a bit more careful.

Compulsory revisions:
1. Introduction and Methods, Study design
   "a prospective case-control study"
The description of the study design is not completely clear, but from what is given, it seems that it is not a case-control study. For instance, there is no untreated control. Information is available on treated patients only, in the form of pre- and post-treatment measurements. What do you mean by "prospective" in this context?

2. Methods
   It would be nice to know exactly when the data from 17 patients were collected (i.e. what is the span of the treatment start for the 17 patients, in calendar time).

3. Results
   "... pressure was 148/76 5/4 mmHg ...
   Is it SEM or standard deviation what is given here? Both SEM and std's are listed at various places of the text, so that it is not clear what is used here. It might be more convenient to list either SEM or std all the time and mention what is used only once, in the Methods section.

4. Results
   "... p=NS by Student's t-test"
First, this is a terrible notation, which appears several times in the text. Second, it is really pity not to use the p-value if it is available (since it carries a lot more information than the simple statement significant or not-significant, at a pre-specified level). By the way, in the text, no level is mentioned, so one might only guess what level is actually meant. Third, what t-test did you used? Did you used a paired one to account for dependency between pre- and post- measurements taken on the same individual?

5. Results
"... p=NS by Fisher's"
Same thing about p=NS
Fisher's what? If you mean Fisher's exact test, it should be stated without saving the last two words. Moreover, if you use pre- and post- results measured on the same individual, how do you take into account their dependency? Standard Fisher's exact test assumes independent samples.

6. Conclusion
"Treatment of anemia ... with subcutaneous erythropoetin, when ... can slow the rate of renal function decline."
This might or might be true, but the study's design and findings are not of that kind that they could prove causality between EPO and the slow-down. So, the wording should be more careful and in a down-to-earth style, perhaps expressing some caution about possible influence of other factors that were beyond control in this study.

Discretionary revisions:

1. Methods
"... dose of ... units depending on the degree of anemia when the patient's hematokrit was less than ..."
It might be interesting to have the dose as a covariate in the regression model. If it could serve as a crude proxy for degree of anemia, it would be interesting to see if the study's results are stable when degree is varying (testing interaction with this covariate, or its' discretized version).
Also, investigating the dose-response relationship for the EPO might be somewhat helpful (at least as a necessary condition) in the process of checking causality of the EPO for the slow-down of renal function deterioration.

2. End points
"Patients were ... until they required dialysis or death (there was none) or lost to follow up (1/17)."
The sentence is potentially confusing. It would be better to have number of patients requiring dialysis listed in parenthesis right after the word "dialysis" instead of listing it in the next paragraph.

3. End points
"... or lost to follow up (1/17)."
How do you treat the missing value for the lost-to-follow-up when computing statistical tests? Do you simply omit it or do you use some kind of replacement/imputation?

4. Results
"When linear regression analysis was applied to pre- and post- EPO 1/creatinine data ..."
More should be said about the regression and resulting estimates (e.g. their units, etc.). On the other hand, it is not necessary to report things like "Z-statistical value" when you report resulting p-value for the test.
In future (especially when you would have more data available), it would be interesting to try to compare pre- and post-treatment rate of decline in a more formal way, e.g. using a linear mixed model with random person effect (or even random, i.e. individual-specific rate of decline, etc.). This
approach might be more sensitive to changes that you are after. It would be also interesting to investigate the nature of the post- versus pre- change. It is hard to imagine, that the treatment effect is immediate. With sufficient data, it would be appealing to study shape of (probably smooth) transition from pre-treatment to post-treatment creatinine rate (by means of a suitable statistical smoothing techniques). The approach that you actually adopted averages within pre- and post-times, so that it is possible that if there are some changes within these periods, it might tend to muddy the view to some extent. Moreover, it does not allow you to look in a detail at the dynamics of that change (for instance, if the deterioration slow-down occurs quickly after the treatment, or if it takes some time to implement, if the treatment effect is transient or permanent, etc. More structured model might help to answer more focused and more complicated questions of practical importance.

**Competing interests:**

None declared.