Cabergoline add-on therapy in patients with uncontrolled acromegaly under somatostatin analogues – a multicenter, retrospective, cohort study of non-irradiated patients applying current criteria for disease control

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Background

- In acromegaly not controlled by somatostatin analogue (SSA) treatment, add-on therapy with cabergoline is a potential approach [1, 2].
- A small number of studies have reported on outcomes of this strategy, with IGF-1 normalization rates ranging between 42 and 60% during follow-up periods of 3 to 55.4 months [3]. However, these studies have included patients who had previously received radiotherapy, a potential confounding factor.
- Furthermore, data on the effectiveness of SSA and cabergoline combination therapy applying the current disease control criteria (normal IGF-1 and GH<1mcg/L) are lacking.

Objective

- To investigate the efficacy of SSA and cabergoline combination therapy in non-irradiated patients with acromegaly not fully responding to SSA treatment alone.

Patients and Methods

- In this multicenter, retrospective cohort study, 26 non-irradiated patients offered cabergoline add-on therapy for uncontrolled acromegaly to ongoing SSA therapy were identified from the registries of four UK Pituitary centers (Birmingham, Bristol, Leicester and Oxford).
- Clinical and laboratory data were collected and analyzed.
- Statistical methods: binary logistic regression, independent samples Mann-Whitney U test.

Results

Table 1: Characteristics of the patients

Characteristic	All	Achievement of normal IGF-1	No achievement of normal IGF-1
n (%)	26	6 (23.1%)	20 (76.9%)
Males / females	12 / 14	2 /4	10 / 10
Age at diagnosis of acromegaly (years), median (range)	47 (21-83)	55 (21-83)	45.5 (23-77)
Prolactin co-secreting adenoma, n	6/25	2/5	4/20
Pituitary surgery prior to starting SSA and cabergoline, n	20/25	2/6	18/19
IGF-1 levels ULN prior to starting cabergoline, median (range)	1.70 (1.03-2.92)	1.36 (1.03-2.92)	1.86 (1.09-2.84)
Duration of SSA treatment prior to cabergoline (months), median (range)	18 (2-118)	55.5 (13-118)	17.5 (2-60)
Concomitant treatment with octreotide LAR, n	9/26	2/6	7/20
Concomitant treatment with lanreotide, n	17/26	4/6	13/20
Duration of combined treatment (months), median (range)	36 (4-139)	66.5 (35-120)	34 (4-139)
Weekly dose of cabergoline at last review, median (range)	2.5 (0.5-4.5)	1.25 (0.5-3)	3 (0.5-4.5)

Table 2: Biochemical outcomes

Outcomes	Values
Normal IGF-1, n (%)	6/26 (23.1%)
IGF-1 ULN at last follow-up, median (range)	1.187 (0.43 - 2.54)
Delta IGF-1 ULN (between before starting cabergoline and at last review), median (range)	0.58 (-1.13 – 2.19)
GH <1mcg/L, n (%)	9/23 (39.1%)
Normal IGF-1 and GH <1mcg/L, n (%)	4/23 (17.4%)

Details of SSA treatment regimens

- Octreotide LAR 20mg/4w n=1; 20mg/6w n=1; 30mg/3w n=1; 30mg/4w n=5; 40mg/4w n=1
- Lanreotide 90mg/4w n=1; 120mg/3w n=7; 120mg/4w n=9

- On univariate regression analysis, IGF-1 x-times ULN prior to starting cabergoline or presence of a prolactin co-secreting tumour was not related with achievement of normal IGF-1.
- There was no significant difference in the median weekly cabergoline dose at most recent review between those achieving or not achieving normal IGF-1.

Discussion and Conclusions

- In our cohort of non-irradiated patients with acromegaly, add-on cabergoline normalised IGF-1 in 23% of those on ongoing SSA therapy, with IGF-1 x ULN levels prior to starting cabergoline not related with this effect.
- Our response rate was lower compared to previous reports, possibly due to the exclusion of previously irradiated tumours.
- Only 17% of the patients achieved both optimal GH and IGF-1 levels, as per current guidelines.

References

1. Katznelson, L. *et al.* Acromegaly: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab*, 2014. **99**(11): p. 3933-51.
2. Melmed, S. *et al.* A Consensus Statement on acromegaly therapeutic outcomes. *Nat Rev Endocrinol*, 2018. **14**(9): p. 552-561.
3. Sandret, L. *et al.* Place of cabergoline in acromegaly: a meta-analysis. *J Clin Endocrinol Metab*, 2011. **96**(5): p. 1327-35.

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