ENEA RESISTANT-PROLACTINOMA STUDY

Title: Epidemiology, clinical profile, and outcomes of patients with prolactinomas taking a high dose cabergoline (≥ 3mg/week): **RESISTANT PROLACTINOMA STUDY**

Background

Prolactinomas constitute the most common pituitary neuroendocrine tumors (PitNETs) with a prevalence ranging from 6–10 to 60 per 100,000 patients (1-4). The management of prolactinomas includes as first-line approach the medical therapy with dopamine agonists (DA) rather than surgery, as opposed to the surgical first-line approach used in all the other pituitary neuroendocrine neoplasms (PitNETs). Recent Guidelines for the Treatment of Hyperprolactinemia recommend cabergoline in preference to other DAs, such as bromocriptine and quinagolide because of the better efficacy and safety profile (5).

A rate as high as 15% of patients with prolactinomas do not respond to standard doses of dopamine agonists (DA) (6-8). Practice guidelines for hyperprolactinemia suggest that a failure to achieve normal prolactin levels on maximally tolerated doses of DAs and a failure to achieve 50% reduction in tumor size implies DA-resistance (5). On the other hand, it is difficult to ascertain the maximally tolerated doses of cabergoline which implies the DA-resistant state according to other authors (9). Generally, it is recommended to switch the treatment from cabergoline to bromocroptine when a DA-resistant state is suspected (5,10,11). In addition, surgical removal or radiotherapy are alternative treatments when standard doses of cabergoline do not control prolactin levels or tumor size (12-14). Additional therapeutic options have been occasionally used; pasireotide, a second-generation somatostatin analogue and molecular targeted treatment (MTT) are under investigation (1,15). On the other hand, the early clinical presentation of malignant prolactinomas is represented by a DA-resistant state (16).

Unmet needs for the management and the treatment of the DA-resistant prolactinomas, imply the necessity of an international study to improve the understanding of the pathophysiology of and the natural history of prolactinomas requiring high doses of cabergoline. In addition, the diagnostic and therapeutic management of DA-resistant prolactinomas have not been investigated so far.

Under this necessity, the RESISTANT PROLACTINOMA STUDY was launched by the ENEA Workshop and Study Committee in order to collect and register data from

the collaboration of ENEA investigators resulting in a large pool of patients taking a high dose cabergoline.

Aim of the study

The purpose of the study is to investigate the clinical and biochemical features, morphological characteristics, diagnostic approaches, treatment regimens and options as well as outcomes of patients taking a high dose cabergoline (≥ 3mg/week).

Objectives

The *primary end-point* is to study the clinical and biochemical features of DA-resistant patients, defined as treated for at least 6 months with at least 3 mg/week cabergoline without achieving prolactin level normalization.

The *secondary end-points* include:

(i) To confirm or refute the commonly acceptable definition of DA-resistant prolactinomas (i.e. doses ≥ 3 mg/week to normalize PRL levels and/or with < 50% reduction in tumor size).

(ii) The assessment of diagnostic approaches and immunohistochemical markers (when surgical specimens are available) in patients taking a dose of cabergoline ≥ 3mg/week in order to achieve the biochemical and radiological control of a prolactinoma.

(iii) The assessment of the impact of surgery, radiotherapy, and additional medical treatment (i.e. bromocriptine, quinagolide, estrogen receptor antagonists, pasireotide, molecular targeted treatment) that have been used in the recruited cohort of patients to achieve the biochemical and radiological control of a DA-resistant prolactinoma.

(iv) The selection of the optimal treatment strategy when a dose of cabergoline exceeds 3mg/week is required in order to achieve the biochemical and radiological control of a prolactinoma.

(v) The formation of a database on DA-resistant prolactinomas.

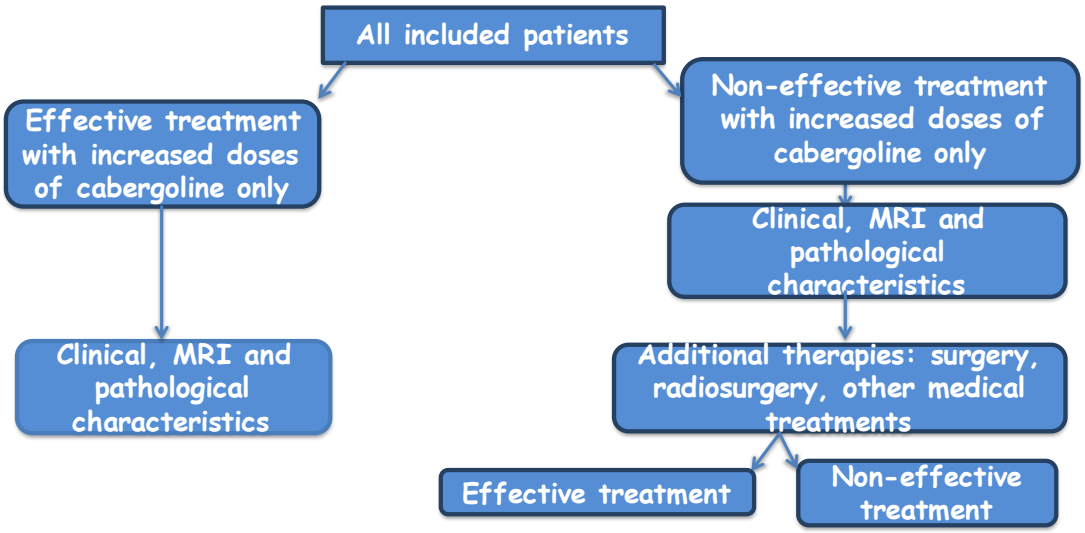
Methods

This is a retrospective observational study. Males and females ≥18 years old with prolactinomas and cabergoline treatment at doses ≥3 mg/week will be recruited and their records will be reviewed. The SYNERGY2GO platform, a comprehensive but simple web application, will be used, including the following data:

1. Gender

2. Age (at diagnosis)
3. Initial prolactin level (at diagnosis)
4. Presence of prolactinoma, size of adenoma (3 dimensions)
5. Adenoma growth extension according to MRI (intrasellar, suprasellar, infrasellar, parasellar)
    a. Parasellar growth grade by Knosp classification
    b. Suprasellar growth grade by Hardy classification
    c. Distance to the chiasm (mm)
6. Pituitary function (hypopituitarism: yes, no) (should be defined more in detail - by axes)
7. Visual morbidity (yes, no) – more specific: visual field defects; oculomotor palsy…
8. Echo-cardiography data (if available) (specify pathology – suggest to put expected US changes and options for answers YES, NO, NA (not applicable)
9. Genetic testing (yes, no),– what does this mean (genetic testing has been performed but results are not available? – suggest to delete)
    a. if YES, give options: AIP; MEN1; …; other (specify….)
10. Estrogen containing therapy (? as a replacement treatment due to hypopit or as a pathogenetic factor BEFORE the PRL-oma was diagnosed? (yes, no, not known?)
11. Cabergoline dose sufficient for prolactin level normalization
12. Cabergoline dose necessary to decrease the size of prolactinoma by at least 50%
13. Maximum cabergoline dose prescribed for at least three months without prolactin level normalization
14. Maximum cabergoline dose for at least three months but without prolactinoma size decrease by at least 50%
15. Alternative treatment (surgery, radiosurgery, tamoxifen, tamoxifen+ bromocriptine, tamoxifen+ cabergoline, raloxifene, temozolomide + cabergoline, pasireotide, molecular targeted treatment, other)
16. Alternative treatment that led to prolactin level normalization (yes, no)
17. Alternative treatment that led to decrease of prolactinoma size by at least 50% (yes, no)
18. Tumor relapse (yes, no)
19. Prolactinoma metastasis (yes, no)

All the cohort will be divided in subgroups according to the outcome as presented in the following figure:



Limitations of the study

An important limitation of the study includes the use of different assays to measure PRL levels. This is a common limitation of multicenter studies than may be overcome by the increase of the population included in the study.

Statistical analysis

A target number of 600 recruited patients has been considered acceptable to achieve a sound conclusion. Any other statistical methods?

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