Author's response to reviews

Title: Prolactinomas, Cushing's disease and acromegaly: debating the role of medical therapy for secretory pituitary adenomas

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Author's response to reviews: see over
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Re: Response to reviewers’ comments on Manuscript 1332064570315130
[Prolactinomas, Cushing's disease and acromegaly: debating the role of medical therapy for secretory pituitary adenomas; Beverly MK Biller, Annamaria Colao, Stephan Petersenn, Vivien S Bonert and Marco Boscaro]

Dear Ms Neilan,

We would like to thank the reviewers for their thoughtful consideration and input. The authors have all agreed on the revisions made in response to these questions and comments and these are outlined below in the following format:

Comment – Each comment is listed verbatim in Arial italic font.

RESPONSE – The authors’ response to each comment is noted in Arial normal font and the page number in the manuscript containing the revised text is noted.

Revised text – The revised text in response to the authors’ comment is quoted below the RESPONSE in Tahoma bold font.

We appreciate the time spent by the reviewers and the editor and believe that the suggested changes have substantially improved the manuscript. We look forward to hearing whether it is now acceptable.

Yours sincerely,

Beverley MK Biller
Reviewer 1: Ferdinand Roelfsema

The manuscript ‘Prolactinomas, Cushing’s disease and acromegaly: debating the role of medical therapy for pituitary adenomas’ is a review on current therapeutic options in these disorders. The manuscript is clearly written and probably intended for the internist and GP. There are a few issues which should be considered by the authors.

1. It is not clear why the authors excluded the under-diagnosed thyrotropinoma and gonadotropinoma from this review. In fact, all functional pituitary adenomas are rare.

RESPONSE – The manuscript reports the content of an independent CME symposium at the 89th Annual Meeting of the Endocrine Society, which did not include presentations on thyrotropinoma and gonadotropinoma. This topic was, therefore, not included in the paper.

2. Nelson’s syndrome is mentioned, although not the associated disturbing hyperpigmentation. The authors do not discuss the treatment of this syndrome.

RESPONSE – As requested, additional detail has been included on page 14:

Nelson’s syndrome is the aggressive growth of a pituitary corticotroph adenoma after bilateral adrenalectomy, and is associated with symptoms such as skin hyperpigmentation, headache and visual impairment, which arise due to the mass effect of the tumor and increased ACTH secretion [41]. Close monitoring by regular MRI scans and measurement of plasma ACTH levels should be undertaken to detect the occurrence of corticotroph tumor progression. Early detection offers the possibility of cure by surgery (microadenoma) or radiotherapy (invasive adenomas).

3. Although extremely uncommon at young age, the treatment of pituitary adenomas in children is not discussed.

RESPONSE – This topic was not discussed at the symposium and we feel that it is outside the scope of the manuscript.

4. A few lines on treatment of adenomas in pregnancy should be considered.

RESPONSE – While this is one of many associated topics of interest, we feel that this also falls outside the scope of the manuscript as it was not discussed at the symposium.
5. A new line of extremely potent drugs for pituitary adenomas, the chimeric drugs developed by Ipsen, is not mentioned.

RESPONSE – Reference to this agent has also been requested by reviewer 2. Discussion of the chimeric somatostatin/dopamine receptor agonist has been added to each of the three sections covering prolactinomas, Cushing’s disease and acromegaly. The following text has been added to the prolactinoma section on page 12:

Because prolactinomas express both D₂ and sst₅ receptors, there is a rationale for the use of chimeric D₂/sst₅ agonists such as BIM23A760, which has high sst₂ and D₂ activity and moderate sst₅ activity [30,31]. A recent *in vitro* study of primary cultures of ten prolactinomas (six responsive to dopamine agonists and four resistant to dopamine agonists) showed that BIM 23A760 and cabergoline produced a similar partial inhibition of prolactin secretion [32].

The following text has been added to the Cushing’s disease section on page 19:

The potential for interaction between somatostatin and dopamine receptors to achieve greater suppression of ACTH levels is being explored with the development of chimeric agents. BIM 23A760 is one such agent, with high sst₂ and D₂ activity and moderate sst₅ activity [30,31]. Observation of a high co-expression of sst₅ and D₂ in the majority of human corticotroph adenomas studied supports the potential for this agent in the treatment of Cushing’s disease; clinical evaluation has not yet been performed [72].

The following text has been added to the acromegaly section on page 28:

The potential for dual somatostatin/dopamine activity in the treatment of patients with acromegaly will be addressed in studies of the chimeric dopamine/somatostatin receptor agonist BIM-23A760. In normal cynomolgus monkeys, BIM-23A760 has been seen to produce potent dose-related GH suppression, with no effect on circulating insulin or glucose levels.[120]
6. Decrease of IGF-I by peripheral actions of somatostatin analogs in liver and other peripheral organs is not discussed. The contribution of liver-derived IGF-I to disease activity etc is not established in man.

RESPONSE – This is a good point, and for completeness we have added a sentence regarding the peripheral action of somatostatin analogues on IGF-1 on page 23:

More recently, it has been suggested that a sst ligand may also act peripherally on the GH/IGF-1 axis by binding to somatostatin receptors on peripheral organs, such as hepatocytes in the liver, to inhibit the secretion of IGF-1 [92].
Reviewer 2: Krystallenia Alexandraki

This is a well written review which summarizes recent advances on medical treatment of the secretory pituitary tumours. The clinical significance of this paper is supported by recent evidence that medical treatment of pituitary tumours challenges the advantages of surgical management. Hence, medical therapy in prolactinomas is now considered the first line treatment; in acromegaly has an increasing input in the management of the disease; finally, in Cushing’s disease (CD) drugs directed to the adrenals are the mainstay of therapy to control hypercortisolaemia, and recent published literature emphasizes on a pituitary-targeted medical therapy. In addition, the value of medical therapy is enhanced since it may be considered in patients who cannot be submitted to surgical procedures because of co-morbidities, or who are unwilling to receive other types of treatment. However, some further points have to be added in this review to include all the current armamentarium for secretory pituitary tumours medical treatment.

Major Compulsory Revisions

I. Management of Prolactinomas

1. Another future possible medical therapy for prolactinomas along with pasireotide might be dopastatin chimeric molecule which targets sst2, sst5 and D2 receptors; hence, a brief report should be useful (1-3).

RESPONSE – Reference to this agent has also been requested by reviewer 1. Discussion of the chimeric somatostatin/dopamine receptor agonist has been added to each of the three sections covering prolactinomas, Cushing’s disease and acromegaly. The following text has been added to the prolactinoma section on page 12:

Because prolactinomas express both D2 and sst5 receptors, there is a rationale for the use of chimeric D2/sst5 agonists such as BIM23A760, which has high sst2 and D2 activity and moderate sst5 activity [30,31]. A recent in vitro study of primary cultures of ten prolactinomas (six responsive to dopamine agonists and four resistant to dopamine agonists) showed that BIM 23A760 and cabergoline produced a similar partial inhibition of prolactin secretion [32].

II. Management of Cushing’s disease

Regarding the Management of Cushing’s disease although the authors report adrenal- and pituitary-directed treatment, they do not mention at all mitotane and etomitade, the glucocorticoid antagonist, mifepristone or the promising future therapy with the ligand dopastatin.
Mitotane has been considered to be highly effective in the long-term suppression of hypercortisolism in patients with CD because of this adrenolytic action (4), with long remissions after cessation of treatment (5). Etomidate has been considered useful since can be administered intravenously resulting in rapid control of cortisol levels when oral therapy cannot be administered as in cases of critically ill patients with CD (6). Mifepristone has been shown to be beneficial in long-term treatment of a macroadenoma, with remission of life-threatening clinical symptoms (7) and more recently this effect has been confirmed (8).

RESPONSE – We thank the authors for pointing out these omissions, which we agree should be added to complete this section. The following text has been added to pages 16 and 19.

Mitotane and etomidate are also sometimes used in the treatment of Cushing’s disease. Mitotane is a derivative of dichlorodiphenyldichloroethane (DDD) that specifically inhibits cells of the adrenal cortex. This adrenolytic action may prove effective in the long term suppression of hypercortisolism in the majority of patients with ACTH-dependent Cushing’s syndrome [45,46]. Its mechanism of action also prevents the risk of escape phenomenon in response to the ACTH rise that occurs in Cushing’s disease when plasma cortisol is decreased. However, its onset of action is slow (weeks or months), and the adverse effects associated with mitotane therapy (mainly digestive and neurological) require careful monitoring of drug levels, and it is routinely used in only a few centers. Etomidate is a non-opioid anesthetic that also induces adrenocortical suppression as one of its main side effects. In situations where rapid control of cortisol levels is required and oral therapy is problematic, iv etomidate therapy may be considered [47-49].

Other approaches
Mifepristone is the only available glucocorticoid receptor antagonist. Although clinical data are currently limited in patients with Cushing’s disease, early clinical data have demonstrated effective treatment of hypercortisolism, but close monitoring of potentially severe hypokalemia, hypertension, and clinical signs of adrenal insufficiency is required [73,74].

Retinoic acid has been shown to be potentially useful in decreasing corticotroph secretion and proliferation in rodent models, and more recently in a dog model of Cushing's disease [75]. However, the effective dose used is high and clinical trial results in humans are not currently available.
3. The recent observation of a high co-expression of sst5 and D2 receptors in the majority of human corticotroph adenomas studied (9) supports the use of the somatostatin-dopamine ligand dopastatin as a trial agent in CD (1,10); hence, a brief report should be useful.

RESPONSE – Discussion of the chimeric somatostatin/dopamine receptor agonist has been added to the Cushing’s disease section on page 19:

The potential for interaction between somatostatin and dopamine receptors to achieve greater suppression of ACTH levels has been investigated with the development of chimeric agents. BIM 23A760 is one such agent, with high sst2 and D2 activity and moderate sst5 activity [30,31]. Observation of a high co-expression of sst5 and D2 in the majority of human corticotroph adenomas studied supports the potential for this agent in the treatment of Cushing’s disease; clinical evaluation has not yet been performed [72].

RESPONSE – Thank you for this very good suggestion. We agree that a discussion of this study would be of benefit in the paper. The following text has been added to page 17:

4. Regarding PPAR-γ ligands the initial enthusiasm based on in vitro studies was not confirmed in recent small-scale clinical trials in patients with CD. However, it might be useful to comment on a recent study that reported: a) a poor expression of PPAR-γ receptor in human pituitary tissue; b) no detection of a specific abnormality in PPAR-γ expression in corticotroph tumours; c) poor immunocytochemical expression in both normal pituitary and pituitary adenomas with only weak cytoplasmic staining; d) the antiproliferative effect of rosiglitazone was shown only at very high doses and these were not blocked by a specific PPAR-γ antagonist (11).

However, evaluation of normal pituitary tissue and pituitary tumors has shown poor expression of PPAR-γ receptor in human pituitary tissue, no detection of a specific abnormality in PPAR-γ expression in corticotroph tumors, poor immunocytochemical expression in both normal pituitary and pituitary adenomas, with only weak cytoplasmic staining [52]. In addition, the antiproliferative effect of rosiglitazone was shown only at very high doses and these were not blocked by a specific PPAR-γ antagonist.
III. Management of Acromegaly

5. Another medical therapy for acromegaly might be dopastatin chimeric molecule which targets sst2, sst5 and D2 receptors; a brief report should be useful (2,3).

RESPONSE – Discussion of the chimeric somatostatin/dopamine receptor agonists have been added to the acromegaly section on page 28:

The potential for dual somatostatin/dopamine activity in the treatment of patients with acromegaly will be addressed in studies of the chimeric dopamine/somatostatin receptor agonist BIM-23A760. In normal cynomolgus monkeys, BIM-23A760 has been seen to produce potent dose-related GH suppression, with no effect on circulating insulin or glucose levels [120].

IV. Summary frame

6. In the first bullet regarding prolactinomas, radiotherapy; should also be mentioned for ‘specific patients’.

RESPONSE – The following text has been added to the first bullet on page 30:

Radiotherapy is indicated for selected patients, such as those who have not responded to medical or surgical treatment.

7. In the second bullet, radiotherapy and adrenal directed therapy should also be mentioned as well as bilateral laparoscopic adrenalectomy for an immediate remission of hypercortisolaemia when all else fails and patients remain intolerant or incompletely treated.

RESPONSE – The following text has been added to bullet 2, page 30:

Additional approaches include radiation therapy and adrenal-directed therapy, as well as bilateral laparoscopic adrenalectomy for immediate remission of hypercortisolemia when other approaches have failed and patients remain intolerant or incompletely treated.

V. Adverse effects

8. Adverse effects that limit or currently precluded the amended treatments should be accordingly added for an homogeneous presentation.
RESPONSE – We agree that a balanced article requires discussion of both the beneficial and adverse effects of any treatments. For each treatment discussed, a summary of the adverse effects of those treatments is presented.

Minor Essential Revisions

Title.

Since the authors are discussing the medical treatment for the secretory pituitary adenomas, it might be more fruitful to underline this fact to the readers as following: ‘Prolactinomas, Cushing’s disease and Acromegaly: debating the role of medical therapy for secretory pituitary adenomas.’

RESPONSE – Thank you for this good suggestion. The title has been amended accordingly.

Prolactinomas, Cushing’s disease and acromegaly: debating the role of medical therapy for secretory pituitary adenomas

Figures

1. Figure 3 is not self-explanatory. It should be written in the legend the type of disease as ‘patients with’ and the synopsis of the study and in the graph the type of disease as ‘patients with’ if this is possible.

RESPONSE – In order to clarify the figure (Figure 2 in the revised manuscript), detail of the study and patient type have been added to the legend as follows:

Phase II study of 29 patients with de novo or persistent Cushing’s disease receiving pasireotide 600 µg sc bid for 15 days. Mean UFC level at baseline and study end (day 15) in each patient (n=29) are shown. The normal range for UFC is 55–276 nmol/24 h (20–100 µg/24 h); the dashed line indicates the upper limit of the normal range. Responding patients (defined as having a UFC level within the normal range at study end) are indicated by the arrows [62].

2. In Figure 4, it should be written in the legend the type of disease as ‘patients with’ and in the graph as well if this is possible.

RESPONSE – The axis of the figure (Figure 3 in the revised manuscript) has been amended to clarify that these data represent patients with acromegaly. The figure legend has been amended as follows:
Effect of somatostatin analogues on pituitary tumor size in patients with acromegaly, showing the percentage of patients with >10% tumor volume reduction after adjuvant or first-line therapy [108]

3. In Figure 2, it should be written in the graph ‘patients with prolactinoma’ if this is possible.

RESPONSE – This query relates to Figure 1 of the submitted manuscript, rather than Figure 2. At the suggestion of Reviewer 3, Figure 1, which showed the changes in cardiac parameters in patients treated with cabergoline, has been removed.

Discretionary Revisions

I. Management of Cushing’s disease

1. A mention of stereotactic radiosurgery could be appropriate to complete the management of CD (12).

RESPONSE – The following text has been added to page 14:

Second-line therapy includes more radical surgery, radiation therapy, including stereotactic radiosurgery, medical therapy and bilateral adrenalectomy [37,38]

2. Regarding ketoconazole a referral to a more recent long term study would be also useful to support its clinical value as safe and efficacious treatment in CD, particularly in patients for whom surgery is contraindicated or has to be delayed during the investigation of an occult adenoma (13).

RESPONSE – Thank you for this good suggestion. The following text describing this retrospective study has been added to page 15:

A recent retrospective analysis of the long-term hormonal effects and tolerance of ketoconazole has been conducted in 38 patients with Cushing’s disease, with a mean follow-up of 23 months. The data demonstrate good tolerability and effective control, particularly in patients for whom surgery is contraindicated, or delayed during the investigation of an occult adenoma [43].

3. A referral on retinoic acid as a promising alternative might be useful after the beneficial effects seen in CD in dogs (14).
RESPONSE – We agree that a brief mention of retinoic acid would complete this section on medical therapy. As requested, the following text has been added to page 20:

Retinoic acid has been shown to be potentially useful in decreasing corticotroph secretion and proliferation in rodent models, and more recently in a dog model of Cushing’s disease [75]. However, the effective dose used in dogs is high and clinical trial results in humans are not currently available.
Reviewer 3: Vera Popovick

The review on medical therapy for pituitary adenomas is aimed to provide information to a broad biomedical audience and is written according to this aim. The review is written by experts who have the necessary experience and who have extensively published on the issue. Some minor revisions:

1. Page 8 instead of nontumoral prolactinomas should be nontumoral hyperprolactinemia

RESPONSE – Thank you for noticing this error. The text has been amended as follows (page 9):

Patients in this study had nontumoral hyperprolactinemia (n=25).

2. Page 11 should be mentioned that resistance to dopamine agonists discussed in this section is partial resistance since true and severe resistance is seen only in prolactin- carcinomas.

RESPONSE – Thank you for bringing this to our attention. A statement has been added, and cited, to the end of the sentence that defined resistance to dopamine agonists. The text has been added on page 11:

Resistance to dopamine agonists can be defined as a failure to achieve normalization of prolactin levels or no reduction in tumor size after 12–24 months of bromocriptine 15 mg/day or cabergoline 0.5 mg/day [6,25-27]; most cases of resistance to dopamine agonists can be considered partial resistance [28].

3. Page 19 In the section Radiotherapy the sentence starting with Stereotactic radiosurgery administered in single dose refers only to (gamma knife). Stereotactic radiotherapy on the other hand includes the use of proton beam and LINAC, so this needs to be corrected.

RESPONSE – the text has been amended as follows (page 22):

Stereotactic radiotherapy administered in a single dose (gamma knife, proton beam and LINAC)

4. Fig 1. Raises safety concerns for cabergoline in terms of developing moderate tricuspid valve regurgitation but as correctly discussed this is still a matter of debate amongst endocrinologists and not yet solved. Since this review is aimed at broad audience I wonder if we need this figure, isn’t the discussion enough for this yet unsettled issue!
RESPONSE – We agree that this figure isn’t a necessity and may give too much weight to an unsettled issue. As such, we have removed this figure from the manuscript.