Reviewer's report

Title: A prospective randomised cross-over study of the effect of insulin analogues and human insulin on the frequency of severe hypoglycaemia in patients with type 1 diabetes and recurrent hypoglycaemia (the HypoAna Trial): Study rationale and design

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Reviewer: Paolo Rossetti

Reviewer's report:

General comments:
This is a much-needed study aimed at clarifying the role of insulin analogues in reducing the incidence of severe hypoglycaemia as compared with human insulins. Indeed, insulin analogues have been claimed to reduce the incidence of hypoglycaemia but patients with hypoglycaemia unawareness/severe hypoglycemia are usually excluded from clinical trials. In particular, insulin detemir appears to be associated with a significantly lower incidence of severe hypoglycaemia as compared to NPH (1). However, evidence from good quality prospective, randomised trials is lacking.

Regarding the four mayor issues of the review process:

1. Will the study design adequately test the hypothesis?

Yes, it is highly probable that it will. Indeed, the prospective, randomised, crossover design is well suited to detect differences, if any exist, in the rate of hypoglycaemia. Additionally, selection of patients prone to hypoglycaemia (those with >2 episodes of severe hypoglycaemia per year) maximizes the chances of detecting differences between human insulin and analogues. However, there are few aspects of the study design that deserve some comments (see below).

2. Are sufficient details provided to allow replication of the work or comparison with related analyses: if not, what is missing?

Yes, details are sufficient.

3. Does the manuscript adhere to the relevant standards for reporting and data deposition: if not, in what ways?

Yes, it does. Consort guidelines have been followed.

4. Is the writing acceptable?

Yes, it is.

The quality of the protocol is good and the objective is relevant to the clinical practice. However, some minor modifications could be done that would improve
Specific comments:

Introduction.
It should be clearly stated that the study focused only on some analogues (namely aspart and detemir). This is particularly relevant for insulin detemir. Indeed, there is some evidence in animals and also in healthy humans (2,3) that detemir may be associated with different responses to hypoglycaemia as compared to human insulin. Thus, results of the HypoANA trial cannot be extrapolated to other insulin analogues and this should be immediately made clear to the reader. (minor essential revision).

Objective.
The same as Introduction: specify the type of insulin analogues used.

Methods.

1. The Authors chose not to adopt a treat-to-target strategy for insulin titration. Instead, insulin doses were adjusted at discretion of the investigators. In my opinion this is the weakest point of the study. Indeed, the study is not blinded and not establishing common and strict titration rules for both the analogues and human insulins may well result in different metabolic control. This may be particularly relevant in the studied population where the fear of hypoglycaemia may influence either the investigators or the patients preventing effective insulin titration, especially in the human insulin group (human insulin is believed to cause more hypoglycaemia than insulin analogues). The consequence may be the achievement of suboptimal metabolic control and possibly lower-than-expected incidence of severe hypoglycaemia. However, as the study is already completed, results (metabolic control, incidence of hypoglycaemia) will tell us ex-post if this methodological limitation affected the quality of the study. (As the study is completed, comments on this point are at the discretion of the Authors).

2. Were there any inclusion criteria regarding the pre-randomisation insulin treatment? Details regarding the pre-randomisation insulin treatment should be given. (Minor essential revision)

3. Severe hypoglycaemia (discretionary revision). For the sake of clarity and for the benefit of the non-expert reader, please when referring to the Whipple’s triad point out that biochemical definition of hypoglycaemia in patients with diabetes is different from the classical definition in healthy subjects.

4. CGM (minor essential revision). Details regarding the use of CGM and the intended analysis of its data should be provided. Was the CGM self-inserted by the patient and calibrated at home with capillary glucose? Or was it calibrated with venous plasma at the Hospital? This has an impact on the accuracy of blood glucose estimations and should be specified. What metrics have the Authors planned to use? Time spent in hypo? What else? How have you planned to cope
with the issue of false positive and false negative hypoglycaemia episodes as reported by the CGM?

5. Power calculation (minor essential revision). It is not clear how MIREDIF was established. The Authors should explain in what sense a 15% difference in the incidence of hypoglycaemia is considered meaningful. Are there data demonstrating (or at least suggesting) that a 15% reduction in the incidence of severe hypoglycaemia has an effect on hard endpoints (mortality, morbidity, cardiovascular events, etc.) or even on quality of life? Alternatively, does a 15% reduction in severe hypoglycaemia make insulin analogues cost-effective as compared to human insulin? If the Authors have planned to perform a cost-effectiveness analysis, details should be provided.

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

The Reviewer does not have any relevant conflict of interest to declare.