Author's response to reviews

Title: Two acromegalic women presenting reversible pegvisomant-related lipohypertrophy and its possible recurrence at the new site of injection, clinical and radiological evidence of body composition change: a case series

Authors:

Vincenzo Rochira (vincenzo.rochira@unimore.it)
Lucia Zirilli (lucia.zirilli@unimore.it)
Chiara Diazzi (chiaradiazzi@gmail.com)
Stefania Romano (s.romano@ausl.mo.it)
Cesare Carani (cesare.carani@unimore.it)

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Author's response to reviews: see over
To: Professor Michael Kidd AM,  
Editor of the Journal of Medical Case Reports  
c/o BioMed Central  
236 Gray’s Inn Road  
London WC1X 8HB  
United Kingdom  
Phone:+44 (0) 20 3192 2009  
Fax :+44 (0)20 3192 2010

Dear Professor Michael Kidd AM

Please find enclosed the revised version of the manuscript entitled “TWO ACROMEGALIC WOMEN PRESENTING REVERSIBLE PEGVISOMANT-RELATED LIPOHYPERTROPHY AND ITS POSSIBLE RECURRENCE AT THE NEW SITE OF INJECTION; CLINICAL AND RADIOLOGICAL EVIDENCE OF BODY COMPOSITION CHANGE. A CASE SERIES” that we are re-submitting to the Journal of Medical Case Reports for publication as Case series.

We revised the manuscript according to Editor’s and Reviewers’ suggestions. All the changes are highlighted in the revised version (the text added is in blue; the text deleted is in red) and in the Point by Point Rebuttal Letter we provided all the details concerning the manuscript changes.

Please, do not hesitate to contact me if you have any problems in reading the manuscript or if you need additional information.

Best Regards  
Modena, 15 July 2011

Vincenzo Rochira and co-Authors
Answers to Editor’s and Editorial Office Comments

1) Please include the ethnicity of the patient in the case presentation section of the manuscript.
The ethnicity of the patients was reported only in the abstract in the first version of the manuscript. We thank the Editor for the comment and we added the ethnicity (both patients are Caucasian) even in the full text in the section Case presentation.

2) Please restructure the authors contribution section.
We rewrote this section according with Editor’s suggestions:
“VR and SR designed the study. VR, SR and CC performed the clinical examinations. LZ and VR analyzed and interpreted patients’ data according with literature and wrote the first draft of the manuscript. CD, SR, VR; LZ contribute to reach the final version of the manuscript. CC supervised the entire work. All authors read and approved the final manuscript.”

3) We would be grateful if you could address the comments in a revised manuscript and provide a cover letter giving a point-by-point response to the concerns.
We enclosed a cover letter giving a point-by-point response.

4) Please also highlight (with ‘tracked changes’/coloured/underlines/highlighted text) all changes made when revising the manuscript to make it easier for the Editors to give you a prompt decision on your manuscript.
All changes are highlighted in the revised manuscript. The text added is in blue; the text deleted is in red.

5) Please also ensure that your revised manuscript conforms to the journal style (http://www.jmedicalcasereports.com/info/instructions/). It is important that your files are correctly formatted.
Done
Answers to Referee 1 Comments

We thank the Reviewer for appreciating the study.

In the revised version of the manuscript all changes are highlighted: the text added is in blue; the text deleted is in red.
Answers to Referee 2 Comments

We appreciated the overall positive comment of the Reviewer and we changed the manuscript according to the Referee’s minor suggestions.

In the revised version of the manuscript all changes are highlighted: the text added is in blue; the text deleted is in red.

1) Page 3; 7th line: “most common clinical relevant’. As far as I know increase of pituitary tumor size and headache are not so frequently observed during pegvisomant therapy. I agree they are clinical relevant.
We agree with the reviewer that pegvisomant-related increase in pituitary tumor and headache are not so common and we apologize for writing the sentence in an incorrect fashion. We changed the sentence as follows:
“A transient increase of liver enzymes [1, 4], the increase in size of the pituitary tumor [1-3, 4-6], and headache [2] are rarely reported, but they are considered as clinically relevant events occurring during pegvisomant administration, with a frequency similar to other treatment regimens [6].”

2) Page 5; 7th line: “cabergo”
We corrected the term into cabergoline.

3) Page 6; line 8-13: The sentence is confusing. Do they always refer to patient 2 (as stated) ? or also patient 1? We apologize for the inaccuracy. We carefully rewrote this sentence as follows:
“Both patient 1 and patient 2 did not experience other side effects, in particular no enlargement in pituitary residual tumor diameter was recorded. Due to the discomfort related to lipohypertrophy, patient 2 decided to stop pegvisomant notwithstanding our advice about the benefits of the treatment and the importance of continuing pegvisomant administration. In patient 2, pegvisomant withdrawal resulted in a progressive disappearance of the lipohypertrophy. Patient 1 was asked to rotate the site of injection over several districts (thighs, abdomen, arms, buttocks), which resulted in a minimal swelling distributed to several districts that is not so evident to impair patient’s compliance to the treatment.”

4) Page 7; line 6-9: The Authors state that the period of injection over the thighs was shorter in comparison to the abdominal site. However, according to medical history phase 1 duration of patient 1 and 2 were 4 and 2 months months respectively while phase 2 duration was 4 months in both subjects. As stated in the ‘Cases Presentation’ Section, lipohypertrophy developed quickly in patient 2 (recorded at physical examination after 2 months from the starting of peg-treatment), while it was observed after 4 months from the starting of peg-treatment in patient 1. The first radiological examination was performed in both patients at least after 8 months from the starting of peg-treatment (Phase 1), independently from the time of development and of observation (at physical examination) of the appearance of lipohypertrophy. It should be considered that lipohypertrophy developed in 2005 (patient 1) and in 2006 (patient 2) when this side effect of the treatment was still not known. Thus, both patients remained in follow-up and a detailed radiological study was planned at least after 8 months from the starting of pegvisomant treatment. With this in view, the period of injection over the thighs was shorter in comparison to the abdominal site. We changed the sentence (page 5, 16) as follows:
“Both patients underwent detailed clinical and radiological investigations at baseline (Phase 1) after at least 8 months from the starting of pegvisomant treatment, when pegvisomant therapy was performed by means of daily abdominal subcutaneous injection at the dose of 10 mg once a day and abdominal lipohypertrophy had been just developed.”

5) Table 1: it would be helpful to report body weight in phase 1 and 2 (both individuals)
We agree with the Referee and we added body weight values obtained from patients’ medical charts. A small increase in body weight was recorded in both patients. This result is concordant with the decrease in IGF-1 serum levels in both patients and allows confirming a greater effect of pegvisomant in Phase 2. We further discussed this issue in the Discussion (see point 8 for details).

6) Table 1: it would be helpful to report DEXA total body fat and fat free mass (both individuals)
We added the DEXA parameters requested. Changes in total body fat and fat free mass were consistent with a greater effect of pegvisomant in Phase 2, a result that is in accordance with the decrease in serum IGF-1 in Phase 2. We further discussed this issue in the Discussion (see point 8 for details).

7) - Figure 1: the quality of the imagine does not allow a larger magnification view nor the reading of measurements
In the revised version of the manuscript the magnification of the figure is improved. If the quality of the image is still not good for publication we might provide each figure of the panel 1 separately in order to further improve the quality of the image.

7a) - Figure 1:
o Abdomen: it seem to me that going from phase 1 to phase 2 there is a decrease of body fat of the anterior abdominal wall and an increase of body fat in the flanks-back areas. I suggest to measure the fat thickness also in these districts
We measured body fat in the flanks-back areas and we found a slight fat increase in these areas in Patient 2, but no changes in Patient 1 (an artifact is present in Patient 2 in Phase 2 resembling an increase in flanks-back areas fat). We reported this result both in the section of Cases presentation and in Figure 1.

o The same observation at the leg level. I suggest to measure change in fat thickness also in the posterior surface of the thighs which seem to be increased as well.
We measured changes in fat thickness also in the posterior surface of the thighs and it was increased in both subjects. We reported this result both in the section of Cases presentation and in Figure 1.

8) Discussion. According to possible new findings coming from the suggested measurements (Table 1, and Figure 1) the Authors could enlarge their discussion mentioning that treating acromegaly and obtaining IGF-I normalization might be also associated with a reduction of fat free mass and augmentation of total body fat mass, independently of therapy.
We updated the discussion according with the results of fat measurements in the back areas of legs and flanks.
We added the following sentence in the discussion:
“The better control of IGF-1 serum levels in both subjects is further substantiated during phase 2 by the increase in body weight, in total body fat mass, in fat redistribution at both abdominal and thigh level (increase in body fat in the posterior areas of the abdomen and the thighs) and by the decrease in total body fat free mass in both patients, independently from therapy (Table 1, Figure 1).”

9) Abstract conclusion: I think that in clinical practice the physical examination is enough for lipohypertrophy detection (I do not suggest radiological examination as a necessary investigation).

Physical examination is probably enough to monitor the site of injection, but radiological examination may be of help in some particular conditions (e.g. when physical examination leads to doubtful interpretation). We do not suggest performing radiological examination in all cases. We changed the sentence as follows:

“In clinical practice, physical examination of the injection site/s should be performed for the early detection of lipohypertrophy during pegvisomant treatment, radiological procedures may be of help for confirming subcutaneous fat changes and for a precise monitoring of fat redistribution, and the rotation of the site of injection may prevent lipohypertrophy.”