MANAGEMENT OF ENDOCRINE DISEASE

Personalized medicine in the treatment of acromegaly

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Abstract

Acromegaly is associated with high morbidity and elevated mortality when not adequately treated. Surgery is the first-line treatment for most patients as it is the only one that can lead to immediate cure. In patients who are not cured by surgery, treatment is currently based on a trial-and-error approach. First-generation somatostatin receptor ligands (fg-SRL) are initiated for most patients, although approximately 25% of patients present resistance to this drug class. Some biomarkers of treatment outcome are described in the literature, with the aim of categorizing patients into different groups to individualize their treatments using a personalized approach. In this review, we will discuss the current status of precision medicine for the treatment of acromegaly and future perspectives on the use of personalized medicine for this purpose.

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Introduction

Acromegaly is a chronic systemic disease associated with high morbidity and increased mortality when not adequately treated (1, 2). Three treatment modalities (surgery, medical therapy and radiotherapy) are available, with surgery being the treatment of choice for most patients as it is the only treatment that can lead to immediate cure (3). Unfortunately, in approximately 50% of cases, surgical cure is not possible, and adjuvant treatment is necessary (4, 5, 6). In these cases, medical treatment is recommended (3, 7). Radiotherapy is considered the third-line treatment and is reserved for aggressive tumors that are not controlled by surgical and medical treatment (3).

Three drug classes are currently used for the treatment of acromegaly: somatostatin receptor ligands (SRL), dopamine agonists and growth hormone (GH) receptor

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antagonists (7). Although all these options are available for the medical treatment of acromegaly, the current recommendations are to use first-generation SRLs (fg-SRL) for the majority of patients in a trial-and-error approach (3). The evolution from the current mode of acromegaly treatment to 'personalized' or a 'precision' medicine would allow the optimization of treatment and a reduction of costs (8, 9). The definition of personalized medicine is broad in the literature, but in general, it refers to the stratification of patients into subgroups in accordance with their disease evolution and response to specific treatments (8, 10). A classic example is the expression of human epidermal growth factor receptor (HER)-2 in some types of breast cancer. These tumors present a more aggressive phenotype, but a specific drug that targets the HER-2 pathway is available (8, 11). Trastuzumab is a monoclonal antibody that targets the external domain of the HER-2 protein (11). Thus, after the identification of HER-2 expression in a subgroup of tumors, patients with these tumors were treated with trastuzumab, with considerable improvement in the treatment efficacy and, consequently, in the disease prognosis (11).

In this review, we will first describe the current approach to treating acromegaly, and then, we will discuss the available biomarkers of response to treatment and putative personalized treatment for acromegaly.

Current treatment of acromegaly: the trial-and-error approach

As previously described, surgery is the treatment of choice for patients with acromegaly, with exceptions for patients with a high surgical risk, those who refuse surgery and those whose tumors are mostly unresectable (e.g., tumors inside the cavernous sinus) (3). However, even in reference centers with experienced skilled neurosurgeons, half of all patients will not achieve surgical cure, and adjuvant treatment will be necessary (4). For the vast majority of these patients, treatment with fg-SRL, octreotide LAR and lanreotide autogel, is indicated according to the most recent guidelines (3, 7). These drugs act through the binding and activation of the somatostatin receptors (sst), mainly by activation of somatostatin receptors type 2 (sst2).

The biochemical response to fg-SRL is evaluated by randomly measuring GH and IGF-I levels, which allows the identification of three patterns of patient response: (i) controlled patients or full responders (approximately 30% of patients), defined as those who attain GH levels below 1.0 µg/L and normal age-matched IGF-I levels; (ii) partial responders (approximately 45–50% of patients), defined as those who present a reduction of GH and/or IGF-I levels ≥50% from baseline (pretreatment) but without normalization and (iii) resistant patients or poor responders (20–25% of patients), defined as those who show a GH and IGF-I reduction of <50% from baseline (12). In addition to biochemical control, fg-SRL can also induce tumor shrinkage; tumors that present a reduction of less than 20% or increase in volume or an increase during treatment are considered resistant to treatment (12). In rare cases, the patient can be biochemically resistant to the fg-SRL treatment according to the previous definition but can present a tumor response to the drug (13). It is important to highlight, however, that tumor volume can be difficult to evaluate in patients who have previously undergone surgery due to the irregularity of the tumor remnant and the presence of postoperative changes such as fibrosis and the presence of surgical material (12, 13).

As mentioned earlier, approximately 20–25% of patients present biochemical resistance to treatment with fg-SRL but are treated with these drugs anyway according to the current treatment algorithms (14, 15, 16). In addition, considering drug initiation and dose up-titration in uncontrolled patients, at least 9–12 months are necessary to assess treatment outcome. This practice means that a high-cost treatment is prescribed for patients who are resistant to this treatment and will be exposed to the deleterious effects of high GH and insulin-like growth factor type I (IGF-I) levels for several months. The availability of biomarkers that could identify these biochemically resistant patients would avoid ineffective treatment with fg-SRL and allow these patients to be started on drugs that are currently considered second-line treatments.

Other options for the medical treatment of acromegaly are the next-generation SRL pasireotide; the dopamine agonist cabergoline (CAB) and the GH receptor antagonist pegvisomant (7). Although they can be used as first-line medical treatments, they are usually reserved for patients whose disease is not controlled by treatment with fg-SRL (3, 7). Pasireotide and pegvisomant can be used in monotherapy for patients who present resistance to fg-SRL, but CAB is usually added to treatment with fg-SRL (combination therapy) when there is a partial response to the latter drug class. Pegvisomant can also be used in combination therapy with fg-SRL with increased efficacy (17).

Cabergoline acts by binding to dopamine receptor type 2 (DR2) and can have anti-secretory and anti-tumoral effects (18, 19). It can be used in monotherapy or

in association with fg-SRL (19). There is limited published experience with CAB treatment for acromegaly, but it seems less effective than other medical treatments (18, 19, 20, 21, 22, 23, 24, 25, 26). Therefore, it is usually recommended for patients with mild disease (IGF-I up to two times the upper limit of the normal range) (7).

Pegvisomant acts by binding to the GH receptor (GHR) without activating the intracellular signaling pathways and thereby leading to a reduction of IGF-I levels (27). This leads to IGF-I normalization in approximately 63–97% of patients but has no action in the somatotropinoma; thus, it is generally reserved for patients who are not controlled with fg-SRL and in whom tumor mass is not a concern (3, 7, 17, 28, 29, 30, 31). Pegvisomant can also be used in monotherapy or in association with fg-SRL (32, 33).

Pasireotide is a next-generation SRL with a higher affinity than octreotide and lanreotide for the somatostatin receptors type 1 (sst1), 3 (sst3) and 5 (sst5), although it can also bind to and activate sst2 with slightly less potency than fg-SRL (34). It is usually only used in monotherapy and has higher efficacy than fg-SRL, controlling disease in 20% of patients who are not controlled with maximum doses of octreotide or lanreotide (35, 36). However, it has a worse safety profile, with more frequent and more intense elevation of glucose levels (35, 36, 37).

In those patients who are treated with fg-SRL and not controlled, the choice of a second-line medical treatment (CAB, pegvisomant, pasireotide, combination treatment) currently usually relies on diverse factors such as the presence of residual tumor, GH and IGF-I levels, the availability of the drug in the health system, patient preference, safety and the experience of each center (7). Frequently, three or four treatments are used before disease control is achieved (38, 39, 40). Therefore, the current trial-and-error approach to acromegaly treatment, in which patients may live with uncontrolled disease for long time before an effective therapy is attained, is not ideal (9).

Biomarkers of treatment response in acromegaly

In some areas of medicine, such as oncology and hematology, treatment has significantly advanced toward precision medicine, in which the right treatment is prescribed for the right patient (8). To achieve that aim, it is important to find biomarkers of response to different treatments. A biomarker is defined by the Biomarkers Definition Working Group as 'a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention' (41). Studies in the literature have examined possible biomarkers of response to treatment in acromegaly, especially for medical treatment with fg-SRL (42).

To evaluate cavernous sinus invasion, the most commonly used methodology is the Knosp–Steiner criteria (43). Tumors that cross the lateral tangent of the intracavernous and supracavernous internal carotid arteries are classified as grades 3A, 3B or 4 and are considered invasive (43). The cure rate for invasive tumors was recently reported to be approximately 47%, compared with approximately 76% in non-invasive tumors (44). Cavernous sinus invasion, evaluated using the Knosp–Steiner criterion, is the main predictor of surgical outcome reported in the literature (4, 5, 45, 46, 47, 48). It is also the most important biomarker as it is currently the only one that does not specify surgery as the first-line treatment (in the case of a grade 4 tumor (an adenoma that completely encases the internal carotid artery) with the epicenter inside the cavernous sinus (3)).

Other predictors of surgical cure have also been suggested, including tumor volume, maximum tumor diameter and age at surgery, but these predictors have inconsistent data in the literature (45, 46, 49, 50, 51, 52). In the majority of the series, pre-operative GH and IGF-I levels were also biomarkers of surgical cure, although the results are not homogeneous in the literature (4, 49, 53, 54, 55, 56).

As previously mentioned, fg-SRL act mainly by binding and activating sst2, which was the most frequently expressed sst in the somatotropinomas in the majority of the series (57, 58). The expression of sst2 at both the mRNA and protein levels has been analyzed in somatotropinomas and correlated with the long-term response to fg-SRL (57, 59, 60). As expected, tumors that express a higher level of sst2 present a greater chance of disease control with fg-SRL treatment, as sst2 is the biomarker of response to fg-SRL for which the most data is available in the literature (57, 59, 60, 61, 62, 63, 64, 65, 66). Somatostatin receptor type 2 expression has mainly a high negative predictive value (reaching 100% in our previous series), with tumors that present low expression showing no response to treatment (59, 60).

Another characteristic of somatotropinomas with a worse response to fg-SRL treatment is a sparsely granulated pattern on immunohistochemistry (analyzed by the expression of the CAM5.2 antibody) (67). Tumors that present a dot-like pattern of CAM5.2 expression are

classified as sparsely granulated and are more invasive and present a worse response to fg-SRL treatment (67, 68, 69). Sparsely granulated tumors present lower sst2 expression than densely granulates tumors, which is probably why they present a worse response to treatment (69, 70). Nevertheless, the granulation pattern itself may be considered a biomarker of response to fg-SRL.

The granulation pattern can also have an expression in the T2-wheighted sequence of the magnetic resonance imaging (MRI) (71). It was described in some studies that a hyperintense signal on the T2-wheighted sequence was associated with a poorer response to fg-SRL and with the sparsely granulated patter in the immunohistochemistry (71, 72, 73, 74). As it is a more easily available evaluation, it can be useful in centers without expertise in the immunohistochemistry or in the patients not submitted to surgery and, therefore, without tumor available for other evaluations.

As previously reported in the presence of a low sst2 expression, a poor response to fg-SRL is usually seen. Nevertheless, in the case of high sst2 expression, a good response is not always observed, likely because of alterations in the proteins involved in the intracellular signaling activated by the binding of fg-SRL to sst2 (42, 59). One of these proteins is the aryl hydrocarbon receptor-interacting protein (AIP). The *AIP* gene is a tumor suppressor gene that is mutated in approximately 20% of patients with familial isolated pituitary adenomas (FIPA) (75, 76, 77, 78). In families with homogeneous FIPA that include only cases of acromegaly and gigantism (isolated familial somatotropinoma), *AIP* mutations are found in approximately 40% of cases (76). Patients who harbor an *AIP* germline mutation are younger and present a more aggressive tumor with worse response to fg-SRL treatment (76, 77, 79). Interestingly, in half of the patients with sporadic acromegaly, low expression of the AIP protein is observed due to mechanisms other than mutations (80, 81, 82, 83). These patients also present a worse response to fg-SRL, as described by our group (81). Furthermore, studies have described that the AIP is involved in the intracellular signaling pathway activated by sst2 and that its presence is essential to the expression of another protein, the zinc finger protein ZAC1 (a zinc finger protein that regulates apoptosis and cell cycle arrest), which also has tumor suppressor features (42, 84, 85). Thus, one reason for a lack of response to fg-SRL in tumors with high sst2 expression is the low expression of AIP. Therefore, AIP expression is also a biomarker of response to fg-SRL (81).

The other biomarkers that have been described in the literature present less robust data and/or are more controversial due to conflicting data. Such biomarkers include the acute octreotide test, the presence of a *gsp* mutation, the expression of E-cadherin, the expression of sst5 and its truncated isoform (sst5TMD4), the expression of miR-34a, the expression of β-arrestin, the Ki-67 labeling index and the Raf kinase expression (57, 68, 72, 83, 86, 87, 88, 89, 90, 91). Additionally, some demographic characteristics, such as younger age, male gender and high pretreatment GH levels were associated with a poor response to fg-SRL in some studies (92, 93, 94).

For the other medical treatments of acromegaly, there is little published data on biomarkers of response. Cabergoline acts through the activation of DR2; therefore, it is expected that the expression of this receptor would be a predictor of response to CAB treatment (19). However, there are no studies analyzing whether this is the case. The co-expression of prolactin in the somatotropinoma is a predictor of response to CAB in monotherapy but not in the case of combination treatment with CAB and fg-SRL (18, 19, 20). In addition, pretreatment GH and IGF-I levels are predictors of response to CAB treatment both alone and in combination therapy in acromegaly, with patients with mild disease (GH levels below 4–5 μg/L and IGF-I levels until 2× the upper limit of normal range) presenting a greater likelihood of disease control (18, 19, 24, 95).

Pasireotide, like fg-SRL, acts by binding to sst but with a different affinity profile; specifically, it has a higher affinity for sst3 and sst5 (96). It has been demonstrated *in vitro* that a better response to pasireotide than to fg-SRL is observed in tumors with a low sst2 expression and a high sst5 expression (96). This was also shown in a small *in vivo* study that found that sst5 expression was a biomarker of response to pasireotide in patients whose disease was not controlled with fg-SRL (97). Somatostatin receptor type 2 expression was also a biomarker of response to pasireotide. In addition, the same study demonstrated that although AIP expression is a biomarker of response to fg-SRL, it did not seem to be a biomarker of the response to pasireotide (97).

Pegvisomant acts in the periphery by blocking the binding of GH to its receptor (27, 98). Therefore, it is not expected that any feature of the somatotropinoma will predict its response to pegvisomant. However, it acts on the GHR, and some patients have a polymorphism of this receptor that leads to a short isoform with a deletion of exon 3 (d3GHR) (99). This isoform may increase the GHR activation by GH, and it has been proposed that

in children with short stature, a better response to GH treatment is observed in patients with the d3GHR than in those with the full-length isoform (flGHR) (100, 101). Thus, GHR isoforms may influence the binding of pegvisomant and the response to the drug. In the first two studies in the literature, which included a total of 63 patients, those who presented the d3GHR isoform had a better response to treatment (i.e., they needed a lower dose of pegvisomant and a shorter treatment to obtain normalization of IGF-I levels) (102, 103). However, more recently, a large multicenter study (111 patients) and a study from our group did not find a difference in the response rates to pegvisomant treatment between patients with the d3GHR and those with the flGHR (31, 104). Additionally, another study described no difference in the response rates to combination therapy with pegvisomant and fg-SRL in patients with the different isoforms of GHR (105). Therefore, current knowledge suggests that d3GHR is not a biomarker of response to pegvisomant.

Some other features may be associated with a better response to pegvisomant, such as lower pretreatment IGF-I levels, lower body mass index (BMI) and the absence of concomitant diabetes mellitus (31, 106, 107).

Personalized medicine in the treatment of acromegaly

Applying the idea of precision medicine to the treatment of acromegaly is very tempting as many medical treatment options are currently available for the disease and some biomarkers of response to each specific drug have been described. This is especially the case for the fg-SRL, which are still considered the first-choice medical treatment for the vast majority of acromegaly patients despite the knowledge that approximately 20–25% of patients will present resistance to the treatment (3, 7). The change to a personalized medicine approach to treating the disease will allow an optimization of therapy, reduce the GH burden (as disease control can be achieved more quickly with the right treatment for each individual patient) and lead to a reduction of costs (by avoiding the use of ineffective, expensive treatments for a considerable period of time for patients who are resistant to them) (9).

If precision medicine has all these advantages, why it is still not being applied for acromegaly? The main limitation of the use of biomarkers to guide medical treatment for acromegaly is the small number of patients included in the studies and the heterogeneity of the data in the literature. The biomarker for which the most published data are available is the expression of sst2 for predicting the response to fg-SRL. However, the published studies have small samples, and the majority are retrospective (59, 60, 66). Moreover, sst2 expression has been analyzed using different methodologies, such as mRNA expression using real-time reverse transcription polymerase chain reaction (RT-PCR) or protein expression using immunohistochemistry (IHC) with different antibodies (57, 59, 60). Even when studies used the same methodology, different analyses were performed; for example, in the case of the measurement of sst2 expression by IHC, some authors only considered membrane expression, while others also considered cytoplasmic expression (59, 60). In addition, some authors only considered the percentage of positive cells, while others also considered the intensity expression (60, 66, 108). Therefore, standardization of the methodology for analyzing sst2 expression and its application to the different pituitary centers will be fundamental for establishing sst2 expression as a biomarker of acromegaly patients' response to fg-SRL treatment in clinical practice.

Despite the previous considerations, current data on biomarkers published in the literature allows the proposal of a more personalized algorithm for the treatment of acromegaly (Fig. 1). Surgery will remain the first-line treatment for the majority of patients as it is the only treatment that allows rapid cure of the disease and

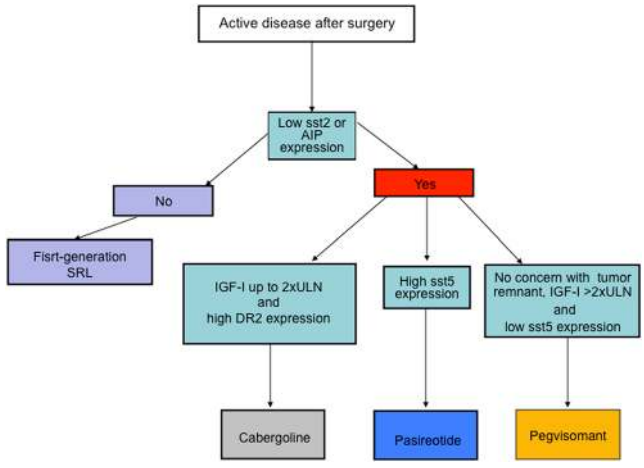


Figure 1

Proposed algorithm for a personalized acromegaly treatment guided by biomarkers of response. AIP, aryl hydrocarbon receptor-interacting protein; CAB, cabergoline; DR2, dopamine receptor type 2; fg-SRL, first-generation somatostatin receptor ligands; sst2, somatostatin receptor type 2; sst5, somatostatin receptor type 5.

obtains tumor tissue for the analysis of the biomarkers with IHC and RT-PCR. In case of surgical failure, a panel of biomarkers, including sst2, sst5, AIP and DR2, can guide the selection of medical treatment, in conjunction with biochemical (GH and IGF-I levels) and tumor data (size of the residual tumor; Fig. 1). This will allow the optimization of treatment.

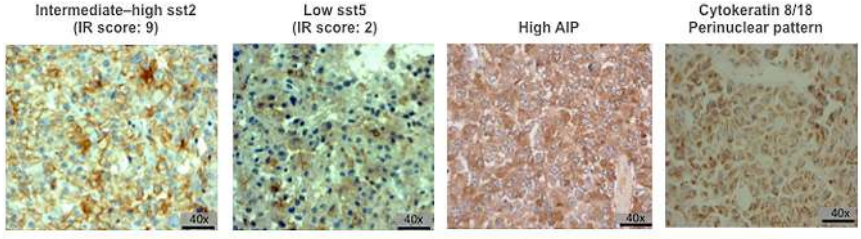
To illustrate the clinical treatment outcomes of patients with different biomarker profiles, we describe two cases in which knowledge of the biomarkers could have helped to change the treatment protocol. The first case is a 53-year-old female patient with typical signs and symptoms of acromegaly. At diagnosis, she presented a macroadenoma of 1.8×0.9×1.0 cm and underwent surgery without cure. The histopathology and IHC analyses revealed a densely granulated somatotropinoma with high sst2 expression, low sst5 expression and high AIP expression (Fig. 2). The patient was treated with octreotide LAR 20 mg every four weeks, and GH and IGF-I levels normalized after three months of treatment. The GH and IGF-I levels at diagnosis, post-surgery and post-octreotide LAR are shown in Fig. 2.

In contrast, the second case is a 42-year-old female patient with a clinical and biochemical diagnosis of acromegaly (Fig. 3) who presented with a macroadenoma of 3.2×2.1×2.2 cm. She underwent surgery without cure, and the histopathology and IHC analyses revealed a sparsely granulated adenoma with low sst2 expression, high sst5 expression and low AIP expression (Fig. 3). The patient was treated with octreotide LAR 30 mg every four weeks for six months and showed resistance to the drug (Fig. 3).

The previous cases describe two female patients who were not cured with surgery and required adjuvant medical treatment. According to the current trial-and-error protocol, an fg-SRL was started for both. The first patient presented an excellent response, as expected according to her tumor characteristics. The second patient, however, showed resistance to the drug, as expected given the biomarker profile of her tumor. In the case of this patient, knowing her biomarker profile would have allowed the optimization of her treatment approach; for example, pasireotide LAR could have been selected as the first-line treatment because it can be more effective in tumors with low sst2 expression, high sst5 expression and low AIP expression (96, 97).

Future perspectives

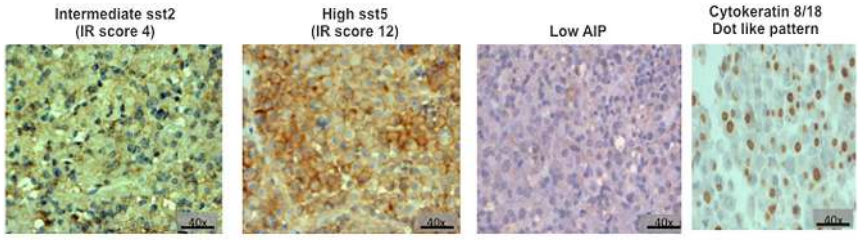
The currently available data in the literature allows the stratification of patients into groups that respond better to different drug classes. However, to increase the accuracy of such predictive stratification, studies with larger samples, such as multicenter studies, are necessary to define the cut-offs for each biomarker to precisely predict the response to the different medical treatments.



	GH (mg/dL)	IGF-I (x ULN)
Diagnosis	23.1	2.82
3 months after surgery	2.8	2.20
6 months of octreotide LAR 20 mg	0.3	0.57

Figure 2

Slides showing the protein expression of sst2, sst5 and AIP and the granulation pattern, analyzed by immunohistochemistry, and the evolution of GH and IGF-I levels throughout the treatment of patient 1. Rabbit monoclonal antibodies against sst2 and sst5 (Abcam, cat. number ab 134152 and ab 109495, respectively) and mouse monoclonal antibodies directed against AIP (Novus Biological, Littleton, CO, USA, cat. number NB100-127) and CAM5.2 (Cell Marque, Rocklin, CA, USA, cat. number 452 M-95) were used. The expression of sst2 and 5, AIP and CAM5.2 were analyzed as previously published (60, 73, 111). The tumor presented high sst2 and AIP expression and low sst5 expression with a densely granulated pattern. AIP, aryl hydrocarbon receptor-interacting protein; sst2, somatostatin receptor type 2; sst5, somatostatin receptor type 5; ULN, upper limit of normality.



	GH (mg/dL)	IGF-I (x ULN)
Diagnosis	24.5	1.97
3 months after surgery	14.2	2.01
6 months of octreotide LAR 30 mg	13.3	2.81

Figure 3

Slides showing the protein expression of sst2, sst5, AIP and the granulation pattern, analyzed by immunohistochemistry, and the evolution of GH and IGF-I levels throughout the treatment of patient 2. Rabbit monoclonal antibodies directed against sst2 and sst5 (Abcam, cat. number ab 134152 and ab 109495, respectively) and mouse monoclonal antibodies directed against AIP (Novus Biological, cat. number NB100-127) and CAM5.2 (Cell Marque, cat. number 452 M-95) were used. The expression of sst2 and 5, AIP and CAM5.2 were analyzed as previously published (60, 73, 111). The tumor presented low sst2 and AIP expression and high sst5 expression with a sparsely granulated pattern. AIP, aryl hydrocarbon receptor-interacting protein; sst2, somatostatin receptor type 2; sst5, somatostatin receptor type 5; ULN, upper limit of normality.

In addition, the standardization of the interpretation of biomarker expression at different centers throughout the world would facilitate data analysis and the proposal of treatment algorithms based on biomarker expression; therefore, standardization is an essential step in the shift toward personalized medicine for the treatment of acromegaly. To this end, it is important to determine reference centers around the world that are willing to use the same standardized methodology to analyze the different biomarkers. These centers must have appropriate facilities for IHC and molecular biology analysis and trained personal dedicated to these time-consuming and difficult analyses.

In some patients, surgery is not indicated or cannot be performed (3). In these patients, primary medical treatment should be started; however, as no tumor sample is available, the analysis of some important biomarkers is not possible. However, in patients with some tumor types, such as breast and lung cancer, the expression of circulating microRNAs (miRNAs) has been described as a biomarker (liquid biopsy) of disease progression and treatment response (109). A previous study described that miRNAs can be secreted by tumor cells in the circulation inside lipid vesicles called exosomes (109). They are small vesicles (30–100 nm) that have been identified in many human fluids, such as saliva and urine plasma (109). Some miRNAs have been previously described to be differentially expressed in somatotropinomas and are related to clinical, tumor and therapeutic outcomes (83, 110, 111, 112, 113). Our group previously found that miR-34a expression is inversely correlated with the response to fg-SRL (83). Considering that the expression of plasma miRNAs has already been described in other tumors, it is possible that in the future, the analysis of circulating miRNAs could provide biomarkers of response to medical treatment in acromegaly, even in those patients who have not undergone surgery.

Conclusion

There are many options available for the treatment of acromegaly, but currently, its treatment is still based on a trial-and-error approach. With the description of biomarkers of treatment outcome, it is possible to categorize patients into different groups, which allows the implementation of targeted treatment. This shift toward personalized medicine allows increased treatment efficacy with more rapid disease control and cost reduction.

Declaration of interest

M R G has received unrestricted research grants and lecture fees from Novartis, Ipsen and Pfizer; has participated on advisory boards for Novartis and Ionis and is a PI in clinical trials by Novartis and Ipsen. L K has received lecture fees from Novartis, Pfizer and Ipsen and has participated as a co-investigator in clinical trials by Novartis and Ipsen. L E W has participated as a co-investigator in clinical trials by Novartis and Ipsen.

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References

1 Holdaway IM, Bolland MJ & Gamble GD. A meta-analysis of the effect of lowering serum levels of GH and IGF-I on mortality in acromegaly. *European Journal of Endocrinology* 2008 **159** 89–95. (https://doi.org/10.1530/EJE-08-0267)

2 Ben-Shlomo A & Melmed S. Acromegaly. *Endocrinology and Metabolism Clinics of North America* 2008 **37** 101–122. (https://doi.org/10.1016/j.ecl.2007.10.002)

3 Katznelson L, Laws ER Jr, Melmed S, Molitch ME, Murad MH, Utz A, Wass JA & Endocrine S. Acromegaly: an endocrine society clinical practice guideline. *Journal of Clinical Endocrinology and Metabolism* 2014 **99** 3933–3951. (https://doi.org/10.1210/jc.2014-2700)

4 Nomikos P, Buchfelder M & Fahlbusch R. The outcome of surgery in 668 patients with acromegaly using current criteria of biochemical 'cure'. *European Journal of Endocrinology* 2005 **152** 379–387. (https://doi.org/10.1530/eje.1.01863)

5 Dallapiazza RF & Jane JA Jr. Outcomes of endoscopic transsphenoidal pituitary surgery. *Endocrinology and Metabolism Clinics of North America* 2015 **44** 105–115. (https://doi.org/10.1016/j.ecl.2014.10.010)

6 Fathalla H, Cusimano MD, Di Ieva A, Lee J, Alsharif O, Goguen J, Zhang S & Smyth H. Endoscopic versus microscopic approach for surgical treatment of acromegaly. *Neurosurgical Review* 2015 **38** 541–548; discussion 548–549. (https://doi.org/10.1007/s10143-015-0613-7)

7 Giustina A, Chanson P, Kleinberg D, Bronstein MD, Clemmons DR, Klibanski A, van der Lely AJ, Strasburger CJ, Lamberts SW, Ho KK *et al*. Expert consensus document: a consensus on the medical treatment of acromegaly. *Nature Reviews Endocrinology* 2014 **10** 243–248. (https://doi.org/10.1038/nrendo.2014.21)

8 Konig IR, Fuchs O, Hansen G, von Mutius E & Kopp MV. What is precision medicine? *European Respiratory Journal* 2017 **50** 1700391.

9 Gadelha MR. A paradigm shift in the medical treatment of acromegaly: from a 'trial and error' to a personalized therapeutic decision-making process. *Clinical Endocrinology* 2015 **83** 1–2. (https://doi.org/10.1111/cen.12797)

10 Jameson JL & Longo DL. Precision medicine – personalized, problematic, and promising. *New England Journal of Medicine* 2015 **372** 2229–2234. (https://doi.org/10.1056/NEJMsb1503104)

11 Krop IE, Kim SB, Martin AG, LoRusso PM, Ferrero JM, Badovinac-Crnjevic T, Hoersch S, Smitt M & Wildiers H. Trastuzumab emtansine versus treatment of physician's choice in patients with previously treated HER2-positive metastatic breast cancer (TH3RESA): final overall survival results from a randomised open-label phase 3 trial. *Lancet Oncology* 2017 **18** 743–754. (https://doi.org/10.1016/S1470-2045(17)30313-3)

12 Colao A, Auriemma RS, Lombardi G & Pivonello R. Resistance to somatostatin analogs in acromegaly. *Endocrine Reviews* 2011 **32** 247–271. (https://doi.org/10.1210/er.2010-0002)

13 Colao A, Pivonello R, Auriemma RS, Briganti F, Galdiero M, Tortora F, Caranci F, Cirillo S & Lombardi G. Predictors of tumor shrinkage after primary therapy with somatostatin analogs in acromegaly: a prospective study in 99 patients. *Journal of Clinical Endocrinology and Metabolism* 2006 **91** 2112–2118. (https://doi.org/10.1210/jc.2005-2110)

14 Colao A, Auriemma RS, Pivonello R, Kasuki L & Gadelha MR. Interpreting biochemical control response rates with first-generation somatostatin analogues in acromegaly. *Pituitary* 2015 **19** 235–247. (https://doi.org/10.1007/s11102-015-0684-z)

15 Mercado M, Borges F, Bouterfa H, Chang TC, Chervin A, Farrall AJ, Patocs A, Petersenn S, Podoba J, Safari M *et al*. A prospective, multicentre study to investigate the efficacy, safety and tolerability of octreotide LAR (long-acting repeatable octreotide) in the primary therapy of patients with acromegaly. *Clinical Endocrinology* 2007 **66** 859–868. (https://doi.org/10.1111/j.1365-2265.2007.02825.x)

16 Colao A, Cappabianca P, Caron P, De Menis E, Farrall AJ, Gadelha MR, Hmissi A, Rees A, Reincke M, Safari M *et al*. Octreotide LAR vs. surgery in newly diagnosed patients with acromegaly: a randomized, open-label, multicentre study. *Clinical Endocrinology* 2009 **70** 757–768. (https://doi.org/10.1111/j.1365-2265.2008.03441.x)

17 Neggers SJ, Franck SE, de Rooij FW, Dallenga AH, Poublon RM, Feelders RA, Janssen JA, Buchfelder M, Hofland LJ, Jorgensen JO *et al*. Long-term efficacy and safety of pegvisomant in combination with long-acting somatostatin analogs in acromegaly. *Journal of Clinical Endocrinology and Metabolism* 2014 **99** 3644–3652. (https://doi.org/10.1210/jc.2014-2032)

18 Sandret L, Maison P & Chanson P. Place of cabergoline in acromegaly: a meta-analysis. *Journal of Clinical Endocrinology and Metabolism* 2011 **96** 1327–1335. (https://doi.org/10.1210/jc.2010-2443)

19 Kasuki L, Vieira Neto L & Gadelha MR. Cabergoline treatment in acromegaly: cons. *Endocrine* 2014 **46** 220–225. (https://doi.org/10.1007/s12020-014-0183-4)

20 Abs R, Verhelst J, Maiter D, Van Acker K, Nobels F, Coolens JL, Mahler C & Beckers A. Cabergoline in the treatment of acromegaly: a study in 64 patients. *Journal of Clinical Endocrinology and Metabolism* 1998 **83** 374–378. (https://doi.org/10.1210/jcem.83.2.4556)

21 Cozzi R, Attanasio R, Lodrini S & Lasio G. Cabergoline addition to depot somatostatin analogues in resistant acromegalic patients: efficacy and lack of predictive value of prolactin status. *Clinical Endocrinology* 2004 **61** 209–215. (https://doi.org/10.1111/j.1365-2265.2004.02082.x)

22 Freda PU, Reyes CM, Nuruzzaman AT, Sundeen RE, Khandji AG & Post KD. Cabergoline therapy of growth hormone & growth hormone/prolactin secreting pituitary tumors. *Pituitary* 2004 **7** 21–30. (https://doi.org/10.1023/B:PITU.0000044630.83354.f0)

23 Moyes VJ, Metcalfe KA & Drake WM. Clinical use of cabergoline as primary and adjunctive treatment for acromegaly. *European Journal of Endocrinology* 2008 **159** 541–545. (https://doi.org/10.1530/EJE-08-0306)

24 Vilar L, Azevedo MF, Naves LA, Casulari LA, Albuquerque JL, Montenegro RM, Montenegro RM Jr, Figueiredo P, Nascimento GC & Faria MS. Role of the addition of cabergoline to the management of acromegalic patients resistant to longterm treatment with octreotide LAR. *Pituitary* 2011 **14** 148–156. (https://doi.org/10.1007/s11102-010-0272-1)

25 Suda K, Inoshita N, Iguchi G, Fukuoka H, Takahashi M, Nishizawa H, Yamamoto M, Yamada S & Takahashi Y. Efficacy of combined octreotide and cabergoline treatment in patients with acromegaly: a retrospective clinical study and review of the literature. *Endocrine Journal* 2013 **60** 507–515. (https://doi.org/10.1507/endocrj.EJ12-0272)

26 Vandeva S, Elenkova A, Natchev E, Kirilov G, Tcharaktchiev D, Yaneva M, Kalinov K, Marinov M, Hristozov K, Kamenov Z *et al*. Treatment outcome results from the Bulgarian Acromegaly Database: adjuvant dopamine agonist therapy is efficient in less than one fifth of non-irradiated patients. *Experimental and Clinical Endocrinology and Diabetes* 2015 **123** 66–71. (https://doi.org/10.1055/s-0034-1389987)

27 Kopchick JJ, Parkinson C, Stevens EC & Trainer PJ. Growth hormone receptor antagonists: discovery, development, and use in patients with acromegaly. *Endocrine Reviews* 2002 **23** 623–646. (https://doi.org/10.1210/er.2001-0022)

28 van der Lely AJ, Biller BM, Brue T, Buchfelder M, Ghigo E, Gomez R, Hey-Hadavi J, Lundgren F, Rajicic N, Strasburger CJ *et al*. Long-term

safety of pegvisomant in patients with acromegaly: comprehensive review of 1288 subjects in ACROSTUDY. *Journal of Clinical Endocrinology and Metabolism* 2012 **97** 1589–1597. (https://doi.org/10.1210/jc.2011-2508)
29 Trainer PJ, Drake WM, Katznelson L, Freda PU, Herman-Bonert V, van der Lely AJ, Dimaraki EV, Stewart PM, Friend KE, Vance ML *et al*. Treatment of acromegaly with the growth hormone-receptor antagonist pegvisomant. *New England Journal of Medicine* 2000 **342** 1171–1177. (https://doi.org/10.1056/NEJM200004203421604)
30 van der Lely AJ, Hutson RK, Trainer PJ, Besser GM, Barkan AL, Katznelson L, Klibanski A, Herman-Bonert V, Melmed S, Vance ML *et al*. Long-term treatment of acromegaly with pegvisomant, a growth hormone receptor antagonist. *Lancet* 2001 **358** 1754–1759. (https://doi.org/10.1016/S0140-6736(01)06844-1)
31 Kasuki L, Machado EO, Ogino LL, Coelho MC, Silva CM, Wildemberg LE, Lima CH & Gadelha MR. Experience with pegvisomant treatment in acromegaly in a single Brazilian tertiary reference center: efficacy, safety and predictors of response. *Archives of Endocrinology and Metabolism* 2016 **60** 479–485. (https://doi.org/10.1590/2359-3997000000210)
32 Marazuela M, Lucas T, Alvarez-Escola C, Puig-Domingo M, de la Torre NG, de Miguel-Novoa P, Duran-Hervada A, Manzanares R, Luque-Ramirez M, Halperin I *et al*. Long-term treatment of acromegalic patients resistant to somatostatin analogues with the GH receptor antagonist pegvisomant: its efficacy in relation to gender and previous radiotherapy. *European Journal of Endocrinology* 2009 **160** 535–542. (https://doi.org/10.1530/EJE-08-0705)
33 Franck SE, Muhammad A, van der Lely AJ & Neggers SJ. Combined treatment of somatostatin analogues with pegvisomant in acromegaly. *Endocrine* 2015 **52** 206–213. (https://doi.org/10.1007/s12020-015-0810-8)
34 Wildemberg LE & Gadelha MR. Pasireotide for the treatment of acromegaly. *Expert Opinion on Pharmacotherapy* 2016 **17** 579–588. (https://doi.org/10.1517/14656566.2016.1146688)
35 Gadelha MR, Bronstein MD, Brue T, Coculescu M, Fleseriu M, Guitelman M, Pronin V, Raverot G, Shimon I, Lievre KK *et al*. Pasireotide versus continued treatment with octreotide or lanreotide in patients with inadequately controlled acromegaly (PAOLA): a randomised, phase 3 trial. *Lancet Diabetes and Endocrinology* 2014 **2** 875–884. (https://doi.org/10.1016/S2213-8587(14)70169-X)
36 Colao A, Bronstein MD, Freda P, Gu F, Shen CC, Gadelha M, Fleseriu M, van der Lely AJ, Farrall AJ, Hermosillo Resendiz K *et al*. Pasireotide versus octreotide in acromegaly: a head-to-head superiority study. *Journal of Clinical Endocrinology and Metabolism* 2014 **99** 791–799. (https://doi.org/10.1210/jc.2013-2480)
37 Henry RR, Ciaraldi TP, Armstrong D, Burke P, Ligueros-Saylan M & Mudaliar S. Hyperglycemia associated with pasireotide: results from a mechanistic study in healthy volunteers. *Journal of Clinical Endocrinology and Metabolism* 2013 **98** 3446–3453. (https://doi.org/10.1210/jc.2013-1771)
38 Portocarrero-Ortiz LA, Vergara-Lopez A, Vidrio-Velazquez M, Uribe-Diaz AM, Garcia-Dominguez A, Reza-Albarran AA, Cuevas-Ramos D, Melgar V, Talavera J, Rivera-Hernandez AJ *et al*. The Mexican acromegaly registry: clinical and biochemical characteristics at diagnosis and therapeutic outcomes. *Journal of Clinical Endocrinology and Metabolism* 2016 **101** 3997–4004. (https://doi.org/10.1210/jc.2016-1937)
39 Howlett TA, Willis D, Walker G, Wass JA, Trainer PJ & Group UKARS. Control of growth hormone and IGF1 in patients with acromegaly in the UK: responses to medical treatment with somatostatin analogues and dopamine agonists. *Clinical Endocrinology* 2013 **79** 689–699.
40 Schofl C, Grussendorf M, Honegger J, Tonjes A, Thyroke-Gronostay D, Mayr B, Schopohl J & participants of German Acromegaly Register. Failure to achieve disease control in acromegaly: cause analysis by a registry-based survey. *European Journal of Endocrinology* 2015 **172** 351–356. (https://doi.org/10.1530/EJE-14-0844)
41 Biomarkers Definitions Working Group. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. *Clinical Pharmacology and Therapeutics* 2001 **69** 89–95. (https://doi.org/10.1067/mcp.2001.113989)
42 Gadelha MR, Kasuki L & Korbonits M. Novel pathway for somatostatin analogs in patients with acromegaly. *Trends in Endocrinology and Metabolism* 2013 **24** 238–246. (https://doi.org/10.1016/j.tem.2012.11.007)
43 Micko AS, Wohrer A, Wolfsberger S & Knosp E. Invasion of the cavernous sinus space in pituitary adenomas: endoscopic verification and its correlation with an MRI-based classification. *Journal of Neurosurgery* 2015 **122** 803–811. (https://doi.org/10.3171/2014.12.JNS141083)
44 Briceno V, Zaidi HA, Doucette JA, Onomichi KB, Alreshidi A, Mekary RA & Smith TR. Efficacy of transsphenoidal surgery in achieving biochemical cure of growth hormone-secreting pituitary adenomas among patients with cavernous sinus invasion: a systematic review and meta-analysis. *Neurology Research* 2017 **39** 387–398. (https://doi.org/10.1080/01616412.2017.1296653)
45 van Bunderen CC, van Varsseveld NC, Baayen JC, van Furth WR, Aliaga ES, Hazewinkel MJ, Majoie CB, Freling NJ, Lips P, Fliers E *et al*. Predictors of endoscopic transsphenoidal surgery outcome in acromegaly: patient and tumor characteristics evaluated by magnetic resonance imaging. *Pituitary* 2013 **16** 158–167. (https://doi.org/10.1007/s11102-012-0395-7)
46 Sun H, Brzana J, Yedinak CG, Gultekin SH, Delashaw JB & Fleseriu M. Factors associated with biochemical remission after microscopic transsphenoidal surgery for acromegaly. *Journal of Neurological Surgery: Part B, Skull Base* 2014 **75** 47–52. (https://doi.org/10.1055/s-0033-1354578)
47 Sarkar S, Jacob KS, Pratheesh R & Chacko AG. Transsphenoidal surgery for acromegaly: predicting remission with early postoperative growth hormone assays. *Acta Neurochirurgica* 2014 **156** 1379–1387; discussion 1387. (https://doi.org/10.1007/s00701-014-2098-5)
48 Babu H, Ortega A, Nuno M, Dehghan A, Schweitzer A, Bonert HV, Carmichael JD, Cooper O, Melmed S & Mamelak AN. Long-term endocrine outcomes following endoscopic endonasal transsphenoidal surgery for acromegaly and associated prognostic factors. *Neurosurgery* 2017 **81** 357–366. (https://doi.org/10.1093/neuros/nyx020)
49 Abosch A, Tyrrell JB, Lamborn KR, Hannegan LT, Applebury CB & Wilson CB. Transsphenoidal microsurgery for growth hormone-secreting pituitary adenomas: initial outcome and long-term results. *Journal of Clinical Endocrinology and Metabolism* 1998 **83** 3411–3418. (https://doi.org/10.1210/jcem.83.10.5111)
50 Bourdelot A, Coste J, Hazebroucq V, Gaillard S, Cazabat L, Bertagna X & Bertherat J. Clinical, hormonal and magnetic resonance imaging (MRI) predictors of transsphenoidal surgery outcome in acromegaly. *European Journal of Endocrinology* 2004 **150** 763–771. (https://doi.org/10.1530/eje.0.1500763)
51 Jane JA Jr, Starke RM, Elzoghby MA, Reames DL, Payne SC, Thorner MO, Marshall JC, Laws ER Jr & Vance ML. Endoscopic transsphenoidal surgery for acromegaly: remission using modern criteria, complications, and predictors of outcome. *Journal of Clinical Endocrinology and Metabolism* 2011 **96** 2732–2740. (https://doi.org/10.1210/jc.2011-0554)
52 Hazer DB, Isik S, Berker D, Guler S, Gurlek A, Yucel T & Berker M. Treatment of acromegaly by endoscopic transsphenoidal surgery: surgical experience in 214 cases and cure rates according to current consensus criteria. *Journal of Neurosurgery* 2013 **119** 1467–1477. (https://doi.org/10.3171/2013.8.JNS13224)
53 Ahmed S, Elsheikh M, Stratton IM, Page RC, Adams CB & Wass JA. Outcome of transphenoidal surgery for acromegaly and its

relationship to surgical experience. *Clinical Endocrinology* 1999 **50** 561–567. (https://doi.org/10.1046/j.1365-2265.1999.00760.x)
54 Starke RM, Raper DM, Payne SC, Vance ML, Oldfield EH & Jane JA Jr Endoscopic vs microsurgical transsphenoidal surgery for acromegaly: outcomes in a concurrent series of patients using modern criteria for remission. *Journal of Clinical Endocrinology and Metabolism* 2013 **98** 3190–3198. (https://doi.org/10.1210/jc.2013-1036)
55 Yildirim AE, Sahinoglu M, Divanlioglu D, Alagoz F, Gurcay AG, Daglioglu E, Okay HO & Belen AD. Endoscopic endonasal transsphenoidal treatment for acromegaly: 2010 consensus criteria for remission and predictors of outcomes. *Turkish Neurosurgery* 2014 **24** 906–912.
56 Shirvani M & Motiei-Langroudi R. Transsphenoidal surgery for growth hormone-secreting pituitary adenomas in 130 patients. *World Neurosurgery* 2014 **81** 125–130. (https://doi.org/10.1016/j.wneu.2013.01.021)
57 Taboada GF, Luque RM, Neto LV, Machado Ede O, Sbaffi BC, Domingues RC, Marcondes JB, Chimelli LM, Fontes R, Niemeyer P *et al*. Quantitative analysis of somatostatin receptor subtypes (1–5) gene expression levels in somatotropinomas and correlation to in vivo hormonal and tumor volume responses to treatment with octreotide LAR. *European Journal of Endocrinology* 2008 **158** 295–303. (https://doi.org/10.1530/EJE-07-0562)
58 Neto LV, Machado Ede O, Luque RM, Taboada GF, Marcondes JB, Chimelli LM, Quintella LP, Niemeyer P Jr, de Carvalho DP, Kineman RD *et al*. Expression analysis of dopamine receptor subtypes in normal human pituitaries, nonfunctioning pituitary adenomas and somatotropinomas, and the association between dopamine and somatostatin receptors with clinical response to octreotide-LAR in acromegaly. *Journal of Clinical Endocrinology and Metabolism* 2009 **94** 1931–1937. (https://doi.org/10.1210/jc.2008-1826)
59 Wildemberg LE, Vieira Neto L, Costa DF, Nasciuti LE, Takiya CM, Alves LM, Rebora A, Minuto F, Ferone D & Gadelha MR. Low somatostatin receptor subtype 2, but not dopamine receptor subtype 2, expression predicts the lack of biochemical response of somatotropinomas to treatment with somatostatin analogs. *Journal of Endocrinological Investigation* 2012 **36** 38–43. (https://doi.org/10.3275/8305)
60 Gatto F, Feelders RA, van der Pas R, Kros JM, Waaijers M, Sprij-Mooij D, Neggers SJ, van der Lelij AJ, Minuto F, Lamberts SW *et al*.Immunoreactivity score using an anti-sst2A receptor monoclonal antibody strongly predicts the biochemical response to adjuvant treatment with somatostatin analogs in acromegaly. *Journal of Clinical Endocrinology and Metabolism* 2013 **98** E66–E71. (https://doi.org/10.1210/jc.2012-2609)
61 Lamberts SW. The role of somatostatin in the regulation of anterior pituitary hormone secretion and the use of its analogs in the treatment of human pituitary tumors. *Endocrine Reviews* 1988 **9** 417–436. (https://doi.org/10.1210/edrv-9-4-417)
62 Hubina E, Nanzer AM, Hanson MR, Ciccarelli E, Losa M, Gaia D, Papotti M, Terreni MR, Khalaf S, Jordan S *et al*. Somatostatin analogues stimulate p27 expression and inhibit the MAP kinase pathway in pituitary tumours. *European Journal of Endocrinology* 2006 **155** 371–379. (https://doi.org/10.1530/eje.1.02213)
63 Taboada GF, Luque RM, Bastos W, Guimaraes RF, Marcondes JB, Chimelli LM, Fontes R, Mata PJ, Filho PN, Carvalho DP *et al*. Quantitative analysis of somatostatin receptor subtype (SSTR1-5) gene expression levels in somatotropinomas and non-functioning pituitary adenomas. *European Journal of Endocrinology* 2007 **156** 65–74. (https://doi.org/10.1530/eje.1.02313)
64 Ferone D, de Herder WW, Pivonello R, Kros JM, van Koetsveld PM, de Jong T, Minuto F, Colao A, Lamberts SW & Hofland LJ. Correlation of in vitro and in vivo somatotropic adenoma responsiveness to somatostatin analogs and dopamine agonists with immunohistochemical evaluation of somatostatin and dopamine receptors and electron microscopy. *Journal of Clinical Endocrinology and Metabolism* 2008 **93** 1412–1417. (https://doi.org/10.1210/jc.2007-1358)
65 Franck SE, Gatto F, van der Lely AJ, Janssen J, Dallenga AHG, Nagtegaal AP, Hofland LJ & Neggers S. Somatostatin receptor expression in gh-secreting pituitary adenomas treated with long-acting somatostatin analogues in combination with pegvisomant. *Neuroendocrinology* 2017 **105** 44–53. (https://doi.org/10.1159/000448429)
66 Casar-Borota O, Heck A, Schulz S, Nesland JM, Ramm-Pettersen J, Lekva T, Alafuzoff I & Bollerslev J. Expression of SSTR2a, but not of SSTRs 1, 3, or 5 in somatotroph adenomas assessed by monoclonal antibodies was reduced by octreotide and correlated with the acute and long-term effects of octreotide. *Journal of Clinical Endocrinology and Metabolism* 2013 **98** E1730–E1739. (https://doi.org/10.1210/jc.2013-2145)
67 Fougner SL, Casar-Borota O, Heck A, Berg JP & Bollerslev J. Adenoma granulation pattern correlates to clinical variables and effect of somatostatin analogue treatment in a large series of patients with acromegaly. *Clinical Endocrinology* 2012 **76** 96–102. (https://doi.org/10.1111/j.1365-2265.2011.04163.x)
68 Larkin S, Reddy R, Karavitaki N, Cudlip S, Wass J & Ansorge O. Granulation pattern, but not GSP or GHR mutation, is associated with clinical characteristics in somatostatin-naive patients with somatotroph adenomas. *European Journal of Endocrinology* 2013 **168** 491–499. (https://doi.org/10.1530/EJE-12-0864)
69 Brzana J, Yedinak CG, Gultekin SH, Delashaw JB & Fleseriu M. Growth hormone granulation pattern and somatostatin receptor subtype 2A correlate with postoperative somatostatin receptor ligand response in acromegaly: a large single center experience. *Pituitary* 2013 **16** 490–498. (https://doi.org/10.1007/s11102-012-0445-1)
70 Mayr B, Buslei R, Theodoropoulou M, Stalla GK, Buchfelder M & Schofl C. Molecular and functional properties of densely and sparsely granulated GH-producing pituitary adenomas. *European Journal of Endocrinology* 2013 **169** 391–400. (https://doi.org/10.1530/EJE-13-0134)
71 Heck A, Ringstad G, Fougner SL, Casar-Borota O, Nome T, Ramm-Pettersen J & Bollerslev J. Intensity of pituitary adenoma on T2-weighted magnetic resonance imaging predicts the response to octreotide treatment in newly diagnosed acromegaly. *Clinical Endocrinology* 2012 **77** 72–78. (https://doi.org/10.1111/j.1365-2265.2011.04286.x)
72 Puig-Domingo M, Resmini E, Gomez-Anson B, Nicolau J, Mora M, Palomera E, Marti C, Halperin I & Webb SM. Magnetic resonance imaging as a predictor of response to somatostatin analogs in acromegaly after surgical failure. *Journal of Clinical Endocrinology and Metabolism* 2010 **95** 4973–4978. (https://doi.org/10.1210/jc.2010-0573)
73 Heck A, Emblem KE, Casar-Borota O, Bollerslev J & Ringstad G. Quantitative analyses of T2-weighted MRI as a potential marker for response to somatostatin analogs in newly diagnosed acromegaly. *Endocrine* 2016 **52** 333–343. (https://doi.org/10.1007/s12020-015-0766-8)
74 Shen M, Zhang Q, Liu W, Wang M, Zhu J, Ma Z, He W, Li S, Shou X, Li Y *et al*. Predictive value of T2 relative signal intensity for response to somatostatin analogs in newly diagnosed acromegaly. *Neuroradiology* 2016 **58** 1057–1065. (https://doi.org/10.1007/s00234-016-1728-4)
75 Vierimaa O, Georgitsi M, Lehtonen R, Vahteristo P, Kokko A, Raitila A, Tuppurainen K, Ebeling TM, Salmela PI, Paschke R *et al*. Pituitary adenoma predisposition caused by germline mutations in the AIP gene. *Science* 2006 **312** 1228–1230. (https://doi.org/10.1126/science.1126100)
76 Igreja S, Chahal HS, King P, Bolger GB, Srirangalingam U, Guasti L, Chapple JP, Trivellin G, Gueorguiev M, Guegan K *et al*. Characterization of aryl hydrocarbon receptor interacting protein (AIP) mutations in familial isolated pituitary adenoma families.

Human Mutation 2010 **31** 950–960. (https://doi.org/10.1002/humu.21292)
77 Daly AF, Tichomirowa MA, Petrossians P, Heliovaara E, Jaffrain-Rea ML, Barlier A, Naves LA, Ebeling T, Karhu A, Raappana A *et al*. Clinical characteristics and therapeutic responses in patients with germ-line AIP mutations and pituitary adenomas: an international collaborative study. *Journal of Clinical Endocrinology and Metabolism* 2010 **95** E373–E383. (https://doi.org/10.1210/jc.2009-2556)
78 Chahal HS, Stals K, Unterlander M, Balding DJ, Thomas MG, Kumar AV, Besser GM, Atkinson AB, Morrison PJ, Howlett TA *et al*. AIP mutation in pituitary adenomas in the 18th century and today. *New England Journal of Medicine* 2011 **364** 43–50. (https://doi.org/10.1056/NEJMoa1008020)
79 Pinho LK, Vieira Neto L, Wildemberg LE, Moraes AB, Takiya CM, Frohman LA, Korbonits M & Gadelha MR. Familial isolated pituitary adenomas experience at a single center: clinical importance of AIP mutation screening. *Arquivos Brasileiros de Endocrinologia and Metabologia* 2010 **54** 698–704. (https://doi.org/10.1590/S0004-27302010000800006)
80 Jaffrain-Rea ML, Angelini M, Gargano D, Tichomirowa MA, Daly AF, Vanbellinghen JF, D'Innocenzo E, Barlier A, Giangaspero F, Esposito V *et al*. Expression of aryl hydrocarbon receptor (AHR) and AHR-interacting protein in pituitary adenomas: pathological and clinical implications. *Endocrine-Related Cancer* 2009 **16** 1029–1043. (https://doi.org/10.1677/ERC-09-0094)
81 Kasuki L, Vieira Neto L, Wildemberg LE, Colli LM, de Castro M, Takiya CM & Gadelha MR. AIP expression in sporadic somatotropinomas is a predictor of the response to octreotide LAR therapy independent of SSTR2 expression. *Endocrine-Related Cancer* 2012 **19** L25–L29. (https://doi.org/10.1530/ERC-12-0020)
82 Kasuki Jomori de Pinho L, Vieira Neto L, Armondi Wildemberg LE, Gasparetto EL, Marcondes J, de Almeida Nunes B, Takiya CM & Gadelha MR. Low aryl hydrocarbon receptor-interacting protein expression is a better marker of invasiveness in Somatotropinomas than Ki-67 and p53. *Neuroendocrinology* 2011 **94** 39–48. (https://doi.org/10.1159/000322787)
83 Denes J, Kasuki L, Trivellin G, Colli LM, Takiya CM, Stiles CE, Barry S, de Castro M, Gadelha MR & Korbonits M. Regulation of aryl hydrocarbon receptor interacting protein (AIP) protein expression by MiR-34a in sporadic somatotropinomas. *PLoS ONE* 2015 **10** e0117107. (https://doi.org/10.1371/journal.pone.0117107)
84 Chahal HS, Trivellin G, Leontiou CA, Alband N., Fowkes RC, Tahir A, Igreja SC, Lupp A, Schulz S, Ansorge O *et al*. Somatostatin analogs modulate AIP in somatotroph adenomas – the role of the ZAC1 pathway. *Journal of Clinical Endocrinology and Metabolism* 2012 **97** E1411–E1420. (https://doi.org/10.1210/jc.2012-1111)
85 Jaffrain-Rea ML, Rotondi S, Turchi A, Occhi G, Barlier A, Peverelli E, Rostomyan L, Defilles C, Angelini M, Oliva MA *et al*. Somatostatin analogues increase AIP expression in somatotropinomas, irrespective of Gsp mutations. *Endocrine-Related Cancer* 2013 **20** 753–766. (https://doi.org/10.1530/ERC-12-0322)
86 Fougner SL, Bollerslev J, Latif F, Hald JK, Lund T, Ramm-Pettersen J & Berg JP. Low levels of raf kinase inhibitory protein in growth hormone-secreting pituitary adenomas correlate with poor response to octreotide treatment. *Journal of Clinical Endocrinology and Metabolism* 2008 **93** 1211–1216. (https://doi.org/10.1210/jc.2007-2272)
87 Duran-Prado M, Gahete MD, Martinez-Fuentes AJ, Luque RM, Quintero A, Webb SM, Benito-Lopez P, Leal A, Schulz S, Gracia-Navarro F *et al*. Identification and characterization of two novel truncated but functional isoforms of the somatostatin receptor subtype 5 differentially present in pituitary tumors. *Journal of Clinical Endocrinology and Metabolism* 2009 **94** 2634–2643. (https://doi.org/10.1210/jc.2008-2564)
88 Theodoropoulou M, Tichomirowa MA, Sievers C, Yassouridis A, Arzberger T, Hougrand O, Deprez M, Daly AF, Petrossians P, Pagotto U *et al*. Tumor ZAC1 expression is associated with the response to somatostatin analog therapy in patients with acromegaly. *International Journal of Cancer* 2009 **125** 2122–2126. (https://doi.org/10.1002/ijc.24602)
89 Kasuki L, Wildemberg LE, 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. *European Journal of Endocrinology* 2013 **169** 217–223. (https://doi.org/10.1530/EJE-13-0349)
90 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. *Journal of Clinical Endocrinology and Metabolism* 2010 **95** 2334–2342. (https://doi.org/10.1210/jc.2009-2197)
91 Gatto F, Biermasz NR, Feelders RA, Kros JM, Dogan F, van der Lely AJ, Neggers SJ, Lamberts SW, Pereira AM, Ferone D *et al*. Low beta-arrestin expression correlates with the responsiveness to long-term somatostatin analog treatment in acromegaly. *European Journal of Endocrinology* 2016 **174** 651–662. (https://doi.org/10.1530/EJE-15-0391)
92 Newman CB, Melmed S, Snyder PJ, Young WF, Boyajy LD, Levy R, Stewart WN, Klibanski A, Molitch ME & Gagel RF. Safety and efficacy of long-term octreotide therapy of acromegaly: results of a multicenter trial in 103 patients – a clinical research center study. *Journal of Clinical Endocrinology and Metabolism* 1995 **80** 2768–2775. (https://doi.org/10.1210/jcem.80.9.7673422)
93 Suliman M, Jenkins R, Ross R, Powell T, Battersby R & Cullen DR. Long-term treatment of acromegaly with the somatostatin analogue SR-lanreotide. *Journal of Endocrinological Investigation* 1999 **22** 409–418. (https://doi.org/10.1007/BF03343583)
94 Eden Engstrom B, Burman P & Karlsson FA. Men with acromegaly need higher doses of octreotide than women. *Clinical Endocrinology* 2002 **56** 73–77. (https://doi.org/10.1046/j.0300-0664.2001.01440.x)
95 Mattar P, Alves Martins MR & Abucham J. Short- and long-term efficacy of combined cabergoline and octreotide treatment in controlling igf-I levels in acromegaly. *Neuroendocrinology* 2010 **92** 120–127. (https://doi.org/10.1159/000317314)
96 Gatto F, Feelders RA, Franck SE, van Koetsveld PM, Dogan F, Kros JM, Neggers S, van der Lely AJ, Lamberts SWJ, Ferone D *et al*. In vitro head-to-head comparison between octreotide and pasireotide in gh-secreting pituitary adenomas. *Journal of Clinical Endocrinology and Metabolism* 2017 **102** 2009–2018. (https://doi.org/10.1210/jc.2017-00135)
97 Iacovazzo D, Carlsen E, Lugli F, Chiloiro S, Piacentini S, Bianchi A, Giampietro A, Mormando M, Clear AJ, Doglietto F *et al*. Factors predicting pasireotide responsiveness in somatotroph pituitary adenomas resistant to first-generation somatostatin analogues: an immunohistochemical study. *European Journal of Endocrinology* 2016 **174** 241–250. (https://doi.org/10.1530/EJE-15-0832)
98 Kopchick JJ. Discovery and mechanism of action of pegvisomant. *European Journal of Endocrinology* 2003 **148** (Supplement 2) S21–S25. (https://doi.org/10.1530/eje.0.148S021)
99 Pantel J, Machinis K, Sobrier ML, Duquesnoy P, Goossens M & Amselem S. Species-specific alternative splice mimicry at the growth hormone receptor locus revealed by the lineage of retroelements during primate evolution. *Journal of Biological Chemistry* 2000 **275** 18664–18669. (https://doi.org/10.1074/jbc.M001615200)
100 Dos Santos C, Essioux L, Teinturier C, Tauber M, Goffin V & Bougneres P. A common polymorphism of the growth hormone receptor is associated with increased responsiveness to growth hormone. *Nature Genetics* 2004 **36** 720–724. (https://doi.org/10.1038/ng1379)
101 Bougneres P & Goffin V. The growth hormone receptor in growth. *Endocrinology and Metabolism Clinics of North America* 2007 **36** 1–16. (https://doi.org/10.1016/j.ecl.2006.08.003)

102 Bianchi A, Mazziotti G, Tilaro L, Cimino V, Veltri F, Gaetani E, Pecorini G, Pontecorvi A, Giustina A & De Marinis L. Growth hormone receptor polymorphism and the effects of pegvisomant in acromegaly. *Pituitary* 2009 **12** 196–199. (https://doi.org/10.1007/s11102-008-0157-8)

103 Bernabeu I, Alvarez-Escola C, Quinteiro C, Lucas T, Puig-Domingo M, Luque-Ramirez M, de Miguel-Novoa P, Fernandez-Rodriguez E, Halperin I, Loidi L *et al*. The exon 3-deleted growth hormone receptor is associated with better response to pegvisomant therapy in acromegaly. *Journal of Clinical Endocrinology and Metabolism* 2010 **95** 222–229. (https://doi.org/10.1210/jc.2009-1630)

104 Filopanti M, Olgiati L, Mantovani G, Corbetta S, Arosio M, Gasco V, De Marinis L, Martini C, Bogazzi F, Cannavo S *et al*. Growth hormone receptor variants and response to pegvisomant in monotherapy or in combination with somatostatin analogs in acromegalic patients: a multicenter study. *Journal of Clinical Endocrinology and Metabolism* 2012 **97** E165–E172. (https://doi.org/10.1210/jc.2011-1769)

105 Franck SE, Van der Lely AJ, Delhanty PJ, Jorgensen JO & Neggers SJ. Pegvisomant in combination with long-acting somatostatin analogues in acromegaly: the role of the growth hormone receptor deletion of exon 3. *European Journal of Endocrinology* 2015 **173** 553–561. (https://doi.org/10.1530/EJE-15-0519)

106 Parkinson C, Burman P, Messig M & Trainer PJ. Gender, body weight, disease activity, and previous radiotherapy influence the response to pegvisomant. *Journal of Clinical Endocrinology and Metabolism* 2007 **92** 190–195. (https://doi.org/10.1210/jc.2006-1412)

107 Sievers C, Baur DM, Schwanke A, Buchfelder M, Droste M, Mann K & Stalla GK. Prediction of therapy response in acromegalic patients under pegvisomant therapy within the German ACROSTUDY cohort. *Pituitary* 2015 **18** 916–923. (https://doi.org/10.1007/s11102-015-0673-2)

108 Chinezu L, Vasiljevic A, Jouanneau E, Francois P, Borda A, Trouillas J & Raverot G. Expression of somatostatin receptors, SSTR2A and SSTR5, in 108 endocrine pituitary tumors using immunohistochemical detection with new specific monoclonal antibodies. *Human Pathology* 2014 **45** 71–77. (https://doi.org/10.1016/j.humpath.2013.08.007)

109 Allegra A, Alonci A, Campo S, Penna G, Petrungaro A, Gerace D & Musolino C. Circulating microRNAs: new biomarkers in diagnosis, prognosis and treatment of cancer (review). *International Journal of Oncology* 2012 **41** 1897–1912. (https://doi.org/10.3892/ijo.2012.1647)

110 D'Angelo D, Palmieri D, Mussnich P, Roche M, Wierinckx A, Raverot G, Fedele M, Maria Croce C, Trouillas J & Fusco A. Altered microRNA expression profile in human pituitary GH adenomas: down-regulation of miRNA targeting HMGA1, HMGA2, and E2F1. *Journal of Clinical Endocrinology and Metabolism* 2012 **97** E1128–E1138. (https://doi.org/10.1210/jc.2011-3482)

111 Bottoni A, Piccin D, Tagliati F, Luchin A, Zatelli MC & degli Uberti EC. miR-15a and miR-16-1 down-regulation in pituitary adenomas. *Journal of Cellular Physiology* 2005 **204** 280–285. (https://doi.org/10.1002/jcp.20282)

112 Bottoni A, Zatelli MC, Ferracin M, Tagliati F, Piccin D, Vignali C, Calin GA, Negrini M, Croce CM & Degli Uberti EC. Identification of differentially expressed microRNAs by microarray: a possible role for microRNA genes in pituitary adenomas. *Journal of Cellular Physiology* 2007 **210** 370–377. (https://doi.org/10.1002/jcp.20832)

113 Mao ZG, He DS, Zhou J, Yao B, Xiao WW, Chen CH, Zhu YH & Wang HJ. Differential expression of microRNAs in GH-secreting pituitary adenomas. *Diagnostic Pathology* 2010 **5** 79. (https://doi.org/10.1186/1746-1596-5-79)

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