Endocrinol Diabetes Nutr. 2018;65(8):428–437

Endocrinología, Diabetes y Nutrición

www.elsevier.es/endo

ORIGINAL ARTICLE

Expert document on management of acromegaly☆

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Received 21 March 2018; accepted 4 May 2018
Available online 16 October 2018

KEYWORDS
Acromegaly;
Recommendations;
Individualized treatment

Abstract
Objectives: To seek a consensus on issues that may generate doubts in management of acromegaly in Spain.
Method: Nominal groups and Delphi. Four experts defined relevant issues in management of acromegaly and generated different assertions and recommendations. Subsequently, a group of 30 additional experts was selected to test agreement with the assertions through two Delphi rounds. The following response categories were established: (1) Totally disagree; (2) Basically disagree; (3) Basically agree; (4) Totally agree. Agreement was defined as ≥70% of answers in categories 1 and 2 (consensus with the disagreement) or 3 and 4 (consensus with the agreement) in the second Delphi round.
Results: Assertions covers various aspects of clinical practice, including: (1) Useful instruments in individualization of treatment (response predictive markers, imaging techniques, etc.); (2) Clinical profiles and relevant comorbidities in treatment individualization; (3) Role of patient in treatment decision-making; (4) Access to treatments (accessibility and equity). The first Delphi round included 35 assertions. Consensus was reached on six of these assertions, two were eliminated, and two were reformulated. Of the 27 assertions included in the second round, consensus was reached on 24 (22 in the agreement, two in the disagreement) and three were eliminated.
Conclusions: This document is intended to solve some common clinical questions and to facilitate decision making in the management of patients with acromegaly.

☆ Please cite this article as: Bernabeu I, Cámara R, Marazuela M, Puig Domingo M. Documento de expertos sobre el manejo de la acromegalia. Endocrinol Diabetes Nutr. 2018;65:428–437.

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https://doi.org/10.1016/j.endien.2018.05.015

PALABRAS CLAVE
Acromegalia;
Recomendaciones;
Tratamiento personalizado

Documento de expertos sobre el manejo de la acromegalia

Resumen
Objetivos: Buscar consenso sobre cuestiones que pueden generar dudas en el manejo de la acromegalia en España.
Método: Grupos nominales y Delphi. Se seleccionaron 4 expertos que definieron cuestiones relevantes en el manejo de la acromegalia sobre las que se formularon distintas aseveraciones y recomendaciones. Posteriormente, se eligió un grupo de 30 expertos adicionales con el que se determinó el grado de acuerdo con las mismas en 2 rondas Delphi. Se establecieron las siguientes categorías de respuesta: 1) totalmente en desacuerdo; 2) básicamente en desacuerdo; 3) básicamente de acuerdo; y 4) totalmente de acuerdo. Se definió acuerdo si, en la segunda ronda Delphi $\geq$ 70% de las respuestas estaban en las categorías 1 y 2 (consenso con el desacuerdo) o 3 y 4 (consenso con el acuerdo).
Resultados: Se generaron aseveraciones y recomendaciones sobre diversos aspectos de la práctica clínica incluyendo: 1) instrumentos de utilidad en la individualización del tratamiento (marcadores predictivos de respuesta, técnicas de imagen, etc.); 2) perfiles clínicos y comorbilidades en la individualización del tratamiento; 3) papel del paciente en la toma de decisiones terapéuticas; y 4) acceso al tratamiento (accesibilidad y equidad). La primera ronda Delphi incluyó 35 aseveraciones, en 6 se alcanzó consenso, 2 fueron eliminadas y 2 reformuladas. En la segunda se incluyeron 27 y se alcanzó consenso en 24 (22 en el acuerdo, 2 en el desacuerdo) y 3 se eliminaron.
Conclusiones: Este documento pretende resolver algunos interrogantes clínicos habituales y facilitar la toma de decisiones en el manejo de la acromegalia.

Introduction

Acromegaly is a disease caused by excess growth hormone (GH) production. It is usually the consequence of a GH-secreting adenoma, though there are also rare cases secondary to ectopic GHRH or GH secretion. The annual incidence of the disease is 3–5 cases per one million inhabitants, and the prevalence is 30–60 cases per one million inhabitants.[1,2]

The clinical manifestations are caused by increased GH and insulin-like growth factor-1 (IGF-1) levels, as well as the compression of structures adjacent to the pituitary tumor and the possible concomitant diminished secretion of other pituitary hormones. The mortality rate can be as high as 30% and is mainly attributable to cardiovascular disease, respiratory disorders and cancer.[3,4]

The therapeutic objectives are to remove the tumor or at least control its volume, avoiding compression symptoms; to normalize the GH and IGF-1 levels; to control the symptoms and comorbidities; and to prevent premature mortality. Surgery remains the treatment of choice in most cases, with radiotherapy being reserved for patients in whom control is not achieved after initial surgery. Disease activity may persist even after surgical removal of the adenoma, thus reflecting the complexity of treatment and the need for a multimodal multidisciplinary and therapeutic approach in order to control GH hypersecretion, normalize the IGF-1 levels, and contain tumor growth.[5] In cases not amenable to surgery or with relapse, the second option is medical treatment with somatostatin analogs (SSAs), dopamine agonists, and GH receptor antagonists. Somatostatin analogs are the preferred option, since they inhibit GH secretion and reduce IGF-1 levels and tumor volume.[1,3] Pharmacological treatment improves left ventricular hypertrophy and dysfunction, as well as hypertension and sleep apnea. However, it has no clear effects upon arthropathy and the soft tissue tumors that characterize acromegaly. Furthermore, SSAs may have a negative influence upon glucose metabolism, while pegvisomant produces beneficial effects. In any case, the control of blood glucose and glycosylated hemoglobin (HbA1c) levels is important in these patients.[5]

Despite the availability of different therapeutic options, there are still unresolved issues in the management of acromegaly. For this reason, a group of experts was convened to produce recommendations with the aim of improving the management of patients with acromegaly, which may prove useful for all professionals involved in their care.

Material and methods

Study design

A qualitative expert opinion study was carried out using nominal group and Delphi methodology. In addition, a narrative review of the literature was made to support the generated assertions.

Selection of experts

The scientific committee of the project consisted of four experts selected according to the following criteria: (1) scientific publications in Medline-indexed journals; (2) studies presented at national and international endocrinology congresses; (3) documented clinical experience in acromegaly; and (4) geographic representativeness. The scientific committee was responsible for project development, the generation of assertions and the drafting of the final document, but was not involved in the consensus generating assessment rounds (Delphi).

Next, the scientific committee selected a total of 30 experts for participation in the two Delphi rounds, guaranteeing: (1) acknowledged experience in acromegaly through membership of the neuroendocrinology working group of the Spanish Society of Endocrinology and Nutrition (SEEN); and (2) representativeness of the different Spanish autonomous communities.

Nominal group meeting

In a first face-to-face meeting, the four experts of the scientific committee defined the objectives and scope, and selected the experts of the neuroendocrinology working group to which the document would be submitted. In addition, they discussed aspects of the management of acromegaly that continue to pose questions in clinical practice, and grouped them into four topics: (1) tools of use for the individualization of treatment (response predictors, imaging techniques, etc.); (2) patient profiles and comorbidities; (3) patient role in decision-making; and (4) access to treatments. Assertions were generated on these topics, which sought to answer the questions posed in clinical practice.

Delphi

The Delphi technique comprises an expert panel consensus seeking method based on analysis and reflection with reference to a defined problem. Delphi methodology has the following characteristics: (a) it is an iterative process (experts issue their opinion more than once, through several rounds, thereby stabilizing opinion); (b) it is anonymous (no member of the group knows to whom a specific response corresponds, thus avoiding the negative influence of dominant members); (c) it is a controlled feedback process (allowing the circulation of information among the experts and the definition of a common language); and (d) the results can be expressed statistically.

Two Delphi rounds were held to establish the degree of agreement with the assertions using an online platform. In the first round, the 30 participants voted using the following response categories: (1) totally disagree; (2) basically disagree; (3) uncertain; (4) basically agree; (5) totally agree. Consensus was established if agreement was observed for at least 70% of the responses in one of the 5 mentioned categories. The assertions that reached adequate agreement were accepted and did not go on to the second round, while those that did not reach adequate agreement were analyzed by the scientific committee, which decided to: (1) remove them; (2) reformulate them; or (3) keep them without changes.

A Delphi second round was performed after this procedure. In this case, the degree of agreement with each assertion was assessed using the following response categories: (1) totally disagree; (2) basically disagree; (3) basically agree; and (4) totally agree. Consensus was established when $\geq$ 70% of the responses corresponded to categories 1 and 2 (disagreement consensus) or 3 and 4 (agreement consensus). Those assertions that did not reach the established level of agreement were removed.

Final editing of the document

After completing the Delphi rounds, a narrative review of the literature was made to support the assertions, and the document was drafted.

Results

In the first Delphi round 35 assertions were evaluated. Consensus was reached on 6, two were eliminated, and another two were reformulated. In the second round, 27 assertions were evaluated, a consensus being reached on 24 (22 agreement consensus, 2 disagreement consensus), while three were removed because the established level of agreement was not reached. The final 30 assertions are described below.

Tools of use for the individualization of treatment

Assertion 1. The acute octreotide suppression test (AOT) is useful for screening acromegalic patients who will not respond adequately to treatment with first generation SSAs (disagreement consensus: 75%).

A significant proportion of patients are resistant to first generation SSAs. Although some studies[6] appear to confirm the usefulness of AOT in predicting the response to subsequent treatment with SSAs, the results are controversial, as is shown by the opinion of the experts consulted in this study.[6]

Assertion 2. In acromegaly, the T2-weighted magnetic resonance imaging (MRI) signal of somatotropic adenomas may be of value in predicting the response to treatment with first generation SSAs (agreement consensus: 93%).

There is important variability in the individual response to treatment with first generation SSAs; this justifies the need to individualize treatment based on response predictors. The role of MRI in relation to this objective has been evaluated. In a study involving newly diagnosed acromegalic patients, a hypointense T2-weighted signal was seen to be a response predictor, with positive and negative predictive values of 81.5% and 77.3%, respectively.[7] These results have been confirmed in other studies.[8–10] Likewise, the presence of a hypointense T2-weighted signal in somatotropic adenomas is associated with an improved response after tumor surgery.[11]

Assertion 3. In somatotropinomas, a scantly granular histological pattern is associated with a poor response to

treatment with first generation SSAs (agreement consensus: 100%).

Growth hormone-secreting pituitary tumors may be dense and scantly granular. Some studies have reported a higher percentage of remission in densely granular tumors.[12,13] The different response to octreotide may be due to increased expression on the part of densely granular tumor cells of somatostatin receptor type 2 (SSTR2), the receptor subtype with the greatest affinity for octreotide.[14]

Assertion 4. In somatotropinomas, the association of a densely granular histological pattern with signal hypointensity in T2-weighted sequencing in the MRI study is predictive of a good response to treatment with first generation SSAs (agreement consensus: 94%).

A number of studies[15,16] have shown an association between a densely granular histological pattern with *gsp* mutations and a good response to SSAs. In addition, a study involving naive patients found T2-weighted signal hypointensity to be correlated to an improved response to octreotide, while hyperintensity was associated with scant granularity and a lesser response to SSAs.[8] Lastly, the results of another study reported greater T2-weighted signal intensity in scantly granular adenomas, generally resistant to first generation SSAs.[10]

Assertion 5. In somatotropinomas, the presence of intense somatostatin receptor 2 expression is predictive of a good response to treatment with first generation SSAs (agreement consensus: 91%).

The relationship between SSTR2 expression and patient response to first generation SSAs has been observed in various publications,[17–19] as evidenced by the biochemical parameters – decreased GH and IGF-1 levels – and by a reduction in tumor size. These findings have established surgical sample SSTR2 expression as a marker of patient response to SSAs, suggesting the need for adjuvant treatment after surgery. These results are not consistent, however. In a study of patients treated and not treated with octreotide before surgery, no relationship was found between SSTR2 or SSTR5 and patient response. In addition, it has been suggested that the preoperative administration of SSAs may modify receptor expression. According to this publication, receptor expression does not guarantee a specific drug response, since other functional aspects of SSA-receptor interaction may intervene, such as the type of dimerization and the signaling cascade.[20]

Assertion 6. In somatotropinomas, the presence of a truncated somatostatin receptor 5 variant predicts a poor response to treatment with first generation SSAs (agreement consensus: 90%).

One study investigated the expression of two truncated SST5 variants (sst5TMD5 and sst5TMD4) in GH-secreting pituitary adenomas and their relationship to a lack of response to SSAs. The results showed a negative association between the truncated sst5TMD4 variant and the response.[21] An attempt has been made to explain this association in terms of an influence of the SSTR5 variants upon the somatostatin receptor signaling pathways[22]; a regulatory influence of the truncated variants upon the effect of somatostatin and its analogs[20]; and greater dependence of the response upon the relative expression of the different receptor subtypes than on the individual levels of any single receptor.[23]

Assertion 7. In somatotropinomas, the presence of intense somatostatin receptor 5 expression may identify acromegalic patients in whom pasireotide may be the best therapeutic option (agreement consensus: 87%).

No differences were seen in maximum tumor diameter, cavernous sinus invasion, or GH and IGF-1 levels at diagnosis or after surgery between those patients who responded and those who did not respond to pasireotide, though SSTR5 expression may predict the response. One study showed that patients with lower SSTR5 expression did not respond to pasireotide, while those with intense receptor expression responded with a greater decrease in IGF-1 levels. No differences were found in the expression of SSTR2a and SSTR3, suggesting that SSTR5 is an important determinant of biochemical response to pasireotide.[24]

Assertion 8. In somatotropinomas, a low expression of somatostatin receptors 2 and 5 identifies acromegalic patients in whom pegvisomant may be the best therapeutic option (agreement consensus: 80%).

The evidence on resistance to treatment with SSAs alone in patients with low SSTR2 expression suggests that a combined regimen of SSAs and pegvisomant, or pegvisomant in monotherapy, should be used in these cases. According to some studies, somatotropic adenomas partially resistant to first generation SSAs, usually requiring combined treatment with pegvisomant, show lower SSTR2 expression.[25] A low SSTR2/SSTR5 ratio also allows identification of these cases.[26]

Assertion 9. In acromegalic patients, Gsp mutations predict a good response to treatment with first generation SSAs (agreement consensus: 87%).

G proteins are involved in the binding of certain hormones and their receptors, and in post-receptor signaling. Mutations of these proteins promote tumor growth by inducing proliferation signals initiated by extracellular factors. Thirty percent of all somatotropinomas carry mutations of the G alpha subunit of the Gsp oncogene. These mutations stabilize the protein in its active conformation and induce a higher Gsp expression that is associated with a better response to first generation SSAs.[27]

Assertion 10. The response of acromegaly to drug treatment is unpredictable (consensus on disagreement: 77%).

There is significant variability in the reported biochemical response rates,[28] due among other factors to population characteristics, the definition of response, per-protocol (PP) or intention-to-treat (ITT) analysis, the type of design, and the biochemical methods used for hormone measurement.[29]

Patient profiles and relevant comorbidities in treatment individualization

Assertion 11. In patients with a partial response to first generation SSAs, cabergoline should be added before other more expensive drugs are prescribed (agreement consensus: 77%).

This assertion is consistent with the Spanish[30] and international guidelines.[31] In patients with a partial response to first generation SSAs, the addition of cabergoline secures the normalization of IGF-1 levels in approximately 50% of the cases. Its efficacy is greater in patients with moderately high IGF-1 levels, and its effect is maintained over time.

Efficacy is scantly significant and is limited to patients with simultaneous prolactin elevation. Its lower cost, good tolerability and oral administration are further arguments in favor of its use.[32–34]

Assertion 12. In second line treatment, the presence of remnant tumor close to the optic chiasm is an indication for pasireotide (agreement consensus: 77%).

In selecting second line treatment, the characteristics of the postoperative remnant tumor must be taken into account. Pegvisomant and pasireotide are available, offering known efficacy and safety,[26,35–37] even in the clinical practice setting, in the case of pegvisomant.[38]

Both drugs have distinct efficacy profiles. Pegvisomant offers greater biochemical efficacy but exerts no antitumor effect. Some cases of tumor growth (2.9–6.7%) have been reported during treatment.[36,39] The risk of growth is lower in irradiated patients and in those subjected to prolonged treatment with SSAs, but there are no clinical, radiological or histological features (Ki67) capable of predicting growth.[39]

Pasireotide has lesser biochemical efficacy,[26] but exerts a highly relevant antitumor effect. This drug reduces tumor size (by 40% on average) in 80% of the cases,[37] and may even offer additional reduction beyond that achieved by first generation SSAs when used as second line therapy.[26,40] Thus, and in the presence of tumor remnants close to the chiasm, pasireotide has been suggested as a priority indication in second line treatment. This recommendation is more prudent than that of the Endocrine Society, which suggests the use of drugs possessing antitumor effects in the presence of tumor remnants with compression of the chiasm or vital centers.[31]

Assertion 13. In the absence of tumor aggressiveness (active growth, invasiveness, local compression), the presence of a tumor remnant does not contraindicate monotherapy with pegvisomant (agreement consensus: 97%).

Experts consider that the presence of a tumor remnant after surgery, without evidence of aggressiveness, does not contraindicate monotherapy with pegvisomant, as contemplated by the guidelines.[31,41] This is in contrast to the clinical practice setting, where pegvisomant is predominantly used in combination with first generation SSAs.[42,43]

Assertion 14. In diabetic acromegalic patients with inadequate metabolic control (HbA1c > 8%), pegvisomant alone or associated with first generation SSAs is more adequate than pasireotide as second line treatment (agreement consensus: 100%).

Altered glucose metabolism is highly prevalent in acromegaly.[44] Another distinguishing characteristic between pegvisomant and pasireotide is their effect upon glucose metabolism. Pegvisomant monotherapy does not affect insulin secretion, improves insulin sensitivity, and reduces endogenous glucose production, lowering basal glycemia and HbA1c, and the need for antidiabetic therapy.[45,46] Pegvisomant therefore has been recommended as the treatment of choice in diabetic acromegalic patients with insufficient metabolic control.[41] However, the effects of pegvisomant upon glucose metabolism are lost during combination therapy with first generation SSAs.[47]

Pasireotide in turn suppresses insulin, glucagon, GLP-1 and GIP secretion, promoting hyperglycemia in 60–65% of all patients. Although hyperglycemia is generally manageable with medication, it may oblige treatment discontinuation in up to 3.5% of the cases.[26,37,48] In the pivotal studies with pasireotide, the presence of poorly controlled diabetes (Hb1c > 8%) was an exclusion criterion.

Assertion 15. Achieving adequate biochemical and tumor control of acromegaly is always a priority concern, and the development of diabetes is therefore not a limiting factor for treatment with pasireotide (agreement consensus: 77%).

Morbidity and mortality in patients with acromegaly are associated with excess GH, and early and effective control of GH hypersecretion is therefore required.[49] On the other hand, diabetes mellitus causes specific morbidity and mortality[50] and, in some older series, was found to be an independent predictor of mortality.[51] Thus, the early control of GH/IGF-I hypersecretion is required without glucose tolerance being significantly altered.

First generation SSAs, in first line therapy, achieve good biochemical control in 50–55% of all patients,[28] without glucose metabolism being significantly affected. In second line treatment, the positive effect of pegvisomant in this regard may be limited by intolerance or contraindication to the drug. In this situation, pasireotide may be effective in controlling GH/IGF-1 secretion and tumor size, but it often induces hyperglycemia. This adverse effect is predictable from the basal glycemia values and prior glucose metabolism,[52] and can be controlled with oral glucose-lowering agents.[52,53] In the pivotal studies, 47% of the patients treated with pasireotide did not require glucose-lowering drugs. In cases of inadequate control (HbA1c > 7%) with metformin, the sequential and/or combined use of DPP4 inhibitors, GLP-1 receptor agonists or insulin is recommended.[53] Based on these considerations, the expert panel considers GH/IGF-I control to be a greater concern than the development of diabetes mellitus, which can be expected to be controlled with adequate treatment.

Assertion 16. In patients with more severe acromegalic disease and a partial response to first generation SSAs, combined therapy in the form of first generation SSAs + pegvisomant is a better option than pegvisomant in monotherapy (agreement consensus: 90%).

In patients with severe disease and partial resistance to first generation SSAs, there is no evidence of additional benefit from combination therapy versus pegvisomant alone in terms of biochemical control.[54,55] However, this treatment modality has clear advantages in other aspects[56]: potential antitumor effect, improved quality of life, lower pegvisomant dosage, lower costs, and greater convenience for the patient when using non-daily regimens. By contrast, combination therapy carries an increased risk of liver problems[56] and loss of the positive effect afforded by pegvisomant monotherapy in relation to glucose metabolism.[47] In the present study, there was a broad consensus that combination therapy is a better option than pegvisomant monotherapy in patients with severe disease and a partial response to SSAs. This recommendation is consistent with those of the leading guides.[31]

Assertion 17. In patients requiring high doses of pegvisomant as monotherapy (25–30 mg/day) it may be more appropriate to combine first generation SSAs and pegvisomant (agreement consensus: 87%).

Studies on the efficiency of the various treatment modalities in acromegaly are scarce.[57–59] However, it is known that combined treatment with SSAs-pegvisomant increases the plasma concentrations of pegvisomant by 20%, reducing the need for doses, and this could lower the cost.[33,55] The expert panel agrees on the convenience of using combination therapy in the form of first generation SSAs and pegvisomant when the latter drug in monotherapy poses a strong demand in terms of dosage.

Assertion 18. Pasireotide is indicated in patients with inadequate tumor response to first generation SSAs (agreement consensus: 93%).

In the head-to-head comparative study of octreotide versus pasireotide, tumor size reduction was recorded in 77.4% and 80.8% of the patients, respectively. The mean reduction was 38% and 40%.[37] In the PAOLA study,[26] second line pasireotide therapy resulted in a tumor reduction of over 25% in 18.5% of the patients previously treated with maximum doses of octreotide, suggesting an antiproliferative effect additional to that of the first generation SSAs. Although the determinants of response have not been identified, the experts agree on the indication of pasireotide in cases of inadequate tumor response to first generation SSAs.

Assertion 19. The normalization of GH and IGF-1 with pasireotide, and of IGF-1 with pegvisomant, has the same long-term impact on survival and mortality (agreement consensus: 94%).

Although the effect of the normalization of GH and/or IGF-1 upon survival and mortality in acromegaly is controversial,[60] it is generally considered to be of prognostic value.[61] There is a broad consensus on biochemical control during the different treatments for acromegaly.[62] In the case of pegvisomant this only comprises the normalization of IGF-1, due to its effect on the secretion of GH and its interference with the analytical methods used to measure it.[63]

Despite the lack of studies on the relationship between biochemical control and morbidity and mortality, the experts consider that the biochemical normalization effect demanded of each drug has the same impact on the prognosis of the disease.

Assertion 20. In patients with no response to first generation SSAs, the treatment of choice is pasireotide or pegvisomant in monotherapy (agreement consensus: 84%).

There is agreement regarding the use of a second line of treatment with pasireotide or pegvisomant, in patients who fail to respond to first generation SSAs.

The affinity profile of pasireotide for the different somatostatin receptor subtypes is very different from that of the first generation SSAs. This justifies its efficacy in a significant percentage of patients resistant to first generation SSAs.[38] In the absence of direct or head-to-head comparative studies, and according to the therapeutic positioning report of the Spanish Agency for Medicinal Products and Medical Devices,[64] the choice of one or the other treatment should be based on the safety profile and the administration route and regimen.

Assertion 21. In patients unresponsive to monotherapy with pasireotide or pegvisomant, combination treatment with both drugs may be considered (agreement consensus: 80%).

The experts consider combination therapy with pegvisomant and pasireotide to be feasible. In 61 patients subjected to combination therapy with first generation SSAs and pegvisomant, and conditioned to the degree of IGF-1 control achieved after 12 weeks, a study was made in which the pegvisomant dose was reduced by 50% and there was a switch to pasireotide plus pegvisomant (if IGF-1 was 1.2 times over the upper limit of normal [ULN]), but there was a switch to pasireotide monotherapy (if IGF-1 persisted up to 1.2 times ULN, which occurred in 24.6% of the cases). Both regimens were effective, and IGF-1 at 24 weeks remained below 1.2 times ULN in 73.8% of the patients (68% for pasireotide plus pegvisomant and 88% for pasireotide monotherapy). Combination therapy was associated with a potential pegvisomant sparing effect (66% dose reduction from the baseline visit) and hyperglycemia in 68.9% of the patients.[65,66]

The role of patients in decision-making in the treatment of acromegaly

Assertion 22. The physician treating the acromegalic patient must explain the advantages and disadvantages of each treatment (surgery, radiotherapy and drugs) in detail and in terms that are easy to understand, so that the patient can make a correct decision (agreement consensus: 100%).

Therapeutic education is essential for patient management. The probability of success and treatment adherence increases when the patient is well informed. The patient must be made aware of the possible complications of the disease and confirm that his or her specialist actively monitors the development of possible complications. The patient should also be informed of the possible treatments that are available and of which is most appropriate for him or her. The possible advantages and disadvantages must also be made known.

Assertion 23. Acromegalic patients have the right to information concerning the experience and outcomes of the center which they attend (agreement consensus: 97%).

Given the variability of our health system, and considering the rights of the patients, the panel considers it important for patients to be informed about the amount of experience in treating the disease and the healthcare outcomes of the management of the disease at their center. There is broad variability in the cure rates of transsphenoidal surgery (50–100%), depending on the center, the surgeon, pituitary adenoma characteristics, and also on the occurrence of complications. It is known that there is a direct relationship between the number of procedures performed by the surgeon and the cure and complications rate. These data should be made known to patients before they decide on a given center or treatment.

Assertion 24. The acromegalic patient has the right to receive a second opinion and care at a reference center for pituitary gland disease (agreement consensus: 97%).

Due to the differences in the amount of experience of the centers in treating this disease, the patient must have the possibility of a second opinion and of being treated in a reference center for the disease, if he or she so chooses.

Assertion 25. Acromegalic patients should be informed about the cost of their treatment in order to promote their treatment adherence (agreement consensus: 87%).

Although it is difficult to report the exact costs of treatment, as these depend on multiple factors, the panel considers that patients should accept responsibility for following the treatment correctly. These measures may increase adherence, facilitate an adequate cost-benefit ratio, and promote system sustainability.

Assertion 26. Acromegalic patient associations help patients make decisions regarding their treatment and resolve doubts (agreement consensus: 93%).

Considering the shortage of time available at the clinic for addressing issues of interest about the disease and its treatments, patient associations can play a very important role in complementing and reinforcing the explanations and indications given by physicians. Such associations have proven to be of great value in improving quality of life and treatment compliance in patients with chronic diseases such as acromegaly.

Access to treatments (accessibility and equity)

Assertion 27. The incorporation of new drugs for the treatment of acromegaly increases the expectations of effective treatment (agreement consensus: 93%).

The experts agree on the possibility of achieving better patient control. As has been commented, pasireotide offers demonstrated efficacy in a significant proportion of acromegalic patients resistant to first generation SSAs.[26]

Assertion 28. Policies regarding the containment of healthcare costs in the different Spanish autonomous communities affect the prescription of new drugs used for acromegaly, due to the high cost of such drugs (agreement consensus: 90%).

The broad consensus on this assertion raises the possibility that bureaucratic or financial obstacles complicate access to treatments with proven efficacy. However, no official data on these potential inequalities are currently available.

Technological and pharmacological innovations pose new challenges to the solvency of healthcare systems, additional to those generated by the current economic crisis. The negative impact of the crisis upon government revenue has led to the adoption of cost containment measures, particularly with reference to drugs. This healthcare management policy threatens the equity of the healthcare system. Scientific bodies and patient associations, as well as the drugs industry and the government regard equity in access to innovative drug therapies as a key aspect on which health policies must be based, provided they are associated with improved clinical outcomes.

Assertion 29. The need for the adequate management of acromegaly should guarantee comprehensive and personalized care of the disease, without limitations due to place of residence or financial situation (agreement consensus: 100%).

Physicians always have the obligation to seek the good of their patients, within the limitations of the clinical situation, of medicine as a human activity, and of the physicians themselves as persons. No social, economic or geographical conditions should influence them.

Assertion 30. Endocrinologists should require acromegalic patients to have access to the most adequate treatment under conditions of equity, without any limitations (agreement consensus: 94%).

The endocrinologist should help his or her patients to manage themselves within the complexity of the healthcare system and ensure access to the best care, without geographical or socioeconomic limitations. According to the great majority of the experts, this implies demanding more adequate care if such care is not being provided.

Discussion

The present Delphi study shows a broad consensus on the need to guarantee comprehensive and personalized care for acromegalic patients, without limitations due to place of residence or economic status. It should also be noted that representative experts from all over Spain participated in this document. Both this fact and the high level of agreement reached clearly validate the assertions made.

The document has addressed aspects of daily practice where there may be more clinical doubts regarding the management of acromegaly, such as the tools used or the type of clinical profiles for the individualization of treatment. The role of the patient in decision making and access to treatments, which are currently very significant issues, have also been addressed.

On the other hand, it is important to emphasize that there were three assertions on which agreement was not reached in the second round. The first assertion was: ''In somatotropinomas, the pathology report allows for the selection of adequate drug treatment in acromegalic patients not cured or with relapsing disease after surgery''. The histological type has been shown to involve differences in tumor phenotypic expression and biological behavior, and contributes prognostic value to the outcome of surgery and the response to medical therapy.[12,67] These results suggest the importance of histopathological data for the prioritization of treatment, but other factors also influence the clinical response. Adequate treatment is therefore established based on a number of factors, not only the pathology report.

The second assertion where no agreement was reached was: ''In patients receiving long-term second line chronic treatment, radiotherapy should be considered because of its better long-term cost-effectiveness ratio''. At present, radiotherapy represents the last line of treatment and is generally used to achieve control of both the tumor and hormonal hypersecretion in patients unresponsive to other treatments. Its main disadvantages are its adverse effects, its limited antisecretory efficacy, and its long latency period. However, the new stereotactic radiotherapy techniques are more effective, rapid and safer than conventional radiotherapy, and allow a significant proportion of patients to achieve remission, thus making chronic medical treatment unnecessary. Radiotherapy has been suggested as an alternative to chronic medical therapy in selected patients.[68] Although most of the panel agreed on this issue (67%), the required level of significance was not reached.

Finally, the last assertion without a consensus was: ''The final treatment decision lies with the acromegalic patient''. The expert panel considers it essential for patients to become involved in therapeutic decision-making, but such decisions cannot fall exclusively upon the patient; rather, they should always be shared with the physician.

Lastly, and while waiting for further evidence to cast more light upon the issues dealt with in this document, the panel hopes that monitoring these assertions will help improve the management and prognosis of patients with acromegaly.

Financial support

This project was funded by Novartis.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Acknowledgments

Thanks are due to Carmen González and Andreu Covas (GOT IT) for facilitating the Delphi project, and to María Jesús García de Yébenes and Estíbaliz Loza (InMusc) for help in the drafting and editing of the document.

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