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Clinical efficacy and safety results for dose escalation of somatostatin receptor ligands in patients with acromegaly: a literature review

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Abstract Acromegaly is a rare disease with a multifaceted clinical presentation. In 90–95% of patients with acromegaly, the disease is caused by a growth hormone (GH)-secreting pituitary adenoma with elevated GH levels that ultimately induce excessive hepatic secretion of insulin-like growth factor-1 (IGF-1). Somatostatin receptor ligands (SRLs) are considered the standard medical choice for the treatment of acromegaly, and normalization of GH and IGF-1 is attainable with effective therapy. This review aims to summarize the literature relative to SRL dose escalation therapy in patients with acromegaly. A United States National Library of Medicine PubMed search of SRL's was conducted using the following search terms: ((((LAR) OR ATG) OR octreotide) OR lanreotide Autogel) AND acromegaly. Related articles in non peer-reviewed journals were excluded. The rationale and benefits of SRL dose optimization therapy were investigated with emphasis on describing the clinical recognition, treatment, and management of patients with acromegaly. We found that dose escalation could provide additional biochemical control of acromegaly in patients who are inadequately controlled with conventional starting doses of octreotide LAR and lanreotide Autogel®. Furthermore, patients should routinely have their GH and IGF-1 levels closely monitored and their SRL dose increased or decreased thereafter according to individual response.

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Introduction

Acromegaly is a rare disease with a multifaceted clinical presentation. The estimated prevalence of acromegaly worldwide is considered to be around 60 cases per million with approximately three new cases per million annually [1, 2]. However, more recent European data pertinent to the prevalence of clinically significant pituitary adenomas suggests that acromegaly could be more common [3]. In most patients with acromegaly the disease is caused by a growth hormone (GH)-secreting pituitary adenoma with elevated GH levels that ultimately induce excessive hepatic secretion of insulin-like growth factor-1 (IGF-1) [4]. The pathologic effects of GH excess are acral overgrowth (i.e., macrognathia, enlargement of the facial bone structure, and enlarged hands and feet); visceral overgrowth, including macroglossia; and enlarged thyroid, liver, kidney, and heart. Compared with healthy subjects, patients with untreated acromegaly experience increased morbidity and mortality [5], which is primarily due to cardiovascular disease [6]. Despite long-term cure of GH excess, patients are also likely to experience a decrease in quality of life [7]. Control of GH/IGF-1 hypersecretion has been shown to reduce mortality rates to levels similar to those in patients without acromegaly [6, 8]. Somatostatin receptor ligands (SRLs) are considered the medical treatment of choice for acromegaly and normalization of GH and IGF-1 is attainable with effective therapy. However, some patients do not achieve biochemical control with a standard dose of a SRL. Recent treatment guidelines and clinical studies suggest that SRL dose titration can improve control of GH and

IGF-1 in patients that have not achieved a full response to an initial SRL dose [9, 10]. In this review we summarize the literature relative to SRL dose escalation therapy in patients with acromegaly. We also discuss clinical evidence in support of optimal medical therapy that requires individual SRL tailoring, including high-dose treatments in acromegaly patients.

Literature search

A United States National Library of Medicine PubMed search was conducted for the following: ((((LAR) OR ATG) OR octreotide) OR lanreotide Autogel) AND acromegaly, through September 2010. Related articles in non peer-reviewed journals were excluded. The studies selected for review included those that evaluated the initial patient response to SRL treatment followed by an attempt to improve patient response with dose optimization therapy, including either higher dose or higher frequency of doses.

Overall treatment goals

Treatment of acromegaly is complex and most cases require a stepwise, multimodality approach to control disease progression. The treatment goals for patients with acromegaly include: inhibiting GH hypersecretion, normalizing IGF-1 levels, reducing tumor mass, and alleviating the comorbidities [4, 9, 11]. Adverse outcomes have been linked to increases in both GH and IGF-1 levels, therefore stringent biochemical criteria have been applied over time (Fig. 1) [12]. Complete biochemical control is defined as serum GH levels of <1 μg/l if tested using a sensitive immunoassay or ≤2.5 μg/l if measured by radioimmunoassay, GH levels of <0.4 μg/l after oral glucose tolerance test (OGTT), and normalization of serum IGF-1 levels compared to age- and sex-matched controls [9, 10, 12]. The algorithm depicted in Fig. 2 represents the current surgical and pharmacological options for the diagnosis and treatment of acromegaly [9, 10]. Surgery is effective as a first-line treatment option for biochemical control in approximately 80% of patients with microadenoma [13–16]. Surgical treatment has the dual advantage of rapidly improving symptoms caused by mass effect of the tumor and significantly reducing or normalizing GH/IGF-1 concentrations. Cure rates with larger and invasive tumors are much smaller (50–60%) and the initiation of medical therapy is recommended after surgery.

Somatostatin receptor ligands

In the last two decades, the development of highly specific and selective synthetic somatostatin analogs that act as ligands for the somatostatin receptor has led to significant progress in the treatment of acromegaly [17]. The leading consensus guidelines for the treatment of acromegaly maintain that SRLs, have emerged as the primary medical therapy for controlling GH excess [18]. In addition, recent results show that octreotide LAR can be a viable option for the first-line treatment of acromegaly as long-term treatment with octreotide LAR does not significantly differ from surgery [19].

SRLs act at four levels to target abnormal GH secretion: (1) suppression of GH secretion from the pituitary and from GH-secreting adenomas, (2) decrease in binding to hepatocyte GH receptors, (3) inhibition of hepatic IGF-1 synthesis, and (4) control of tumor growth [20]. Two commercially available SRLs; octreotide LAR and lanreotide Autogel (ATG), have unique therapeutic effects based on their different pharmacokinetic properties and

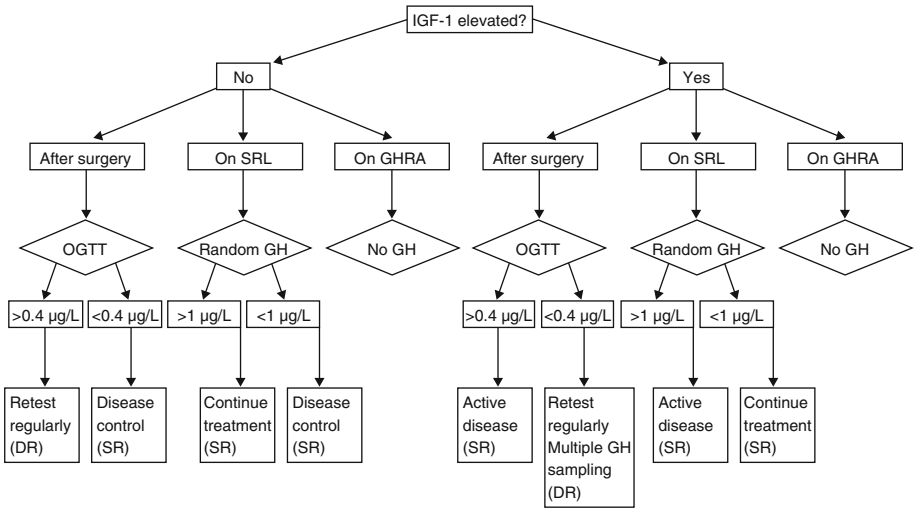

Fig. 1 Interpretation of GH and IGF-1 levels in acromegaly. © 2010, The Endocrine Society, reproduced with permission. Giustina et al. [12]. *GHRA* growth hormone receptor antagonist, *OGTT* oral glucose tolerance test, *DR* discretionary recommendation, *SR* strong recommendation

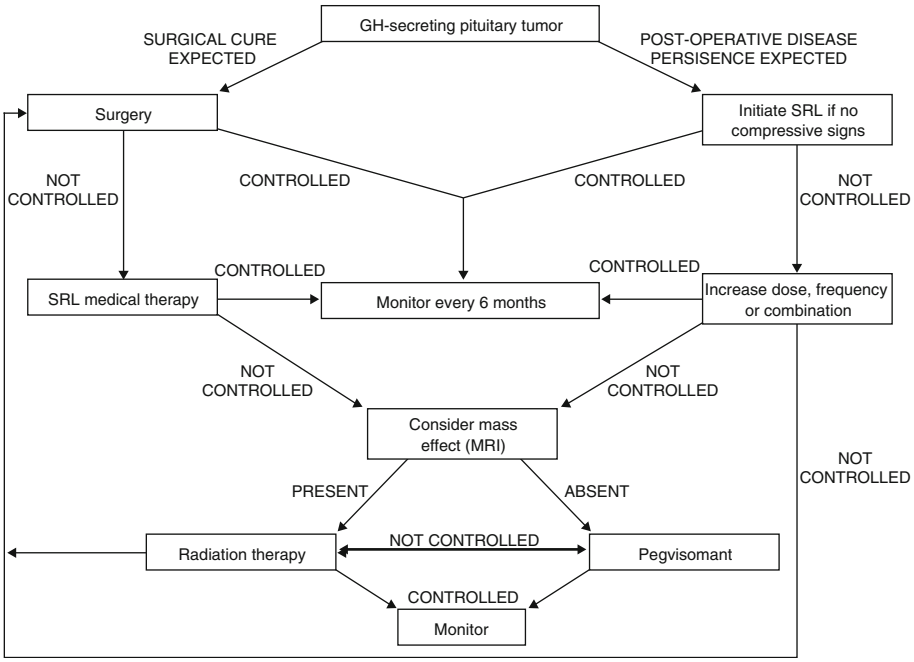

Fig. 2 The management strategy for the treatment of acromegaly. Disease control is defined as attaining the GH and IGF-1 levels outlined in the text. First level, surgery or medical therapy (*SRL*); second level, *SRL* therapy, dose adjustment, and monitor disease progression; third level, MRI; fourth level, radiation or pegvisomant therapy; fifth level, monitor disease progression or return patient to surgery. © 2009, The Endocrine Society, reproduced with permission. Melmed et al. [10]

patterns of receptor affinity. They each bind with varying affinity to the five somatostatin receptors (SSTRs) but both bind preferentially to SSTR2 [21]. Resistance to SRL therapy that is reported in some patients could be explained, in part, by variable tumor expression and/or decreased density of SSTR2 expression [22]. Currently, there are other SRLs in clinical trials: the next generation SRL, pasireotide (SOM230) is in phase 3 development and a chimeric molecule, dopamine-SRL (dopastatin), is in phase 2 development. Pasireotide is a novel multi-ligand SRL with a unique structure, potent in vitro and in vivo inhibitory effects on GH and IGF-1 release, and a high binding affinity to SSTR1, -2, -3, and -5 with up to a 40-fold greater affinity for SSTR5 than octreotide. Based on phase 2 results in patients with acromegaly [23], pasireotide is considered a promising therapeutic candidate with several potential advantages over currently used SRLs in GH-secreting adenomas that are either unresponsive or resistant to current therapy [24].

The use of octreotide LAR for the treatment of patients with acromegaly is supported by more than 20 years of clinical research and experience [18]. The usual starting dose for octreotide LAR is 20 mg with titration down to 10 mg or up to 30, 40 or 60 mg, based on the need to attain biochemical control [25]. An initial study that evaluated the efficacy, tolerability, and pharmacokinetics of octreotide LAR determined that a 10 mg dose was considerably less effective than a 20 or 30 mg dose, and that an interval of 60 days between injections seemed too long. Much better control was achieved by delivering either a 20 or 30 mg dose every 28 or 42 days [26, 27].

A more recent development has been the introduction of lanreotide ATG, a supersaturated aqueous formulation in a prefilled syringe that requires deep subcutaneous administration every 28 days [28]. The usual starting dose of lanreotide ATG is 90 mg every 4 weeks with further titration up to 120 mg or down to 60 mg after 3 months based on the degree of biochemical response [29]. Longer intervals between injections have also been suggested [29, 30].

A large variability in the clinical response to SRL therapy is reported in the published literature. Clinical results of treatment with conventional doses of octreotide LAR (20–30 mg/month) show that complete biochemical control (GH levels $\leq$2.5 μg/l and IGF-1 normalization) is achieved in between 38 and 85% and 33–75% of patients, respectively [31–37]. Lanreotide slow release (SR) at conventional doses reduced plasma GH levels (<5 μg/l) in 54–68% of patients and normalized IGF-1 levels in 35–63% of patients [38, 39].

Additionally, the selection of patients who are expected to benefit from treatment with SRLs [31] and the optimal time to evaluate their response has changed over time. Consequently, Cozzi et al. suggested that clinicians evaluate patients 3–6 months after starting octreotide LAR therapy rather than discontinuing treatment at 3 months since the change in GH and IGF-1 levels after 6 months of treatment can predict the patients' response to treatment [34]. Elevated baseline GH and IGF-1 levels were not found to be accurate predictors of patient response to SRL therapy and thus SRL treatment should be also considered in such patients [34]. Most importantly,

there is an ever-increasing quantity of clinical evidence that supports dose optimization with SRLs [40–42]. Recently updated guidelines state that patients should be continually monitored and, if necessary, recommend that dose optimization of SRL therapy should be performed at 3-month intervals based on the patient response [10, 43]. Collectively, these reports demonstrate that dose escalation, including high-dose treatment, improves the symptoms and comorbidities in patients with acromegaly without significant change to the safety and adverse events observed with conventional doses.

In patients with different treatment histories (mixed populations), the efficacy of octreotide LAR appears to be generally similar to that of lanreotide ATG and slightly better than that of lanreotide SR, according to data from switching or crossover studies [44, 45]. Patients who had previously responded to treatment with subcutaneous octreotide showed the greatest response. A number of studies have been carried out to compare the biochemical efficacy of octreotide LAR and lanreotide SR. However, these studies are almost exclusively open-label, prospective studies with varying inclusion criteria. A meta-analysis of the results from 44 available trials that compared the efficacy of octreotide LAR and lanreotide SR determined that the biochemical efficacy of octreotide LAR is greater than that of lanreotide SR among subjects not selected for prior SRL responsiveness [46]. Other reviews of SRL therapy suggest that lanreotide ATG and octreotide LAR are of equivalent efficacy; however, a robust analysis is not possible given the limited power of the studies reviewed [44, 45]. The efficacy of SRLs should continue to be evaluated in prospective, randomized trials evaluating efficacy with respect to GH control and tumor shrinkage.

Rationale and benefits of SRL dose optimization therapy

In patients with insufficient biochemical response to a specific SRL dose, both dose optimization and/or addition of another therapy have been suggested [36, 44]. Treatment guidelines recommend evaluation of biochemical control and dose titration of the SRL every 3 months if appropriate [43]. Combination therapy has inherent advantages, but it is outside the focus of the present review.

Control of GH and IGF-1 diminishes and reduces mortality to expected levels [8, 47, 48]. In select cases such as large residual tumors with cavernous sinus invasion, elevated baseline GH and IGF-1, multiple co-morbidities, and longer duration of the disease, our approach is to start treatment with octreotide LAR 30 mg or lanreotide ATG 120 mg every 28 days for 3 months. Subsequent dose titration, either up or down, is based on the biochemical results and the patient's clinical response. If the patient's response is inadequate, the octreotide LAR dose is increased to 40 mg/month. This treatment approach is similar to other established endocrinology centers [40]. Presently, our experience at the Northwest Pituitary Center at Oregon Health & Science University with high-dose SRL treatment is limited to octreotide LAR. If the patient does not respond to the higher dose we proceed to combination therapy without discontinuation of SRLs, albeit at lower doses.

A selection of recent clinical reports describing the benefit of dose-optimization therapy with octreotide LAR and lanreotide ATG are summarized in Tables 1 and 2, respectively. In one of the earliest studies, Lancranjan et al. demonstrated that dose escalation with octreotide LAR from 20 to 30 mg/month in 22 patients reduced the mean GH level by 26% at 48 weeks [36]. In a 2-year study of 36

Table 1 Benefits of octreotide LAR dose optimization therapy

Reference	Highest dose (mg/month)	Patients on this dose (%)	Total number of patients (n)	Duration of treatment	Patients with GH ≤2.5 μg/l (%)	Patients with normalized IGF-1 (%)
Lancranjan et al. [36]	30	15	151	12 months	69.8	65.8
Colao et al. [32]	30	33	36	12–24 months	69.4	61.1
	40	19				
Cozzi et al. [34]	30	38	110	4 years	72	75
	40	4				
Colao et al. [51]	30	27	56	24 months	86	84
	40	30				
Colao et al. [19]	30	82 (of safety population)	40 (protocol completers)	50 weeks	27.5 (Patients achieving both GH and IGF-1 control)	
Giustina et al. [56]	60	11	26	24 weeks	27*	36
	30 (every 3 weeks)	15			0	0

* GH <2 μg/l

Table 2 Benefits of lanreotide ATG dose optimization therapy

Reference	Highest dose (mg/month)	Patients on this dose (%)	Total number of patients (n)	Duration of treatment	Patients with GH ≤2.5 μg/l (%)	Patients with normalized IGF-1 (%)
Caron et al. [29]	120 mg	48	130	1 year	68	50
Ronchi et al. [30]	120 mg/8 week	27	6	42 weeks	62	43
	120 mg/6 week	18	4	36 weeks		
	120 mg/4 week	55	12	34 weeks		
Attanasio et al. [58]	180 mg	4	26	1 year	42	54
Chanson et al. [49]	120 mg	73	63	48 weeks	85	43
Melmed et al. [65]	120 mg	65	99	52 weeks	38	54

patients with acromegaly by Colao et al., 43% of patients achieved control of both GH and IGF-1 levels when the starting dose of octreotide LAR (20 mg/month) was increased to 30 mg/month and an additional 20% achieved biochemical control upon an increase to 40 mg/month [32]. Another trial conducted on 110 patients treated for up to 54 months with octreotide LAR reported that dose optimization may provide a significant benefit for patients with acromegaly [34]. Dose titration was based on IGF-1 normalization and increasing the starting dose of octreotide LAR from 20 to 30 mg/month significantly decreased IGF-1. At the end of the study 38% of patients (n = 42) were being treated with octreotide LAR 30 mg/month, 4% were treated with 40 mg/month while 33% continued on the starting dose (20 mg/month).

The efficacy of titrated versus fixed doses of lanreotide ATG has been compared and the same improvement in patient outcome with dose optimization was reported. After 1 year of treatment, the mean plasma GH and IGF-1 concentrations in 130 patients were significantly lower for titrated lanreotide ATG than with fixed doses of lanreotide ATG (Fig. 3) [29]. The efficacy of lanreotide ATG in decreasing GH and IGF-1 has also been confirmed in patients previously treated with octreotide LAR. After a washout period, patients were switched to lanreotide ATG (120 mg) and the time between doses was adjusted based on the GH and IGF-1 response. Based on the need for additional treatment, the frequency was increased in 12/23 patients to every 4 weeks, 4/23 patients remained on the original starting dose every 6 weeks, and 6/23 patients were reduced to treatment every 8 weeks. At the end of the study, the number of patients that achieved GH <2.5 μg/l and normalized IGF-1 was 62 and 43% patients, respectively [30]. In another study, 63 patients with acromegaly were treated with lanreotide ATG (90 mg/4 weeks) with the dose adjusted to achieve normalized, age- and sex-matched, levels of IGF-1. By the end of the study 73% of patients required an increase to 120 mg [49]. A randomized placebo-controlled study in an unselected population of 99

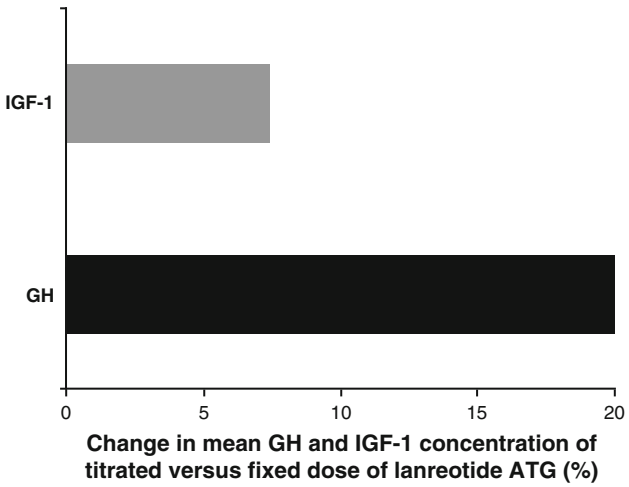

Fig. 3 Percent reduction of GH and IGF-1 concentrations at 12 months in patients with acromegaly treated with titrated versus fixed doses of lanreotide ATG

patients published in 2010 showed that lanreotide ATG was effective in controlling both GH and IGF-1 hypersecretion: 54% of patients had normalized IGF-1 and 38% achieved a combined criterion of GH level ≤2.5 μg/l and normalized IGF-1. Unsurprisingly, at the end of the open-label phase, 65/99 patients were on the highest dose (120 mg every 4 weeks) [50].

Use of SRLs as primary therapy

Of late, much interest has surrounded the use of SRLs in primary therapy or preoperative treatment to improve surgical outcomes, and dose optimization therapy has also proven beneficial in first-line treatment of patients with acromegaly. A 2-year dose-escalation study by Colao et al. using octreotide LAR as the first-line therapy in 56 patients with acromegaly demonstrated that 32/56 (57%) required a

dose increase from the starting dose of 20 mg/month (group A) to either 30 mg/month (group B) or 40 mg/month (group C) to achieve control of GH and IGF-1 levels. At 24 months, control of GH and IGF-1 was achieved in 24/56 (42.9%) patients treated with octreotide LAR 20 mg/month, 15/56 (26.8%) patients receiving 30 mg/month and 6/56 (10.7%) patients who had their octreotide LAR dose increased to 40 mg/month (Fig. 4) [51]. Overall, dose optimization clearly benefited the patients in this study such that 86% of patients achieved GH levels of ≤2.5 μg/l and 84% achieved normalized IGF-1 levels. More importantly, a third of the patients that were not controlled on a lower dose achieved remission after increasing their dose. A different approach was tried in another 12-month, open-label, prospective study [52]. Twenty-six newly diagnosed patients with acromegaly were treated with lanreotide ATG (120 mg/4 weeks). The interval between injections was increased to every 6–8 weeks in patients that achieved biochemical control (GH ≤2.5 μg/l and normalized IGF-1). After 12 months, biochemical control was achieved in 14/26 (54%) patients with nine patients still receiving the lanreotide dose every 4 weeks, while the dosage was delayed to every 6 weeks in eight patients and every 8 weeks in nine patients. This dosing regimen also induced at least 25% tumor shrinkage in 77% of the patients in the study.

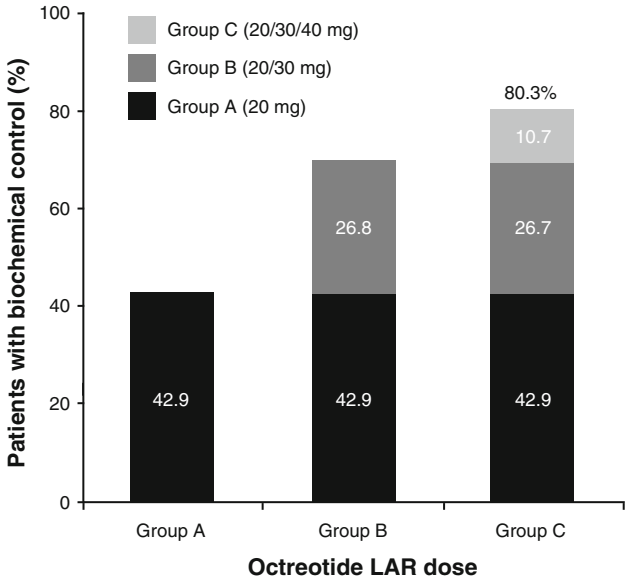

Fig. 4 Increase in the proportion of octreotide LAR patients with control of GH and IGF-1 after dose optimization therapy. *Group A* represents patients that were started and remained on the 20 mg/month dose. *Group B* represents patients whose starting dose was increased to 30 mg/month. *Group C* represents patients whose dose was increased further to 40 mg/month

Tumor volume reduction

There is clear evidence that SRL treatment induces tumor volume reduction in the majority of patients [53]. However, definitions of significant tumor reduction and optimal measurement are still under debate. Unsurprisingly, higher doses of SRLs were found to be more efficacious. Colao et al. in 2007 demonstrated that mean pituitary tumor volume was decreased by 68% after 24 months in patients treated with octreotide LAR at doses of up to 40 mg/month [51]. Furthermore, higher tumor volume reduction was detected at 24 months in patients who had their octreotide LAR dose increased to 40 mg/month (Fig. 5) [51]. These results led to a hypothesis and possible advantage of using initial high doses of octreotide LAR for macroadenomas [40]. In a 5-year study of patients with acromegaly, tumor shrinkage was 75 and 78% in the octreotide LAR (30-40 mg, every 28 days) and lanreotide ATG (60-120 mg, every 21–28 days) groups, respectively [54]. A systematic review of 22 studies published in 2010 found that 33% of patients experienced a variable degree of tumor volume reduction (from 10 to 77%) during lanreotide SR or ATG treatment [55]. As expected, tumor reduction was more frequently observed in patients that were naïve to SRLs and had macroadenomas. No obvious correlation between biochemical response and tumor volume reduction has been noted in patients treated with lanreotide ATG. The observation that dose optimization can increase the number of patients achieving biochemical control [19] has been

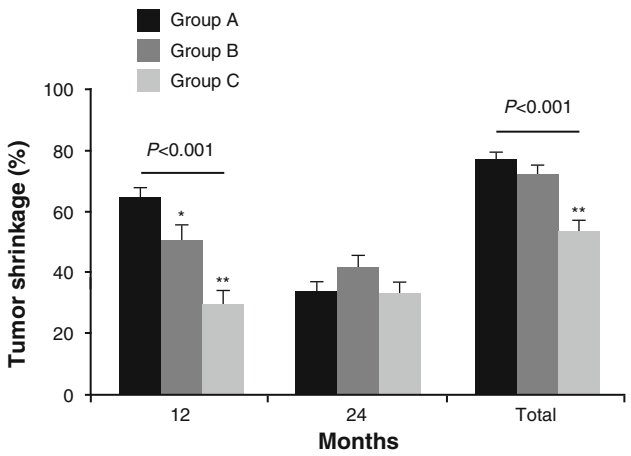

Fig. 5 Percent tumor volume reduction from baseline to 12 months of treatment (12), from 12 to 24 months of treatment (24) and total tumor shrinkage (from baseline to 24 months of treatment) in patients with acromegaly. *Group A* represents patients that were started and remained on the 20 mg/month dose. *Group B* represents patients whose starting dose was increased to 30 mg/month. *Group C* represents patients whose dose was increased further to 40 mg/month. © 2007, The European Society of Endocrinology, reproduced with permission. Colao et al. [51]. *$P < 0.01$ versus same time Group A; **$P < 0.01$ versus same time Group A and B

confirmed in another recent study. A randomized, 50-week trial designed to determine the benefit of first-line octreotide LAR treatment versus surgery demonstrated that 42/51 (82%) patients initially randomized to octreotide LAR 20 mg required a dose increase to 30 mg during the study in order to achieve biochemical control**.** In addition to biochemical control, at week 24, the mean tumor volume for the octreotide LAR-treated group decreased by 21% from baseline, and by 35% by week 48. Seventy-three percent of octreotide LAR-treated patients had significant (>20%) tumor shrinkage over the 48-week study period.

Efficacy of "high-dose/high-frequency" SRLs

More recently, in patients inadequately controlled on conventional doses of octreotide LAR (20–30 mg/month), both higher dose (>40 mg/month) or higher frequency administration (30 mg every 3 weeks) has been tested to determine if disease control can be improved [56]. In a prospective, open-label multicenter study, 28 patients who were responsive to conventional-dose SRL therapy but did not achieve biochemical control were treated with either high-dose (60 mg/month) or high-frequency octreotide LAR. After 24 weeks of treatment, 27% (3/11) of patients treated with high-dose octreotide LAR achieved control of GH (<2 μg/l) and 36% (4/11) achieved normalization of IGF-1 [56]. More importantly, in the high-dose group, 90% of patients had noticeable decreases in IGF-1 levels (Fig. 6) [56].

Experience with high-dose (>120 mg/month) or high-frequency (every 3 weeks) lanreotide ATG treatment is limited to case reports. In two patients with acromegaly who were not suitable for surgery, Wuster et al. increased the dose of lanreotide ATG sequentially up to 180 mg every 3–4 weeks for 3–6 months if the biochemical response of the patient was unsatisfactory [57]. Tumor volume reduction was observed with no drug-related adverse events. Clinical use of high-dose lanreotide ATG therapy was reported for an additional six patients who were titrated up to 180 mg/month in two separate clinical studies [58, 59].

Safety and tolerability of SRLs is maintained at higher doses

SRLs are well tolerated in most patients and treatment discontinuations due to adverse events are generally related to transient gastrointestinal (GI) disturbances [43]. The most commonly reported adverse events are injection-site discomfort and erythema, GI disturbances (such as diarrhea, abdominal pain, nausea and vomiting), biliary sludge or gallstones, and abnormal glucose metabolism [60]. However, most adverse events are transient and of mild-to-moderate intensity. SRL treatment can create conditions that favor precipitation of microcrystals and stone formation; however, gallbladder sludge and gallstones are usually asymptomatic and do not require surgery [61], which was confirmed using ultrasound surveillance of patients with acromegaly treated with octreotide LAR [36]. Glucose metabolism in patients with acromegaly treated with SRLs is very complex. Excess of GH in acromegaly is frequently associated with insulin resistance [4]. SRLs significantly

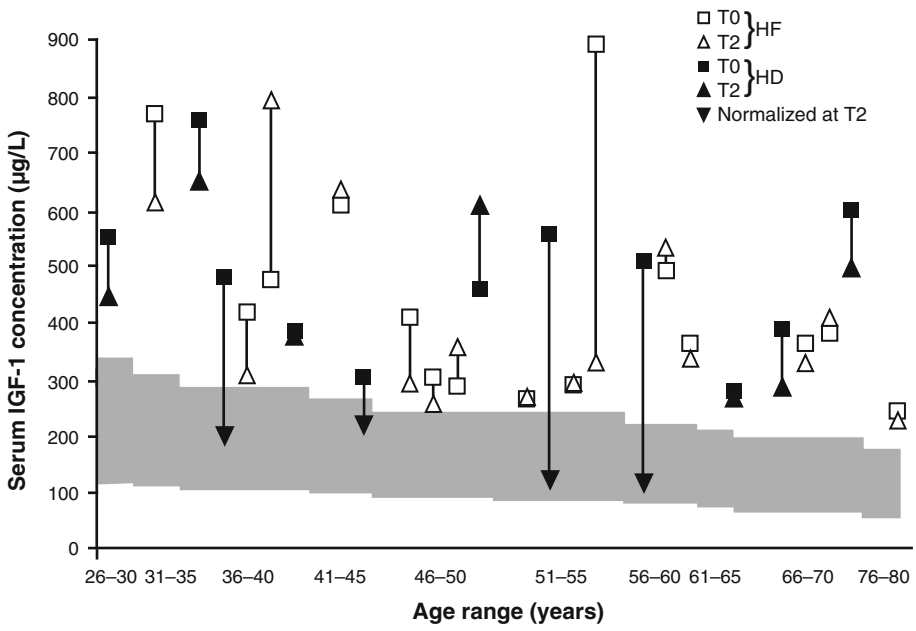

Fig. 6 Patient IGF-1 levels at baseline (*T0*) and week 24 (*T2*) in patients receiving either high-frequency octreotide therapy (HF; 30 mg every 21 days) or high-dose octreotide (HD; 60 mg every 28 days) therapy. Shaded area indicates normal IGF-1 concentration range for age. © 2009, The European Society of Endocrinology, reproduced with permission. Giustina et al. [56]

improve GH thus increasing insulin sensitivity, but experimental and clinical evidence suggests that this treatment could have negative effects on β-cell function [62]. Hypoglycemia has also been reported. A recent meta-analysis of 31 studies in patients treated with SRLs showed a statistically significant decrease in fasting plasma insulin, but without any significant change in fasting plasma glucose [63]. Clinical results from studies of patients with acromegaly treated with doses of octreotide LAR up to 60 mg/month show a similar safety profile to that reported with conventional treatment (20–30 mg/month) with octreotide LAR. The adverse events reported from patients in the dose-optimization studies discussed above were very similar to conventional therapy with octreotide LAR and report mild adverse events mostly involving the gastrointestinal tract [32, 36, 51, 64]. Some studies reported non-significant increases in gallstones or gallbladder sludge [32, 51, 56]. A Japanese study evaluating octreotide LAR 40 mg/month for a duration of 40 months in patients with acromegaly reported that treatment was safe and did not effect glycosylated hemoglobin (HbA_{1c}) levels negatively [64]. Giustina et al. 2009 demonstrated no dose–response effect in terms of adverse events. A slight decrease in median HbA_{1c} was observed in the high-dose group (60 mg/month) but not in the high-frequency group (30 mg every 3 weeks) [56]. Studies of patients treated with doses of lanreotide ATG up to 120 mg also report mainly GI adverse events. The case reports of patients treated with lanreotide ATG doses $\geq$120 mg every 4 weeks revealed no unexpected adverse events [57].

Conclusions

Treatment approach should be individualized to take into consideration a patient's tumor size and location, symptoms, comorbid conditions, and preferences. Novel medical treatments with different therapeutic regimens using SRLs are gaining importance while a second wave of more effective drugs is in development. Careful monitoring of the medical therapy of acromegaly, both primary and adjuvant, plays an important role in successfully controlling the signs and symptoms of the disease. The current review of published clinical studies demonstrates that dose escalation could provide additional biochemical control of acromegaly in patients who are inadequately controlled with conventional starting doses of octreotide LAR (20 mg/month) and lanreotide ATG (90 mg every 4 weeks). Therefore, patients should routinely have their GH and IGF-1 levels monitored and their SRL dose increased or decreased thereafter according to their individual response. Furthermore, multiple studies have now proven that higher doses of octreotide LAR could provide additional efficacy without significantly changing the safety and adverse events seen with conventional doses. The potential long-term use of SRLs at doses higher than the maximum labeled dose should still be evaluated in prospective, randomized trials with respect to GH control, tumor shrinkage and safety profile. It is important to also consider the cost:benefit ratio of high-dose compared with combination therapy and the overall burden of uncontrolled disease and complications.

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