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Magnetic resonance imaging as a predictor of therapeutic response to pasireotide in acromegaly

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Abstract

Objective: Hyperintensity signal in T2-weighted magnetic resonance imaging (MRI) has been related to better therapeutic response during pasireotide treatment in

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acromegaly. The aim of the study was to evaluate T2 MRI signal intensity and its relation with pasireotide therapeutic effectiveness in real-life clinical practice.

Design, Patients and Measurements: Retrospective multicentre study including acromegaly patients treated with pasireotide. Adenoma T2-weighted MRI signal at diagnosis was qualitatively classified as iso-hyperintense or hypointense. Insulin-like growth factor (IGF-I), growth hormone (GH) and tumour volume reduction were assessed after 6 and 12 months of treatment and its effectiveness evaluated according to baseline MRI signal. Hormonal response was considered 'complete' when normalization of IGF-I levels was achieved. Significant tumour shrinkage was defined as a volume reduction of ≥25% from baseline.

Results: Eighty-one patients were included (48% women, 50 ± 1.5 years); 93% had previously received somatostatin receptor ligands (SRLs) treatment. MRI signal was hypointense in 25 (31%) and hyperintense in 56 (69%) cases. At 12 months of follow-up, 42/73 cases (58%) showed normalization of IGF-I and 37% both GH and IGF-I. MRI signal intensity was not associated with hormonal control. 19/51 cases (37%) presented a significant tumour volume shrinkage, 16 (41%) from the hyperintense group and 3 (25%) from the hypointense.

Conclusions: T2-signal hyperintensity was more frequently observed in pasireotide treated patients. Almost 60% of SRLs resistant patients showed a complete normalization of IGF-I after 1 year of pasireotide treatment, regardless of the MRI signal. There was also no difference in the percentage tumour shrinkage over basal residual volume between the two groups.

KEYWORDS
acromegaly, IGF-1, magnetic resonance imaging, pasireotide, somatostatin receptor ligands, T2-weighted signal intensity

1 | INTRODUCTION

Acromegaly is caused by excessive secretion of growth hormone (GH) and insulin-like growth factor (IGF-I) generally as a result of a GH-secreting pituitary adenoma.[1,2] The treatment of patients with acromegaly aims to normalize IGF-I and GH plasma levels, control tumour mass as well as reduce morbidity and mortality rates.[3] Transsphenoidal surgery is offered as the first line treatment for most of patients with acromegaly for its potential curative effect.[4] However, pharmacologic therapy is currently an important treatment option for patients with persistent disease after surgery and in those with contraindications or who refuse surgery.[1] Medical treatments include somatostatin receptor ligands (SRLs), dopamine agonists and the GH receptor antagonist Pegvisomant.[3] First-generation SRLs have been considered as the first-line medical therapy until now.[4] However, these compounds achieve biochemical control only in about 50% of patients, with a high variability depending on the series[5]; SRLs also induce tumour shrinkage in about half of treated patients.[6] Pasireotide is a multireceptor SRL, with a higher affinity for somatostatin receptor subtype SST5 than SST2, followed by SST3 and SST1.[7] It is still considered a second treatment line although it has demonstrated that it can normalize hormonal control and may reduce tumour size in a substantial part of cases inadequately controlled with first-generation SRLs.[8,9]

In recent years, efforts have been performed to identify biomarkers that can predict therapeutic response of either acromegaly drug available, with the objective of a therapeutic approach towards personalized medicine, avoiding a delay in disease control and improving prognosis and quality of life.[10–15] Furthermore, the T2-weighted magnetic resonance imaging (MRI) signal of the tumour has also been recognized as a reasonable predictor biomarker of response to first-generation SRLs. A hypointense T2-weighted MRI signal is associated with greater IGF-I decrease after 6 and 12 months of treatment with first-generation SRL.[16–20] Histologically, most of hypointense T2 tumours show predominantly a densely granulated pattern and high SST2 expression.[15,18] Conversely, an increase in hyperintense T2-weighted MRI signal during pasireotide treatment has been recently linked to a better hormonal response in a series of patients with acromegaly.[21] The aim of the present study was to evaluate the prevalence of this radiological feature and its association with therapeutic response to pasireotide in clinical practice in a large cohort of acromegaly patients.

2 | SUBJECTS AND METHODS

2.1 | Cohort description

This is a retrospective multicentre study performed in 18 tertiary university hospitals in Spain and Portugal. The information was obtained from the clinical records of the electronic histories. We evaluated 81 subjects with active acromegaly that failed surgical treatment or did not respond adequately to maximal doses of first-generation SRLs, in which pasireotide was indicated according to current clinical guidelines recommendations.[22] First-generation SRLs were suspended at least 3 months before starting pasireotide. The exclusion criterion was the absence of the required clinical information at the three time-points data collection: before starting pasireotide, and 6 and 12 months after initiation of pasireotide. The study protocol was conducted according to the principles of the Declaration of Helsinki and approved by the Hospital Germans Trias i Pujol Research Ethics Committee.

2.2 | Clinical and laboratory evaluations

Demographic and clinical variables including time since diagnosis of acromegaly and other treatments performed before starting pasireotide (surgery, radiotherapy and/or medical therapies) were registered. The IGF-I value before the initiation of pasireotide treatment was used as basal IGF-I. Total serum IGF-I concentrations were analyzed using a chemiluminescence immunoassay (Liaison XL; DiaSorin) in 15 centres (for the other three centres we do not have data). IGF-I values are expressed as percentage above the upper limit of normal (ULN) adjusted for age and sex, thus allowing comparability between centres. A complete response to pasireotide was considered when IGF-I achieved normal age and gender values from local laboratories, partial response when IGF-I values decreased ≥50% from baseline without normalizing, and poor response when IGF-I values decreased from baseline was <50%. GH value was obtained from a morning random measurement.

2.3 | MRI evaluation

Images corresponding to the time of somatotropinoma diagnosis were used as basal images for intensity category evaluation although regarding the effects upon tumour volume during pasireotide treatment, the last image before the treatment was started was used as basal measurement. Gadolinium-enhanced pituitary MRI images were evaluated by each local neuroradiological service of participating hospital under the supervision of an experienced neuroradiologist (J. P.) from the coordinating centre. He supervised the quality and standardization of the acquisition protocol. Namely, T2-weighted MRI signal intensity of the solid portion of the pituitary adenomas was compared with the cerebral grey and white matter in the adjacent temporal lobe. Signal intensity was categorically classified as hypointense, when the MRI signal was mostly equal to or lower than the signal intensity of white matter and lower than that of grey matter, and as hyperintense when the signal was equal to or higher than that of grey matter. An isointense signal was defined as a signal intensity between white and grey matter.[23] No quantification of signal intensity was performed. Those tumours in which the image characteristics was highly heterogeneous and do not allowed to define a clear hyper, iso or hypointense patterns, were considered as indeterminate and were discarded for association and correlation analyses but not for hormonal control and tumour reduction evaluation. Tumour volume was calculated using the following formula: height × width × length. Significant tumour shrinkage was defined as a decrease of ≥25% from baseline.

2.4 | Statistical analysis

A descriptive analysis was performed. Normal distribution of continuous variables was assessed by the Kolmogorov–Smirnov test. Numerical data are presented as mean ± standard error. Categorical data are expressed using numerical values and percentages. Differences among groups were evaluated using χ^2 test or Student's *t*-test/Mann–Whitney *U* test, as appropriate. The significance level was defined as a p value < 0.05. All the analyses were performed with the SPSS 23.0 statistical package.

3 | RESULTS

3.1 | Patient's clinical characteristics before pasireotide treatment

Eighty-one patients with active acromegaly on treatment with pasireotide for a period of 9–12 months were included. Their baseline characteristics are presented in Table 1. More than 90% of patients had previously undergone unsuccessful treatment with first-generation SRL (Table 1), according to the clinical guidelines and normative use of pasireotide; 24 out of 81 patients (30%) had been previously treated under a combination modality including first-generation SRLs with cabergoline and 17 (21%) with pegvisomant, without reaching adequate control; of these 41 patients, 13 and 5, respectively, continued with these treatments in equal or lower doses. Radiotherapy was given before pasireotide in 29 out of 81 cases (36%), in a period that ranged from 2 months to 20 years (mean: 70 ± 17 months) before initiation of pasireotide. Basal T2-weighted MRI showed that signal intensity was iso/hyperintense in almost 70% of the patients included before starting pasireotide. The mean value of basal IGF-I before initiation of pasireotide, expressed as % ULN, was 178 ± 8.2, without differences by T2-weighted MRI signal categories. The tumour volume before pasireotide treatment showed a statistical trend ($p = 0.08$) towards being greater in the iso/hyperintense T2-weighted MRI signal group (Table 1).

TABLE 1 Baseline characteristics of all patients, hypointense group and iso/hyperintense group.

	All patients (n = 81)	Hypointense T2-weighted MRI signal (n = 25 [31%])	Iso/hyperintense T2-weighted MRI signal (n = 56 [69%])	p
Age	50 ± 1.5	47 ± 2.6	51 ± 1.9	0.28
Female patients	39 (48%)	6 (24%)	33 (59%)	<0.01
BMI	24.9 ± 0.8	25.5 ± 1.1	24.6 ± 1.0	0.61
Time since diagnosis (months)	72 ± 8.9	70 ± 21	73 ± 10	0.85
Extrasellar extension	47 (58%)	13 (52%)	34 (61%)	0.76
Previous surgery	65 (80%)	23 (92%)	42 (75%)	0.13
Previous radiotherapy	29 (36%)	7 (28%)	22 (39%)	0.45
Time since radiotherapy (months)	70 ± 17.7	46 ± 21.5	77 ± 22.1	0.34
Previous first-generation SRL treatment	75 (93%)	23 (92%)	52 (93%)	1.00
IGF-I, % ULN	178 ± 8.2	165 ± 12	184 ± 11	0.27
GH (mcg/L)	19 ± 9	11 ± 5	22 ± 12	0.08
Tumour volume $(mm)^3$	12431 ± 3259	6001 ± 2425	15003 ± 4419	0.08

Note: Data are shown as mean ± standard error or number (percentage).

Abbreviations: BMI, body mass index; GH, growth hormone; IGF-I, insulin-like growth factor; SRL, somatostatin receptor ligand; ULN, upper limit normal.

3.2 | Hormonal response to pasireotide treatment

IGF-I levels were evaluated after 6 and 12 months of treatment with pasireotide. IGF-I achieved normal age and gender values in 44 out of 81 patients (54%) at 6 months. In 7 patients cabergoline was added during these 6 months of follow-up and only in 1 of these patients IGF-I was normalized; this patient was included in the poor response group. No combination with pegvisomant was reported during this period. Thus, at 6 months, a complete response to pasireotide was observed in 43 patients from 81 cases (53%); partial response was observed in 2 (2%), and poor response in 36 (45%).

At 12 months, of these 43 patients who had normalized IGF-1 at 6 months, 35 continued to present biochemical control, 5 presented an escape phenomenon with high IGF-I values, and 3 other patients were lost of follow-up and not included in the assessment due to lack of data. Moreover, 9 patients who presented an insufficient response at 6 months showed a complete hormonal response at 12 months, thus leading to 44 patients under complete control at 12 months from a total of 73 cases (60%) in which full follow-up information was available (5 additional cases were excluded due to insufficient data). Of these 73 patients, from the period between 6 and 12 months of follow-up, 3 started cabergoline and 4 pegvisomant, and of these new combination treatment cases 2 out of 7 achieved normal IGF-I, and were included in the poor pasireotide response group. Thus, a complete response to pasireotide was observed in 42 cases (58%), while 4 (5%) and 27 (37%) patients presented a partial and poor response, respectively. We did not find relationship between T2-weighted MRI signal intensity and biochemical response (complete hormonal response in 50% vs. 60%, for the hypointense vs. hyperintense group, respectively) (Table 2). There was also no correlation between age, gender and the baseline volume of the tumour and the biochemical response to pasireotide.

Considering also GH levels in addition to IGF-I for hormonal control, 25 patients out of 67 evaluable cases (37%) achieved a complete normalization of IGF-I and GH < 1 mcg/L, and 30 patients (45%) normal or ≥50% decreased IGF-I levels and GH < 2.5 mcg/L.

3.3 | Glucose metabolism

At baseline, 11 of the 81 patients (14%) had a glycated haemoglobin (HbA1c) ≥ 6.5%. At 12 months of follow-up, 45 (56%) had a HbA1c ≥ 6.5% with different diabetes treatment modalities which allowed an acceptable glycaemic control while drug titration was stabilized. Most of the cases included treatment with iDPP-4 or GLP-1 receptor agonists and/or insulin, added to metformin and there was no relationship of the development of disglycaemia with the intensity of tumour image.

3.4 | Tumour volume response to pasireotide treatment

Table 3 shows the tumour volume response at 6 and 12 months during pasireotide treatment. At 12 months, MRI imaging was available in

TABLE 2 Relationship between IGF-I hormonal response to pasireotide treatment and T2-weighted MRI signal.

	Total evaluable cases	Hormonal response	Hypointense T2-weighted MRI signal	Iso/hyperintense T2-weighted MRI signal	*p*
% IGF-I reduction over ULN at 6 months	81	38 ± 3	32 ± 5	40 ± 3	0.10
Complete normalization of IGF-I at 6 months	81	43 (53%)	12/25 (48%)	31/56 (55%)	0.63
% IGF-I reduction over ULN at 12 months	73[a]	37 ± 4	26 ± 13	41 ± 3	0.44
Complete normalization of IGF-I at 12 months	73	42 (58%)	10/20 (50%)	32/53 (60%)	0.44
Normal IGF-1 and GH < 1 mcg/L at 12 months	67	25 (37%)	7/17 (41%)	18/50 (36%)	0.76

Note: Data are shown as mean ± standard error or number (percentage).

Abbreviations: GH, growth hormone; IGF-I, insulin-like growth factor; MRI, magnetic resonance imaging; ULN, upper limit normal.

[a]At 12 months, were excluded 8 patients due to insufficient data.

TABLE 3 Relationship between tumour response to pasireotide treatment and T2-weighted MRI signal.

	Total evaluable cases	Volume reduction	Hypointense T2-weighted MRI signal	Iso/hyperintense T2-weighted MRI signal	*p*
Tumour shrinkage (≥ 25%) at 6 months	55[a]	22 (40%)	5/16 (31%)	17/39 (44%)	0.38
Tumour shrinkage (≥ 25%) at 12 months	51[b]	19 (37%)	3/12 (25%)	16/38 (41%)	0.32
Absolute tumour shrinkage (mm^3) at 6 months	55	1921 ± 884	596 ± 582	2410 ± 1150	<0.01
Absolute tumour shrinkage (mm^3) at 12 months	51	2005 ± 1004	189 ± 142	2517 ± 1273	0.04
% tumour shrinkage over basal residual volume at 6 months	55	24 ± 5	19 ± 10	25 ± 5	0.07
% tumour shrinkage over basal residual volume at 12 months	51	24 ± 4	22 ± 11	25 ± 5	0.19

Note: Data are shown as mean ± standard error or number (percentage).

Abbreviation: MRI, magnetic resonance imaging.

[a]At 6 months, from the total of patients, 26 were excluded because no MRI imagine was available.

[b]At 12 months, from the total of patients, 30 were excluded because no MRI imagine was available.

51 out of the 81 cases (see Table 3). Significant tumour shrinkage was observed in 19 out of the 51 cases (37%). Of these 19, 16 showed iso/hyperintense signal and the remaining 3 were hypointense. None of the 3 hypointense cases in which a significant volume decrease was observed presented a change towards a hyperintense signal, remaining all of them hypointense. Of the remaining 22 initial hypointense tumours, 3 presented a change towards hyperintensity and in 2 of them IGF-I levels normalized. Despite the greater absolute tumour volume reduction in the iso/hyperintense group, there were no significant differences between groups in the percentage of tumours which reduced the volume ≥25% in relation to signal intensity. Thus, the effect of pasireotide in this regard was similar irrespective of the MRI signal as well as for the remnant tumour volume. Tumour volume increased in 5 patients (10%) of which only in one, a hypointense tumour, the increase was ≥25%.

The overall effective control using the combined criterion which includes normalization of IGF-I and a decrease of tumour volume ≥25% from basal value was observed in 12 cases from 69 (17%) in which the whole information was available.

4 | DISCUSSION

In the last decade, T2-weighted MRI signal of the somatotroph adenomas has been recognized as a non-invasive biomarker with a reasonable ability to predict response to first-generation SRL therapy in acromegaly.[16,17] Thus, imaging tumour characteristics may help the clinician in identifying patients with an expectable good or less optimal response to SRLs, allowing to prescribe another medical treatment in those later cases, particularly in the presurgical situation, but also when surgical cure has not been achieved.[15] In non-cured surgical cases, the addition of specific molecular profiling information obtained from the somatotropinoma tissue may add relevant and potential predictive data for single cases.[11]

Somatotroph adenomas with hypointense T2-weighted signal intensity have been described as smaller and less invasive, and predominantly have a densely granulated pattern when cytoqueratin analyses are performed, as well as higher expression of SST2 receptors compared to adenomas with high T2-signal intensity, which show the opposite characteristics.[18,24] Hypointense tumours have also higher GH and IGF-I levels at diagnosis and usually depict greater hormonal reductions from baseline after months of SRLs treatment than patients with T2-iso or hyperintense adenomas.[16–19] In our series, in which patients had failed to achieve biochemical cure by surgical treatment or presented an insufficient response to first-generation SRLs, hyperintense tumours had a large residual tumour volume before starting pasireotide treatment, which was higher than those showing hypointensity, but hormonal values were similar.

This is the first acromegaly Spanish–Portuguese cohort analyzing the response to pasireotide in real life and is one of the largest cohorts obtained from clinical practice so far using this medical treatment. Our results show that in patients with active acromegaly treated with pasireotide, basal T2-weighted MRI signal intensity was associated with a substantial chance of tumour shrinkage, which is very relevant for larger remnants, while hormonal control of the disease was similar irrespective of MRI signal. Thus, unlike with first-generation SRLs, in which a hypointense signal is associated with a good response and a hyperintense signal with an insufficient response, in the case of pasireotide both hyperintense and hypointense tumours do not differ regarding the hormonal control effectiveness of the treatment at 12 months of follow-up. A recent study by Coopmans et al. showed that a quantitative increase in T2-signal intensity during pasireotide treatment showed a positive correlation with both shrinkage effect and hormonal control.[21] In our series, hyperintense signal was more frequently represented and it was associated to larger remnant basal tumour volumes, and to a striking mass reduction after 6 and 12 months of pasireotide therapy. However, hypointense tumours, which had not previously responded to first-generation SRLs, were also as good responders in both hormonal normalization and relative reduction of volume outcomes. Hormonal control obtained with pasireotide was similar in both groups and a remarkable percentage of good response was observed irrespective of MRI T2-signal intensity, as almost 60% of patients achieved normalization of IGF-1. Control of both GH < 1 mcg/L and normal IGF-I occurred in 37% of the patients. This differences may be due to the effect of pasireotide on peripheral target tissues via SSTRs - mostly hepatic tissue- to reduce GH-induced IGF-I production.[8,25]

In our cohort, 29 patients (36%) had previously received radiotherapy in a period ranging between a few months and 20 years before starting pasireotide; of those, 4 patients were treated with radiotherapy more than 10 years before pasireotide treatment, so they could be considered as radiotherapy failures, and in 2 cases it was performed within the year before starting pasireotide. As we could not rule out that in the remaining 23 patients, who were similarly distributed in both groups, some of the enhanced pasireotide response could be favoured by the effect of radiotherapy, we performed the analysis excluding these 23 patients and obtained no differences in the results.

Overall, there was still about 40% of cases in our study, in which adequate hormonal control was not obtained with pasireotide. This confirms that SRLs treatment failure selects the more challenging cases of somatotropinomas with the requirement of next generation drugs, sometime in combination to accelerate achievement of successful control. This subset of uncontrolled cases did not present specific clinical or radiologic characteristics that could make them identifiable from the rest of the cohort before the initiation of medical treatment. The percentage of pasireotide failure is therefore near to the one described for pegvisomant in clinical practice, which is about 30%.[26] This is relevant, as until now pegvisomant was considered the most effective drug for acromegaly treatment and has been extensively and successfully used as combination with SRLs. Thus, as it is currently approved, pasireotide would be a very solid therapeutic option as indicated by the fact that almost 60% of patients who normalized IGF-I levels in cases of previous failure with first-generations SRL, a result which is clearly substantially better than what was observed in pivotal studies.[9]

In our series, almost 40% of the patients had significant tumour shrinkage, 16 (41%) from the hyperintense group and 3 (25%) from the hypointense. These results are in line with those previously published.[27] Another relevant aspect of the imaging analysis of the tumour in patients with acromegaly treated with pasireotide is the dynamic changes observed over time, as described by Coopmans et al.[21] In this later study, sequential imaging while on pasireotide treatment showed that a number of cases presented an increment in the hyperintense signal and this increase correlated with the magnitude of shrinkage effect as well as the hormonal control. The interpretation was that a cytolytic effect would apply in those patients, leading to a tumour mass reduction and in parallel to an amelioration of hormonal hypersecretion, probably also related to a decrease in viable somatotroph cellular mass. In our study, the concordance of tumour decrease ≥25% from basal volume and hormonal control was observed in 17% of cases, while hormonal control was obtained in an additional 40%. This means that in some cases tumour mass reduction may contribute to amelioration/normalization of hormonal hypersecretion but specific occupancy of SST2 and 5 is the principal mechanism involved in normalization of hormonal values in acromegaly resistant to SRLs. In the present study, we only observed changes in the categorical signal intensity in 2 patients who presented a complete hormonal response but none presented a significant tumour shrinkage. We could not evaluate this parameter in those hyperintense tumours since we did not quantify the signal intensity. However, no change towards a hypointense category was observed in hyperintense cases, irrespective of their hormonal and tumour volume response to pasireotide.

Other approaches in the search for new imaging biomarkers include the use of radiomics which allows a much deep image-typing, and potentially able to elucidate responsiveness to medical treatments as well as biological disease evolution.[28–30] In this regard, some recent investigations have shown that radiomic analyses may identify different subsets of granularity with an accuracy of about 70%,[29] which would be very helpful before surgery. At present, the assessment of basal and 6–12 months image characteristics, when accurately evaluated under experienced neuroradiologists and using a standardized methodology for imaging evaluation, may be of substantial value.

Strengths and limitations should be acknowledged in our study. One of the strengths is the relatively large number of patients included, especially considering the prevalence of acromegaly first-line treatment failure cases and that pasireotide is, until now, always indicated as a second line of prescription. Thus, the number of subjects included is of value. In addition, virtually all cases were treated using a very similar protocol of dose escalation. The study, however, has some limitations. First, the retrospective nature includes some selection biases. The first one is that most of the patients had previously received first-generation SRLs and this may eventually modify the SST receptor population in a heterogeneous way. Moreover, as the majority of hyperintensity tumours present an insufficient response to SRLs, it was expected that in the present study the hyperintense group was overrepresented. Some selection bias may apply in the present study and in some cases, combination treatment with cabergoline and pegvisomant did not facilitate the evaluation of pasireotide effectiveness. However, the whole results with a relatively high number of cases offer a consistent picture of the value of this compound in real life practice in challenging acromegaly cases.

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CONFLICTS OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

Some or all data sets generated during and/or analyzed during the current study are not publicly available but would available from the corresponding author on reasonable request.

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REFERENCES

1. Colao A, Grasso LFS, Giustina A, et al. Acromegaly. *Nat Rev Dis Primers*. 2019;5(1):20.
2. Melmed S. Acromegaly. *N Engl J Med*. 2006;355(24):2558-2573.
3. Melmed S, Bronstein MD, Chanson P, et al. A consensus statement on acromegaly therapeutic outcomes. *Nat Rev Endocrinol*. 2018;14(9):552-561.
4. Giustina A, Barkhoudarian G, Beckers A, et al. Multidisciplinary management of acromegaly: a consensus. *Rev Endocrine Metabolic Disorders*. 2020;21(4):667-678.
5. Carmichael JD, Bonert VS, Nuño M, Ly D, Melmed S. Acromegaly clinical trial methodology impact on reported biochemical efficacy rates of somatostatin receptor ligand treatments: a meta-analysis. *J Clin Endocrinol Metabolism*. 2014;99(5):1825-1833.
6. Giustina A, Mazziotti G, Torri V, Spinello M, Floriani I, Melmed S. Meta-analysis on the effects of octreotide on tumor mass in acromegaly. *PLoS One*. 2012;7(5):e36411.
7. Schmid HA. Pasireotide (SOM230): development, mechanism of action and potential applications. *Mol Cell Endocrinol*. 2008;286(1-2):69-74.
8. Colao A, Bronstein MD, Freda P, et al. Pasireotide versus octreotide in acromegaly: a head-to-head superiority study. *J Clin Endocrinol Metabolism*. 2014;99(3):791-799.
9. Gadelha MR, Bronstein MD, Brue T, et al. Pasireotide versus continued treatment with octreotide or lanreotide in patients with inadequately controlled acromegaly (PAOLA): a randomised, phase 3 trial. *Lancet Diabetes Endocrinol*. 2014;2(11):875-884.

10. Fougner SL, Casar-Borota O, Heck A, Berg JP, Bollerslev J. Adenoma granulation pattern correlates with clinical variables and effect of somatostatin analogue treatment in a large series of patients with acromegaly. *Clin Endocrinol*. 2012;76(1):96-102.
11. Puig-Domingo M, Gil J, Sampedro-Nuñez M, et al. Molecular profiling for acromegaly treatment: a validation study. *Endocr Relat Cancer*. 2020;27(6):375-389.
12. Fougner SL, Lekva T, Borota OC, Hald JK, Bollerslev J, Berg JP. The expression of E-cadherin in somatotroph pituitary adenomas is related to tumor size, invasiveness, and somatostatin analog response. *J Clin Endocrinol Metabolism*. 2010;95(5):2334-2342.
13. Kasuki L, Wildemberg LEA, Neto LV, Marcondes J, Takiya CM, Gadelha MR. Ki-67 is a predictor of acromegaly control with octreotide LAR independent of SSTR2 status and relates to cytokeratin pattern. *Eur J Endocrinol*. 2013;169(2):217-223.
14. Lim DST, Fleseriu M. Personalized medical treatment of patients with acromegaly: a review. *Endocrine Practice*. 2022;28(3):321-332.
15. Puig-Domingo M, Bernabéu I, Picó A, et al. Pasireotide in the personalized treatment of acromegaly. *Front Endocrinol*. 2021;12. doi:10.3389/fendo.2021.648411
16. Puig-Domingo M, Resmini E, Gomez-Anson B, et al. Magnetic resonance imaging as a predictor of response to somatostatin analogs in acromegaly after surgical failure. *J Clin Endocrinol Metabolism*. 2010;95(11):4973-4978. https://pubmed.ncbi.nlm.nih.gov/20739382/
17. Potorac I, Petrossians P, Daly AF, et al. T2-weighted MRI signal predicts hormone and tumor responses to somatostatin analogs in acromegaly. *Endocr Relat Cancer*. 2016;2311:871-881. https://erc.bioscientifica.com/view/journals/erc/23/11/871.xml
18. Heck A, Ringstad G, Fougner SL, et al. Intensity of pituitary adenoma on T2-weighted magnetic resonance imaging predicts the response to octreotide treatment in newly diagnosed acromegaly. *Clin Endocrinol*. 2012;77(1):72-78.
19. Bonneville F, Rivière LD, Petersenn S, et al. MRI T2 signal intensity and tumor response in patients with GH-secreting pituitary macroadenoma: PRIMARYS post hoc analysis. *Eur J Endocrinol*. 2019;1803:155-164. https://eje.bioscientifica.com/view/journals/eje/180/3/EJE-18-0254.xml
20. Nista F, Corica G, Castelletti L, et al. Clinical and radiological predictors of biochemical response to first-line treatment with somatostatin receptor ligands in acromegaly: a real-life perspective. *Front Endocrinol*. 2021;12:1.
21. Coopmans EC, Schneiders JJ, El-Sayed N, et al. T2-signal intensity, SSTR expression, and somatostatin analogs efficacy predict response to pasireotide in acromegaly. *Eur J Endocrinol*. 2020;182(6):595-605.
22. Fleseriu M, Biller BMK, Freda PU, et al. A pituitary society update to acromegaly management guidelines. *Pituitary*. 2021;24(1):1-13. https://link.springer.com/10.1007/s11102-020-01091-7
23. Hagiwara A, Inoue Y, Wakasa K, Haba T, Tashiro T, Miyamoto T. Comparison of growth hormone–producing and non–growth hormone–producing pituitary adenomas: imaging characteristics and pathologic correlation. *Radiology*. 2003;228(2):533-538. doi:10.1148/radiol.2282020695
24. Potorac I, Petrossians P, Daly AF, et al. Pituitary MRI characteristics in 297 acromegaly patients based on T2-weighted sequences. *Endocr Relat Cancer*. 2015;222:169-177. https://erc.bioscientifica.com/view/journals/erc/22/2/169.xml
25. Murray RD, Kim K, Ren SG, Chelly M, Umehara Y, Melmed S. Central and peripheral actions of somatostatin on the growth hormone-IGF-I axis. *J Clin Invest*. 2004;114(3):349-356.
26. Fleseriu M, Führer-Sakel D, van der Lely AJ, et al. More than a decade of real-world experience of pegvisomant for acromegaly: ACROSTUDY. *Eur J Endocrinol*. 2021;185(4):525-538. https://eje.bioscientifica.com/view/journals/eje/185/4/EJE-21-0239.xml
27. Mondin A, Manara R, Voltan G, et al. Pasireotide-induced shrinkage in GH and ACTH secreting pituitary adenoma: a systematic review and meta-analysis. *Front Endocrinol (Lausanne)*. 2022;13. doi:10.3389/fendo.2022.935759
28. Kocak B, Durmaz ES, Kadioglu P, et al. Predicting response to somatostatin analogues in acromegaly: machine learning-based high-dimensional quantitative texture analysis on T2-weighted MRI. *Eur Radiol*. 2019;296:2731-2739. https://link.springer.com/article/10.1007/s00330-018-5876-2
29. Park YW, Kang Y, Ahn SS, et al. Radiomics model predicts granulation pattern in growth hormone-secreting pituitary adenomas. *Pituitary*. 2020;23(6):691-700. https://link.springer.com/article/10.1007/s11102-020-01077-5
30. Wildemberg LE, Da Silva Camacho AH, Miranda RL, et al. Machine learning-based prediction model for treatment of acromegaly with first-generation somatostatin receptor ligands. *J Clin Endocrinol Metab*. 2021;106(7):2047-2056. https://pubmed.ncbi.nlm.nih.gov/33686418/

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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