Reviewer's report

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

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Reviewer: Krystallenia Alexandraki

Reviewer's report:

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).

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.

2. 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).
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.

4. Regarding PPAR-# 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-# receptor in human pituitary tissue; b) no detection of a specific abnormality in PPAR-# 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-# antagonist (11).

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).

IV. Summary frame

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

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’.

V. Adverse effects

8. Adverse effects that limit or currently precluded the amended treatments should be accordingly added for an homogeneous presentation.

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’

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.

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.

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

I. Management of Cushing’s disease

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

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 been delayed during the investigation of an occult adenoma (13).

3. A referral on retinoic acid as a promising alternative might be useful after the beneficial effects seen in CD in dogs (14).

References


**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

'I declare that I have no competing interests'