Author's response to reviews

Title: Randomised Prospective Study for the Effect of Therapy on Residual Beta Cell Function in Type-1 Diabetes Mellitus

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PDF covering letter
Reviewer Anders Green

Discretionary revisions
A1. Owners of the data will be the participating investigators. Data are managed at the Justus-Liebig University of Giessen by the authors. They will be also collectively responsible for further publications.
A2. No interim analyses are planned to avoid power reduction of the final analysis. The results of the pilot study (Linn, 1996) did not lead us to expect a conclusion to be obtained earlier.

Compulsory Revisions

B1 Dr. Green questions the ethical justification of the study design. For the following reasons the authors believe that the study is justified on ethical grounds:

1) Ethical Committees of the following institutions have given their consent to the study protocol. Copies of the original statements may be provided to the reviewer or the editor by request.
   - Ethical Committee of Justus Liebig University, Giessen
   - Institutional Review Board of the Physician’s Chamber of the Federal State of Hessia, Wiesbaden
   - Ethical Review Committee of Otto-von-Guericke University of Magdeburg

2) In contrast to the Diabetes Control and Complications Trial (DCCT) authors have reported that in their hands (one-center randomized controlled pilot study) conventional therapy was equivalent to intensive insulin therapy concerning glycosylated hemoglobin (Ghb, HbA1c) during the first three years after diagnosis of diabetes (Linn, 1996, Ref. 8 of this manuscript). The attached figure shows the HbA1c time course of this cohort of newly diagnosed consecutive patients either on conventional or intensive therapy.

We think that there are several reasons for the obvious discordance of our observations compared to the DCCT. First, patients with high insulin reserve (C-peptide > 0.5 nmol/l) were excluded from the DCCT, but not from our study. Second, DCCT patients had their diagnosis from one year onward, while we had followed our patients from diagnosis onward. Third, the DCCT’s conventional therapy allowed up to two and our conventional therapy up to three insulin injections. Fourth, we started off using a one-week training program with structured curriculum for all patients while the DCCT training was not not standardized and more less the matter of each of the 30 study centers. This educational program is standardized for type 1 diabetes, evaluated in most German diabetes centers, and will also be used for future multi-center study protocols.

3) In our pilot study we achieved Ghb levels in the normal non-diabetic range in more than 50% of the patients irrespective of the choice of therapy – conventional or intensive – in the first place. By comparison, only 5% of the DCCT patients on intensive therapy maintained normal Ghb levels.

4) According to the present study protocol insulin therapy of patients with Ghb increased above the normal (!) range ( > 6.3% HbA1c at the central study lab) twice within 6 months must be changed. For example, a patient on conventional therapy with HbA1c 6.7 % at visit 1 and 7.4% and visit 2 must be switched to intensive therapy. This patient will be classified as “therapy failure” in the data bank.
5) The DCCT was not designed to measure the association of C-peptide with G hb. All the same, the DCCT report on this association published in 1998 (Ref. 5 of the manuscript). This report is flawed because DCCT investigators used identical data sets to answer the questions of their main hypothesis (therapeutic strategy and G hb) and several secondary hypotheses. This approach involves multiple testing with the result of lowering alpha values in the subsequent statistical tests. Unfortunately, no alpha corrections were described in this particular publication. Therefore, we believe that the results of the DCCT may imply at best a beneficial effect of intensive insulin therapy on C-peptide but are by no means confirmative for this particular question. Without a confirmative level of evidence intensive insulin therapy should not be turned into clinical practice for protection of C-peptide decay.

6) Patients will be informed on conflicting results of different trials on the effect of therapy on C-peptide. On the basis of this information patients may decide not to enter the randomised trial. These patients will be offered to join the observational groups of conventional or intensive therapy without randomisation. The patient chooses therapy together with his physician. This procedure will give the opportunity to every patient to participate without being randomised. Using this procedure we will be able to estimate the effect of patient preference on outcome of insulin therapy in type 1 diabetes mellitus.

B2
BMI is included into the randomization procedure. Antibodies is a good point. We will include the determination of ICA and GAD by the central laboratory. However, we want to point to the fact that in an adult cohort of type 1 diabetic patients not more than one-third of the plasma samples can be expected to contain one or both of the specific antibodies.

B3
C-peptides are measured every six months, i.e. 6x during the 3-year study period. Therefore, there is a redundancy of C-peptide levels making it possible to sort out patients with rapid or slow C-peptide decrease during the study.

B4
Diagnostic techniques of neuropathy: Careful clinical examination (Vibration test with a tuning fork) and nerve velocity measurements are both standardized and have been used in diabetes studies before. Statistically, it is no problem to correct for C-peptide levels at primary and secondary end points at the same time. However, we have to admit, that it is mathematically somewhat more complicated. This problem will be solved by the Statistics Workgroup of Giessen University.

B5
BMI, age, and sex are important confounding factors and will be taken into consideration in the statistical analysis.

B6
Hypoglycemia is included as a secondary endpoint (page 10, bottom).
Reviewer Erifili Hatziagelaki

Answer to Specific Comments

1) Are non compliant patients continued to be followed and C-peptide levels assessed in accordance with the intent-to-treat principle?

Yes, non-compliant patients will be also followed for three years. Non-compliance is defined on page 8. See also page 12: Patients who change their therapy will be analysed as randomised.

2) The mix of the randomized study ... Why wouldn’t everyone opt to be simply followed and not randomized?

We cannot totally exclude at this point that a majority of patients do not want to be randomized. In fact, we are aiming at randomizing a minimum of 50% of the recruited patients.

Also it tends to be a problem to the site investigators, as to their own ethical viewpoints with regard to the value of intensive treatment and therefore willingness to encourage people to be randomized.

Investigators have agreed upon the importance of randomization. The participating physicians will aim for optimal glucose control in every single study patient independent from the kind of therapy. They can change any insulin regimen if glycosylated hemoglobin is increased over normal (> HbA1c 6.3%) twice within a 6-month time span.
Figure legend
Glycosylated hemoglobin (HbA1c) concentrations (mean, SD) measured every six months in newly diagnosed type 1 diabetic patients on conventional (open circles) or intensive (closed circles) insulin therapy (Figure taken from Linn et al.: Intensive therapy in adult …, Metabolism 45:1508-1513, 1996).
Note that the patients were followed from diagnosis onward (initial HbA1c 12.6 ± 2.5%). HbA1c was reduced to near normal levels within 6 months subsequent to the start of insulin injection. This effect was independent from the type of insulin therapy. Only after three years the HbA1c curves start diverging from each other. At 5 years the difference between HbA1c in the conventional and the intensive treatment cohorts became statistically significant.