Author's response to reviews

Title: Sitagliptin is effective and safe as add-on to insulin in patients with absolute endogenous insulin-deficient diabetes; an observational three case studies

Authors:

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Author's response to reviews: see over
Tokyo, December 5, 2010

Dear Editorial Team,

Thank you for your important comments. They have been reflected in the new version. The followings are the specific responses how they have been handled. All the changes made were colored with red. I hope this revised version is OK with you.

Best regards,

Eiji Kutoh.

The title has been changed.

>1 As sitagliptin was not used as a sole treatment modality in
your patients, so it is advised to change the title to; sitagliptin is effectivas and safe as add-on treatment in patients with absolute insulin-deficient diabetis, an observational three case studies.

Spelling and grammatical errors have been corrected as much as possible.

>2 Spelling errors are much and has to be corrected such: increatin - vial - been injecting - it not clear.

It appears that there are 3 different subtypes of type 1 diabetes: autoimmune, non-autoimmune fulminant and non-autoimmune non-fulminant. The autoimmune type 1 diabetes mellitus comprises about 60% of the patients in Japan. In general, this type can occur rather quickly but still preserves certain levels of endogenous insulin at
diagnosis. However, it is unclear why this patient got acute onset of diabetes with absolute insulin deficiency. I think this is an atypical case. This is discussed in the case presentation section. In any case, this will not change the conclusion of the paper; sitagliptin is effective with absolute insulin-deficient subjects (irrespective of type 1 or type 2 diabetes).

The non-autoimmune fulminant type 1 diabetes comprises about 10% of patients in Japan. This type of T1DM is rare in Caucasian populations. The 30 year old case 2 patient may be this type. This is discussed in the case presentation section.

>3 The authors did not discussed why the first case with 91 years old got acute onset of diabetes with absolute insulin deficiency.
The statement has been revised as you have suggested.

- Please revise the consent statement to confirm that informed written consent was received for publication of the manuscript and figures? Written informed consent was obtained from the patient(s) for publication of this manuscript and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

The author’s contribution section has been included (page 11).

- Please include the authors contribution section. We suggest the following kind of format (please use initials to refer to each author's contribution): FC analyzed and interpreted the patient data regarding the hematological disease and the
transplant. RH performed the histological examination of the kidney, and was a major contributor in writing the manuscript. All authors read and approved the final manuscript.

*The nationality of each patient has been included in the case presentation section.*

- Please include the ethnicity of each patient in the case presentation section of the manuscript.

*Response to reviewer 1*

*The title and the conclusion of the manuscript have been changed.*

> Therefore, please revise this over-riding conclusion and the title of the paper accordingly.
The fact that there was no change in diet/exercise management during the observed period has been included in the case presentation section.

>-Multiple mechanisms, for example exercise and diet management, may influence in A1c in addition to the pharmacological agencies used in this study. Please discuss this.

These have been included at the end of discussion (page 10).

>-The strengths and limitations of the study should be mentioned.

Response to reviewer 2

The fact that this kind of therapy should be used as add
on is now stated in the title and briefly discussed in the Conclusion section (page 10).

>1) Recently in Japan, it was reported that liraglutide (one of the GLP-1 analogs) was switched from insulin and the patients had severe DKA (diabetic keto-acidosis). One should keep in mind that incretin-related therapies can not replace insulin with the those who has no insulin secretion. With such subjects, this kind of therapy can be used as add on to insulin. Therefore, to make sure that the readers of this paper will get this point, the author should stress this in discussion.

They have been included in the abbreviations section in the first page.

>2) All abbreviations should be explained when they first
used or should be included in the abbreviations section.

**Blood pressure (BP) was measured at each visit but it was very variable and one cannot draw any conclusion. So the data of BP is not included.**

> 3) The author investigated the change of glycemic parameters as well as body weigh and gastro-intestinal problems. Did the author check if some other basic measures (for example blood pressure) were influenced after sitagliptin?

*As you can see in the revised version, the discussion has been expanded and other DPP-4 inhibitors are also discussed (page 10)*

> 4) The discussion needs to be tidied up and expanded a bit and there should probably be some further discussion of other DDP-IV inhibitors.
The title has been changed.

>5) In my opinion, the conclusion made by the author is too solid based on observational study with 3 cases. Consider re-writing.

Rev 3

A possibility that sitagliptin may have effects on peripheral glucose utilization distinct from that of insulin/glucagon is discussed in the Discussion section (page 10)

>I think this case report is important demonstrating the role of Incretins in the control of blood glucose not only by enhancing Insulin secretion but also by decreasing hepatic glucose output whether in type 1 or type 2 diabetes. Who knows they may have a role in the peripheral glucose utilisation different from that of insulin action.
More specific details regarding the “extra-pancreatic effect of sitagliptin” are discussed in the Discussion section (Page 10)

>the author's speculation that "the glycemic effects of sitagliptin [in these cases?] may be through mechanisms that are independent of the GLP-1 axis" should be made more specific to possibly relate to the type of patients described in this clinical case study.

The title has been changed.

Minor points

>1. The title states "a case report", when in fact there are 3 cases reported; also the common denominator is more that
these patients are relatively or absolutely insulin-deficient, not whether they have strictly-speaking type 1 or type 2 diabetes, and I would suggest changing the title to reflect that point.

*The spelling errors have been corrected as much as possible.*

2. There are multiple spelling errors throughout – introduction "incretin", "vital?"