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New treatment guidelines on Cushing's disease

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Abstract

It is important to treat patients with Cushing's disease as rapidly as possible to limit its long-term mortality and morbidity. Selective transphenoidal pituitary adenomectomy remains the treatment of choice but, unfortunately, the rate of cure at long-term follow-up is suboptimal and recurrences are high, even in the hands of expert neurosurgeons. Treatment options for persistent or relapsed disease include repeat trasphenoidal pituitary surgery, radiotherapy or bilateral adrenalectomy. Medical treatment, a second-line treatment option, may have either a primary or adjunctive role if the patient cannot safely undergo surgery, if surgery fails, or if the tumor recurs. Cabergoline and pasireotide (SOM230), two pituitary tumor-directed drugs, are the most exciting news in the human pharmacological approach. However, the use of these drugs in clinical practice and their real impact in the management of patients is yet to be determined. The treatment of patients with Cushing's disease is complex and requires a multidisciplinary and individualized approach to patient management using cost-benefit analyses.

Introduction and context

Cushing's disease (CD) results from a chronic excess of cortisol secretion caused by a adrenocorticotropic hormone (ACTH)-secreting pituitary adenoma [1,2]. The goal of treatment is the complete surgical removal of corticotroph tumors. Selective transphenoidal pituitary adenomectomy remains the treatment of choice for CD but, unfortunately, the rate of cure at long-term follow-up is suboptimal and recurrences are high, even in the hands of expert neurosurgeons [3]. Immediate remission rates range from 65-90%, with recurrence rates reaching about 25% after 10 years [4-8]. Remission rates are lower and recurrence rates higher in patients with macroadenomas and in patients with cavernous sinus or dura invasion.

The use of endoscopic surgery is of interest but a comparison on outcome between microscopic and endoscopic techniques cannot be made [3]. Treatment options for persistent or relapsed CD include repeat trasphenoidal pituitary surgery, radiotherapy or bilateral adrenalectomy. In specialized centers, repeat pituitary surgery has been shown to be efficacious in approximately 50-70% of patients, especially if an adenoma was identified at the first surgery [3,9,10]. However, a second pituitary surgery carries increased risk of hypopituitarism, particularly when a more extensive surgical excision has been performed.

Radiation therapy (conventional or stereotactic radiosurgery) should be reserved for second- or third-line treatment; it results in remission in approximately 60% of patients within 3-5 years [3,11-13]. The main drawbacks of radiotherapy include long time-to-effect and risk of delayed hypopituitarism (in up to 70% of patients). The possible causative link between radiation therapy and cerebrovascular events and neurocognitive dysfunctions is still unclear. The incidence of hypopituitarism appears to be similar between different types of radiotherapy [11-13]. At present, there are insufficient data to determine whether radiosurgery has a more rapid effect than conventional radiation therapy and whether any particular radiotherapeutic technique is preferable [3].

Bilateral adrenalectomy, preferably employing a minimally invasive laparoscopic technique, provides an immediate final cure in cases where other treatments fail [3,14-16]. However, apart from surgical risks, this treatment requires lifelong glucocorticoid and mineralocorticoid-replacement therapy (which is often suboptimal) and carries with it the risk of Nelson's syndrome, the prevalence of which ranges from 8-29% [17].

According to the recent consensus conference, medical therapy represents a second-line treatment in patients with persistent or recurrent disease as well as in patients treated with radiotherapy in whom the beneficial effects are delayed, prior to adrenalectomy and in all patients not suitable for surgery [3]. Of note, additional medical therapy may be useful in patients undergoing pituitary surgery (especially in the presence of diabetes, hypertension, and marked coagulation abnormalities).

Many drugs have been tentatively employed in the treatment of CD but none has been proven fully satisfactory. These may act at the hypothalamic-pituitary level and decrease ACTH secretion, at the adrenal level, inhibiting cortisol synthesis (steroidogenesis inhibitors), or at the peripheral level by competing with cortisol (glucocorticoid receptor antagonist) [3].

Recent advances

There is controversy regarding the definition of apparent cure after surgery for CD, and remission rates vary according to the criteria used and the time of assessment [1,3]. The definition of cure and the prognostic effect of subtle or unrecognized residual hypercortisolism have a major clinical impact on the follow-up and therapeutic decisions for patients. Recently, a consensus statement recommended the measurement of morning cortisol during the first postoperative week: hypoadrenalism (serum cortisol below 2 μg/dl) is probably the best index of remission, but even when this is the case, late relapses may occur. When serum cortisol is between 2 and 5 μg/dl the patient can be considered in remission, whereas serum cortisol above 5 μg/dl for up to 6 weeks is indicative of persistent disease and requires further evaluation [1,3]. It is noteworthy that no single test can rule out the possibility of future recurrence after surgery so patients should be followed up for many years. The measurement of cortisol in saliva, a useful screening test for hypercortisolism, could have some advantages: it is easy to perform at home and is noninvasive [18,19]. A recent study suggested that measurement of midnight salivary cortisol can be a very good marker for predicting remission and future relapse [20]. However, further and larger studies are needed to confirm this interesting finding considering that, using various assays, a strict standardization of both collection and analysis methods is necessary and normal reference ranges and diagnostic cut-offs should be validated in each laboratory before being applied to a large population [18].

The treatment of CD is very complex and represents a challenge for clinicians, requiring a multidisciplinary and individualized approach to patient management using cost-benefit analyses. In the case of failure after surgery or relapse (late relapses have been reported at 20 years after surgery) no treatment has proven to be fully satisfactory during the lengthy progression of this chronic and devastating disease. According to the recent consensus conference, the treatment recommendation may, in part, depend on the treatment option available as well as the acceptability of the relative risks. In general, experts favor repeat pituitary surgery as the initial therapy for persistent or recurrent disease, then radiotherapy (conventional or radiosurgery) if this is unsuccessful [3].

So far, medical therapy has been considered a transient and palliative treatment. However, recently there has been renewed interest in this topic due to new insights into the pathogenetic mechanisms of corticotroph tumors [21-23]. Cabergoline and pasireotide (SOM230), two pituitary tumor-directed drugs, are the most exciting news in the pharmacological approach to human CD [3,24].

Recently, Pivonello *et al.* [25] evaluated long-term efficacy and safety in 20 patients with persistent CD during long-term treatment with cabergoline. At 24-month follow-up, eight (40%) patients were persistently controlled at a median cabergoline dose of 3.5 mg/week. In addition, the clinical picture improved during treatment and significant tumor shrinkage was observed in 20% of patients [25].

Pasireotide exhibits a unique profile with high affinity for four of the five somatostatin receptors (ssts), especially sst type 5, which is the most prevalent sst in corticotroph tumors [22-24,26,27]. In a recent phase II open-label single-arm multicenter study, 39 patients with *de novo* persistent or recurrent CD were treated with pasireotide 600 mcg subcutaneously twice daily for 15 days [28]. Of the 29 patients included in the primary efficacy population, 22 patients (76%) showed a reduction of 24-hour urinary free cortisol, of which 5 (17%) had normalized 24-hour urinary free cortisol (responders). Overall, the mean 24-hour urinary free cortisol level decreased from baseline by 44.5% at the end of the short period of treatment. Worsening of glucose metabolism (14 patients with hyperglycemia)

was commonly observed with initial drug exposure but, generally, was transient. Pharmacokinetic analysis showed that a steady-state plasma concentration was achieved within 5 days. Responders appeared to have higher pasireotide exposure than non-responders.

Currently, the most exciting news with regard to pharmacological approaches to human CD is the efficacy of cabergoline and pasireotide; however, prolonged treatment and more data will be needed to evaluate their long-term therapeutic efficacy and safety.

Implications for clinical practice

It is important to treat CD as rapidly as possible to limit its long-term mortality and morbidity. In the case of failure of pituitary surgery no treatment has been proven fully satisfactory. There is controversy regarding the definition of apparent cure after surgery. Early identification of patients with persistent or recurrent disease is very important to minimize the effects of subtle or unrecognized residual hypercortisolism. Midnight salivary cortisol, a useful screening test for diagnosing hypercortisolism, could be a very good marker for predicting remission and future relapse. Medical treatment, a second-line treatment option, may have either a primary or adjunctive role if the patient cannot safely undergo surgery, if surgery fails, or if the tumor recurs. The use of cabergoline and pasireotide in clinical practice and their real impact in the management of patients with CD are yet to be determined.

Abbreviations

ACTH, adrenocorticotropic hormone; CD, Cushing's disease; sst, somatostatin receptor.

Competing interests

The authors declare that they have no competing interests.

References

1. Arnaldi G, Angeli A, Atkinson AB, Bertagna X, Cavagnini F, Chrousos GP, Fava GA, Findling JW, Gaillard RC, Grossman AB, Kola B, Lacroix A, Mancini T, Mantero F, Newell-Price J, Nieman LK, Sonino N, Vance ML, Giustina A, Boscaro M: **Diagnosis and complications of Cushing's syndrome: a consensus statement.** *J Clin Endocrinol Metab* 2003, **88:**5593-602.
2. Newell-Price J, Bertagna X, Grossman AB, Nieman LK: **Cushing's syndrome.** *Lancet* 2006, **367:**1605-17.
3. Biller BM, Grossman AB, Stewart PM, Melmed S, Bertagna X, Bertherat J, Buchfelder M, Colao A, Hermus AR, Hofland LJ, Klibanski A, Lacroix A, Lindsay JR, Newell-Price J, Nieman LK, Petersenn S, Sonino N, Stalla GK, Swearingen B, Vance ML, Wass JA, Boscaro M: **Treatment of adrenocorticotropin-dependent Cushing's syndrome: a consensus statement.** *J Clin Endocrinol Metab* 2008, **93:**2454-62.
4. Patil CG, Prevedello DM, Lad SP, Vance ML, Thorner MO, Katznelson L, Laws ER Jr: **Late recurrences of Cushing's disease after initial successful transsphenoidal surgery.** *J Clin Endocrinol Metab* 2008, **93:**358-62.
5. Prevedello DM, Pouratian N, Sherman J, Jane JA Jr, Vance ML, Lopes MB, Laws ER Jr: **Management of Cushing's disease: outcome in patients with microadenoma detected on pituitary magnetic resonance imaging.** *J Neurosurg* 2008, **109:**751-9.
6. Hammer GD, Tyrrell JB, Lamborn KR, Applebury CB, Hannegan ET, Bell S, Rahl R, Lu A, Wilson CB: **Transsphenoidal microsurgery for Cushing's disease: initial outcome and long-term results.** *J Clin Endocrinol Metab* 2004, **89:**6348-57.
7. Hofmann BM, Fahlbusch R: **Treatment of Cushing's disease: a retrospective clinical study of the latest 100 cases.** *Front Horm Res* 2006, **34:**158-84.
8. Atkinson AB, Kennedy A, Wiggam MI, McCance DR, Sheridan B: **Long-term remission rates after pituitary surgery for Cushing's disease: the need for long-term surveillance.** *Clin Endocrinol* 2005, **63:**549-59.
9. Patil CG, Veeravagu A, Prevedello DM, Katznelson L, Vance ML, Laws ER Jr: **Outcomes after repeat transsphenoidal surgery for recurrent cushing's disease.** *Neurosurgery* 2008, **63:**266-70.
10. Mullan KR, Atkinson AB: **Endocrine clinical update: Where are we in the therapeutic management of pituitary-dependent hypercortisolism?** *Clin Endocrinol (Oxf)* 2008, **68:**327-37.
11. Castinetti F, Nagai M, Dufour H, Kuhn JM, Morange I, Jaquet P, Conte-Devolx B, Regis J, Brue T: **Gamma knife radiosurgery is a successful adjunctive treatment in Cushing's disease.** *Eur J Endocrinol* 2007, **156:**91-8.
12. Jagannathan J, Sheehan JP, Pouratian N, Laws ER, Steiner L, Vance ML: **Gamma Knife surgery for Cushing's disease.** *J Neurosurg* 2007, **106:**980-7.
13. Petit JH, Biller BM, Yock TI, Swearingen B, Coen JJ, Chapman P, Ancukiewicz M, Bussiere M, Klibanski A, Loeffler JS: **Proton stereotactic radiotherapy for persistent adrenocorticotropin-producing adenomas.** *J Clin Endocrinol Metab* 2008, **93:**393-9.
14. Gumbs AA, Gagner M: **Laparoscopic adrenalectomy.** *Best Pract Res Clin Endocrinol Metab* 2006, **20:**483-99.
15. Chow JT, Thompson GB, Grant CS, Farley DR, Richards ML, Young WF Jr: **Bilateral laparoscopic adrenalectomy for corticotrophin-dependent Cushing's syndrome: a review of the Mayo Clinic experience.** *Clin Endocrinol* 2008, **68:**513-9.
16. Thompson SK, Hayman AV, Ludlam WH, Deveney CW, Loriaux DL, Sheppard BC: **Improved quality of life after bilateral laparoscopic adrenalectomy for Cushing's disease: a 10-year experience.** *Ann Surg* 2007, **245:**790-4.
17. Assie G, Bahurel H, Coste J, Silvera S, Kujas M, Dugue MA, Karray F, Dousset B, Bertherat J, Legmann P, Bertagna X: **Corticotroph tumor progression after adrenalectomy in Cushing's disease: a reappraisal of Nelson's syndrome.** *J Clin Endocrinol Metab* 2007, **92:**172-9.

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18. Nieman LK, Biller BM, Findling JW, Newell-Price J, Savage MO, Stewart PM, Montori VM: **The diagnosis of Cushing's syndrome: an Endocrine Society Clinical Practice Guideline.** *J Clin Endocrinol Metab* 2008, **93:**1526-40.
19. Nunes ML, Vattaut S, Corcuff J-B, Rault A, Loiseau H, Gatta B, Valli N, Letenneur L, Tabarin A: **Late-night salivary cortisol for diagnosis of overt and subclinical Cushing's syndrome in hospitalized and ambulatory patients.** *J Clin Endocrinol Metab* 2009, **94:**456-62.
20. Carrasco CA, Coste J, Guignat L, Groussin L, Dugué MA, Gaillard S, Bertagna X, Bertherat J: **Midnight salivary cortisol determination for assessing the outcome of transsphenoidal surgery in Cushing's disease.** *J Clin Endocrinol Metab* 2008, **93:**4728-34.

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21. de Bruin C, Feelders RA, Lamberts SW, Hofland LJ: **Somatostatin and dopamine receptors as targets for medical treatment of Cushing's syndrome.** *Rev Endocr Metab Disord* 2009, **10:**91-102.

22. de Bruin C, Pereira AM, Feelders RA, Romijn JA, Roelfsema F, Sprij-Mooij DM, van Aken MO, van der Lelij AJ, de Herder WW, Lamberts SW, Hofland LJ: **Coexpression of dopamine and somatostatin receptor subtypes in corticotroph adenomas.** *J Clin Endocrinol Metab* 2009, **94:**1118-24.

23. Batista DL, Zhang X, Gejman R, Ansell PJ, Zhou Y, Johnson SA, Swearingen B, Hedley-Whyte ET, Stratakis CA, Klibanski A: **The effects of SOM230 on cell proliferation and adrenocorticotropin secretion in human corticotroph pituitary adenomas.** *J Clin Endocrinol Metab* 2006, **91:**4482-8.

F1000 Factor 3.0 *Recommended*
Evaluated by Gunter Stalla 05 Jul 2007

24. Arnaldi G, Cardinaletti M, Trementino L, Tirabassi G, Boscaro M: **Pituitary-directed medical treatment of Cushing's disease.** *Expert Rev Endocrinol Metab* 2009, **4:**263-72.

25. Pivonello R, De Martino MC, Cappabianca P, De Leo M, Faggiano A, Lombardi G, Hofland LJ, Lamberts SW, Colao A: **The medical treatment of Cushing's disease: effectiveness of chronic treatment with the dopamine agonist cabergoline in patients unsuccessfully treated by surgery.** *J Clin Endocrinol Metab* 2008, **94:**223-30.

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26. Schmid HA: **Pasireotide (SOM230): development, mechanism of action and potential applications.** *Mol Cell Endocrinol* 2008, **286:**69-74.

27. Lesche S, Lehmann D, Nagel F, Schmid HA, Schulz S: **Differential effects of octreotide and pasireotide on somatostatin receptor internalization and trafficking in vitro.** *J Clin Endocrinol Metab* 2009, **94:**654-61.

F1000 Factor 3.0 *Recommended*
Evaluated by Giovanni Tulipano 12 Dec 2008

28. Boscaro M, Ludlam WH, Atkinson B, Glusman JE, Petersenn S, Reincke M, Snyder P, Tabarin A, Biller BM, Findling J, Melmed S, Darby CH, Hu K, Wang Y, Freda PU, Grossman AB, Frohman LA, Bertherat J: **Treatment of pituitary-dependent Cushing's disease with the multireceptor ligand somatostatin analog pasireotide (SOM230): a multicenter, phase II trial.** *J Clin Endocrinol Metab* 2009, **94:**115-22.

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