Medical Therapies for Acromegaly

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KEYWORDS

• Acromegaly • Somatostatin receptor ligand • Dopamine agonist
• GH receptor antagonist • New drugs

KEY POINTS

- Surgery is the primary treatment for acromegaly; however, approximately half of patients require adjuvant medical therapy.
- Three drug classes are available for treatment: somatostatin receptor ligands, dopamine agonists and growth hormone receptor antagonists, which are used as either monotherapy or in combination.
- First-generation somatostatin receptor ligands are the mainstay of medical treatment, achieving biochemical control in approximately 50% of patients.
- New drugs with novel mechanisms of action or administration routes are currently being developed, with an aim of increasing biochemical control and improving patients' quality of life.

INTRODUCTION

Acromegaly is a chronic disease with increased morbidity and mortality rates; this disease is caused by a growth hormone (GH)-secreting adenoma in 99% of cases.[1–3] Fortunately, adequate treatment significantly reduces morbidity and normalizes mortality rates.[2,4] Surgery is the first-line treatment for the majority of patients; however, it

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Abbreviations	
AE	adverse effects
AIP	aryl hydrocarbon receptor-interacting protein
CAB	cabergoline
DA	dopamine agonists
fg-SRL	first-generation somatostatin recperot ligands
GH	growth hormone
GHR	GH receptor
GLP1-RA	glucagon-like peptide-1 receptor agonist
IGF-I	insulin-like growth factor type I
LAN-ATG	lanreotide autogel
OCT-LAR	octreotide long-acting repeatable
OOC	oral octreotide capsules
PAS-LAR	pasireotide long-acting release
PRL	prolactin
QoL	quality of life
SC	subcutaneous
SRL	somatostatin receptor ligands
SST	somatostatin receptors
ULN	upper limit of normal

leads to a disease cure in approximately 50% of cases, based on data from reference centers.[5] Thus, medical treatment is necessary as an adjuvant therapy for a significant proportion of patients and as a primary treatment in few cases (high surgical risk, refusal to undergo surgery or a tumor being almost exclusively located in the cavernous sinus).[3,6,7]

Currently, 3 drug classes are available for acromegaly treatment: somatostatin receptor ligands (SRL), dopamine agonists (DA), and GH receptor (GHR) antagonists (**Table 1**).[6] In this article, current options for medical therapy are reviewed, and future perspectives on the medical treatment of acromegaly are discussed.

SOMATOSTATIN RECEPTOR LIGANDS

GH-secreting pituitary adenomas express 4 types of somatostatin receptors (SST)—including SST1, SST2, SST3, and SST5, with SST2 and SST5 being the 2 most highly expressed receptor types. The SRL exert effects via interactions with these receptors; currently, 2 first-generation SRL (fg-SRL) (octreotide and lanreotide) and 1i second-generation SRL (pasireotide) are available for use.[8]

First-Generation Somatostatin Receptor Ligands: Injectable and Oral Options

Two injectable fg-SRL known as octreotide long-acting repeatable (OCT-LAR) and lanreotide autogel (LAN-ATG) primarily bind to SST2, as well as to SST5 (to a lesser extent).[8] These SRL are considered the first-line medical treatment for patients with persistent disease after surgical tumor resection or when surgery is not an option, as previously cited.[6] In some cases of macroadenomas with parasellar extension (in which total resection is not possible), surgery remains the first-line treatment, as tumor debulking enhances postoperative responsiveness to medical therapy.[9] The routine use of fg-SRL as a presurgical treatment is discouraged. Although some studies have reported positive short-term tumor reduction and biochemical control effects after 3 to 6 months of medication treatment, no positive long-term outcomes have been described in the literature.[10,11] However, the use of preoperative fg-SRL can be attempted in patients with severe pharyngeal thickening and/or sleep apnea, as well as patients with high-output heart failure, to reduce surgical risks.[6]

Table 1
Drugs approved for the treatment of acromegaly

Drug	Drug Class	Administration Route	Doses	IGF-I Normalization	Side Effects
Lanreotide autogel	SRL (first-generation)	Deep SC injection	60, 90 or 120 mg every 4–8 wk	50%–60%	Gastrointestinal disturbances (abdominal pain, diarrhea, and nausea), cholelithiasis
Octreotide long-acting repeatable	SRL (first-generation)	Intramuscular injection	10, 20 or 30 mg every 4 wk[b]	50%–60%	Gastrointestinal disturbances (abdominal pain, diarrhea, and nausea), cholelithiasis
Oral octreotide capsules	SRL (first-generation)	Oral	20–40 mg twice a day	58%–91%[a]	Gastrointestinal disturbances (abdominal pain, diarrhea, and nausea), cholelithiasis
Pasireotide long acting release	SRL (second-generation)	Intramuscular injection	20, 40, or 60 mg every 4 wk	58%	Gastrointestinal disturbances (abdominal pain, diarrhea, and nausea), cholelithiasis, hyperglycemia
Cabergoline	Dopamine agonist	Oral	0.5 mg/day 3–7 days/week	20%	Nausea, dizziness, hypotension, impulse control disorders
Pegvisomant	GH receptor antagonist	SC injection	10–30 mg/day	70%	Injection site reactions, elevated transaminases

[a] In patients previously controlled with injectable fg-SRL.
[b] 40 mg approved in some countries.

OCT-LAR is intramuscularly administered by a health care professional, initiating usually at 20 mg every 4 weeks, which can be increased up to 40 mg if biochemical control is not achieved; moreover, this dose can be decreased to 10 mg in cases of intolerance or if IGF-I levels are observed in the lower half of the normal range. LAN-ATG is initiated at 90 mg every 4 weeks and is administered via deep subcutaneous (SC) injection (which can be administered by a health care professional, by a caregiver or via self-administration), with dose adjustments occurring from 60 mg to 120 mg per month. Longer dosing intervals of 120 mg every 6 or 8 weeks can be considered if the patient is adequately controlled.[12] Moreover, efficacy assessments should be performed by measuring the levels of insulin-like growth factor type I (IGF-I) after 3 doses in the week prior to the next injection.[13] Once the level of IGF-I is normalized, biochemical assessments should be performed every 6 to 12 months.[13]

Previous disease control criteria included both GH and IGF-I levels (random GH levels <1.0 mcg/L and normal age-matched IGF-I levels). Using these criteria, biochemical remission is achieved in approximately 30% to 40% of patients.[14] In the recent consensus on the criteria for acromegaly diagnosis and remission, the criteria are currently solely based on the levels of IGF-I.[13] Patients are considered to be controlled if they exhibit normal age-adjusted IGF-I levels.[13] By adopting this criterion, control rates have been demonstrated to be increased to 50% to 60%.[14,15] A partial response can be considered when there is an IGF-I level decrease greater than or equal to 50% without normalization; otherwise, patients are considered to be resistant.[16] A partial response was observed in 16.2% to 23.6% of patients, whereas resistance was observed in 27.9% to 30.6% of patients.[15] Importantly, although biochemical assessment is the primary criterion of remission, signs and symptoms of acromegaly should also be considered.[13] Additionally, IGF-I levels should be maintained in the upper half of the normal range to avoid GH deficiency.[13]

Another effect observed during treatment with fg-SRL is tumor reduction.[17] A large meta-analysis including 41 studies and 1172 patients revealed that 53% of the patients (95% CI: 45.0%–61.0%) demonstrated tumor reduction following treatment with OCT (either as an adjuvant or primary treatment).[18] The mean tumor reduction was observed to be 37.4% (95% CI: 22.4%–52.4%).[18] Treatment with LAN (adjuvant or primary) was also associated with tumor reduction in 32.8% of patients.[19] This reduction seems to be more important in primary treatment than in adjuvant treatment.[17] In patients treated with OCT-LAR as first-line therapy, tumor reduction occurred in 82.1% of patients, with a median percentage decrease of 62 $\pm$ 31% being observed.[20] Among patients treated with LAN-ATG as first-line therapy, 76.9% of the patients exhibited tumor shrinkage, with a median reduction of 48·4 $\pm$ 27·6% being observed.[21] In contrast, tumor growth was observed to occur only in a minority of patients treated with fg-SRL (2.2% of patients), particularly in young patients with large tumors.[22] Routine imaging is not recommended for patients who have achieved biochemical control of the disease unless disease progression is observed or different management strategies are considered.[13]

These medications are generally well tolerated and are rarely discontinued due to adverse effects (AE). The most common AE are gastrointestinal effects, including nausea, vomiting, diarrhea, and abdominal distension or pain, which are observed in approximately 50% of patients. However, these AE are usually self-limited and tend to resolve after few injections.[8] Additionally, asymptomatic cholelithiasis occurs in 15% of cases.[8] In general, the effect on glucose metabolism is neutral.[23]

Although fg-SRL treatment improves signs and symptoms of acromegaly, some patients may continue to experience symptoms that impact their quality of life (QoL), even with adequate biochemical control.[24–26] The total or partial irreversibility of

some complications (such as arthropathy or sleep apnea) is likely the most important contributing factor to this finding. However, injection site reactions or the recrudescence of symptoms in the days preceding the next injection may also contribute to this phenomenon.[27]

Life-long treatment with fg-SRLs is usually needed; however, a small number of studies have evaluated treatment withdrawal.[28–30] One study evaluated this phenomenon in patients who were considered to be optimally controlled (safe GH levels and IGF-I levels in the lower normal range) and who received low to median doses of fg-SRL (OCT-LAR at 10 or 20 mg every 28 days, LAN-ATG at 60 mg every 28 days or LAN-ATG at 120 mg every 42 days).[28] Among 29 patients for whom treatment was withdrawn, 79.3% of the patients experienced disease relapse after a median of 6 months following drug discontinuation.[28] Drug discontinuation may be considered in carefully selected patients who are highly sensitive to fg-SRL with well-controlled disease and IGF-I levels in the lower half of the normal range; however, long-term remission is not maintained in most patients.[28,29]

In patients who are controlled with injectable fg-SRL, the oral formulation of octreotide (oral octreotide capsules [OOC]) may be considered, thereby potentially improving QoL in patients who experience injection site reactions. The starting dose for OOC is 20 mg twice daily taken 1 hour before or 2 hours after meals, with dose adjustments performed every 2 to 4 weeks based on the IGF-I levels and symptoms. OOC can be initiated at any time after the last fg-SRL injection and before the expected date of administration of the next dose.[31] In a phase 3 trial, patients with IGF-I levels less than 1.0 x upper limit of normal (ULN) who were receiving fg-SRL treatments were randomized to receive either OOC or placebo. After 36 weeks, 58% of the patients in the OOC group demonstrated normal IGF-I levels, whereas 19% of the patients in the placebo group exhibited normal IGF-I levels (P=.008).[32] Additionally, the safety profile for OCC has been observed to be similar to that of injectable fg-SRL.[32–34] If a complete response is not achieved, adherence to meal timing recommendations should be assessed.[31] Moreover, coadministration of medications that alter gastric pH, such as proton pump inhibitors, may affect absorption and require higher OOC doses.[31]

Second-Generation Somatostatin Receptor Ligand: Pasireotide Long-Acting Release

Pasireotide long-acting release (PAS-LAR) is a second-generation SRL that exhibits a broader pattern of interaction with SST, whereby it binds to SST5 with the highest affinity, followed by SST2, SST3, and SST1. It is intramuscularly administered by a health care professional every 4 weeks starting at a dose of 40 mg, with the possibility of increasing the dose to 60 mg or decreasing to 20 mg based on patient response and tolerability.[35] In the first phase 3 trial investigating this drug, PAS-LAR was compared with OCT-LAR in medical treatment-naïve patients.[36] In this study, biochemical control (defined as a GH level <2.5 ng/mL and normal age-adjusted IGF-I level) was achieved in 31.3% of patients treated with PAS-LAR and 19.2% of those treated with OCT-LAR (P=.007). Normal IGF-I levels were observed in 38.6% and 23.6% of patients treated with PAS-LAR and OCT-LAR, respectively (P=.002). Additionally, a significant reduction in tumor volume (≥20%) was achieved in 80.8% and 77.4% of patients treated with PAS-LAR and OCT-LAR, respectively.[36] In the PAOLA study, which included patients not controlled with fg-SRL, 15% to 20% of the patients achieved a mean GH level less than 2.5 ng/mL and normal IGF-I levels after 6 months of treatment.[37] IGF-I normalization was observed in 25% and 26% of patients treated with 40 and 60 mg PAS-LAR, respectively. Moreover, a tumor volume reduction

greater than 25% was observed in 10.8% of patients receiving 60 mg PAS-LAR and in 18.5% of those receiving 40 mg.[37] In an extension study, biochemical control (GH levels <1.0 ng/mL and normal IGF-I levels) was achieved in 37.0% of patients after a follow-up of 5.8 years.[38]

In a long-term study performed in a real-world setting, normal IGF-I levels were achieved in 54% of 50 patients who were treated for up to 10 years.[39] Among these patients, 44 (88%) were resistant or partially responsive to fg-SRL. A tumor volume reduction of greater than 25% was observed in 62% of patients with evaluable imaging data. Additionally, acromegaly symptoms improved after treatment, especially in patients who were biochemically controlled. Similarly, QoL improved in patients that were biochemically controlled.[39]

Recently, the results of a meta-analysis of real-world studies (including 12 studies and 409 patients who were not controlled with fg-SRL) were demonstrated.[40] Normal IGF-I levels were observed in 57.9% (95% CI: 48.4%–66.8%) of the patients. Furthermore, clinically relevant tumor shrinkage was achieved in 33.3% (95% CI: 19.7%–50.4%) of the patients.[40]

Most AE that are experienced by patients treated with PAS-LAR are similar to those observed with fg-SRL, except for a higher frequency and severity of hyperglycemia and potential occurrence of QT interval prolongation.[36,37] Pasireotide should be used with caution in at-risk patients, especially those patients using drugs that are known to prolong the QT interval. In these patients, electrocardiograms should be performed before drug initiation and at regular intervals.

Pasireotide-induced hyperglycemia occurs because pasireotide decreases insulin secretion while exerting a less pronounced effect on glucagon secretion, whereas fg-SRL inhibit both insulin and glucagon secretion in a similar manner.[41] Pasireotide also inhibits the incretin response but has no effect on insulin sensitivity.[41] In a head-to-head study, hyperglycemia-related AE were reported in 57.3% of patients treated with PAS-LAR and 21.7% of those treated with OCT-LAR.[36] In the PAOLA study, these events were reported in 67% of patients treated with 40 mg PAS-LAR, 61% of those treated with 60 mg PAS-LAR and 30% of patients in the active control group (fg-SRL).[37] Hyperglycemia usually occurs early after PAS-LAR initiation (typically during the first 3 months).[42] Although hyperglycemia is frequently observed in patients treated with PAS-LAR, it is manageable with antidiabetic medication and reversible upon drug discontinuation.[39] The main risk factors for glucose increase include preexisting elevated glucose levels and/or HbA1c, in combination with advanced age, hypertension, dyslipidemia, and increased body mass index.[42]

Monitoring for hyperglycemia is mandatory for patients treated with PAS-LAR.[43] Due to the fact that most hyperglycemic events occur at early points in time during treatment, more intensive self-monitoring of blood glucose is indicated during the first 3 months of treatment, particularly in patients exhibiting greater risks of glucose impairment.[43] Glucose and HbA1c levels should be routinely monitored every 3 months.[43] Moreover, all patients should be advised on lifestyle modifications and the risk of hyperglycemia. For patients with diabetes, patients with prediabetes, or patients at risk for developing diabetes, metformin should be initiated if not already in use, and a glucagon-like peptide-1 receptor agonist (GLP1-RA) or a dipeptidyl peptidase-4 inhibitor may be considered.[43] Given the physiopathology of pasireotide-related hyperglycemia, GLP1-RA appears to be the most appropriate treatment.[44]

PAS-LAR may induce cystic degeneration of somatotropinomas, thus suggesting an antitumor effect of the drug.[45] Interestingly, dose reduction has been described after long-term treatment with PAS-LAR, which could be related to this antitumor

effect.[45–49] In fact, among 27 patients for whom conditions were controlled with PAS-LAR, it was possible to reduce the doses in 20 patients.[46] The dose reduction was associated with a decrease in glucose and HbA1c levels. Therefore, in patients controlled with PAS-LAR, dose reduction should be considered, particularly in those who develop hyperglycemia.[46]

Biomarkers of the Response to Somatostatin Receptor Ligands

Several biomarkers of the response to SRL (particularly to fg-SRL) are available.[8] These biomarkers include demographic, clinical, biochemical, molecular, histopathological, and imaging factors that have been associated with responses to treatment. Male sex and younger ages are associated with a worse response to fg-SRL.[50] Moreover, higher GH and IGF-I levels before the initiation of therapy are associated with a worse response to fg-SRL and PAS-LAR.[51]

As expected, the expression of SST in somatotropinomas represents one of the most important biomarkers. It has been extensively demonstrated that low SST2 expression is strongly associated with a poor response to fg-SRL.[52–56] Additionally, SST5 expression seems to be associated with the response to PAS-LAR in patients that are not controlled with fg-SRL (either resistant or partially responsive patients).[57]

Another important biomarker is the aryl hydrocarbon receptor-interacting protein (AIP). This protein seems to be involved in the SST2 signaling pathway, and patients with pathogenic variants in the *AIP* gene, as well as patients harboring tumors with low AIP protein expression, demonstrate worst response to fg-SRL.[58,59] Conversely, AIP expression does not appear to influence the response to PAS-LAR.[57] Data regarding OOC are still lacking.

Other important tumor characteristics are as follows: (1) cytokeratin granulation pattern, with sparsely granulated tumors exhibiting a worst responses to fg-SRL and better response to PAS-LAR; (2) E-cadherin expression, with low expression associated with a poor response to fg-SRL; and (3) signal intensity in the T2-weighted MRI sequence, with hyperintense tumors being less responsive to fg-SRL (but not to PAS-LAR).[51,60]

Artificial intelligence has been used to improve both the identification and application of these biomarkers.[61,62] A large multicenter Brazilian study including 153 patients developed a machine learning prediction model that is able to predict the response to fg-SRL with high accuracy (86.3%).[61]

Recently, a prospective study was performed, in which a trial-and-error approach was compared with a personalized approach based on various biomarkers, including short acute octreotide test results, T2 signal intensity and invasiveness on MRI, and E-cadherin expression.[63] In this study, patients treated with the personalized approach were 2.53 times more likely to achieve normal IGF-I levels [hazard ratio: 2.53 (95% CI: 1.30–4.80)]. They also achieved normal IGF-I levels sooner than patients treated with the trial-and-error approach [182 (92–365) days versus 305 (137–365) days, P=.06].[63]

DOPAMINE AGONISTS: CABERGOLINE

Cabergoline (CAB) is the only drug in the DA class that is used to treat acromegaly, even though its use is off-label.[6] It acts by binding to dopamine receptor type 2 (DR2), which is expressed in somatotropinomas.[64] It is an oral drug that is usually administered at an initial dose of 0.5 mg 3 days per week, with possible adjustments being performed up to 7 days per week.[6,65] To improve patient tolerance, CAB should be initiated at one capsule per week, with a gradual increase.

The published literature on the use of CAB in patients with acromegaly is much more scarce than that concerning other drugs, and there are no prospective controlled trials evaluating this drug.[65] Additionally, no studies have compared the effects of CAB with those of other drugs used to treat acromegaly. Nevertheless, CAB monotherapy appears to be less effective in achieving biochemical control, with success rates of approximately 20% to 30% being observed.[66–68] In the largest single-center study available in the literature, our group demonstrated disease control (random GH levels <1.0 mcg/L and normal age-matched IGF-I levels) in 6 out of 28 patients (21%).[68] One patient exhibited escape from treatment 16 months after disease control, thus resulting in long-term disease control in 18% of patients with respect to GH and IGF-I levels; moreover, 32% of the patients achieved normal IGF-I levels. Importantly, this was a retrospective study with selection bias, as we only initiated CAB monotherapy for patients with mild disease (IGF-I levels up to 1.5–2.0 × ULN), as these patients benefit more from the treatment. Thus, CAB is recommended for patients not cured by surgery who demonstrate these levels of IGF-I.[6] In addition to lower pretreatment IGF-I levels, the coexpression of prolactin (PRL), hyperprolactinemia, and lower pretreatment GH levels are predictors of a better response to CAB monotherapy.[66,68] Furthermore, tumor reduction was reported in 35% of patients in a previous meta-analysis.[66]

CAB can also be used in combination with fg-SRL in patients who are partially responsive to these drugs. In a meta-analysis of previous studies, the addition of CAB elicited IGF-I normalization in 52% of patients. However, in some of these studies, patients were preselected based on their previous responses to DA treatment.[66] In more recent studies, a lower rate of disease control with the combination of CAB and fg-SRL has been reported.[68–70] Our group reported IGF-I normalization in 52% of 62 patients during short-term follow-up; however, treatment escape occurred in 3 patients, thereby resulting in long-term disease control in 46% of patients when considering only IGF-I levels and in 23% of patients when considering both normal age-matched IGF-I levels and random GH levels less than 1.0 ng/mL.[68]

Similar to monotherapy, the main predictor of the response to combination therapy is pretreatment IGF-I levels, with a greater chance of disease control being observed with IGF-I levels less than 2.0 x ULN before treatment.[66] Unlike monotherapy, in combination therapy, the presence of hyperprolactinemia or the coexpression of PRL does not predict a better response to treatment.[66,68]

Cabergoline exhibits a good safety profile, with the most frequent AE being nausea, dizziness, orthostatic hypotension, and constipation, which can occur in up to 10% of patients.[66] Cardiac valvular fibrotic disease has been reported in patients with Parkinson's disease receiving higher doses of the drug (up to 3.0 mg/day). However, subsequent studies evaluating the doses used for the treatment of pituitary adenomas (mostly in hyperprolactinemia, in which lower doses are generally used) have not demonstrated clinically significant valvular disease.[71–75] Nevertheless, echocardiographic monitoring is recommended for patients receiving doses greater than 2.0 mg/week.[6] More recently, impulse control disorders have also been described as possible AE of CAB; however, the frequency of these disorders is currently unknown due to the scarcity of studies.[76–78] Nevertheless, attention should be given to the possible occurrence of this side effect.

GROWTH HORMONE RECEPTOR ANTAGONIST: PEGVISOMANT

Pegvisomant (PEG) is the only available drug for the treatment of acromegaly among GHR antagonists.[6] This drug is a genetically engineered analog of GH with 2 modifications that confer its activity and effects as a GHR antagonist.[79] The first

modification involves a single amino acid substitution at binding site 2 of GH to GHR (G120K), which confers the antagonist effect of the molecule.[80] The second modification consists of 8 substitutions at binding site 1, which provides a competitive binding advantage over wild-type GH.[79] The addition of several polyethylene glycol molecules prolongs its serum half-life from 30 minutes to more than 100 hours.[80] This drug is usually administered SC once daily at doses ranging from 10 to 30 mg/day. However, studies evaluating once-weekly administration have demonstrated similar efficacy.[81–83]

The first clinical trial involving this drug was a 12-week, randomized, double-blind study with 3 different doses of PEG (10, 15, and 20 mg/day) and placebo.[84] A total of 112 patients were included, and disease control (normal age-matched IGF-I levels) was achieved in 89% of patients in the 20 mg group, with no serious AE (except for injection site reactions in 5% of patients and elevation of transaminase levels in 1 patient) being observed. A second study included 152 patients who were treated with PEG for up to 18 months, with a mean dose of 19.6 mg/day being utilized.[81] In patients treated for 12 months or more (n = 90), disease control was achieved in 97% of the patients. Injection site reactions occurred in 11% of the patients, and 2 patients exhibited elevated liver enzyme levels requiring cessation of the treatment.

In the largest real-world study (ACROSTUDY), the normalization of IGF-I levels was observed in 75.4% of 2221 patients treated with PEG monotherapy after a 10-year follow-up.[85] The safety profile was similar to that of the initial clinical trials, with injection site reactions reported in 3.2% of the patients and increased transaminase levels above 3 x ULN being observed in 3.2% of the patients, thereby leading to drug discontinuation in 1.7% of the patients. When considering the possibility of an increase in transaminase levels, regular monitoring is recommended after the initiation of treatment, with monthly assessments being performed during the first 6 months of use.[86] It is important to emphasize that no serious hepatitis or liver failure has been reported to date.

An increase in tumor size was a concern when the drug started to be used, as it does not act on the tumor and reduces the negative feedback of IGF-I on the tumor, thus, an increase could occur via a mechanism similar to corticotroph tumor progression after adrenalectomy.[79,87] However, this phenomenon was not observed in clinical practice, with tumor enlargement being observed in only 3.0% of patients, which is a percentage that is similarly observed compared with other acromegaly treatments.[85] Routine imaging examinations are not recommended; however, an individualized approach may be appropriate, particularly if changes in biochemical responses are observed.[13]

Some studies have evaluated predictors of the response to PEG monotherapy, such as pretreatment GH and IGF-I levels, sex, age, body mass index, and the presence of the d3GH isoform of the GHR.[88–94] Among these factors, the most consistently demonstrated predictor is pretreatment IGF-I levels, with higher levels predicting a worse chance of disease control.[95]

In addition to monotherapy, PEG has been used in combination with drugs that act on tumors in previous studies.[96–99] The majority of the studies that evaluated PEG in association with injectable fg-SRL demonstrated an efficacy greater than 90%. This drug combination offers the advantages of a mean dose reduction of PEG of 50% and of the effect of fg-SRL on the tumor, with tumor reduction being observed in 20% of the patients in the combination treatment.[96,97] The safety profile of the combination therapy is similar to that of PEG monotherapy, with the exception of an elevation of transaminases (3 x ULN), which is observed in approximately 10% of patients; however, this elevation is generally transitory and does not lead to drug interruption.[97]

The combination of PEG and CAB was previously described in 19 patients who were initially treated with CAB without disease control.[99] Upon the addition of 10 mg/day PEG, normal IGF-I levels were achieved in 68% of patients. When CAB was discontinued, only 26% of the patients maintained normal IGF-I levels with PEG monotherapy. In another small study including 9 patients not controlled under PEG monotherapy (median dose of 20.7 $\pm$ 6.8 mg/day), the addition of CAB resulted in normalization of IGF-I levels in 28% of patients and a mean reduction in IGF-I levels of $-18 \pm 27\%$.[100] Moreover, the safety profile was similar to that of PEG monotherapy in both studies.[99,100]

The combination of PEG and PAS-LAR was assessed in the PAPE study, which included 61 patients who demonstrated IGF-I levels less than 1.2 x ULN due to treatment with fg-SRL and PEG. In these patients, fg-SRL were switched to PAS, and the PEG dose was reduced by 50%. After 12 weeks, those patients who maintained IGF-I levels less than 1.2 x ULN were switched to PAS-LAR monotherapy (24.6% of the patients), and those with IGF-I levels greater than 1.2 x ULN were maintained with combination therapy. After 24 weeks, the PEG dose could be reduced by 66%.[101] The safety profile was similar to that of combination of PEG and fg-SRL, with the exception of the occurrence of hyperglycemia (with the frequency of diabetes mellitus increasing from 32% at baseline to 69% at 24 weeks).

ACROMEGALY AND PREGNANCY

During pregnancy, placental GH begins to appear in the circulation in the second trimester, which results in elevated IGF-I levels and the inhibition of pituitary GH secretion; this phenomenon does not occur in patients with acromegaly during pregnancy.[102] Therefore, during the late stage of pregnancy, both placental and pituitary GH levels are elevated in the circulation.[103] Nevertheless, IGF-I levels may decrease in patients with acromegaly even without any treatment, due to the fact that high estrogen levels observed during pregnancy decrease liver sensitivity to GH.[104,105] Some comorbidities associated with acromegaly (such as diabetes mellitus or hypertension) can be exacerbated during pregnancy; however, this scenario does not commonly occur.[102] Furthermore, tumor enlargement rarely occurs.[103,106]

In a previous meta-analysis including 19 studies with a total of 273 pregnancies in 211 women, 62% of the patients were controlled, whereas an increase in tumor size was observed in 9% of the patients.[102] The worsening of diabetes or development of gestational diabetes occurred in 9% of the patients, whereas worsening of hypertension or preeclampsia/eclampsia occurred in 6% of patients.[102] Furthermore, premature births, miscarriages, small sizes for gestational age and fetal anomalies were less commonly observed compared to the same changes described in population studies of women without acromegaly.[102]

During pregnancy, medical treatment should be withdrawn.[107] Thorough follow-ups, along with a visual field evaluation being performed every trimester, are warranted in patients with macroadenomas. Patients who are at high risks of tumor enlargement can be maintained on medical therapy with DA or fg-SRL. In case of tumor growth, transsphenoidal surgery during the second trimester is indicated. If the pregnancy is uneventful, breastfeeding is allowed until medical therapy is initiated.[107]

If a woman with acromegaly is planning to conceive, long-acting SRL and pegvisomant should be discontinued 2 months before attempting to conceive, with short-acting octreotide being used if necessary.[108] Cabergoline can be used until pregnancy is confirmed.[109] Moreover, the use of gonadotropin-releasing hormone for ovary stimulation may be associated with a risk of apoplexy, which should be considered before in vitro fertilization.[109]

FUTURE PERSPECTIVES

Two drugs are currently in the late stages of development and are expected to be available for use in the near future: CAM2029 (octreotide subcutaneous depot) and paltusotine.

CAM2029 is a new octreotide formulation that allows for monthly SC administration.[110] This drug comes in a ready-to-use pen (without the need for reconstitution or refrigeration), and it can be self-administered. A phase 3 study (ACROINNOVA 1) included patients who were controlled with stable doses of injectable fg-SRL for at least 3 months and who were randomized to either CAM2029 or placebo treatment groups.[111] After 24 weeks of treatment, more patients in the active treatment arm (72.2%) exhibited normal IGF-I levels compared with the patients in the placebo arm (37.5%). Additionally, there was an improvement observed in the acromegaly index of severity and QoL. Patients who chose to self-administer the medication reported improved "satisfaction with the current way of taking the medication".[111]

Patients who terminated participation in the ACROINNOVA 1 trial were permitted to migrate to the ACROINNOVA 2 trial.[112] In this study, all of the patients who were previously allocated to the placebo group and 89.3% of the patients who were previously allocated to the CAM2029 group exhibited normal IGF-I levels at 50 to 52 weeks. Patients receiving stable doses of injectable fg-SRL and with IGF-I levels $\leq$2 x ULN could also be included in ACROINNOVA 2.[113] Among these patients, 14.8% of the patients exhibited normal IGF-I levels at the time of entry into the study, which increased to 33% at the time of analysis. The most frequently observed AE included injection site reactions (erythema and swelling) and headaches. In general, CAM2029 demonstrated a safety profile similar to that of the standard fg-SRL treatment.[112,113]

Paltusotine is a selective nonpeptide SST2 agonist that is orally administered.[114] This drug was evaluated in 2 phase 3 clinical trials known as PATHFNDR 1 and PATHFNDR 2.[114] PATHFNDR 1 included patients with acromegaly who were treated with injectable fg-SRL with normal IGF-I levels.[115] After 36 weeks, 83% of the patients in the paltusotine arm and 3.6% of the patients in the placebo arm exhibited normal IGF-I levels. Moreover, acromegaly symptoms were stable in the paltusotine arm but were worsened in the placebo arm.[115]

PATHFNDR 2 included 2 patient profiles: patients who were not medically treated (medically naïve or medical therapy terminated at least 4 months prior to screening) with IGF-I levels $\geq$1.3 $\times$ ULN at screening and patients who were biochemically controlled (normal IGF-I levels) while receiving injectable fg-SRLs who agreed to a washout period.[116] Significantly more patients in the paltusotine arm (55.6%) exhibited normal IGF-I levels after 24 weeks compared with patients in the placebo group (5.3%) (OR = 42.81; 95% CI: 8.44–455.8, P<.0001). Furthermore, acromegaly symptoms were improved in the active treatment arm and worsened in the placebo arm (P=.004).[116]

The main AE reported in the paltusotine group included arthralgia, headache, diarrhea, and abdominal pain, which were mostly mild to moderate in intensity. More patients in the placebo group experienced AE that were determined by the investigators to be related to acromegaly compared with patients in the paltusotine group (85.7% vs 30.0%). Gastrointestinal events were usually resolved without the need for drug discontinuation.[115]

Other drugs exhibiting different mechanisms of action or different forms of administration are also being investigated.[117] A prolonged release formulation of lanreotide (LAN-PRF), which can be subcutaneously administered every 12 weeks, is currently being evaluated.[118] In a phase 2 study, to evaluate the maximum tolerated dose and the pharmacokinetics of this drug, no dose-limiting toxicities were observed.[118]

The mean half-life varied from 54.2 to 63.1 days (depending on the utilized dose). Overall, IGF-I levels remained stable during the study period. Moreover, the most frequently reported AE included diarrhea, cholelithiasis, fatigue and headache.[118]

An octreotide formulation known as Debio 4126 has also been developed, which can be intramuscularly administered every 12 weeks.[117] In a phase 1B study, IGF-I levels remained relatively stable, with 9 (75%) out of 12 patients who initially exhibited normal IGF-I levels remaining controlled.[119] The safety profile was similar to that of other injectable fg-SRL.[119]

Another GHR antagonist known as ALXN2420 (formerly known as AZP-3813) is also being investigated.[117] This drug was evaluated in a phase 1 study involving healthy individuals.[120] In this study, a dose-dependent decrease in IGF-I levels was observed after a single injection, with a more prolonged reduction observed at higher doses, which persisted for up to 72 hours. In the group treated for 14 days, the decrease in IGF-I levels was more pronounced than that in patients treated with a single dose.[120]

A pasireotide subcutaneous depot formulation known as CAM4071 has also been developed.[117] This drug has been evaluated in a phase 1 trial with healthy individuals.[121] Dose-dependent IGF-I suppression was observed, which was demonstrated to be 58.9 $\pm$ 12.7% at the higher dose (80 mg). A 60 mg dose of PAS-LAR exerted a suppression effect comparable to that of 40 mg CAM4071. Additionally, the half-life of CAM4071 was observed to vary from 1050 hours (44 days) at the 5 mg dose to 311 hours (13 days) at the 80 mg dose, thereby indicating that CAM4071 may be administered once a month.[121] The most frequently observed AE included gastrointestinal symptoms (43.6%) and injection site reactions (43.6%).[121]

Finally, drugs with different mechanisms of action are currently being evaluated: antisense oligonucleotides targeting the GH receptor (Cimderlisen, ATL1103), a SST3-and SST5-selective SRL (HTL0030310), and a monoclonal antibody against GH (Hu-13H02m).[122–125]

SUMMARY

In conclusion, surgery remains the first-line therapy for acromegaly. However, even in specialized centers, approximately half of patients require adjuvant medical therapy. There are currently several drug options available for the medical management of acromegaly, with good safety profiles and different efficacies being observed. The primary option for medical treatment includes the use of fg-SRL, which may control approximately 50% of patients. Other options include PAS-LAR, CAB, and PEG, which can be used either as monotherapy or as combination treatments. Despite achieving biochemical control, some patients continue to experience impaired QoL. Novel drugs are currently under development that target different mechanisms of action (which can improve control rates) or offer different and less bothersome administration routes or dosing regimens, thereby potentially improving QoL.

CLINICS CARE POINTS

- Surgery is the primary treatment for most patients with acromegaly; however, approximately half of patients do not achieve a cure, even in reference centers, thus necessitating the use of medical treatment for a significant proportion of patients.
- Biochemical control assessments should be based on IGF-I measurements; moreover, in adequately controlled patients, these assessments can be performed at extended intervals (6–12 months).

- First-generation SRL, including octreotide and lanreotide, are the first-line medical treatment for the majority of patients, and they can achieve IGF-I normalization in approximately 50% of patients.
- Biomarkers (particularly SST2 expression) can help to predict a better response to fg-SRL.
- Cabergoline monotherapy is mainly indicated for patients experiencing mild disease after surgery (IGF-I levels as high as 1.5–2.0 x ULN). In combination with fg-SRL, CAB is recommended for patients exhibiting a partial response to these drugs and mild disease, with control rates of 32% demonstrated in monotherapy and 46% demonstrated in combination treatments.
- Pasireotide, which is a second-generation SRL, is indicated for patients who are partially controlled or resistant to fg-SRLs; moreover, it achieves disease control in approximately 50% of these patients. Due to the risk of hyperglycemia, close monitoring and timely intervention are needed.
- PEG can be used in monotherapy or in combination with SRL and is indicated for patients in whom disease is not controlled with fg-SRL and for whom tumor size is not a concern.
- Two new drugs with more convenient administration routes are in late-stage development: CAM2029 (octreotide SC depot) and paltusotine. These drugs are expected to improve adherence and quality of life.

DISCLOSURE

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