Author's response to reviews

Title: Insulin secretion in patients with latent autoimmune diabetes (LADA): half way between type 1 and type 2 diabetes. Action LADA 9

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Author's response to reviews: see over
Dear Editor,

Please, find enclosed the new version of the manuscript entitled ‘Insulin secretion in patients with latent autoimmune diabetes (LADA): half way between type 1 and type 2 diabetes. Action LADA 9’. The response to the reviewers’ comments is included below.

Sincerely,

Didac Mauricio, MD, PhD
RESPONSE TO THE REVIEWERS' COMMENTS

Each reviewer's question is followed by the corresponding response, including the changes that were made. We have arranged the response according to the order on the reviewers’ reports.

Reviewers' comments

Reviewer #1: Bernhard O. Boehm

Major revisions:

1. As requested by the reviewer, this information is now included in the Methods section. A total of 11 study subjects were included in Hospital de Sant Pau (4 with LADA and 7 with type 1 diabetes). All other subjects were included in the other centre (Hospital Arnau de Vilanova). The statistician, a co-author (JRM), confirmed that the inclusion of subjects from 2 participating centres does not affect the statistical power of this study.

2. As recommended by the reviewer, we performed an additional analysis to compare C-peptide responses between patients with LADA and type 2 diabetes under insulin treatment, and also between those non-insulin treated LADA and type 2 diabetic subjects. These results are now included in the results section. Please, note that all comparisons showed statistical difference between LADA and type 2 diabetes. See the last paragraph under Results of the current version of the paper. Also, we included a statement on this finding in the 2nd paragraph of the Discussion. Please, note that as insulin-treatment is actually closely associated with diabetes duration (as expected, all groups show a progressive loss of C-peptide secretion), we did not analyze the difference between insulin and non-insulin treated subjects within each group. This issue has been well characterized in previous studies for all types of diabetes.

3. The number of patients treated with sulphonylureas was 5 in the LADA group (3 of them with combined use of insulin) and 6 in the group of type 2 diabetes (2 of them also with insulin). The number of subjects is not different between groups. Also, the number of subjects precludes any additional comparison. We included the information on sulphonylurea treatment under Results (also in Table 1). Only 1 patient was treated with a DPP-IV inhibitor (sitagliptin) in the LADA group. This information has also been included under Results. Please, note that gliptins were introduced in Spain later than in other European countries and were not available for clinical use during most of the recruitment period of the study. See 2nd paragraph and last paragraph under Results.

Minor revisions:

1. This has now been changed.
2. We have included additional information on the study subjects (also requested by reviewer 2) in the title and footnote of Figure 1. Please, see also the last comment of reviewer 2.

Reviewer #2: T. Tuomi

Major revisions

1. Under Methods, we referred the reader to a detailed description of the patient characteristics described in a recent publication (reference 8). We now include a statement concerning the diagnostic criteria of the different groups which specifically indicates the reference also for this. There are previous publications that indicate that a significant proportion of patients with type 1 diabetes show some preservation of insulin secretion years after the onset. This is especially so in adult-onset subjects. Please, for instance, check the recent publication by Sherr et al (Diabetes Metab Res Rev 2014; 30: 154–162), where even in younger-onset patients stimulated C-peptide above the 0.2 nmol/l threshold is present in 64% of subjects 2 – 5 years after diagnosis and in 42% of those with more than 5 years of disease duration. We are open to introduce a comment on this issue if the reviewer considers that this is necessary.

2. As described under Methods, we followed the procedures described in the European C-peptide trial (reference 13), in which our group had previously participated. The procedure indicates that subjects should withhold short-acting insulin for 6 hours before the test. We have included this in the description of the procedure. Concerning the rest of the comment, please see the response to comment 2 of reviewer 1.

3. The reviewer is absolutely right. We changed this throughout the text, including the Abstract.

4. Again, we agree with the reviewer. The short paragraph in the Discussion that included this comment has now been deleted.

5. Under Results, we have included a paragraph with the description of the number of insulin-treated patients in LADA and type 2 diabetes according to disease duration. Also, we included the number of type 1, type 2 and LADA patients in the footnote to figure 1. We also refer here the reader to table 1 and supplementary tables for further details.

6. We include now tables 2 and 3 as Additional files (now Additional files 1 and 2). We still think that it is important to include this information as online available information as this may be useful to any researchers willing to use this data (i.e. for sample calculations of future studies, data metanalysis). We include information on
insulin-treatment in the figure legend. Also, information on insulin treatment is provided on the footnote of Additional files 1 and 2 (former tables 2 and 3).