Reviewer’s report

Title: Switching patients with acromegaly from octreotide to pasireotide improves biochemical control: crossover extension to a randomized, double-blind, Phase III study

Version: 0 Date: 26 Oct 2015

Reviewer: Mark Gurnell

Reviewer's report:

Summary

The authors report a planned extension to a previous core study in which patients with acromegaly were randomised to treatment with pasireotide LAR 40 mg every 28 days or octreotide LAR 20 mg every 28 days. In the original study, titration to pasireotide LAR 60 mg or octreotide LAR 30 mg was permitted at 3 or 7 months, but not mandatory. At completion of the core study (month 12) patients could continue into the extension study, at which point those with unsatisfactory biochemical control could switch treatment to either Pasireotide LAR 40 mg every 28 days or octreotide LAR 20 mg every 28 days. Among those patients who crossed over, one dose escalation to Pasireotide LAR 60 mg every 28 days or octreotide LAR 30 mg every 28 days was permitted but not mandatory at month 17 or 20. It is the findings of this arm of the extension study that are reported here. A separate manuscript has already reported the results of the extension phase for those patients who achieved satisfactory control at month 12 in the core study.

Comments

For the most part the manuscript is clearly written and complements previous publications by the Investigators reporting the findings of the original core study and one arm of the extension phase. I have only minor points to raise:

1. As stated in the introduction, a GH target of <2.5 mcg/L is based on earlier studies which used radioimmunoassays to measure GH. However, modern guidelines/consensus criteria favour GH < 1mcg/L. Given that the study has used a modern immunometric assay to determine GH, the authors should more openly acknowledge this limitation and discuss its consequences for extrapolation of their findings in to current clinical practice.
2. In Table 3 - Adverse events - disorders of glucose homeostasis are divided into 'hyperglycaemia' and 'diabetes mellitus' - this continues to seem an unusual distinction - and the risk of presenting data in this way is that it makes it more difficult for the reader to gain a full appreciation of the extent of glycaemic disturbance in the pasireotide group - which is of course the major concern of therapy with this agent. The authors do combine these in the text - which helps to emphasise the differences between pasireotide and octreotide - and so it would seem sensible to do the same in the table?

3. Tumour volumes were determined by hand drawing around the tumour circumference on coronal slices, and then multiplying the area by slice thickness - but it appears that a variable slice thickness was allowed - if so, can the authors confirm the range? Ideally, a standardised slice thickness/protocol should have been adopted across centres - and preferably 1mm thickness to provide the most accurate estimate of tumour volume.

4. The header for the GH and IGF-1 measurement and assays section in the supplementary methods is incorrect.
Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
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Yes

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