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Original Research

Efficacy of cabergoline in non-irradiated patients with acromegaly: a multi-centre cohort study

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Abstract

Objective: This study aimed to elucidate the efficacy (as per current biochemical criteria) of cabergoline monotherapy or as addition to long-acting somatostatin receptor ligand (SRL) in patients with acromegaly and no previous pituitary radiotherapy.

Design: Multi-centre, retrospective, cohort study (four UK pituitary centres: Birmingham, Bristol, Leicester, and Oxford).

Methods: Clinical, laboratory, and imaging data were analysed.

Results: Sixty-nine patients on cabergoline monotherapy were included (median insulin-like growth factor 1 [IGF-1] × upper limit of normal [ULN] pre-cabergoline 2.13 [1.02-8.54], median treatment duration 23 months, and median latest weekly dose 3 mg); 31.9% achieved normal IGF-1 (25% growth hormone [GH]-secreting and 60% GH+prolactin co-secreting tumours); median weekly cabergoline dose was similar between responders and non-responders. Insulin-like growth factor 1 normalization was related with GH+prolactin co-secreting adenoma (B 1.50, P = .02) and lower pre-cabergoline IGF-1 × ULN levels (B −0.70, P = .02). Both normal IGF-1 and GH < 1 mcg/L were detected in 12.9% of cases and tumour shrinkage in 29.4% of GH-secreting adenomas.

Twenty-six patients on SRL + cabergoline were included (median IGF-1 × ULN pre-cabergoline 1.7 [1.03-2.92], median treatment duration 36 months, and median latest weekly dose 2.5 mg); 23.1% achieved normal IGF-1 (15.8% GH-secreting and 33.3% GHprolactin co-secreting tumours). Normal IGF-1 and GH < 1 mcg/L were detected in 17.4%.

Conclusions: In non-irradiated patients, cabergoline normalizes IGF-1 in around one-third and achieves both IGF-1 and GH targets in approximately one out of ten cases. SRL + cabergoline is less efficient than previously reported possibly due to differences in study methodology and impact of confounding factors.

Keywords: cabergoline, dopamine agonist, acromegaly, non-irradiated patients

Significance

In the largest to date series of patients with acromegaly not previously irradiated for their pituitary tumour, we elucidated the biochemical efficacy of cabergoline. Cabergoline monotherapy in cases with pre-treatment median insulin-like growth factor 1 (IGF-1) × upper limit of normal (ULN) 2.13 normalizes IGF-1 in 32% of them (25% of growth hormone [GH]-secreting and 60% of GH+prolactin co-secreting adenomas). Biochemical control according to currently used criteria (normal IGF-1 and GH < 1 mcg/L) is achieved in only 13% of the patients. The specificity of IGF-1 × ULN < 2.05 in predicting IGF-1 normalization is low (63%). Cabergoline as addition to ongoing long-acting somatostatin receptor ligand therapy has lower efficacy than previously reported (normal IGF-1 in 23% of patients with pre-cabergoline median IGF-1 × ULN 1.7) and leads to both normal IGF-1 and GH < 1 mcg/L in 17% of the cases.

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Introduction

Active acromegaly is associated with several co-morbidities and increased mortality[1,2] necessitating prompt biochemical control of the disease. First-line treatment is the removal of the tumour usually by trans-sphenoidal surgery (TSS).[3-5] In cases of persistent disease post-operatively or in poor surgical candidates, medical therapy is a potential management option.[3-5]

Dopamine agonists (DAs) are included in the treatment algorithm of acromegaly and have been the first medications offered for this condition.[3-5] Their efficacy is associated with the expression of dopamine receptor subtype 2 (DR2) in the tumour cells,[6] and their advantages include the oral application and low cost.[3] Cabergoline is currently the most widely used DA due to its higher effectiveness, more favourable side effects profile, and longer duration of action, as compared with bromocriptine.[7] It has been offered as monotherapy or in combination mainly with long-acting somatostatin receptor ligand (SRL), but the reported biochemical outcomes show considerable variability. Indeed, with cabergoline monotherapy, normalization of insulin-like growth factor 1 (IGF-1) has been described to be achieved in between 0% and 100% of the patients during follow-up periods from 2.6 to 24 months.[8-17] Studies on the addition of cabergoline to ongoing SRL therapy demonstrate normalization of IGF-1 in between 23% and 60% of the cases during follow-up intervals from 3 to 55.4 to months.[17-24] Randomized-controlled trials evaluating the role of DA in acromegaly are lacking. A meta-analysis by Sandret et al.[25] in 2011 reported IGF-1 normalization in 34% of the patients on cabergoline as single-agent therapy and in 52% of those with cabergoline added to SRL treatment. In a later study analysing the outcomes of patients from the Mexican Acromegaly Registry, amongst the cases treated with a combination of SRL and cabergoline, control of the disease was achieved in 19% of them during a median follow-up of 36.5 months; in this report, control was defined as a basal growth hormone (GH) < 1 ng/mL and IGF-1 < 1.2 × upper limit of normal (ULN).[26] Drawbacks of the published studies include their small sample size,[8-11,13-15] the application of variable criteria for disease control,[12,26] and, importantly, the inclusion of patients who had previously received pituitary radiotherapy confounding the results on the efficacy of medical treatment.[8,9,11-17,27,28]

The aim of this multi-centre UK retrospective cohort study was to elucidate the efficacy (according to currently recommended biochemical criteria)[3] of cabergoline offered as monotherapy or as addition to ongoing SRL therapy in a large series of patients with active acromegaly who had no pituitary radiotherapy prior to or during this medical treatment. With this approach, we aimed to eliminate the impact of irradiation on the biochemical response and assess the true effect of these agents.

Patients and methods

This was a multi-centre, retrospective, cohort study involving 4 UK Pituitary centres (Queen Elizabeth Hospital, University Hospitals Birmingham NHS Foundation Trust, Birmingham; Oxford Centre for Diabetes, Endocrinology and Metabolism, Oxford University Hospitals NHS Foundation Trust, Oxford; Leicester Royal Infirmary, University Hospitals of Leicester NHS Trust, Leicester; Bristol Royal Infirmary, University Hospitals Bristol and Weston NHS Foundation Trust, Bristol).

Patients with active acromegaly offered cabergoline for at least 3 months either as monotherapy (without any prior medical treatment) or as add-on to ongoing SRL treatment were identified from the registries of the participating centres. Patients who had received pituitary irradiation prior to or during cabergoline administration or those on concomitant treatment with pegvisomant were excluded. Clinical, biochemical, and imaging data were collected. The monitoring period started from the time of cabergoline initiation until the last assessment whilst on this agent. In the event of a change in the management approach (eg, commencing on a new medical treatment, pituitary surgery, or radiotherapy), the follow-up was terminated just prior to the treatment amendment. The diagnosis of a GH+prolactin co-secreting adenoma relied on the presence of hyperprolactinaemia and positive immunostaining for prolactin in cases of surgical excision. In the absence of immunohistochemical data, prolactin levels at diagnosis were used to determine if these were most likely attributed to "stalk effect" based on cut-offs from previous literature (prolactin levels of >2000 mU/L in the presence of a macroadenoma are extremely unlikely to be associated with stalk effect).[29] Criteria for acromegaly control were defined as age-normalized IGF-1 levels and random GH < 1 mcg/L.[3] Tumour shrinkage was based on radiological reports and was assessed only in patients on cabergoline monotherapy aiming to exclude the effect of concomitant SRL treatment on the adenoma size. In cases in which cabergoline was initiated immediately after pituitary surgery, the imaging data were not used in the analyses to avoid confounding by immediate post-operative changes.

There was no intervention beyond routine delivery of patient care and each participating centre had institutional approval before the contribution of anonymized data; all centres had patient consent waivers. The audit reference number for the co-ordinating centre was Clinical Audit Registration and Management System—15286 (University Hospitals Birmingham NHS Foundation Trust). The research complied with the Declaration of Helsinki.

Hormonal assessments

Hormonal measurements were performed at each participating centre (details on assays are shown in Tables S1-S3). Insulin-like growth factor 1 times the ULN (IGF-1 × ULN) was used in the statistical analyses.

Statistical analyses

Percentages were estimated for categorical data and medians with ranges for continuous variables. Comparisons of continuous variables were performed by Mann–Whitney *U* test and of discrete variables by the chi-square test. Regression analysis was applied to investigate the association between various parameters and biochemical response. The most optimal value of IGF-1 × ULN prior to starting cabergoline that predicted IGF-1 normalization was assessed by constructing receiver operating characteristic (ROC) curve and plotting sensitivity and 1-specificity (the Youden index was used). The level of significance was set at $P < .05$.

Analyses were conducted with IBM SPSS statistics for Windows (version 28; IBM, Armonk, NY, United States) and GraphPad Prism (Version 9.3.1; GraphPad Software, Boston, MA, United States).

Table 1. Characteristics of patients on cabergoline monotherapy and biochemical outcomes.

Characteristic/biochemical outcome	Total group of patients	Patients achieving normal IGF-1	Patients not achieving normal IGF-1
Number	69[a]	22	47
Age at diagnosis of acromegaly (years), median (range)	50.5 (28-78)	49 (30-72)	51 (28-78)
Males/females, number (%)	45/24 (65.3%/34.7%)	14/8 (36.4%/63.6%)	31/16 (34.0%/66.0%)
Macroadenoma/microadenoma at diagnosis, number (%)	50/13(79.4%/20.6%)[1]	14/5 (73.7%/26.3%)	36/8 (81.8%/18.2%)
Prolactin co-secreting *vs* purely GH secreting adenoma, number (%)	15 (27.3%) *vs* 40 (72.7%)[2]	9/15 (60%) *vs* 10/40 (25%)[b]	6/15 (40%) *vs* 30/40 (75%)[b]
TSS prior cabergoline initiation *vs* no TSA prior cabergoline initiation, number (%)[c]	34 (49.3%) *vs* 35 (50.7%)	11/34 (32.4%) *vs* 11/35 (31.4%)	23/34 (67.6%) *vs* 24/35 (68.6%)
Imaging results prior to starting cabergoline			
Residual tumour max diameter ≥1 cm, number (%)	32 (48.5%)[3]	11/32 (34.4%)	21/32 (65.6%)
Residual tumour max diameter <1 cm, number (%)	17 (25.8%)[3]	7/17 (41.2%)	10/17 (58.8%)
No visible tumour, number (%)	10 (15.2%)[3]	2/10 (20%)	8/10 (80%)
Residual tumour size unknown, number (%)	7 (10.6%)[3]	1/7 (14.3%)	6/7 (85.7%)
IGF-1 ×ULN prior to starting cabergoline, median (range)	2.13 (1.02-8.53)[4]	1.70 (1.12-6.41)[b]	2.58 (1.02-8.54)[b]
GH (mcg/L) prior to starting cabergoline, median (range)	4.3 (0.4-222)[5]	2.8 (0.4-104)[b]	5.45 (0.6-222)[b]
Maximum weekly dose of cabergoline (mg), median (range)	3 (0.25-7)	3 (0.5-7)	3.5 (0.25-7)
Weekly dose of cabergoline at last review (mg), median (range)	3 (0.25-7)[6]	2.5 (0.25-4)	3 (0.25-7)
Total duration of cabergoline treatment (months), median (range)	23 (3-252)	79.5 (5-237)	11 (3-252)
IGF-1 normalization, number (%)	22 (31.9%)		
IGF-1 ×ULN at last follow-up, median (range)	1.36 (0.33-6.10)[7]		
GH < 1 mcg/L, number (%)	16 (25.8%)[8]		
Normal IGF-1 and GH < 1 mcg/L, number (%)	8 (12.9%)[8]		
Normal IGF-1 and GH > 1 mcg/L, number (%)	12 (19.4%)[8]		
High IGF-1 and GH < 1 mcg/L, number (%)	8 (12.9%)[8]		

Data are available for [1]63 patients; [2]55 patients; [3]66 patients; [4]64 patients; [5]63 patients; [6]69 patients; [7]64 patients; and [8]62 patients.
Abbreviations: ULN, upper limit of normal; TSS, Trans-sphenoidal surgery.
[a]From 2000 onwards on cabergoline treatment, 64 patients.
[b]$P < .05$.
[c]In 2 patients, cabergoline was initiated 4 and 6 months after TSS (both were non-responders); in the remaining ones, cabergoline started at least 9 months after TSS (in all patients, median 20 months, range 4-120).

Results

Cabergoline monotherapy

Sixty-nine patients were included (median age at diagnosis of acromegaly 50.5 years [range 28-78], 45 males/24 females). In 15 cases, the tumour was GH+prolactin co-secreting. Cabergoline monotherapy was offered as first-line treatment in 35 (50.7%) patients, and in the remaining 34 (49.3%) ones, it was initiated after TSS. Prior to commencing on cabergoline, median IGF-1 × ULN was 2.13 (range 1.02-8.54). The median duration of cabergoline treatment was 23 months (range 3-252). The median weekly dose at the most recent review was 3 mg (0.25-7). The reason for cessation of this agent later was lack of biochemical response combined or not with side effects in all cases, except in two of them; in the latter two patients, in whom, notably, IGF-1 had normalized, the reasons were patient's choice to stay off medical treatment and option for surgery. Characteristics of the patients are shown in Table 1.

Biochemical response

Normal IGF-1 was achieved in 31.9% (22/69) of the total group of patients (in 25% of those with purely GH-secreting adenoma [10 out of 40 cases] and 60% of GH prolactin co-secreting adenoma [9 out of 15 cases], $P = .02$) (Table 1). From the cases with no IGF-1 normalization, detailed IGF-1 × ULN values just prior to the initiation of cabergoline were available in 37, and 83.8% (31) of them had reduction of their IGF-1 (median decrease of IGF-1 × ULN 0.77 [range 0.08-4.68]). The course of the IGF-1 × ULN values for each individual patient is shown in Figure 1A. Overall, in the patients showing reduction in their IGF-1 after starting cabergoline (including both those achieving and not achieving normal

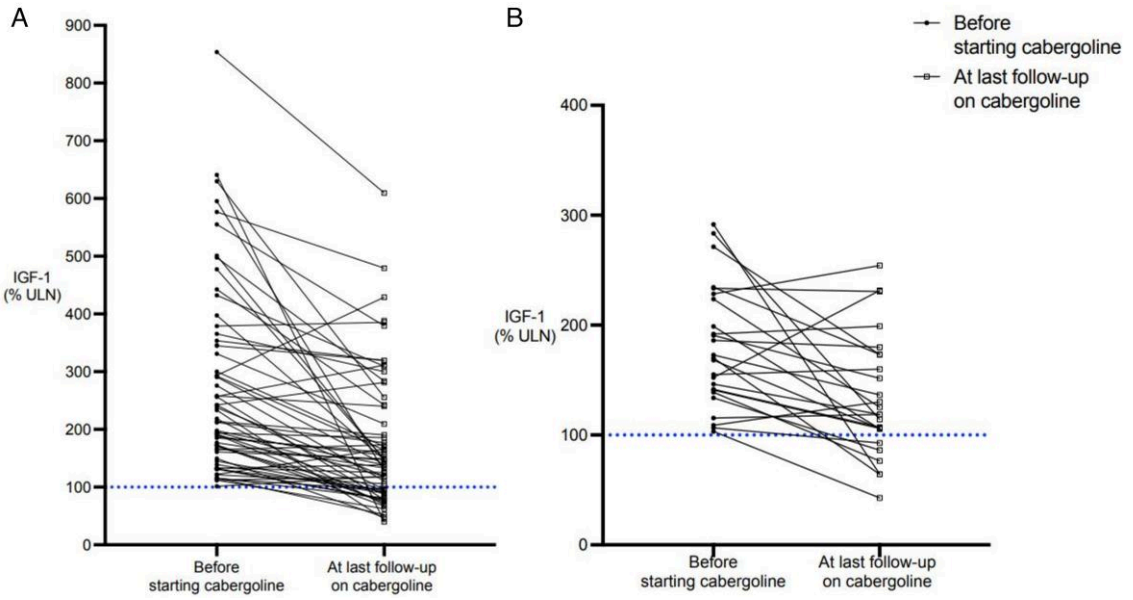

Figure 1. (A) Individual IGF-1 levels expressed as percentage of the ULN prior to (circles) and after treatment with cabergoline monotherapy (open squares) (individual values for both time points were available for 62 patients). (B) Individual IGF-1 levels expressed as percentage of the ULN prior to (circles) and after treatment with cabergoline as addition to ongoing long-acting somatostatin receptor ligand therapy (open squares) (individual values for both time points were available for 25 patients). IGF-1, insulin-like growth factor 1; ULN, upper limit of normal.

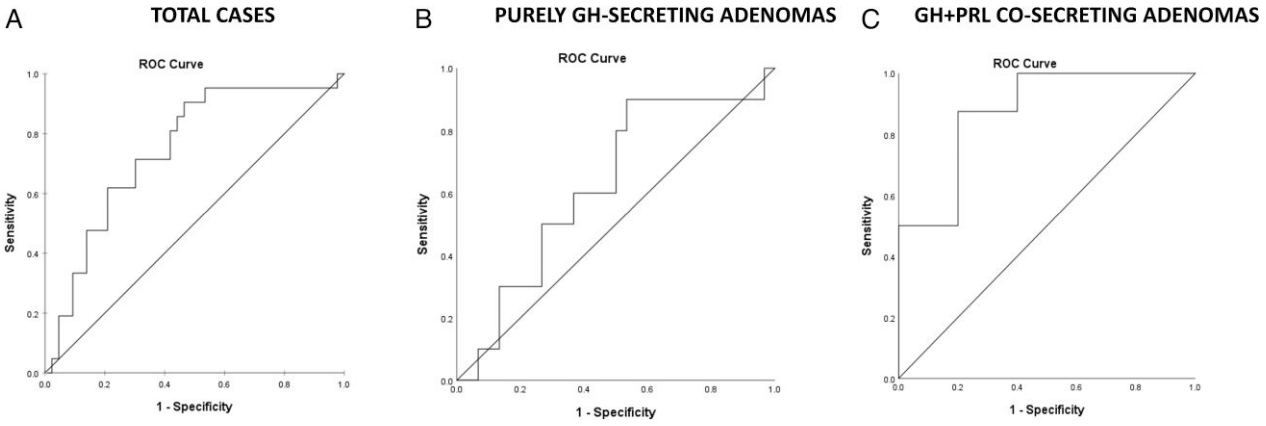

Figure 2. ROC curve analysis of IGF-1 ULN levels prior to starting cabergoline in predicting achievement of normal IGF-1. (A) Total cases (AUC 0.75; 95% CI, 0.62-0.87), (B) purely GH-secreting adenomas (AUC 0.62; 95% CI, 0.43-0.82), (C) GH+prolactin co-secreting adenomas (AUC 0.88; 95% CI, 0.67-1.00). AUC, area under the curve; GH, growth hormone; IGF-1, insulin-like growth factor 1; ROC, receiver operating characteristic; ULN, upper limit of normal.

IGF-1), median IGF-1 × ULN fell from 2.13 (range 1.12-8.54) to 1.31 (range 0.40-6.10) ($P < .001$); the median IGF-1 × ULN reduction was 0.90 (range 0.05-6.01) and was related with the pre-cabergoline IGF-1 × ULN levels (B −0.54, $P < .001$) but not with the latest cabergoline dose. There was no difference in the weekly dose of cabergoline between those achieving and those not achieving normal IGF-1 (median 2.5 mg [range 0.25-4] *vs* 3 mg [range 0.25-7], respectively). On ROC analysis, IGF-1 × ULN < 2.05 had a sensitivity of 71% and a specificity of 63% in predicting IGF-1 normalization (area under the curve [AUC] 0.75; 95% CI, 0.62-0.87) (Figure 2A). The most optimal cut-off was found for IGF-1 × ULN < 1.93, and it had a sensitivity of 71% and a specificity of 70%. When performing ROC analysis according to tumour subtype, the most optimal cut-offs were for purely GH-secreting adenomas, IGF-1 × ULN < 2.57 (sensitivity 90%, specificity 47%, AUC 0.62; 95% CI, 0.43-0.82), and for GH+prolactin co-secreting ones, IGF-1 × ULN < 2.49 (sensitivity 88%, specificity 80%, AUC 0.88; 95% CI, 0.67-1.00) (Figure 2B and C). Univariate regression analysis showed that achievement of normal IGF-1 was significantly related with the presence of a GH+prolactin co-secreting adenoma (B 1.50, $P = .02$) and lower pre-cabergoline IGF-1 × ULN levels (B −0.70, $P = .02$). No relation was found between IGF-1 normalization and age at acromegaly diagnosis, sex, latest cabergoline dose, and random GH and adenoma size (≥1 or <1 cm or no visible tumour) prior to starting cabergoline.

GH < 1 mcg/L was found in 25.8% (16/62) of patients, while 12.9% (8/62) of them had both GH < 1 mcg/L and normal IGF-1 (Table 1). The rates of discordant GH and IGF-1 results are shown in Table 1. On univariate regression analysis, there was a trend for a significant negative relation

between the achievement of GH < 1 mcg/L and latest cabergoline dose (B −0.506, $P = .05$), IGF-1 × ULN levels (B −0.566, $P = .06$), and random GH values prior to starting cabergoline (B −0.205, $P = .05$). No relation was found between the achievement of GH < 1 mcg/L and age, sex, presence of a GH+prolactin co-secreting adenoma, and tumour size (≥1 or <1 cm or no visible tumour) prior to initiating cabergoline.

Tumour shrinkage

Data on tumour shrinkage were available in a subset of 37 patients on cabergoline monotherapy (median age at diagnosis of acromegaly 51 years [range 30-78]; 26 males/11 females). During a median imaging monitoring period of 21 months (range 3-184), reduction in the tumour size was reported in 16 (43.2%) cases. Amongst the tumours with available information on subtype, the reduction was reported in 7/11 (63.6%) GH+prolactin co-secreting (median imaging follow-up 38 months [range 7-165]) and in 5/17 (29.4%) purely GH-secreting adenomas (median imaging follow-up 20 months [range 3-98]).

Cabergoline as addition to ongoing long-acting SRL therapy

Twenty-six patients were included (median age at diagnosis of acromegaly 47 years [range 21-83], 12 males/14 females). Adenoma subtype was known in 25 cases, and in 6 of them (24%), it was a GH+prolactin co-secreting adenoma. The median duration of long-acting SRL treatment prior to starting cabergoline was 18 months (range 2-118; 2 months in 1 patient and longer than 6 months in the remaining ones). Nine patients were treated with octreotide long-acting release and 17 with lanreotide. Before commencing on cabergoline, median IGF-1 × ULN was 1.70 (range 1.03-2.92). The median duration of the combination therapy was 36 months (range 4-139; in all except 1 patient, this was between 7 and 139 months). The median weekly dose of cabergoline at the last review was 2.5 mg (range 0.5-4.5). The reason for the cessation of cabergoline later was lack of biochemical response combined or not with side effects. Characteristics of the patients are shown in Table 2.

Normal IGF-1 was achieved in 23.1% (6/26) of the total group of patients (in 15.8% of the purely GH-secreting adenomas [3 out of 19 cases] and 33.3% of GH+prolactin co-secreting ones [2 out of 6 cases]) (Table 2). From the cases with no IGF-1 normalization, detailed IGF-1 × ULN values prior to initiation of cabergoline were available in 19, with 68% (13) of them showing the reduction in the IGF-1 (median decrease of IGF-1 × ULN 0.39 [range 0.03-1.69]). The course of the IGF-1 × ULN values for each individual patient is shown in Figure 1B. Overall, in the patients showing reduction in their IGF-1 after starting cabergoline (including both those achieving and not achieving normal IGF-1), median IGF-1 × ULN fell from 1.73 (range 1.03-2.92) to 1.07 (range 0.43-2.31) ($P < .001$); the median IGF-1 × ULN reduction was 0.60 (range 0.03-2.28) and was related with the pre-cabergoline IGF-1 × ULN levels (B −0.65, $P = .002$) but not with the latest cabergoline dose.

GH < 1 mcg/L was detected in 39.1% (9/23) of patients. Combination of normal IGF-1 and GH < 1 mcg/L was found in 17.4% (4/23) of the cases. The rates of GH and IGF-1 discordant results are shown in Table 2.

Discussion

To our knowledge, this is the largest series to date investigating the efficacy of cabergoline monotherapy in normalizing IGF-1 in patients with acromegaly not previously irradiated for their pituitary tumour. Normal IGF-1 was achieved in 31.9% of the cases and this effect was associated with the presence of a GH+prolactin co-secreting adenoma and lower pre-cabergoline IGF-1 × ULN levels. In purely GH-secreting adenomas, IGF-1 normalization was achieved at a rate of 25%. Both GH < 1 mcg/L and normal IGF-1 were found in 12.9% of the patients. Interestingly, a cut-off of pre-treatment IGF-1 × ULN < 2.05 had a sensitivity of 71% and a specificity of only 63% in predicting normal IGF-1 on cabergoline monotherapy. Tumour shrinkage was reported in 29.4% of the purely GH – secreting tumours. The efficacy of cabergoline in achieving normal IGF-1 as an add-on treatment to long-acting SRL in non-irradiated patients was only 23.1% in the total group and 15.8% in the purely GH – secreting adenomas.

Data on the effectiveness of cabergoline in acromegaly are derived from studies with rather small sample size, with variable definition of disease control,[8-17] and, importantly, with cohorts including cases previously offered pituitary radiotherapy.[8,9,11-14,17] Sandret et al.[25] in a meta-analysis of 10 studies looking at outcomes of patients treated with cabergoline alone found that age-adjusted normal IGF-1 was achieved in 34% (51 of 149) of the cases. The median duration of cabergoline administration was 7.5 months and the mean maximal weekly dose was 2.6 mg. In this study, information on rates of patients achieving GH < 1 mcg/L was not available. A number of patients had received prior radiotherapy and the impact of this was confirmed on multivariate analysis demonstrating that previous irradiation was a predictor of IGF-1 normalization (20% in the irradiated and 36% in the non-irradiated, with no baseline characteristics analysed separately for each subgroup). Furthermore, the outcomes of purely GH – secreting adenomas were not reported.

Notably, we did not identify the association between the latest dose of cabergoline and the rate of normal IGF-1 achievement; the median weekly dose of respondents was 2.5 mg and of non-respondents 3 mg. This is possibly explained by the variable expression and functionality of the DR2 in the adenomatous cells impacting the efficacy of this agent. In agreement with previous studies,[17,25,30] we confirmed that higher baseline IGF-1 levels are negatively associated with IGF-1 normalization. This has led to the suggestion that cabergoline is most likely to be beneficial in patients with modest IGF-1 elevation. Nonetheless, on ROC analysis, we found that IGF-1 × ULN < 2.05 or IGF-1 × ULN < 1.93 had rather low sensitivity (both 71%) and specificity (63% and 70%, respectively) in predicting achievement of normal IGF-1, potentially reflecting the impact of other factors implicated in the biochemical response. In addition, the presence of a tumour co-secreting GH+prolactin was associated with a more optimal IGF-1 response to cabergoline. Data in the literature on the predictive role of hyperprolactinaemia remain contradictory,[17,25,30] and whether, in the various series, the increased prolactin was due to stalk effect or due to true tumoural hypersecretion was often not clearly defined. In our cohort, the rate of IGF-1 normalization was 60% in the GH+prolactin co-secreting tumours as opposed to 25% in the purely GH-secreting adenomas.

Table 2. Characteristics of patients with cabergoline addition to ongoing somatostatin receptor ligand therapy and biochemical outcomes.

Characteristic/biochemical outcome	Values Total group of patients	Values Patients achieving normal IGF-1	Values Patients not achieving normal IGF-1
Number	26[a]	6 (23.1%)	20 (76.9%)
Age at diagnosis of acromegaly (years), median (range)	47 (21-83)	55 (21-83)	45.5 (23-77)
Males/females, number (%)	12/14 (46.2%/53.8%)	2/4 (33.3%/66.7%)	10/10 (50%/50%)
Macroadenoma/microadenoma at diagnosis, number (%)	20/5 (80%/20%)[1]	4/2 (66.7%/33.3%)	18/1 (5.3%/94.7%)
Prolactin co-secreting *vs* purely GH secreting adenoma, number (%)	6 (24%) *vs* 19 (76%)[1]	2/6 (33.3%) *vs* 3/19 (15.8%)	4/6 (66.7%) *vs* 16/19 (84.2%)
TSS prior cabergoline initiation *vs* no TSA prior cabergoline initiation, number (%)	19 (73.1%) *vs* 7 (26.9%)[2]	3/19 (15.8%) *vs* 3/7 (42.9%)	16/19 (84.2%) *vs* 4/7 (57.1%)
Duration of somatostatin receptor ligand treatment before starting cabergoline, (months), median (range)	18 (2-118)	55.5 (13-118)	17.5 (2-60)
Concomitant treatment with octreotide LAR, number (%)[b]	9 (34.6%)	2/9 (22.2%)	7/9 (77.8%)
Concomitant treatment with lanreotide, number (%)[c]	17 (65.4%)	4/17 (23.5%)	13/17 (76.5%)
IGF-1 × ULN prior to starting cabergoline, median (range)	1.70 (1.03-2.92)[1]	1.36 (1.03-2.92)	1.86 (1.09-2.84)
GH prior to starting cabergoline, median (range)	2.55 (0.5-39.9)[3]	0.7 (0.55-39.9)	2.7 (0.5-16.8)
Maximal weekly dose of cabergoline (mg), median (range)	3 (0.5-4.5)	2 (0.5-3)	3 (0.5-4.5)
Weekly dose of cabergoline at last review (mg), median (range)	2.5 (0.5-4.5)	1.25 (0.5-3)	3 (0.5-4.5)
Duration of combined treatment (months), median (range)	36 (4-139)	66.5 (35-120)	34 (4-139)
IGF-1 normalization, number (%)	6 (23.1%)		
IGF-1 × ULN at last follow-up, median (range)	1.19 (0.43-2.54)		
GH < 1 mcg/L, number (%)	9 (39.1%)[4]		
Normal IGF-1 and GH < 1 mcg/L, number (%)	4 (17.4%)[4]		
Normal IGF-1 and GH > 1 mcg/L, number (%)	1 (4.3%)[4]		
High IGF-1 and GH < 1 mcg/L, number (%)	5 (21.7%)[4]		

Data available for [1]25 patients; [2]26 patients; [3]22 patients; and [4]23 patients.
Abbreviations: LAR, long-acting release; ULN, upper limit of normal.
[a]From 2000 onwards on cabergoline and somatostatin receptor ligand therapy, 26 patients.
[b]Seven patients on 30-40 mg every 3-4 weeks and 2 patients on 20 mg every 4 weeks.
[c]16 patients on 120 mg every 3-4 weeks and 1 patient on 90 mg every 4 weeks.

Disease control by applying currently accepted biochemical criteria (GH < 1 mcg/L and normal IGF-1) was achieved in only a small percentage of patients (12.9%). Discordant results were found in 32.3% of the cases. Overall, discordant results may relate with discrepancies in the assays used or with various biological factors (eg, abnormalities in glucose metabolism and liver dysfunction); alternatively, they may reflect mild disease activity the impact of which on the long-term prognosis of the patients remains to be elucidated.[5,31,32]

Data on tumour shrinkage during cabergoline therapy are scarce[8-12] and the interpretation of their results is confounded by the inclusion of patients who had previously received radiotherapy, the often very short duration of treatment with cabergoline and the variable rates of GH+prolactin co-secreting tumours included in each series. In our cohort, 43% of the tumours showed shrinkage with this effect, as probably expected, been more prominent in GH+prolactin co-secreting tumours (63.6% *vs* 29.4% of the purely GH-secreting adenomas).

In our study, the combination therapy of SRL and cabergoline led to normal IGF-1 in 23.1% of the patients during a 36-month median duration of treatment. This rate was only 15.8% in the purely GH-secreting adenomas. In earlier reports, including, however, previously irradiated patients and variable ratios of GH+prolactin co-secreting tumours, this percentage has ranged between 35% and 73%.[17,18,21,22,30,33] Sandret et al.[25] in a meta-analysis of 5 studies with 77 subjects (median duration of combined treatment 6 months and mean weekly cabergoline dose 2.5 mg) reported IGF-1 normalization in 52% of them; notably, 29% of the patients had previously received radiotherapy and amongst 46 cases with available immunohistochemistry for their excised tumour, nearly half of them (47%) had a mixed GH-prolactin adenoma.

When applying the currently proposed criteria for biochemical control (GH < 1 mcg/L and normal IGF-1), we found success rates as low as 17.4%, in accord with the outcomes reported from the Mexican Acromegaly Registry (19% with GH < 1 ng/mL and IGF-1 < 1.2 × ULN).[26] Interestingly, *in vitro* studies assessing the GH anti-secretory effects in cultures of human pure GH-secreting tumours have shown that the efficacy of 72-h incubation with octreotide and cabergoline was

almost superimposable to that of octreotide alone exposure; in cultures of GH+prolactin co-secreting tumours, octreotide and cabergoline treatment demonstrated higher efficacy compared with octreotide alone, although the difference was not statistically significant due to the small sample size (in all experiments, the drugs were tested at a concentration of 10 nM).[34] The small number of cases on combination therapy did not allow us to perform analyses to identify predictors of biochemical response. Nonetheless, the predictive value of baseline IGF-1 has been previously established.[25]

Advantages of our study include the exclusion of previously irradiated patients, the large number of subjects on the cabergoline monotherapy group, and the long duration of cabergoline treatment in the whole cohort. Further strengths are the analysis of the efficacy based on both IGF-1 and GH levels criteria (as per current guidelines) and the provision of data for pure GH or GH+prolactin co-secreting tumours elucidating their distinct biochemical responses. Limitations relate with the retrospective nature of the study with management/monitoring decisions and approaches based on the clinicians' preference rather than on a standard protocol. The mildly elevated pre-treatment IGF-1 levels of the patients indicate a possible selection bias. The variation of the assays between the participating centres is another drawback, the impact of which we tried to minimize by using the times of the ULN of the IGF-1 for the statistical analyses. Finally, for the assessment of tumour shrinkage, we relied on imaging reports; this approach could be subject to variation in scan interpretation amongst radiologists and did not allow accurate quantification of the changes in adenoma size. Nonetheless, we were able to identify the reduction in tumour size in a number of patients with both tumour subtypes.

In conclusion, our results represent "real-world" data on the biochemical efficacy of cabergoline in acromegaly. In our large cohort of non-irradiated patients with median IGF-1 around 2.1 times the ULN, we have shown that cabergoline monotherapy can normalize IGF-1 in around one-third of the cases and achieve biochemical control according to currently used criteria in approximately only 1 in 10. The specificity of IGF-1 × ULN < 2.05 in predicting IGF-1 normalization is low (63%) suggesting that this treatment option may be successful not only in patients with biochemically mild disease. The efficacy of cabergoline addition to ongoing SRL therapy was related with lower efficacy rate (23.1% normalization of IGF-1) than previously reported and could be explained by differences in the groups of patients studied potentially confounding the outcomes. Overall, the IGF-1 response rates are lower in purely GH-secreting adenomas, as opposed to GH +prolactin co-secreting ones. Clinical, pathological, and molecular criteria guiding decisions on cabergoline administration in patients with acromegaly remain to be further elucidated.

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Supplementary material

Supplementary material is available at *European Journal of Endocrinology* online.

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Authors' contributions

Sandrine Urwyler (Data curation [supporting], Formal analysis [equal], Funding acquisition [lead], Project administration [supporting], Writing—original draft [equal], Writing—review & editing [equal]), Irene Samperi (Data curation [supporting], Formal analysis [supporting], Project administration [supporting], Writing—review & editing [supporting]), Kirstie Lithgow (Data curation [supporting], Project administration [supporting], Writing—review & editing [supporting]]), Akash Mavilakandy (Data curation [supporting], Writing—review & editing [supporting]), Mike Matheou (Data curation [supporting], Writing—review & editing [supporting]), Karin Bradley (Data curation [supporting], Writing—review & editing [supporting]), Aparna Pal (Data curation [supporting], Writing—review & editing [supporting]), Narendra Reddy (Data curation [supporting], Writing—review & editing [supporting]), John Ayuk (Writing—review & editing [supporting]), and Niki Karavitaki (Conceptualization [lead], Data curation [lead], Formal analysis [equal], Funding acquisition [supporting], Project administration [lead], Supervision [lead], Writing—original draft [equal], Writing—review & editing [lead]).

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