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Annales d'Endocrinologie 76 (2015) 43–58

Annales d'Endocrinologie
Annals of Endocrinology

Review

Medical therapies in pituitary adenomas: Current rationale for the use and future perspectives

Traitements médicaux des adénomes hypophysaires : thérapies actuelles et futures perspectives

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Abstract

Pituitary adenomas (PA) represent in the majority of cases, benign tumors whose treatment currently associate surgery, medical therapies and radiotherapy in a multidisciplinary approach. While trans-sphenoidal surgery remains, except for prolactin-secreting adenomas, the first-line treatment of PA, it can considerably be hampered by the existence of an invasive and/or aggressive tumor for which medical therapies are often requested. In this review, we extensively discuss, both at molecular and clinical levels, the medical therapies currently used and in development in the different phenotypes of pituitary adenomas.

Keywords: Pituitary adenomas; Somatostatin analog; Dopamin agonist; Acromegaly; Cushing's disease

Résumé

Les adénomes hypophysaires (AH) représentent, pour la majorité d'entre eux, des tumeurs bénignes dont la stratégie thérapeutique associe de nos jours, chirurgie, traitement médicaux et radiothérapie, au travers d'une approche multidisciplinaire. Alors que la chirurgie trans-sphénoïdale demeure, à l'exception des prolactinomes, le traitement de 1ère intention de la plupart des AH, elle peut se révéler problématique en cas de tumeur invasive et/ou aggressive pour laquelle un traitement médical (néo)adjuvant est souvent requis. Dans cette revue, nous revenons en détail sur les traitements médicaux actuellement disponibles, ou les molécules en cours de développement, dans les différents types d'AH, en combinant à la fois l'approche fondamentale à l'impact tel qu'il observé en pratique clinique.

Mots clés : Adénomes hypophysaires ; Analogues de la somatostatine ; Agonistes dopaminergiques ; Acromégalie ; Maladie de Cushing

1. Introduction

Pituitary adenomas (PA) represent a heterogeneous group of tumors, which originate from cells of the anterior pituitary gland, with a reported prevalence of 1:1000 of the general population [1,2]. Mostly benign, PA can severely affect the patient health status, either because of the associated hormonal secretion depending on the tumor phenotype, or due to the local

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http://dx.doi.org/10.1016/j.ando.2014.10.002
0003-4266/

compression of critical adjacent structures, such as the optic chiasma, as well as important vascular pathways. With the exception of prolactinoma patients, surgery remains, when it is feasible and indicated, the first-line treatment of PA. However, in a significant proportion of unresectable cases, in patients with remnant or relapsing tumors, or in those cases of experiencing an uncontrolled hormonal hypersecretion, medical therapies should be considered. Current treatments available for pituitary tumors can be divided into two subgroups:

- directly targeting the tumoral cells, effects can be exerted at both the antiproliferative and the anti-secretory levels;
- indirectly, by treatments developed to control the physical symptoms and complications due to hormonal hypersecretion, especially in Cushing's disease and acromegaly.

Nowadays, a deeper understanding of pituitary tumor pathophysiology appears as a must, as most of the new pharmacological compounds directly act on specific molecular disruptors of the tumoral cells. In this extensive review, we attempt to describe the different medical therapies currently available in pituitary tumors, as well as to discuss the ones that showed encouraging results in experimental studies or already in initial phases of clinical practice. For this purpose, we analysed the drugs, or the class of drugs, already available and incoming for each different histotype of PA.

2. Prolactinomas

2.1. Dopamine agonist therapy

Prolactin (PRL) secreting adenomas, commonly named prolactinomas, represent around 40% of PA with a prevalence of 5/10,000 inhabitants [3]. Most of prolactinomas express a high level of dopamine receptor subtype 2 (D2DR) [4], and ligand-induced activation of D2DR results in an overall inhibition of the prolactin synthesis, secretion, as well as cellular proliferation [4–6]. Consequently, dopamine agonists (DAs) have been widely used to treat prolactinomas, resulting in an even higher rate of PRL normalization compared to trans-sphenoidal surgery [7,8]. Three different DAs are currently available: quinagolide, bromocriptine and cabergoline. The latest two are ergot derivatives, while quinagolide is an octahydrobenzyl(*g*)-quinoline non-ergot oral DA [9]. Note that pergolide, initially distributed in USA, has been withdrawn in 2007 because of an increased risk of heart valve disease (www.fda.gov). Since the introduction in the clinical practice, cabergoline became the DA of choice because of its high D2DR affinity (IC_{50} – defined in this case by the concentration of the drug necessary to induce the half maximal inhibition of prolactin secretion – of 0.1 nmol/L vs 3.4 nmol/L for bromocriptine) [10] and its long half-life, allowing a weekly oral administration [11]. Moreover, previous studies showed that cabergoline was more effective than bromocriptine in normalizing PRL levels, with an overall success rate of nearly 90% [12,13]. Nonetheless, a minority of patients present with resistance to DAs, defined as the failure to achieve normal PRL levels or a tumor size reduction of at least 50% with maximal conventional doses of medication (i.e. 7.5 mg/day of bromocriptine or 2.0 mg/week of cabergoline) [14]. Of note, a dissociated response to DA treatment can occur, with the normalization of PRL secretion and no effects on tumor mass, or vice versa. Although several mechanisms have been proposed to explain the resistance to DAs in prolactinomas, such as the decrease of the D2DR density on the lactotroph membrane, decrease in D2DR mRNA expression or dysfunctions in the G-protein machinery that couples the D2DR [15–18], the molecular aspects of DA resistance are still incompletely understood.

In a retrospective study, Vroonen et al. showed that patients with DA-resistant (DA-R) prolactinomas presented with invasive macroadenomas in 80% of cases [19] and, among the male population, a majority was diagnosed with giant prolactinomas (Fig. 1). Recently, giant prolactinomas have been defined by Maiter and Delgrange as:

- PA with a maximum diameter more than 40 mm (in any direction) and massive extrasellar extension;
- very high baseline PRL concentration, usually above or equal to 1000 ng/mL, evaluated using a modern and well-standardized assay;
- exclusion of concomitant GH or ACTH secretion [20].

Nowadays, therapeutic strategies in DA-R prolactinomas are limited: surgery can be unfeasible in case of extrasellar and/or cavernous sinus invasion, while radiotherapy exposes patients to a high risk of develop subsequent hypopituitarism and local adverse events, such as optic chiasm damages. The option of systemic medical therapies still remains, however the benefit to switch from one DA to another in case of resistance, as proposed in the past [21], is limited, since a majority of patients are treated since the beginning with cabergoline, the more effective DA currently available in clinical practice. Increasing the DA dose is most frequently applied by clinicians, but it can be limited by the appearance of drug-related side effects. However, the long-time debated hypothesis of an increased incidence of valvular abnormalities under DA treatment has been clarified by a recent cross sectional study conducted in UK, which did not show significant association between the use of DAs in prolactinoma patients and the finding of cardiac valvulopathies [22]. In conclusion, according to the high efficacy of DAs (mainly cabergoline), associated with low-mild side effects and an easy manageable oral administration, the current challenge in the medical therapy of prolactinomas rather concern the resistant cases to DA treatment, *a fortiori* because of their frequent association to an aggressive behaviour. A part of the use of other medical therapies (see below), the option of debulking trans-spehnoidal surgery in case of DA-resistant prolactinomas is successful in some cases and needs to be considered. Indeed, in the study by Vroonen et al. already mentioned, the surgical debulking led to a significant decrease of PRL values compared to preoperative values of PRL at significantly lower weekly CAB dose [19]. This better control of PRL secretion after surgical debulking was also described in a previous clinical study where nearly half of the