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ORIGINAL

Efficacy of combined octreotide and cabergoline treatment in patients with acromegaly: a retrospective clinical study and review of the literature

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Abstract. Although somatostatin analogues are effective medical therapy for acromegaly, the serum insulin-like growth factor-I (IGF-I) levels remain uncontrolled in 35% of patients. Combined therapy with octreotide LAR and cabergoline has been reported to normalize IGF-I levels in 42–56% of Caucasian patients with acromegaly. However, it remains to be clarified whether combination therapy is effective in Japanese patients and on tumor shrinkage. We conducted a retrospective study on combined therapy in patients with octreotide-resistant acromegaly. Ten patients with acromegaly who showed octreotide-resistance were enrolled in this study. Cabergoline was added in doses of 0.25–2.0mg/week. Serum GH and IGF-I levels and tumor volume were assessed before and after treatment, and factors correlated with effect of the combined therapy were analyzed. Although serum GH levels did not decrease, serum IGF-I levels significantly decreased by 20% after 6 months of combined therapy compared with baseline ($p < 0.05$). As a result, serum IGF-I levels normalized in 30% of the patients. Tumor volume after combined therapy also significantly decreased ($p < 0.01$). There were no correlations between the decrease of serum IGF-I levels during combined therapy and the response of GH in a bromocriptine test, random GH, IGF-I, and PRL levels, the tumor volume, and the expression of PRL and dopamine D2 receptor in the tumor. In conclusion, we demonstrated that the addition of cabergoline to octreotide LAR is a beneficial option in Japanese patients with octreotide-resistant acromegaly, irrespective of serum PRL levels and the response of GH levels in a bromocriptine test.

Key words: Acromegaly, Octreotide, Cabergoline, Combined therapy, Prolactin (PRL)

ACROMEGALY is a chronic disease caused by unrestrained hypersecretion of GH and insulin-like growth factor-I (IGF-I) [1]. Patients with active acromegaly (shown by high IGF-I and/or GH levels) have increased mortality compared to the general population (mean standardized mortality ratio (SMR) 1.72). Importantly, biochemical normalization of GH and IGF-I restores increased mortality [2]. Surgery remains the first-line treatment, but 20% of patients with microadenoma and 40–60% of patients with macroadenoma are not cured by surgery and require adjuvant medical therapy [3, 4].

Long–acting somatostatin analogs (SSAs) have been widely accepted as the best medical option for the treatment of acromegaly [5]. Nevertheless, at least 35% of patients are considered to be resistant to commercially available SSAs (octreotide LAR and lanreotide autogel) as they do not achieve IGF-I normalization [5, 6]. Dopamine agonists, such as bromocriptine and cabergoline, have long been known to suppress GH secretion in patients with acromegaly. Although cabergoline has a higher potency than bromocriptine, it has been shown to normalize IGF-I levels in only up to 39% of acromegalic patients treated with this drug as monotherapy [7, 8]. Cabergoline efficacy is greater in subjects with concomitant hyperprolactinemia and when the elevation of IGF-I and GH levels is only mild or

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moderate [9-11]. Furthermore, very little data are available regarding tumor shrinkage in patients with acromegaly who are receiving dopamine agonist therapy. Combined results from a number of studies revealed that 29% of patients had some tumor shrinkage and the majority of these patients were also hyperprolactinemic [10]. As another option for medical therapy, pegvisomant, a new drug that acts as a GH receptor antagonist, normalizes IGF-I levels in 63–97% of patients but do not induce tumor shrinkage [12, 13].

To overcome the limitations of monotherapy for acromegaly, combined medical therapy has been proposed. Recently, addition of cabergoline to octreotide LAR has been shown to normalize IGF-I levels in 42–56% of acromegalic patients not controlled by octreotide LAR alone [14-19]. All these studies were performed in Caucasian populations and there have been no reports in the Asian population. In this study, we analyzed the biochemical effect of combination therapy with octreotide LAR and cabergoline in Japanese patients with acromegaly who showed resistance to octreotide LAR monotherapy. We also analyzed the effect on tumor shrinkage and the factors correlated with the effect on decrease in serum IGF-I.

Patients and Methods

Patients

Ten patients with active acromegaly (4 men and 6 women; mean age: 39.0 ± 12.5 years) who were treated with octreotide LAR monotherapy for more than 8 months in Kobe University Hospital between 2005 and 2012 and showed octreotide-resistance were enrolled in this study and analyzed retrospectively. Octreotide-resistance was defined as serum GH levels of more than 1μg/L or serum IGF-I levels of more than 2 SD of age and sex matched reference subjects in a Japanese population [20], and no significant changes in GH or IGF-I levels for at least 6 months, irrespective of treatment with 20 mg or more- per month of octreotide LAR. The bromocriptine test was performed with a single oral 2.5 mg administration; and plasma GH levels were measured both before and 2–12 h after bromocriptine and nadir GH levels were recorded.

Protocols

Plasma GH and IGF-I levels were assessed at 6 months before as well as at baseline, and 1, 3, and 6 months after combined treatment with octreotide LAR and cabergoline. Cabergoline was initially administered at 0.25–1.0 mg/week and progressively increased to 2.0 mg/week.

Assays

Serum GH and IGF-I levels were measured by immunoradiometric assay (IRMA) (Tosoh, Chiba, Japan and Diagnostic System Laboratories, TX, USA). Serum PRL levels were measured with a 2-site immunochemiluminescent assay (ADVIA Centaur, NJ, USA).

Tumor volume calculation

Tumor diameters were measured in 3 MRI orthogonal planes, and tumor volume was calculated using the Di Chiro and Nelson formula (volume = height × width × depth × π/6), as previously described [21]. MRI was performed before octreotide LAR monotherapy, before the combined therapy, and 6–12 months after the addition of cabergoline.

Immunohistochemical staining

Immunohistochemistry for paraffin-embedded tumor samples was performed at the same time for the comparison by using avidin-biotin-peroxidase complex (ABC). The following primary antisera were used: polyclonal antibodies to GH (1:2000; Dako, A0570), PRL (1:500; Dako, A0569), cytokeratin (CAM5.2, Becton-Dickinson, Mountain View, USA), somatostatin receptor subtype 2 and 5 (SSTR2, 5) (SS-800 and SS-838, Gramsch Lab. Germany), and dopamine D2 receptor (DRD2). Semiquantitative scoring for the SSTRs [22, 23] and DRD2 [24] protein was performed by the experienced pathologist as previously described.

Statistical analysis

Values are expressed as mean ± SD. Statistical analysis was performed using JMP 8 software (SAS Institute, Cary, NC, USA). Analysis of variance (ANOVA) and Student's *t*-test for paired data was used where appropriate. Correlations between numerical variables were studied using Spearman's correlation test. *p*-values of less than 0.05 were considered significant.

Results

GH and IGF-I levels after addition of cabergoline to octreotide

Ten patients with active acromegaly who showed octreotide-resistance were treated with a combined therapy of octreotide LAR and cabergoline (Table 1).

Eight patients had undergone surgery, and 2 patients received radiotherapy before the combined therapy. MRI revealed intersellar or parasellar remnant tumors in 6 patients, and empty sella in 3 patients. MRI examination was not performed in 1 patient because of a past history of clipping surgery for cerebral aneurysm. Immunohistochemical analysis was performed in 4 patients and 3 of them were positive for PRL (Table 1). The mean values of serum random GH, nadir GH in an oral glucose tolerance test, and IGF-I levels at diagnosis were 38.3 ± 35.0 ng/mL, 20.9 ± 20.0 ng/mL, and 643 ± 386 ng/mL, respectively. The mean duration of octreotide LAR treatment was 37.1 ± 24.9 (8–51) months. Before the addition of cabergoline, the mean values of serum random GH, PRL, and IGF-I were 4.3 ± 3.9 ng/mL, 14.3 ± 10.0 ng/mL, and 407 ± 142 ng/mL, respectively (Table 1). The mean dose of cabergoline at 6 months was 1.8 ± 0.4 mg/week. As shown in Fig. 1a, serum IGF-I levels between 6 months before the addition of cabergoline and those at 0 month were not changed, suggesting the presence of octreotide-resistance. Although serum IGF-I levels at 1 and 3 months were not changed as compared with baseline, after the addition of cabergoline, those at 6 months were significantly decreased (Fig. 1a, 20% reduction as compared with baseline). With respect to individual IGF-I levels, serum IGF-I levels were decreased in 8 patients after 6 months of combined therapy (Fig. 1b). Serum IGF-I levels after 6 months were within the normal range(≤|2SDS|) in 3 patients (30%); IGF-I level normalized with the combined therapy in 2 patients (patient 6 and 9), while the other patient was treated with combined therapy irrespective of normal IGF-I levels due to elevated GH levels and a remnant macroadenoma (patient 10, details were shown in Fig. 2b). On the other hand, changes in serum random GH levels during the combined therapy were not significant (Fig. 1c); however, random GH levels in 6 patients decreased after 6 months of combined therapy (Fig. 1d).

Tumor shrinkage after the combined therapy

The remnant tumor volume before and after octreotide LAR monotherapy and after combined therapy was evaluated in 6 patients. The tumor volume evaluated by MRI before and after octreotide LAR monotherapy was not significantly changed (Fig. 2a, $p = 0.07$), suggesting a presence of octreotide-resistance. Intriguingly, significant shrinkage of tumor volume after combined therapy was observed (Fig. 2a, $p = 0.009$). The mean tumor volumes before and after combined therapy were 33.4 ± 40.6 mm^3 and 20.9 ± 20.8 mm^3, respectively. In particular, 2 patients who showed marked decrease in IGF-I demonstrated obvious tumor shrinkage (patient 6 and 10). The patient 10 had a giant tumor of Knosp grade 4 with severe headache (Fig. 2b, left). Since a surgical cure was not expected, the patient was treated with octreotide LAR 30 mg/month for 17 months. The patient's symptoms rapidly improved and the tumor shrank substantially (Fig. 2b, middle); however, serum GH levels remained high and the size of the tumor remained unchanged at the successive MRI examination on octreotide LAR monotherapy. We then performed combined therapy. After the addition of cabergoline 2 mg/ week, serum GH and IGF-I levels were normalized and surprisingly, the tumor shrank drastically and the most of it disappeared (Fig. 2b, right).

Table 1 Clinical characteristics of 10 acromegalic patients

No.	Age	Sex	prior treatment			tumor at MRI	IHC	GH (ng/mL)	IGF-I (ng/mL)	PRL (ng/mL)	octreotide LAR			cabergoline	
			NS	RT	DO						length (month)	dose range (mg/month)	side effect	dose range (mg/week)	side effect
1	30	M	+	-	-	remnant	NA	14.1	636	10.6	19.3	20-40		0.5-2	
2	51	F	+	+	-	remnant	GH/PRL	6.7	574	5.8	10.6	20-40		0.5-2	
3	55	F	+	-	-	remnant	GH	2.2	517	16.2	8.1	20		2	
4	45	F	-	-	+	empty sella	NA	1.2	410	32.7	50.6	30-40	debris	0.25-2	
5	30	M	+	-	+	remnant	NA	3.2	447	2.2	32.8	20		1	
6	47	F	+	-	+	empty sella	NA	1.6	289	8.4	80.5	20		2	
7	18	M	+	+	+	empty sella	GH/PRL	1.2	437	21.9	50.6	30-40		2	
8	44	F	+	-	-	remnant	GH/PRL	3.9	241	17.8	32.3	20		1	
9	46	M	+	-	+	NA	NA	3.5	230	3.3	69.1	20-40		2	
10	24	F	-	-	-	macroadenoma	NA	4.8	287	23.9	17.0	20-30		0.25-2	nausea

NS, neurosurgery; RT, radiotherapy; DO, daily octreotide; IHC, immunohistochemistry; NA, not applicable

Predictors of response to the combined therapy

A couple of reports suggested that a good response to combined therapy might be correlated with serum PRL levels. We analyzed the correlation of the parameters with the changes in the ratio of IGF-I levels before and after combined therapy (Fig. 3). However, no significant correlation was found between changes in IGF-I levels and the response of GH in a bromocriptine test (Fig. 3a), random GH levels (Fig. 3b), IGF-I levels (Fig. 3c), random PRL levels (Fig. 3d), and tumor volume (Fig. 3e) before treatment.

Adverse effects in the combination therapy

No patient was withdrawn from combination therapy because of adverse effects. With octreotide treatment alone, 1 patient showed mild debris in the gallbladder detected by ultrasonography. One patient complained of mild nausea during combination therapy, but this was tolerated after a couple of weeks of continuing treatment.

SSTR and DRD2 expression in the tumor

To explore the underlying mechanisms, we performed immunohistochemical analysis of the tumor derived from patient 2, 3, 7, and 8. We evaluated the immunoreactivity of somatostatin receptor (SSTR) 2, 5, and dopamine D2 receptor (DRD2), which were defined by the ratio of positive cells as previously described [22-24]. SSTR2 immunoreactivity was scored as (++) in patient 7 and as (+) in patient 2, 3, and 8 (Fig. 4a). SSTR5 immunoreactivity was scored as (+++) in patient 3 and 7, and as (+) in patient 2 and 8. DRD2 immunoreactivity was scored as (+++) in all the patients. CAM5.2 staining showed typical fibrous body patterns in patient 3, indicating the sparsely granulated cell type (Fig. 4a). Patient 2, 7, and 8 showed

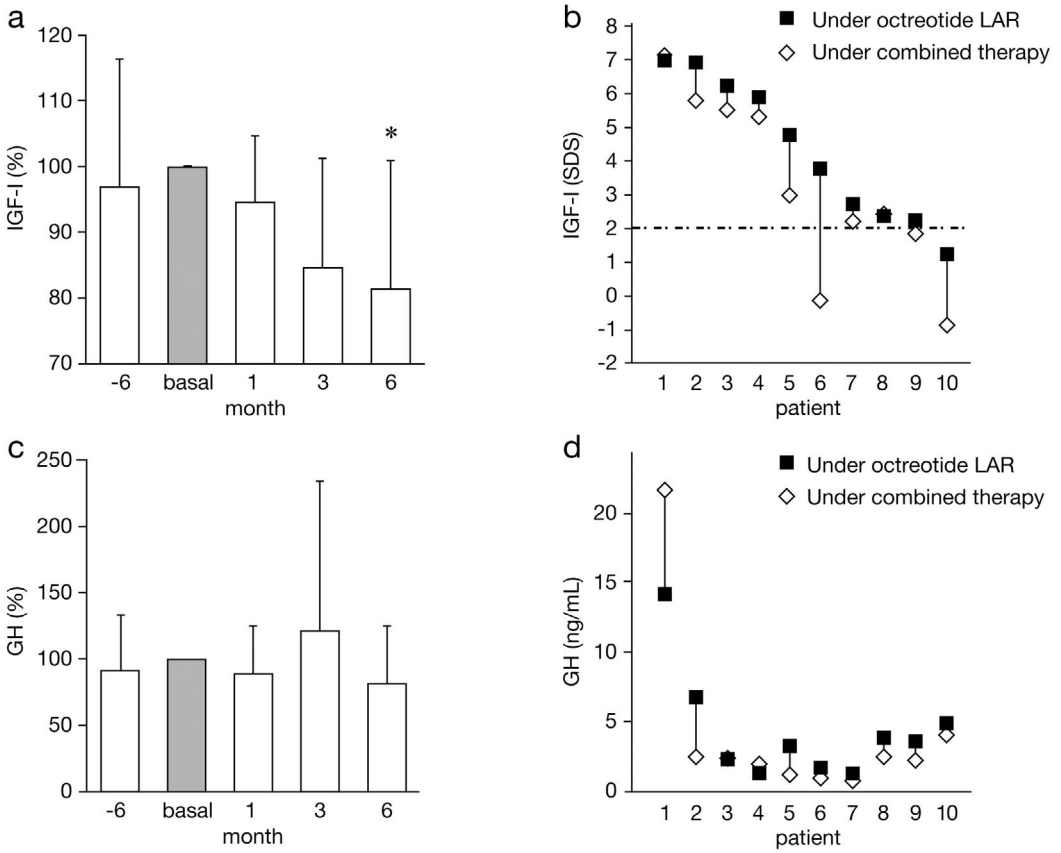

Fig. 1 (a) Mean IGF-I (%) levels before and during combined therapy of octreotide LAR and cabergoline. Values are expressed as mean ± SD. *$p<0.05$ *vs.* baseline. (b) Individual SD scores (SDS) of serum IGF-I levels at 0 and 6 months after combined therapy. (c) Mean random GH (%) levels before and during combined therapy with octreotide LAR and cabergoline. Values are expressed as mean ± SD. (d) Individual serum GH levels (ng/mL) at 0 and 6 months after combined therapy.

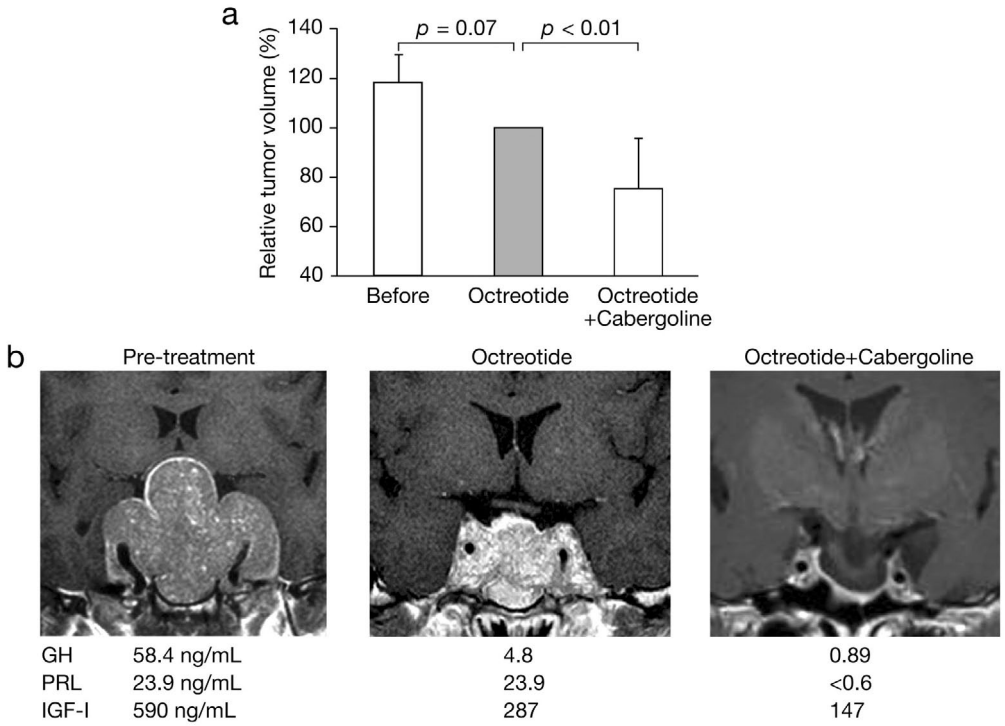

Fig. 2 (a) Changes in the relative tumor volume. Tumor volume (%) was significantly decreased after combined therapy. (b) A representative effective case of combined therapy. Pituitary MRI in patient 10 revealed a giant tumor encasing the internal carotid artery before treatment (Knosp grade 4) (left panel). After octreotide treatment, the tumor shrank obviously but thereafter, the size of the tumor was unchanged at the successive MRI examination (middle panel). The addition of cabergoline drastically shrank the tumor and normalized serum levels of GH and IGF-I (right panel).

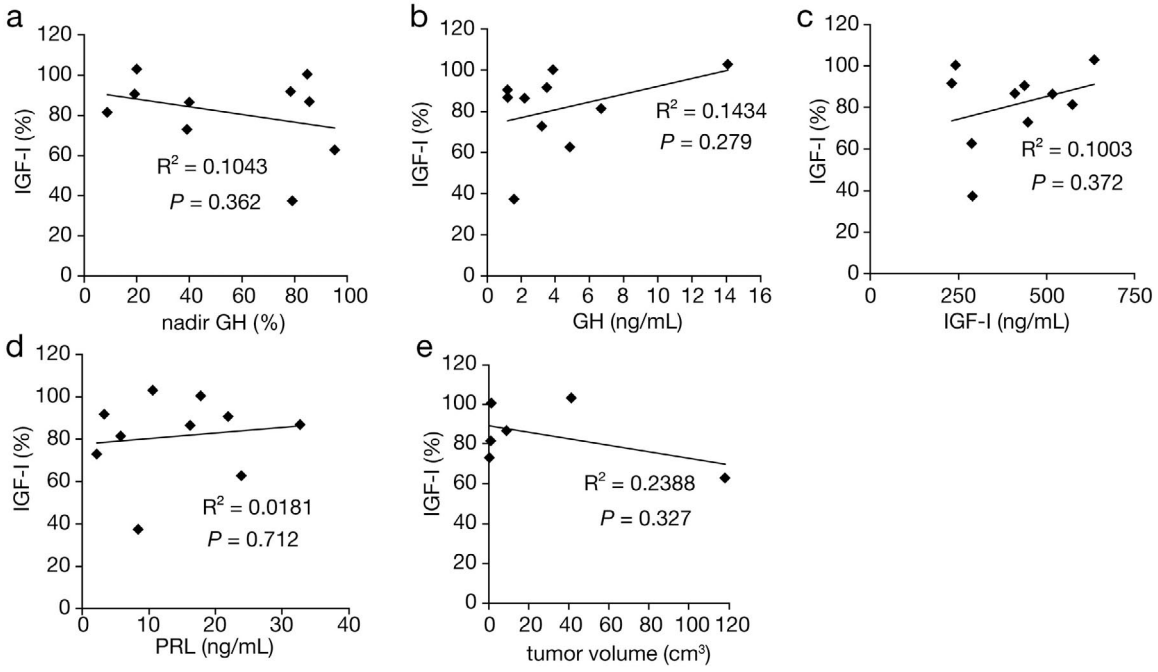

Fig. 3 Correlation with the ratio of serum IGF-I levels before and after combined therapy and (a) response of GH (%) in a bromocriptine test, (b) basal random GH levels, (c) basal IGF-I levels, (d) serum PRL levels, and (e) tumor volume before combined therapy. No correlations with the response of serum IGF-I and these factors were observed.

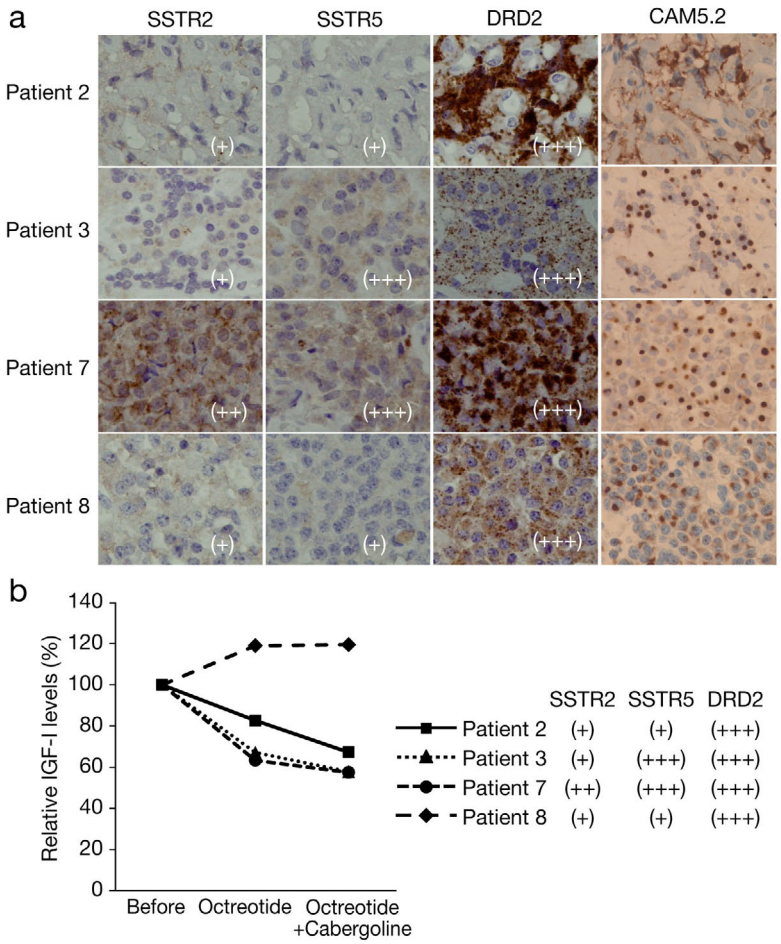

Fig. 4 (a) Immunohistochemical analysis of SSTR2, 5, DRD2, and cytokeratin (CAM5.2) of the tumor. (b) The changes in the individual IGF-I levels (%) during octreotide LAR monotherapy and combined therapy together with the score of immunoreactivity of SSTR2, 5, and DRD2.

atypical CAM5.2 staining pattern, indicating the monomorphous GH and PRL cell adenoma with fibrous bodies. We then analyzed the relationship between the changes of IGF-I levels during the combined therapy and SSTR2, 5, and DRD2 expression of the tumor (Fig. 4b). We found a tendency that when SSTR2 or 5 was highly expressed, the serum IGF-I levels were well responded to octreotide monotherapy (patient 7); however, the responses to combined therapy were not necessarily correlated with the immunoreactivity of DRD2.

Discussion

In this study, we demonstrated that the addition of cabergoline to octreotide LAR in Japanese patients with octreotide-resistant acromegaly significantly decreased IGF-I levels after 6 months. IGF-I levels were decreased by 20% compared with baseline. In addition, tumor volume was significantly reduced by combined therapy.

In 6 previous studies, cabergoline was added to a SSA that had failed to normalize IGF-I (Table 2). Five prospective studies involved 134 patients [14, 15, 17-19], and 1 retrospective study involved 9 patients [16]. The mean duration of combined treatment was 7.5 months. The cabergoline dose ranged between 1 and 3.5 mg/week (mean dose, 2.2 mg/week) (Table 2). Sandret *et al.* reported a meta-analysis of 5 previous studies, showing that 40 patients (52%) achieved normal IGF-I levels on combined treatment [25]. The mean decreases in IGF-I and GH levels were 30% and 19%, respectively. The effect of cabergoline was related to baseline IGF-I levels, but not to the dose of cabergoline, the duration of treatment, or baseline PRL levels. In the present

Table 2 Characteristics of the published studies evaluating the effect of combined therapy in patients with acromegaly

	Marzullo *et al.*[14] 1999	Cozzi *et al.*[15] 2004	Gatta *et al.*[16] 2005	Jallad *et al.*[17] 2009	Mattar *et al.*[18] 2010	Vilar *et al.*[19] 2011	Present study
N	10	19	9	34	19	52	10
Neurosurgery*	10/10	8/19	6/9	27/34	19/19	32/52	8/10
Radiotherapy*	0/10	2/19	5/9	14/34	4/19	6/52	2/10
IHC positive PRL	5/10	4/8	3/6	11/21	4/9	7/15	3/4
Elevated plasma PRL	2/10	2/19	0/9	13/34	0/19	17/52	5/10
SSA type OCT	0/10	13/19	8/9	34/34	19/19	52/52	10/10
SR or ATG	SR 10/10	ATG 6/19	ATG 1/9	0/34	0/19	0/0	0/10
SSA dose	SR 60-90mg	OCT 30mg	OCT 30mg	OCT 30mg	OCT 30mg	OCT 30mg	OCT 20-40mg
Mean duration	6 month	9-12 month	27 month	24 month	24 month	12 month	36 month
CAB dose	1.5-3mg/w	1-3.5mg/w	mean 1.8mg/w	1.5-3.5mg/w	1-3.5mg/w	1-3mg/w	1-2mg/w
Mean duration	3 month	3-18 month	8.44 month	6 month	4-12 month	6-12 month	6 month
GH normalization	40% (4/10)	21% (4/19)	44% (4/9)	71% (24/34)	NA	46% (24/52)	20% (2/10)
IGF-I normalization	50% (5/10)	42% (8/19)	44% (4/9)	56% (19/34)	37% (7/19)	40% (21/52)	30% (3/10)

IHC, immunohistochemistry; SSA, somatostatin analog; OCT, octreotide LAR; SR, lanreotide slow-release; ATG, lanreotide autogel; CAB, cabergoline; NA, not applicable; *, prior treatment

study, IGF-I levels were decreased by 20% with combined therapy and the IGF-I levels were normalized in 30% of patients, indicating that the combined therapy was slightly less effective compared with the previous studies. As a reason, the serum baseline IGF-I levels in the present study might be higher than those in the previous study. Also, it is possible that the dose of cabergoline used in this study (1.4 mg/week compared with 2.5 mg/week in the previous study) might be relatively small to exert the maximum effect. In addition, 8 out of 10 patients showed a decrease in serum IGF-I levels; however, this did not reach to the normal range in 4 patients, suggesting that a prolonged treatment may improve the ratio of normalization.

Very little data have been reported concerning tumor shrinkage in response to combined therapy. The effect of cabergoline monotherapy on tumor volume was examined in several studies [10, 26, 27]. Tumor shrinkage by cabergoline was associated with a higher baseline PRL level, a higher baseline IGF-I level, and previous treatment [25]; however, the factors that affect the response to a combined therapy of SSAs and cabergoline may be different from those that are related in cabergoline monotherapy. In the current study, we demonstrated that combined therapy might be effective for the tumor shrinkage. The interpretation of the clinical course is difficult with this design because long-term treatment with octreotide LAR *per se* continues to decrease GH and IGF-I levels and induces tumor shrinkage at least in some cases [28, 29]. We have shown that the tumor volume was significantly decreased after the combined therapy in contrast to the changes in the tumor volume before and after octreotide LAR monotherapy, which was not significant. However, it cannot be ruled out that prolonged treatment with octreotide LAR rather than the addition of cabergoline was efficacious against the tumor shrinkage because of the decreased tendency before and after octreotide monotherapy. Nevertheless, as shown in patient 10 (Fig. 2b), combined therapy was obviously beneficial in some cases. It is important to discriminate cases that are responsive to combined therapy from those that are not. Most previous reports have demonstrated that the effect of combined therapy was not correlated with serum PRL levels [25]. We analyzed the factors associated with the decrease in serum IGF-I levels caused by combined therapy; however, no obvious correlations were observed between decreased IGF-I levels and nadir GH levels in a bromocriptine test, tumor volume, or serum PRL levels.

Immunohistochemical analysis of the tumor showed that PRL was expressed in 3 out of 4 patients (Table 1). In patient 8, the tumor exhibited a PRL expression as well as GH; however, the response in serum IGF-I was not observed during combination therapy, suggesting that expression of PRL may not predict the response. DRD2 was highly expressed in all 4 patients. Irrespective of the high expression of DRD2, patient 8 revealed a blunted response to combined therapy, suggesting that the expression levels of DRD2 may also not predict the response to combined therapy. However,

the pattern of DRD2 expression was obviously different among these tumors, suggesting that expression pattern may be related with the functional property of DRD2. It has been reported that the expression levels of SSTR2 were associated with the normalization of serum GH and IGF-I levels in response to octreotide therapy [30]. In the present study, patient 7 revealed a relatively high expression of SSTR2, in which serum IGF-I levels were decreased by 36% with octreotide LAR monotherapy. On the other hand, patient 2, 3, and 8 showed relatively low expressions of SSTR2, in which serum IGF-I levels were decreased by 33-17%, suggesting an association between the response to octreotide in serum IGF-I and the expression levels of SSTR2.

When a patient reveals an octreotide-resistant status, there are several options for medical therapy. The first is to increase the dose of octreotide up to 40 mg/month because dose escalation may be effective especially in young patients with large tumors [31]. The second is to administer a combined therapy of SSAs and cabergoline as shown in the current study. The third is an alternative combined therapy of SSAs and pegvisomant. Collating the available results, combined therapy of SSAs and cabergoline is considered to be beneficial in cases with slightly elevated IGF-I levels irrespective of SSA treatment; and this is also a cost-effective treatment.

In conclusion, we demonstrated that the addition of cabergoline to octreotide LAR is beneficial in Japanese patients with octreotide-resistant acromegaly. Although it is important to clarify the predictors of the effectiveness of combined therapy, present data demonstrates that combination therapy with octreotide LAR and cabergoline is an important option for the treatment of octreotide-resistant acromegaly.

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Conflicts of Interest

The authors declare no conflict of interest.

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