Reviewer's report

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

Version: 2 Date: 14 August 2003

Reviewer: Anders Green

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This paper contains a protocol addressing primarily the issue of preserving remaining insulin reserve by intensive insulin treatment in the beginning of the course of Type 1 diabetes (T1D). The protocol represents an open clinical randomised trial, performed as a multi-centre study in Germany. Eligible patients who accept randomization will be assigned to either intensive treatment, incl. multiple insulin injections and more intensive patient education, or conventional insulin treatment and patient education. Those patients who decline randomisation will, after having granted permission so, be monitored on an observational basis in two similar arms of the protocol.

The primary end point is specified as the difference in c-peptide level between base-line and after three years of follow-up. A range of additional outcomes, incl. occurrence of signs of neuropathy and retinapathy, will comprise secondary end points.

The protocol addresses an important issue in clinical diabetology, however it appears to be associated with ethical as well as methodological problems, as indicated below.

a) Discretionary revisions

a1. At least according to some traditions, a protocol on a clinical trial must contain sections describing ownership to data and rather detailed plans for publication.

a2. Similarly, specification of rules for independent interim analyses of data and corresponding "stopping rules" (in case that a conclusion should be obtained earlier than expected) may be considered needed, but are not mentioned in the paper.

b) Compulsory revisions

b1. The greatest concern relates to the ethical foundation of the protocol. Given the fact that, from a clinical and scientifical point of view,
intensive insulin treatment is superior to "old-fashioned" conventional in terms of improving glucose metabolism in T1D and by reducing the risk of long-term complication (albeit at the cost of increased risk of hypoglycaemia), it is hardly ethically justified to ask newly diagnosed patients to be randomised - with the chance of belonging to conventional treatment for the first several years in their life with diabetes. The protocol states that approval has been obtained from relevant institutional review boards, and the protocol contains a comprehensive section of bias handling in which a discussion of the influence of preferences (from patients as well as from caregivers) are presented. Yet, there is no specific section with a precise and balanced account on the ethical aspects. Personally, I find it hardly justified to perform this trial in order to throw light on the natural history of betacell-function and its determinants - a subject that to a large extent can be examined in carefully designed observational studies.

b2. With the diagnostic criteria outlined in the protocol (ie. the lack of considering body mass index and the decision of not considering immune markers) one must expect that quite many younger patients with Type 2 diabetes will be enrolled. There is no indication in the protocol to the respect of how this source of serious confounding will be dealt with.

b3. The primary end point is specified as the difference in c-peptide level between base-line and after three years of follow-up. Nothing is indicated as to how frequently c-peptide levels are examined. This crude operational definition of the primary end point will imply that the outcome for a patient with rapidly declining c-peptide be similar to the outcome of a patient with the same drop in c-peptide but where the drop first takes place immediately before the follow-up examination. Important scientific information is lost this way, unless methods like "area under the curve" or similar approaches are used here.

b4. The protocol does not contain an otherwise needed account of the examination/diagnostic techniques and operational definitions of neuropathy and retinopathy - both conditions appearing as elements of the secondary end points. Also concerning the secondary end points, decreasing c-peptide levels are included here. It seems inappropriate that c-peptide levels appear as components of both primary end point and the secondary end point.

b5. Age and Body Mass Index may be considered important confounding factors in a study like this. The authors have opted for adjusting for these factors by balancing them out between the various arms at the level of randomisation. It is much to be preferred to handle age and BMI as individual "secondary" study variables, to control for confounding effects at the level of statistical analysis. This will most likely provide much more clinically relevant information.

b6. Hypoglycaemia is an important side-effect to insulin treatment, particularly in an intensive regimen. The protocol explicitly states an
interest in looking at the incidence of hypoglycaemia in relation to the c-peptide level at baseline. Nevertheless, hypoglycaemia is not listed among the end points - which it should be, with corresponding definitions of what hypoglycaemia is in operational terms and how this information will be retrieved.

b7. Other "secondary" study variables, like patients’ psychical situation, are introduced in the section dealing with handling of bias. However, if such variables are relevant for the study, they should be presented with full specifications of operational definitions and corresponding classification rules.

b8. Different terms (some places "type-1 diabetes", other places "IDDM") are used for T1D in the paper. A common terminology should be adopted.

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

Level of interest: A paper of limited interest

Quality of written English: Acceptable