Journal of the Endocrine Society, 2022, **6**, 1–6
https://doi.org/10.1210/jendso/bvac114
Advance access publication 04 August 2022
Mini-review

Preoperative Medical Treatment for Patients With Acromegaly: Yes or No?

Frederique Albarel,[1,2,3,*] Thomas Cuny,[1,2,3,*] Thomas Graillon,[1,2,4] Henry Dufour,[1,2,4] Thierry Brue,[1,2,3,†] and Frederic Castinetti[1,2,3,†]

[1]Aix Marseille Univ, INSERM, MMG, Marseille, France
[2]French Reference Center for rare Pituitary Diseases, Department of Endocrinology, La Conception Hospital, Marseille, France
[3]Department of Endocrinology, Assistance Publique Hopitaux de Marseille, Marseille, France; and
[4]Department of Neurosurgery, Assistance Publique Hopitaux de Marseille, Marseille, France

*Joint first authors.
†Joint senior authors.
Correspondence: Frederic Castinetti, MD, PhD, Department of Endocrinology, La Conception Hospital, 147 Boulevard Baille, 13385 Marseille Cedex 05, France. Email: Frederic.castinetti@ap-hm.fr.

Abstract

Transsphenoidal surgery is the first-line treatment for acromegaly. However, several factors can modify surgical remission rates, such as the initial hormone levels, the size and invasiveness of the tumor, and the degree of experience of the surgeon. Physicians treating patients with acromegaly should thus consider how to improve surgical remission rates. As stated in recent guidelines, the major point is to consider that any patient with acromegaly should be referred to an expert neurosurgeon to maximize the chances of surgical sure. The benefits of presurgical medical treatment, mainly using somatostatin receptor ligands (SRLs), given 3 to 6 months before surgery, remain controversial. By normalizing growth hormone and insulin-like growth factor 1 levels, SRLs may improve the overall condition of the patient, thus decreasing anesthetic and surgical complications. By decreasing the tumor size and modifying the consistency of the tumor, SRLs might also make surgical excision easier. This is however theoretical as published data are contradictory on both points, and only limited data support the use of a systematical presurgical medical treatment. The aim of this review is to analyze the potential benefits and pitfalls of using presurgical medical treatment in acromegaly in view of the contradictory literature data. We also attempt to determine the profile of patients who might most benefit from this presurgical medical treatment approach as an individualized therapeutic management of acromegaly.

Key Words: acromegaly, somatostatin analogs, surgery, cabergoline, anesthesia, growth-hormone, IGF-1

Abbreviations: GH, growth hormone; IGF, insulin-like growth factor; PSMT, presurgical medical treatment; SRL, somatostatin receptor ligand; SST, somatostatin receptor subtype

Acromegaly is a rare disease usually caused by a growth hormone (GH)–secreting pituitary tumor. It leads to several comorbidities, including left ventricular hypertrophy, hypertension, diabetes, and sleep apnea. When left untreated (or undiagnosed), acromegaly leads to an increased mortality rate [1]. Over the last 20 years, therapeutic management of acromegaly has changed, with a reduction in the use of radiation techniques and increased use of a combination of medical treatments, as is shown by the French Acromegaly Registry [2]. However, transsphenoidal surgery still represents the first-line treatment for acromegaly. It is a low-risk procedure when carried out by experienced surgeons [3, 4], with an efficacy that varies from 20% to 80%, depending on the size of the tumor, its invasiveness, the initial hormone levels (frequently correlated with tumor size), and the degree of experience of the surgeon. Surgery is currently the only treatment (apart from radiotherapy, which can lead to remission after a prolonged period) that can result in cure for the patient [5-7]. The aims of physicians treating patients with acromegaly should thus be to maximize the chances of obtaining a surgically induced remission and to avoid prolonged and costly medical treatment, and this first requires an expert neurosurgeon in an expert center. Since the original description of the use of somatostatin receptor ligands (SRLs) before transsphenoidal surgery [8] more than 20 years ago, the benefits of presurgical medical treatment (PSMT) in improving the rate of surgical cure have remained controversial. This subject has been explored by several original papers and has remained a matter of discussion in all the guidelines published over the last 15 years. The aim of this review will thus be to determine the potential benefits and pitfalls of using PSMT in patients with acromegaly.

First-generation SRLs represent the first-line medical treatment of choice in acromegaly [5, 6]. They are recommended as first-line therapy in patients who are not suitable for surgery or who are unlikely to be cured by surgery owing to the tumor invading the cavernous sinus [5]. Moreover, preoperative SRLs are considered in cases of severe acromegaly-related comorbidities that increase the risk of anesthesia [9]. Their antisecretory and antitumor efficacy likely explains why they are considered as almost the sole option for PSMT. After a brief overview of their antisecretory and antitumor efficacy,

Received: 5 June 2022. **Editorial Decision:** 11 July 2022. **Corrected and Typeset:** 11 August 2022

and their tolerance in acromegaly, we will focus on their potential benefits for perioperative and postoperative outcomes of acromegaly. Cabergoline, a D2 receptor agonist, will also be briefly discussed as another potential PSMT.

Somatostatin Analogs: Overview of Efficacy and Tolerance in Acromegaly

While native somatostatin binds to the 5 different somatostatin receptor subtypes (SST1-5), SRLs exhibit a strong binding affinity for SST2, and, to a lesser extent, for SST5 and SST3 [10]. SST2 and SST5 are the most abundantly expressed subtypes of somatostatin receptor in GH-secreting pituitary tumors [11]. At the cellular level, binding of SRLs to SST2 results in inhibition of adenylyl cyclase and decreased cyclic adenosine monophosphate synthesis. This then leads to a reduction in the intracellular calcium concentration and inhibition of both GH secretion and somatotroph proliferation [12].

In acromegaly, the precise antisecretory efficacy of SRLs for the control of both GH and insulin-like growth factor (IGF)-1 secretion is still debated, as large differences in terms of hormonal efficacy have been reported between different case series, probably due to different patient profiles (naïve vs already treated), or to different remission criteria [13]. In a meta-analysis that included the largest population of acromegalic patients thus far (n = 4464), an overall biochemical control rate of 56% for GH and 55% for IGF-1 for SRLs was reported [14]. In a prospective study assessing the efficacy of lanreotide (120 mg every 28 days) as first-line therapy for patients with acromegaly (n = 90), a total of 35% and 43.5% of patients had both GH ≤2.5 µg/L and normalized IGF-1 levels after 24 and 48 weeks of treatment, respectively. However, when considering stringent criteria of cure (GH ≤ 1 µg/L and normalized IGF-1), biochemical control decreased to 23.4% and 30.6% of patients at 24 and 48 weeks, respectively [15]. Interestingly, the biochemical response to lanreotide occurred in the short term (12 weeks) and remained sustained over the long term. In cases of partial biochemical response to SRLs, increasing the dose and/or frequency is a potential option that may further improve biochemical control rates [16, 17].

The efficacy of SRLs is influenced by both clinical and paraclinical parameters: for example, young male patients with high GH levels at diagnosis are usually less responsive to SRL [18]. Patients with T2 hypointense tumors on magnetic resonance imaging generally show a better response to SRLs than patients with iso- or hyperintense tumors [19, 20]. The explanation for this is that T2 hypointensity is a condition known to be associated with a densely granulated pattern of the tumor and a higher density of SST2 receptors on the cell membranes of somatotroph tumor cells [21].

Besides having antisecretory effects, SRLs also show antiproliferative actions. In vivo evidence for the antiproliferative effects of SRLs has been shown by a significantly lower Ki-67 labeling index in somatotroph tumor tissue obtained from patients who were pretreated with octreotide compared with those patients who were not [22-25]. This effect could be observed in the first 3 months following the introduction of octreotide [24]. In the clinical setting, a significant antitumoral effect (≥20% from baseline tumor volume) was achieved in 63% of patients with acromegaly treated with first-line subcutaneous lanreotide for a year [15]. More than half (54%) of patients benefited from this antitumoral effect in the first 12 weeks following the introduction of lanreotide. A meta-analysis based on 41 studies, including a total of 1685 patients, found a roughly similar proportion of patients (66%) who had a significant reduction in tumor volume with octreotide long-acting release. The mean percentage reduction in tumor size in these studies was reported to be 50.6% (95% CI 42.7-58.4%) [26]. The expected antitumoral effect observed with SRLs also depended on the sequence of treatment in the patient. Primary therapy with either lanreotide or octreotide was accompanied by a higher degree of tumor shrinkage compared with secondary therapy (ie, after radiotherapy or primary surgery) [27].

Side effects of SRLs consisted mostly of gastrointestinal symptoms (nausea, flatulence, cramps, and diarrhea), which occurred in around 30% of patients [28]; however, these were mostly transient and mild to moderate. Gallbladder abnormalities (sediment, sludge, microlithiasis, and gallstones) occurred in up to 35% of acromegalic patients treated with SRLs, usually after more than 3 to 6 months. However, they are seldom symptomatic and rarely prompt acute surgery. At the metabolic level, SRLs can impair insulin secretion [29, 30], and hyperglycemia, usually mild in severity, is observed in about 15% of acromegalic patients treated with first-generation SRLs [31]. Other side effects may be encountered, such as pain at the injection site [32]. Lastly, disturbances in liver function, hepatitis, hair loss, and anaphylaxis have been more rarely reported.

The use of a PSMT with SRLs would be expected to have 2 potential types of benefits. Firstly, reducing the tumor volume and modifying its consistency could facilitate complete removal accompanied by lower perioperative surgical complications. This is however controversial as only 50% of tumors will respond with a 20% shrinkage of the tumor after 3 to 6 months of PSMT, a difference for which a change in surgical outcome is uncertain. Secondly, lower presurgical GH levels could improve the surgical condition of the patient and decrease the risks of anesthesia, but this would concern patients with severe comorbidities at the time of surgery. While it could be assumed that the complete removal of a smaller lesion should be easier and less complicated for the neurosurgeon, a direct correlation between tumor shrinkage and complete resection has not yet been shown [33].

SRLs as PSMT in Acromegaly: Perioperative Outcome

The antitumor efficacy of SRLs was discussed in the first section of this review. A more controversial aspect is the way in which SRLs can modify the tumor consistency, and how this might impact on tumor removal [8, 34-38]. Indeed, while previously published observations have shown that PSMT made the adenoma softer [8, 35], 2 other studies have reported that PSMT may also increase the firmness of the tumor in some patients after 3 to 6 months of SRL treatment [38, 39]. For example, Li et al reported a difference in a prospective study on 49 patients with acromegaly (including 24 pretreated for 3 months with lanreotide). In their study they reported 6/23 vs 0/22 had a firm consistency in the pretreated vs nonpretreated tumors, respectively [39]. While the authors suggested that firmer tumors might make it easier to distinguish between the adenoma and surrounding tissue, they also showed that

this modified consistency did not increase the rate of surgical complications. Finally, in a recent retrospective study of 40 patients with GH-secreting macroadenomas (including 17 who had a PSMT), Araujo-Castro et al found no significant difference in tumor consistency, regardless of their PSMT exposure. Remission rates and surgical complications were similar between soft or firm tumors (45.5% vs 48.3% remission, and 18.2% vs 20.7% complications, in soft vs firm tumors, respectively) [40].

Difficult intubation can occur in up to 20% of patients with acromegaly [41-43]. In selected patients, PSMT can allow a disinfiltration of the tissues, reducing tongue volume and laryngeal edema and improving obstructive sleep apnea [44, 45], which could facilitate anesthesia. Several studies have compared surgical complications in patients with or without PSMT. In a retrospective study on 286 patients (including 143 who had PSMT), no significant difference was observed in terms of surgical morbidity, difficult intubation requiring a stay in an intensive care unit, or hypoxemia during anesthesia [34]. Mao et al found no significant difference in 98 patients, including 49 with PSMT: in the subgroup of 12 patients presenting with perioperative morbidity, 14.3% had received a PSMT, while 10.2% had not [46]. A similar result was reported by Carlsen et al in 62 patients (n = 32 with 6 months of octreotide PSMT) [38], and by Li et al in 24 patients with PSMT vs 25 without [39]. Interestingly, in a prospective randomized study on 39 patients, Shen et al reported a lower risk of cerebrospinal fluid leak in patients who had PSMT (2/19 patients with PSMT vs 9/20 without, $P = .031$) [47]. In our experience of 110 operated patients with acromegaly of whom 64 received PSMT, we observed no significant difference between patients with or without PSMT in terms of severe complications, especially concerning cerebrospinal fluid leaks (in only 1 patient who had not had PSMT). Unexpectedly, we noticed significantly more transient postoperative hyponatremia in patients with PSMT (13 with PSMT vs 1 without) [48]. It is important to note that anesthesia and surgical complications were not the main aim of all these studies; most of the time, these points were analyzed retrospectively based on medical records, which might have biased the exhaustivity of the data.

Patients with acromegaly may also have higher morbidity with anesthesia due to increased hemodynamic changes and higher blood glucose levels. Obtaining normal GH secretion with PSMT may improve glycemic control, hypertension, and left ventricular hypertrophy prior to surgery [8, 33, 49, 50]. According to some authors, this could also lead to a decreased hospital stay after surgery, but this point remains controversial. For example, Colao et al reported the cardiac and metabolic evolution in 59 patients with acromegaly before surgery (22 with octreotide PSMT for 3-6 months before surgery) and showed that electrocardiogram abnormalities (sinus arrhythmia and ventricular or supraventricular tachycardia, and 1 anomaly in the repolarization phase) disappeared in 7/11 patients with PSMT, while metabolic parameters (blood glucose, triglyceride, and cholesterol) and systolic and diastolic blood pressure were all lower in PSMT patients at the time of surgery. The average duration of hospitalization after surgery was significantly longer in patients without PSMT (8.6 vs 5.6 days). They hypothesized that this could be due to a lower frequency of cardiac arrhythmia, respiratory impairment, and respiratory infections after surgery in patients with PSMT [51]. Conversely, 2 studies reported no significant difference in postoperative hospital stay between patients with or without PSMT (3.7 vs 3.6 days, and 4.5 vs 4.8 days in PSMT vs no PSMT patients) [38, 46]. These data can be difficult to analyze as in some centers the duration of hospital stay is "standardized" to allow postsurgical hormonal evaluation, making it impossible to analyze a potential impact on hospital stay [48].

SRLs as a PSMT in Acromegaly: Postoperative Outcome

Several groups have proposed PSMT using SRLs to optimize the postoperative outcome. In a meta-analysis, a significant benefit of PSMT was found when only prospective randomized controlled trials were included, 3 such trials having been performed at that time [52]. However, previously published studies reported conflicting results on the effect of PSMT on overall outcomes, in terms of achieving and sustaining normalization of IGF-1 normalization, with some studies reporting improved remission rates [8, 38, 39, 46, 47, 51] while others did not [34, 36, 37, 53, 54].

In our experience [48], based on a cohort of 110 consecutive newly diagnosed patients with a median follow-up period of 39.4 months, remission rates were significantly different in patients who had PSMT vs patients without PSMT (61.1% vs 36.6%, respectively, at long-term evaluation), while both groups were comparable for the main confounding factors, with the exception of higher IGF-1 at diagnosis in PSMT patients, a factor that would likely have been in favor of the non-PSMT group. Our study differed from previously reported studies in both the longer time of follow-up and the use of stringent remission criteria, as has been recommended by several guidelines [6, 7, 9]. Another potential confounding factor between studies may be the duration of SRL pretreatment that varied widely from one study to another, from a few weeks [37, 39, 46, 47] to several months [35, 52]. In our study [48], the duration of PSMT (range 3-18 months, median 5 months) was similar in pretreated patients in remission and those not in remission.

A review by Jacob and Bevan, based on 4 prospective randomized controlled trials on operated somatotroph macroadenomas, showed improvement in the short-term remission rate [55]. With a "moderate quality" grading level, the most recently published consensus paper stated that "randomized studies suggest improvement in postoperative remission after pretreatment with SRL for 3–6 months" [6]. However, data concerning long-term remission after PSMT appeared less optimistic, suggesting that despite improvement in short-term remission rates, this favorable outcome was not consistently found to persist in the long term [49]. For example, in a 2019 single-center retrospective study based on 135 patients followed for at least 2 years after surgery (mean follow-up time of 50.9 ± 25.7 months), the early remission of patients with PSMT (61.5%) was significantly higher than in patients without PSMT (31.2%), but no significant difference was maintained between groups in terms of late remission [56]. A meta-analysis by Zhang et al based on 3 long-term follow-up studies (2 prospective and 1 retrospective), including patients on subcutaneous SRL treatment, showed a benefit of PSMT for short-term but not long-term remission [57]. A prospective study that used stringent remission criteria did not show any significant advantage of PSMT in

terms of remission at the 1- and 5-year evaluations, although the authors did not exclude a clinically relevant response in macroadenomas. Indeed, although it did not reach statistical significance, twice as many patients were in remission in the pretreated group [54]. In a systematic review and meta-analysis of comparative studies published in 2019, 5 randomized controlled trials and 7 nonrandomized comparative studies were included [58]. Among a majority of macroadenomas, only the short-term cure rate, but not the long-term cure rate, was significantly improved by PSMT. These findings confirmed meta-analyses performed earlier based on a more limited number of studies [49, 57, 59]. Accordingly, a consensus conference concluded in 2020, with the evidence judged "low quality," that PSMT results "in many instances were not sustained during long-term follow-up" [6].

Noncomparative studies may also shed some light on the effect of PSMT on remission rates, as they do for other potential predictive factors of remission. However, 3 recent large studies, based on 659, 546, and 266 surgical cases of acromegaly, reported contradictory results for PSMT as a predictive factor of remission [60-62]: only 1 reported a predictive role of PSMT with an odds ratio of 2.32 (95% CI 1.46-3.70; $P < .001$), among several well-known predictors of biochemical remission (lower preoperative growth hormone level, smaller size, or noninvasive character of the adenoma). The experience of the neuroendocrine unit of the Massachusetts General Hospital (Boston, USA) showed no benefit of PSMT in 266 patients with follow-up >5 years. Interestingly, PSMT was administered in 17.4% of patients, "usually with the intention of reducing perioperative risk in those with severe comorbidities." This modality was significantly more common among patients managed after 2006 than the earlier cohort.

As has been proposed elsewhere, it may thus be concluded from the current evidence that "select patients may be candidates for preoperative medical therapy" [63]. If this is correct, what are the predictive factors of a beneficial effect of PSMT on remission rates? In a meta-analysis, PSMT was found to be especially beneficial in centers with lower postsurgery remission rates (<50%) [52]. However, precise prognostic factors of response to pretreatment, such as characteristics of the tumor, thresholds of tumor size, or levels of GH, to allow for individualized care for each patient are currently lacking. In terms of long-term remission, in our study no patient with an adenoma size greater than 18 mm, or a mean GH exceeding 35 ng/mL at diagnosis was cured by surgery alone (ie, without PSMT), while in the PSMT group, 8 patients with adenomas greater than 18 mm in diameter and 9 patients with mean GH exceeding 35 ng/mL at diagnosis were cured after surgery. Moreover, radiological invasiveness was also associated with a significant benefit of PSMT [48], a factor that had been previously reported in other studies for short-term remission [39, 47], and more recently by Lv et al for long-term remission [64]. This latter point obviously does not apply to massively invasive lesions that are very unlikely to be cured after surgery alone, even after PSMT [65].

Cabergoline as a Presurgical Medical Treatment

Cabergoline is a long-acting dopamine agonist that is more effective and better tolerated than bromocriptine in patients with hyperprolactinemia. Cabergoline binds the dopamine receptor subtype 2, which is expressed in somatotroph adenomas [66]. In acromegaly, cabergoline has a limited role in the treatment strategy. When given as monotherapy, cabergoline can result in biochemical control in 35% of acromegalic patients; however, most of these patients received previous therapies (surgery, SRLs, radiotherapy) before being treated with cabergoline. A recent meta-analysis [67] showed that among the 150 patients with acromegaly treated with cabergoline in monotherapy in 10 different clinical trials, cabergoline was used before any other treatment in only 29/136 (21%) patients. In a study which included 15 acromegalic patients, 5 were naive to any previous therapies and treated with cabergoline (mean dose 3.8 ± 2.3 mg/week) [68]. Mean GH and IGF-1 decreased from 5.5 ± 4.4 ng/mL to 1.35 ± 1.27 ng/mL and 538.4 ± 194.2 to 319.4 ± 260 ng/mL, respectively, suggesting that cabergoline could be considered in a case-by-case approach as part of PSMT in acromegaly. However, the evidence remains very poor given the low number of patients who have been evaluated in this setting.

Conclusions

Published data are contradictory concerning the potential benefits of PSMT given 3 to 6 months before surgery. The theoretical benefits might be visible in terms of surgical and anesthetic morbidity. In patients with severe comorbidities leading to uncontrolled metabolic parameters, or difficult intubation (those with severe pharyngeal thickness and sleep apnea or high output heart failure), PSMT might improve the general condition of the patient before surgery. The benefits might also be visible in terms of postsurgical remission. However, data on remission rates are very controversial, and difficult to interpret due to different patient profiles, different lengths of follow-up, or different durations of medical treatment: while short-term remission seems to be improved with PSMT, long-term remission rates do not support PSMT as a systematic approach. Decreasing the size of the tumor does not mean decreasing its invasiveness, and this likely explains why despite some antitumor efficacy, SRLs given as PSMT did not systematically modify the long-term outcome of operated patients. In our experience, with an expert neurosurgeon in favor of PSMT, surgical remission rates were significantly increased by PSMT. This led us to rethink our therapeutic strategy with a selection of patients who, we think, might gain some benefits from PSMT. In this setting, it is likely that patients with severe acromegaly-induced comorbidities, as well as those with macroadenomas and no confirmed cavernous sinus invasion, might be the best candidates for PSMT. However, with the persistent lack of conclusive data on the benefits of PSMT, we cannot recommend its systematic use; as mentioned in recent guidelines, the expertise of the neurosurgeons remains the major point to consider before surgery, and this should lead clinicians to send their patients to expert centers. If this is not possible, or in cases of delayed surgery, PSMT with SRLs should be proposed while waiting for surgery by an expert neurosurgeon to be possible. As a large long-term prospective study might be difficult to perform, we think that an individualized approach with an expert team is the optimal way in which to determine whether a patient should be pretreated with SRLs; importantly, this should not lead to surgery being declined in patients with effective SRL treatment, as surgery should remain the first-line treatment for all patients with acromegaly.

Funding

No funding.

Disclosures

The authors received consultancy fees and research grants from Ipsen Pharma, Recordati rare diseases, and Pfizer Pharmaceuticals.

Data Availability

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

References

1. Colao A, Grasso LFS, Giustina A, *et al*. Acromegaly. *Nat Rev Dis Primers*. 2019;5(1):20.
2. Maione L, Brue T, Beckers A, *et al*. Changes in the management and comorbidities of acromegaly over three decades: the French Acromegaly Registry. *Eur J Endocrinol*. 2017;176(5):645-655.
3. Swearingen B, Barker FG 2nd, Katznelson L, Biller BM, Grinspoon S, Klibanski A, *et al*. Long-term mortality after transsphenoidal surgery and adjunctive therapy for acromegaly. *J Clin Endocrinol Metab*. 1998;83(10):3419-26
4. Goyal-Honavar A, Sarkar S, Asha HS, *et al*. Impact of experience on outcomes after endoscopic transsphenoidal surgery for acromegaly. *World Neurosurg*. 2021;151:e1007-e1015.
5. Fleseriu M, Biller BMK, Freda PU, *et al*. A Pituitary Society update to acromegaly management guidelines. *Pituitary*. 2021;24(1):1-13.
6. Giustina A, Barkhoudarian G, Beckers A, *et al*. Multidisciplinary management of acromegaly: a consensus. *Rev Endocr Metab Disord*. 2020;21(4):667-678.
7. Melmed S, Bronstein MD, Chanson P, *et al*. A consensus statement on acromegaly therapeutic outcomes. *Nat Rev Endocrinol*. 2018;14(9):552-561.
8. Stevenaert A, Beckers A. Presurgical octreotide: treatment in acromegaly. *Metabolism*. 1996;45(8 Suppl 1):72-74.
9. Katznelson L, Laws ER Jr., Melmed S, *et al*. Acromegaly: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab*. 2014;99(11):3933-3951.
10. Oberg K, Lamberts SW. Somatostatin analogues in acromegaly and gastroenteropancreatic neuroendocrine tumours: past, present and future. *Endocr Relat Cancer*. 2016;23(12):R551-R566.
11. Casar-Borota O, Heck A, Schulz S, *et al*. 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. *J Clin Endocrinol Metab*. 2013;98(11):E1730-E1739.
12. Peverelli E, Treppiedi D, Mangili F, Catalano R, Spada A, Mantovani G. Drug resistance in pituitary tumours: from cell membrane to intracellular signalling. *Nat Rev Endocrinol*. 2021;17(9):560-571.
13. Gadelha MR, Wildemberg LE, Kasuki L. The future of somatostatin receptor ligands in acromegaly. *J Clin Endocrinol Metab*. 2022;107(2):297-308.
14. Carmichael JD, Bonert VS, Nuno M, Ly D, Melmed S. Acromegaly clinical trial methodology impact on reported biochemical efficacy rates of somatostatin receptor ligand treatments: a meta-analysis. *J Clin Endocrinol Metab*. 2014;99(5):1825-1833.
15. Caron PJ, Bevan JS, Petersenn S, *et al*. Tumor shrinkage with lanreotide autogel 120 mg as primary therapy in acromegaly: results of a prospective multicenter clinical trial. *J Clin Endocrinol Metab*. 2014;99(4):1282-1290.
16. Giustina A, Mazziotti G, Cannavo S, *et al*. High-dose and high-frequency lanreotide autogel in acromegaly: a randomized, multicenter study. *J Clin Endocrinol Metab*. 2017;102(7):2454-2464.
17. Giustina A, Bonadonna S, Bugari G, *et al*. High-dose intramuscular octreotide in patients with acromegaly inadequately controlled on conventional somatostatin analogue therapy: a randomised controlled trial. *Eur J Endocrinol*. 2009;161(2):331-338.
18. Gadelha MR, Kasuki L, Korbonits M. Novel pathway for somatostatin analogs in patients with acromegaly. *Trends Endocrinol Metab*. 2013;24(5):238-246.
19. Potorac I, Petrossians P, Daly AF, *et al*. T2-weighted MRI signal predicts hormone and tumor responses to somatostatin analogs in acromegaly. *Endocr Relat Cancer*. 2016;23(11):871-881.
20. 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(2):333-343.
21. Swanson AA, Erickson D, Donegan DM, *et al*. Clinical, biological, radiological, and pathological comparison of sparsely and densely granulated somatotroph adenomas: a single center experience from a cohort of 131 patients with acromegaly. *Pituitary*. 2021;24(2):192-206.
22. Thapar K, Kovacs KT, Stefaneanu L, *et al*. Antiproliferative effect of the somatostatin analogue octreotide on growth hormone-producing pituitary tumors: results of a multicenter randomized trial. *Mayo Clin Proc*. 1997;72(10):893-900.
23. Losa M, Ciccarelli E, Mortini P, *et al*. Effects of octreotide treatment on the proliferation and apoptotic index of GH-secreting pituitary adenomas. *J Clin Endocrinol Metab*. 2001;86(11):5194-5200.
24. Cap J, Cerman J, Nemecek S, Marekova M, Hana V, Frysak Z. The influence of treatment with somatostatin analogues on morphology, proliferative and apoptotic activity in GH-secreting pituitary adenomas. *J Clin Neurosci*. 2003;10(4):444-448.
25. Selek A, Cetinarslan B, Canturk Z, *et al*. The effect of somatostatin analogues on Ki-67 levels in GH-secreting adenomas. *Growth Horm IGF Res*. 2019;45:1-5.
26. Giustina A, Mazziotti G, Torri V, Spinello M, Floriani I, Melmed S. Meta-analysis on the effects of octreotide on tumor mass in acromegaly. *PLoS One*. 2012;7(5):e36411.
27. Freda PU, Katznelson L, van der Lely AJ, Reyes CM, Zhao S, Rabinowitz D. Long-acting somatostatin analog therapy of acromegaly: a meta-analysis. *J Clin Endocrinol Metab*. 2005;90(8):4465-4473.
28. Newman CB, Melmed S, Snyder PJ, *et al*. Safety and efficacy of long-term octreotide therapy of acromegaly: results of a multicenter trial in 103 patients—a clinical research center study. *J Clin Endocrinol Metab*. 1995;80(9):2768-2775.
29. Steffin B, Gutt B, Bidlingmaier M, Dieterle C, Oltmann F, Schopohl J. Effects of the long-acting somatostatin analogue lanreotide autogel on glucose tolerance and insulin resistance in acromegaly. *Eur J Endocrinol*. 2006;155(1):73-78.
30. Verges B. Effects of anti-somatostatin agents on glucose metabolism. *Diabetes Metab*. 2017;43(5):411-415.
31. Baldelli R, Battista C, Leonetti F, *et al*. Glucose homeostasis in acromegaly: effects of long-acting somatostatin analogues treatment. *Clin Endocrinol (Oxf)*. 2003;59(4):492-499.
32. Hage M, Marin C, Gaillard S, Raffin-Sanson ML, Cazabat L. Local myofascitis: an unusual adverse reaction to lanreotide autogel injection. *Ann Endocrinol (Paris)*. 2019;80(4):260-261.
33. Ben-Shlomo A, Melmed S. Clinical review 154: The role of pharmacotherapy in perioperative management of patients with acromegaly. *J Clin Endocrinol Metab*. 2003;88(3):963-968.
34. Losa M, Mortini P, Urbaz L, Ribotto P, Castrignano T, Giovanelli M. Presurgical treatment with somatostatin analogs in patients with acromegaly: effects on the remission and complication rates. *J Neurosurg*. 2006;104(6):899-906.
35. Abe T, Ludecke DK. Effects of preoperative octreotide treatment on different subtypes of 90 GH-secreting pituitary adenomas and outcome in one surgical centre. *Eur J Endocrinol*. 2001;145(2):137-145.
36. Lucas T, Astorga R, Catala M; Spanish Multicentre Lanreotide Study Group on Acromegaly. Preoperative lanreotide treatment for GH-secreting pituitary adenomas: effect on tumour volume and

predictive factors of significant tumour shrinkage. *Clin Endocrinol (Oxf)*. 2003;58(4):471-481.
37. Kristof RA, Stoffel-Wagner B, Klingmuller D, Schramm J. Does octreotide treatment improve the surgical results of macroadenomas in acromegaly? A randomized study. *Acta Neurochir (Wien)*. 1999;141(4):399-405.
38. Carlsen SM, Lund-Johansen M, Schreiner T, *et al*. Preoperative octreotide treatment in newly diagnosed acromegalic patients with macroadenomas increases cure short-term postoperative rates: a prospective, randomized trial. *J Clin Endocrinol Metab*. 2008;93(8):2984-2990.
39. Li ZQ, Quan Z, Tian HL, Cheng M. Preoperative lanreotide treatment improves outcome in patients with acromegaly resulting from invasive pituitary macroadenoma. *J Int Med Res*. 2012;40(2):517-524.
40. Araujo-Castro M, Pian H, Ruz-Caracuel I, Acitores Cancela A, Pascual-Corrales E, Rodriguez Berrocal V. Presurgical somatostatin receptor ligand treatment does not affect tumor consistency in GH-secreting pituitary macroadenomas. *Endocr Connect*. 2021;10(1):102-109.
41. Seidman PA, Kofke WA, Policare R, Young M. Anaesthetic complications of acromegaly. *Br J Anaesth*. 2000;84(2):179-182.
42. Schmitt H, Buchfelder M, Radespiel-Troger M, Fahlbusch R. Difficult intubation in acromegalic patients: incidence and predictability. *Anesthesiology*. 2000;93(1):110-114.
43. Nemergut EC, Dumont AS, Barry UT, Laws ER. Perioperative management of patients undergoing transsphenoidal pituitary surgery. *Anesth Analg*. 2005;101(4):1170-1181.
44. Annamalai AK, Webb A, Kandasamy N, *et al*. A comprehensive study of clinical, biochemical, radiological, vascular, cardiac, and sleep parameters in an unselected cohort of patients with acromegaly undergoing presurgical somatostatin receptor ligand therapy. *J Clin Endocrinol Metab*. 2013;98(3):1040-1050.
45. Garcia-Alvarez M, Climent V. Sleep apnea and cardiovascular complications of the acromegaly. Response to the medical treatment. *Minerva Endocrinol*. 2019;44(2):159-168.
46. Mao ZG, Zhu YH, Tang HL, *et al*. Preoperative lanreotide treatment in acromegalic patients with macroadenomas increases short-term postoperative cure rates: a prospective, randomised trial. *Eur J Endocrinol*. 2010;162(4):661-666.
47. Shen M, Shou X, Wang Y, *et al*. Effect of presurgical long-acting octreotide treatment in acromegaly patients with invasive pituitary macroadenomas: a prospective randomized study. *Endocr J*. 2010;57(12):1035-1044.
48. Albarel F, Castinetti F, Morange I, *et al*. Pre-surgical medical treatment, a major prognostic factor for long-term remission in acromegaly. *Pituitary*. 2018;21(6):615-623.
49. Fleseriu M, Hoffman AR, Katznelson L, Neuroendocrine A, Pituitary Scientific C. American Association of Clinical Endocrinologists and American College of Endocrinology disease state clinical review: management of acromegaly patients: what is the role of pre-operative medical therapy? *Endocr Pract*. 2015;21(6):668-673.
50. Colao A, Pivonello R, Galderisi M, *et al*. Impact of treating acromegaly first with surgery or somatostatin analogs on cardiomyopathy. *J Clin Endocrinol Metab*. 2008;93(7):2639-2646.
51. Colao A, Ferone D, Cappabianca P, *et al*. Effect of octreotide pretreatment on surgical outcome in acromegaly. *J Clin Endocrinol Metab*. 1997;82(10):3308-3314.
52. Pita-Gutierrez F, Pertega-Diaz S, Pita-Fernandez S, *et al*. Place of preoperative treatment of acromegaly with somatostatin analog on surgical outcome: a systematic review and meta-analysis. *PLoS One*. 2013;8(4):e61523.
53. Plockinger U, Quabbe HJ. Presurgical octreotide treatment in acromegaly: no improvement of final growth hormone (GH) concentration and pituitary function. A long-term case-control study. *Acta Neurochir (Wien)*. 2005;147(5):485-93; discussion 493.
54. Fougner SL, Bollerslev J, Svartberg J, Oksnes M, Cooper J, Carlsen SM. Preoperative octreotide treatment of acromegaly: long-term results of a randomised controlled trial. *Eur J Endocrinol*. 2014;171(2):229-235.
55. Jacob JJ, Bevan JS. Should all patients with acromegaly receive somatostatin analogue therapy before surgery and, if so, for how long? *Clin Endocrinol (Oxf)*. 2014;81(6):812-817.
56. Polat Korkmaz O, Gurcan M, Nuhoglu Kantarci FE, *et al*. The effects of pre-operative somatostatin analogue therapy on treatment cost and remission in acromegaly. *Pituitary*. 2019;22(4):387-396.
57. Zhang L, Wu X, Yan Y, Qian J, Lu Y, Luo C. Preoperative somatostatin analogs treatment in acromegalic patients with macroadenomas. A meta-analysis. *Brain Dev*. 2015;37(2):181-190.
58. Yang C, Li G, Jiang S, Bao X, Wang R. Preoperative somatostatin analogues in patients with newly-diagnosed acromegaly: a systematic review and meta-analysis of comparative studies. *Sci Rep*. 2019;9(1):14070.
59. Nunes VS, Correa JM, Puga ME, Silva EM, Boguszewski CL. Preoperative somatostatin analogues versus direct transsphenoidal surgery for newly-diagnosed acromegaly patients: a systematic review and meta-analysis using the GRADE system. *Pituitary*. 2015;18(4):500-508.
60. Freda PU. How effective are current therapies for acromegaly? *Growth Horm IGF Res*. 2003;13(Suppl A):S144-S151.
61. Yao S, Chen WL, Tavakol S, *et al*. Predictors of postoperative biochemical remission in acromegaly. *J Neurooncol*. 2021;151(2):313-324.
62. Ghajar A, Jones PS, Guarda FJ, *et al*. Biochemical control in acromegaly with multimodality therapies: outcomes from a pituitary center and changes over time. *J Clin Endocrinol Metab*. 2020;105(3):e532-e543.
63. Ershadinia N, Tritos NA. Diagnosis and treatment of acromegaly: an update. *Mayo Clin Proc*. 2022;97(2):333-346.
64. Lv L, Hu Y, Zhou P, *et al*. Presurgical treatment with somatostatin analogues in growth hormone-secreting pituitary adenomas: a long-term single-center experience. *Clin Neurol Neurosurg*. 2018;167:24-30.
65. Albarel F, Castinetti F, Morange I, *et al*. Outcome of multimodal therapy in operated acromegalic patients, a study in 115 patients. *Clin Endocrinol (Oxf)*. 2013;78(2):263-270.
66. Stefaneanu L, Kovacs K, Horvath E, Buchfelder M, Fahlbusch R, Lancranjan L. Dopamine D2 receptor gene expression in human adenohypophysial adenomas. *Endocrine*. 2001;14(3):329-336.
67. Sandret L, Maison P, Chanson P. Place of cabergoline in acromegaly: a meta-analysis. *J Clin Endocrinol Metab*. 2011;96(5):1327-1335.
68. Moyes VJ, Metcalfe KA, Drake WM. Clinical use of cabergoline as primary and adjunctive treatment for acromegaly. *Eur J Endocrinol*. 2008;159(5):541-545.