Acromegaly: the effect of somatostatin analogues on tumour volume shrinkage

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ABSTRACT

Acromegaly is a rare disease, caused by growth hormone (GH) hypersecretion and secondarily elevated insulin-like growth factor 1 (IGF-1) level. Nearly all patients with acromegaly suffer from somatotroph pituitary adenoma. The main goal of treatment is to normalise both GH and IGF-1 levels, which reduces symptoms, complications and mortality. Transsphenoidal selective adenomectomy performed by an experienced neurosurgeon is the first-line therapy. Therapy with somatostatin analogues (SSA) is used as a neoadjuvant treatment prior to surgery and in a persistent disease following the surgery.

The long-acting somatostatin analogues reduce serum GH/IGF-1 levels and tumour volume. In this clinical review, mechanisms and role of 1st and 2nd generation somatostatin analogues in the treatment of patients with acromegaly are presented, with particular emphasis on the effects on somatotroph pituitary adenoma volume reduction.

KEY WORDS: pasireotide, lanreotide, octreotide, long-acting somatostatin analogues, tumour volume reduction, insulin-like growth factor 1, growth hormone, acromegaly, somatotroph pituitary adenoma

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INTRODUCTION

Acromegaly is a rare disease caused by hypersecretion of growth hormone (GH) and secondarily elevated insulin-like growth factor 1 (IGF-1) level. In nearly all patients, acromegaly symptoms are associated with the presence of a somatotroph pituitary adenoma. In some patients, mixed somatotroph/prolactin tumours occur which in addition to GH also secrete prolactin (PRL). Acromegaly symptoms are very rarely induced by hypothalamic tumours or neuroendocrine tumours that secrete somatoliberin (growth hormone–releasing hormone, GH-RH) or GH [1]. Excessive release of GH and IGF-1, not only leads to typical acromegaly symptoms but also to other complications, including cardio-vascular and metabolic complications (prediabetes and diabetes) that increase morbidity and mortality associated with acromegaly and considerably impact the quality of life. Acromegaly, when not controlled adequately, is associated with a risk of mortality twice as high as that of the general population [1–3].

The purpose of this clinical review is to present the current views on the effect of somatostatin analogues on the reduction in somatotroph pituitary adenoma volume.

KEY PRINCIPLES OF TREATING ACROMEGALY

According to the guidelines of the Endocrine Society from 2014 and the Polish guidelines, transsphenoidal selective adenomectomy is the first-line treatment in case of acromegaly [1, 2]. It is the only method known to cure this rare albeit devastating disease. However, in case of large, invasive tumours that infiltrate the cavernous sinuses and internal carotid artery or lead to destruction of the bottom of sella turcica and the sphenoid sinus walls, a preoperative therapy with somatostatin analogues may reduce both the tumour volume and clinical symptoms. This option is definitely beneficial in case of planning a neurosurgical treatment. A long-term exposure to surgical somatostatin analogues is also indicated in case of [1–3]:

- persistent acromegaly following a non-complete surgery
- patient not consenting to removal of the pituitary adenoma
- high risk associated with the general anaesthesia.

Other than by using somatostatin analogues, acromegaly may also be treated with pegvisomant, a growth hormone receptor antagonist. When injected, it reduces secretion of IGF-1, thus improving the symptoms. However, it has no effect on the size of the pituitary tumour. In addition, the elevated GH blood level seen in patients taking pegvisomant makes it difficult to precisely determine the dose. In some cases in which acromegaly is not fully controlled by somatostatin analogues, pegvisomant may be combined with octreotide or lanreotide. In Poland, the drug is not reimbursable which limits its use.

Another agent which is sometimes used in acromegaly is cabergoline, a derivative of ergot alkaloids. This selective dopamine D2 receptor agonist may be used as monotherapy in acromegaly, however, its efficacy in this setting is definitely lower than that of somatostatin analogues (30–40% efficacy) or when used in combination with octreotide or lanreotide. Dopamine agonists, in particular cabergoline, play a more significant role in case of mixed tumours that secrete both GH and PRL [1–4].

SOMATOSTATIN ANALOGUES' MECHANISM OF ACTION AT CELL LEVEL

Under physiological conditions, an elevated serum GH level increases secretion of somatostatin which, as a result of a negative feedback mechanism, inhibits GH release. Native somatostatin is correlated with 5 subtypes of somatostatin receptors (sst_{1-5}) and has a very short half-life. An autonomous somatotroph adenoma that causes acromegaly symptoms escapes the control by the negative feedback mechanism, which results in excessive release of growth hormone and triggers clinical symptoms of the disease. Somatotroph pituitary tumours display a varied expression of the different subtypes of somatostatin receptors. Immunohistochemical studies have shown that subtypes 1 and 5 (sst_1 and sst_5) are the most frequent somatostatin receptor subtypes in somatotroph pituitary tumours while subtypes 2a, 2b and 3 (sst_{2a}, sst_{2b} and sst_3) are less common [5].

Somatostatin analogues are able to reduce the volume of somatotroph pituitary adenomas by inhibiting the specific signalling pathways that promote cell proliferation and growth. Somatostatin analogues also increase expression of proteins responsible for inhibiting cell proliferation and apoptosis or arresting cell cycle at phase G1.

By acting on somatostatin receptors, including in particular subtype sst_2, somatostatin analogues activate phosphoprotein phosphatases (PTPs). Initiating a cascade of pathways that activate secondary messengers results in inhibition of extracellular signal-regulated kinase (ERK) 1/2 (mitogen-activated protein kinase (MAP), and increases expression of cyclin-dependent kinase inhibitors such as p21 and p27 [6].

Another antiproliferative mechanism of somatostatin analogues is the activation of *Zac1* gene expression which is responsible

for inhibiting tumour growth. *Zac1* has been discovered quite recently and is a zinc-finger protein that inhibits the cell cycle and induces apoptosis. Under physiological conditions, *Zac1* gene expression in the frontal lobe of the pituitary gland is high but decreases in the presence of pituitary adenomas. Some somatotroph tumours have been seen to show a high expression of *Zac1* gene, sometimes comparable to that of normal tissue [8]. Theodoropoulou et al. detected a strong positive correlation between *Zac1* immunoreactivity of tumour tissue and IGF-1 level normalization as well as pituitary tumour volume reduction attributable to octreotide. It seems to confirm that the *Zac1* gene demonstrates antiproliferative activity which is induced by the use of somatostatin analogues in acromegaly. Theodoropoulou et al. also demonstrated that the connecting link between octreotide and the increased expression of *Zac1* is the phosphoinositide 3-kinase/protein kinase B (PI3K/PKB) pathway also referred to as Akt. When activated, PI3K catalyses phosphorylation of phosphatidylinositol 4,5-bisphosphate (PIP2) into phosphatidylinositol-(3,4,5)-trisphosphate (PIP3), which leads to the activation of Akt kinase. The latter controls cell growth, apoptosis and proliferation. It has been demonstrated that octreotide inhibits phosphatidylinositol-dependent kinase (that catalyses PIP2 transformation into PIP3) and Akt phosphorylation. Inhibition of PI3K/Akt pathway increases the expression of *Zac1* gene [7–9].

SOMATOSTATIN ANALOGUES AS THE FIRST-LINE OF TREATMENT IN ACROMEGALY AND THEIR EFFECT ON PITUITARY TUMOUR SIZE

There are numerous reports about the positive effect of somatostatin analogues (when used as the first line of treatment) manifested by a reduction of somatotroph pituitary tumour volumes. In a retrospective study, Colao et al. confirmed a 25% reduction in tumour volume after only 3 months of exposure to octreotide LAR [10]. A multi-centre prospective study conducted by Mercado et al. into the use of octreotide LAR in doses of 10–30 mg every 28 days showed a reduction in tumour volume by at least 20% in over 60% subjects after 24 weeks and in over 75% subjects after 48 weeks of therapy [11]. In both studies, a shrinkage in volume occurred more often in case of microadenomas and small intrasellar macroadenomas (ca. 70%) and significantly less often in case of invasive macroadenomas with suprasellar invasion (approx. 35%). In case of particularly difficult invasive somatotroph tumours that cannot be controlled by treatment with 30 mg octreotide LAR, one may consider increasing the dose to 40 mg, with administration every 4 weeks. Efficacy of this method in terms of biochemical improvement and further reduction in somatotroph pituitary tumour volume was confirmed by Colao et al. in 2007. According to the authors of the paper, dose escalation may be particularly beneficial for young patients with large, invasive pituitary tumours. In addition, a dose increase to 40 mg of octreotide LAR does not lead to further impairment of carbohydrate metabolism [12].

Lanreotide Autogel may also significantly reduce the volume of pituitary adenomas in acromegaly. In a recent multi-centre prospective PRIMARYS study, a similar reduction in somatotroph tumour volumes by over 20% was seen in over 50% patients after 3 months and over 60% patients after 12 months of exposure to lanreotide Autogel used as the first line of treatment in acromegaly [13]. A similar report was published for the previous form of lanreotide SR 60 mg by Attanasio et al. [14].

SOMATOSTATIN ANALOGUES AS PRE-OPERATIVE TREATMENT

The views on whether somatostatin analogues should be routinely used as pre-operative treatment are polarised. According to classic papers from the 1990s that reported on the neoadjuvant use of short-acting subcutaneous octreotide in doses of 150–1500 μg/24 h, the somatostatin analogue displayed a beneficial effect in terms of biochemical improvement, reduction in clinical symptoms and shrinkage of the pituitary tumour. Studies from that time also showed a beneficial effect on the tumour consistency (the tumour became less firm) which was expected to make neurosurgeries easier [15–17]. A similar reduction in tumour volume up to 50% along with a beneficial effect on tumour consistency was also demonstrated by studies involving lanreotide SR [18, 19].

However, a prospective randomised POTA (*Preoperative Octreotide Treatment of Acromegaly*) study conducted later, in 2008, did not discover any noticeable changes between somatotroph tumour consistency in patients that were pre-treated with octreotide LAR for 6 months prior to their surgery and tumour consistency in patients operated on without a prior treatment with a somatostatin analogue. The study indeed showed that patients with macroadenomas pre-treated with octreotide LAR before surgery experienced early postoperative remission significantly more often than non-pretreated patients but there were no differences between the remission subgroup and the persistent acromegaly subgroup with respect to reduction in the pituitary tumour volume achieved by pharmacotherapy [20].

It seems that preoperative treatment of acromegaly with somatostatin analogues should not be used routinely but may be indicated for some patients on an individual basis, as suggested by the guidelines of the Endocrine Society from 2014 and the Polish guidelines on acromegaly treatment. Somatostatin analogues may be considered as an option in case of acromegaly caused by macroadenomas, in particular those infiltrating adjacent structures and showing clinical and radiological signs of invasiveness [1, 2].

SOMATOSTATIN ANALOGUES AS ADJUVANT TREATMENT IN ACROMEGALY

As mentioned earlier, surgery is the only therapy that offers a chance to cure acromegaly. Its efficacy is highest in case of microadenomas and intrasellar macroadenomas, and significantly lower in case of invasive, infiltrating macroadenomas [1, 2]. From the neurosurgeon's point of view, the latter type of somatotroph tumours is the most difficult to treat. Assessment of patient's eligibility for surgical treatment which – due to tumour morphology – is not likely to be a complete removal despite pre-treatment with somatostatin analogues seems to be a significant clinical issue.

In 2006, Italian authors published a paper which suggested that incomplete, or the so-called debulking pituitary adenoma surgery performed on patients who responded poorly to pre-operative treatment with somatostatin analogues (octreotide or lanreotide) increases the likelihood of biochemical control (normalisation of GH and IGF-1 levels). In that paper, removal of more than 3/4 of tumour mass enabled a satisfactory control of the disease in more than half of the patients who had been previously inadequately treated by the same somatostatin analogue. The treatment did not significantly increase the frequency of pituitary gland function impairment relative to pre-operative period [21]. Subsequently, other authors also presented similar reports on the beneficial effect of somatostatin analogues in adjuvant treatment of acromegaly, including reduction in pituitary adenoma volume [22].

Figure 1 shows an MRI (*magnetic resonance imaging*) scan of an invasive somatotroph pituitary tumour pre-treated with a somatostatin analogue prior to surgery, and a scan after a debulking neurosurgery.

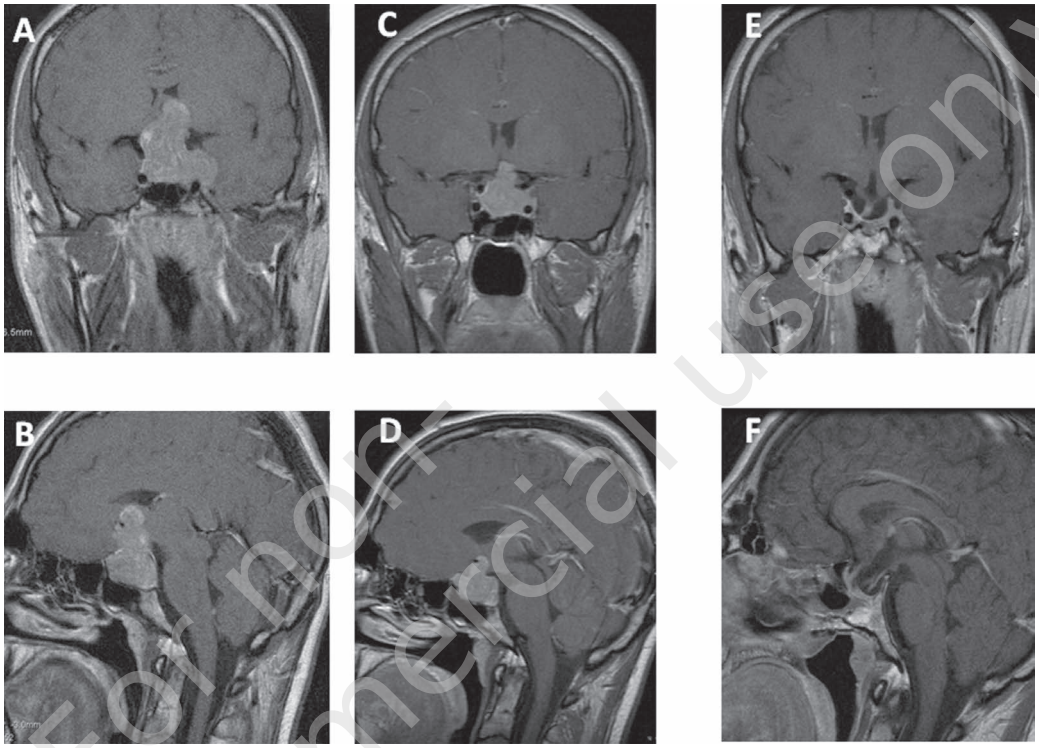
PREDICTIVE FACTORS OF TUMOUR VOLUME REDUCTION IN THE COURSE OF TREATMENT WITH SOMATOSTATIN ANALOGUES

In 2006, Colao et al. published findings from a prospective observational study into the effect of long-acting 1st generation somatostatin analogues on somatotroph pituitary tumour volume reduction. Treatment-naïve patients with somatotroph pituitary tumours (of whom most had macroadenomas) received octreotide LAR in a dose of 20–30 mg or lanreotide 60–90 mg every 28 days. After 12 months of therapy, 42.4% of patients experienced a full biochemical control of acromegaly (GH ≤ 2.5 μg/dl and IGF-1 level normal for the sex and age group). A significant reduction in tumour volume (by more than 75%) was seen in 14% patients, a moderate reduction (by 50–75%) was experienced by 30% patients and a slight reduction (by 25–50%) was achieved in 31% patients while the tumour volume remained stable (shrank by less than 25%) in 22% patients. Only 2% patients experienced a clinically relevant increase in tumour volume [23].

The study confirmed that 1st generation somatostatin analogues are efficacious in reducing pituitary tumour volume in acromegaly. A reduction by at least 25% was reported in more than 75% patients with acromegaly. Interestingly, no correlation was demonstrated to exist between the relative reduction in somatotroph adenoma volume and the tumour volume prior to treatment. No difference was identified between octreotide LAR and lanreotide with respect to their ability to shrink tumour size. However, a decline in the IGF-1 level was shown to have a significant effect on the tumour volume reduction: the IGF-1 level achieved after 12 months of treatment turned out to be the strongest predictive factor of tumour size reduction. Other predictive factors included the patient's age (reverse dependency) and a decrease in the GH level after 12 months of treatment with a 1st generation somatostatin analogue [23].

In a retrospective study conducted at the same centre a little later, Italian authors demonstrated that a relative reduction in tumour volume (and its maximum measurement) after 12 months of treatment with variable doses of octreotide LAR (20 mg every 28 days for three months, followed by a dose adjustment to individual patient's needs) depends mostly on the relative reduction in tumour volume after 3 months of treatment with octreotide LAR and the levels of GH and IGF-1 achieved in that period. The findings from the study are particularly important for clinical practice. After only 3 doses of somatostatin analogue it is possible to identify the patients

FIGURE 1.
Invasive somatotroph pituitary macroadenoma with extrasellar expansion, infiltrating cavernous sinuses and pressing on the optic chiasm (coronal and sagittal planes). Initial image prior to treatment (A, B); reduction in tumour mass after 6 months of treatment with 30 mg octreotide LAR (C, D); MRI scan after non-complete transsphenoidal surgery– residual tumour mass near cavernous sinuses and the bottom of sella turcica – further treatment based on somatostatin analogue, satisfactory biochemical control and retained pituitary gland function (E, F).



who will benefit from pharmacotherapy the most [10]. In the group of patients showing an early response, a prolonged use of somatostatin analogues should translate into an increasingly higher reduction in tumour volume, which was also confirmed by a paper published by Ben-Shlomo and Melmeda around the same date [24].

At this point it should be noted that even though a biochemical improvement goes hand in hand with tumour shrinkage in the majority of patients displaying a positive response to pharmacotherapy based on somatostatin analogues, the dependency is not absolute. There are publications which report on cases where hormones returned to normal levels but no significant reduction in tumour volume was evidenced by MRI scans, as well as cases where the tumour shrank without GH and IGF-1 returning to normal levels [25]. These irregularities are most likely caused by the different cell mechanisms that inhibit GH secretion and the antiproliferative action of somatostatin analogues.

PASIREOTIDE AND ITS ROLE IN ACROMEGALY TREATMENT

Pasireotide (SOM 230) is a 2nd generation somatostatin analogue which influences somatostatin receptor subtypes $sst_{1,2,3}$ and sst_5. Pasireotide's potency on subtypes sst_1, sst_3 and sst_5 is 30, 11 and 158 times higher, respectively, than that of octreotide, and on subtype sst_2 – 7 times lower. Thus, the molecule should be mostly used to treat somatotroph tumours which show an expression of other receptor subtypes than sst_2. A targeted use of pasireotide is difficult because the expression of various somatostatin receptor subtypes is not routinely assessed by immunohistochemical studies, and no pathologists are present on the medical teams managing pituitary adenomas (particularly in Poland).

Registration studies of short-acting pasireotide (administered subcutaneously twice a day) showed that it reduces the volume of somatotroph pituitary adenomas by over 20% after 3 months of use and by over 50% after 6 months of use [26]. According to a study published by Colao et al. in 2014, octreotide LAR and pasireotide LAR showed a similar efficacy in reducing pituitary

tumour volume by over 20% in treatment-naïve patients with acromegaly (77 vs 81%; NS) despite pasireotide's significantly higher efficacy in achieving a biochemical control of the disease (normal GH and IGF-1 levels) [27].

In 2014, results of a multi-centre PAOLA (*Efficacy and Safety of Pasireotide Long Acting Release (LAR) Versus Octreotide LAR or Lanreotide Autogel (ATG) in Patients With Inadequately Controlled Acromegaly*) study were published. The study compared pasireotide LAR in doses of 40 and 60 mg against the so-called active control which consisted in the prolonged use of a 1st generation somatostatin analogue (octreotide LAR 30 mg or lanreotide Autogel 120 mg). Both pasireotide and 1st generation somatostatin analogues were administered to patients with acromegaly whose condition was not adequately controlled despite receiving high doses of 1st generation somatostatin analogues for over 6 months. In the study group selected in this way, pasireotide proved to be superior to 1st generation somatostatin analogues both in relation to biochemical control and reduction of tumour volume. Both effects achieved by pasireotide were dependent on the dose. The tumour volume shrank by more than 25% in 18.5% and 11% patients receiving, respectively, pasireotide LAR 40 mg and 60 mg relative to 1.5% patients in the active-control group [28]. In view of the findings from the PAOLA study, pasireotide LAR may be considered a valuable therapeutic option primarily for patients with acromegaly who require a prolonged pharmacotherapy because their disease could not be adequately controlled by maximum doses of 1st generation analogues. It should be noted that patients receiving pasireotide experienced abnormal carbohydrate metabolism and diabetes decompensation secondary to acromegaly more often than patients receiving octreotide or lanreotide [28]. This piece of information should draw our attention to the fact that all patients with acromegaly, particularly those who are scheduled to receive subcutaneous pasireotide or LAR, should have their carbohydrate metabolism parameters monitored and carefully normalized.

SUMMARY

Somatostatin analogues are the standard pharmacotherapy in acromegaly. They are used both in the neoadjuvant setting and as the adjuvant therapy following unsuccessful or incomplete neurosurgery. Their beneficial effect is manifested by a reduced secretion of GH and secondarily lower level of IGF-1, which improves the clinical outcome and decreases both morbidity and mortality in acromegaly, as well as reduces the volume of pituitary tumours, minimising neuro-ophthalmological symptoms. The key predictive factors of reduction in tumour volume include:

- a lower IGF-1 level
- younger age
- a lower GH level.

When 1st generation analogues (octreotide LAR and lanreotide Autogel) are not efficacious, one may consider using pasireotide, a new, multi-receptor 2nd generation somatostatin analogue.

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Marta Gutowska: 50%.