Archives of the Balkan Medical Union
vol. 53, no. 1, pp. 117-125
March 2018

MINIREVIEW

NEW CROSS-ROADS FOR SECOND LINE MEDICAL THERAPY IN ACROMEGALY

Adina Ghemigian[1], Andra Cocolos[1], Eugenia Petrova[1], Ana Valea[2], Nicoleta Dumitru[1], Mara Carsote[1]

[1] „Carol Davila" University of Medicine and Pharmacy, „C.I. Parhon" National Institute of Endocrinology, Bucharest, Romania
[2] „Iuliu Hatieganu" University of Medicine and Pharamacy, Clinical County Hospital, Cluj-Napoca, Romania

Abstract

Acromegaly is a complex disorder caused by growth hormone excess mostly due to a pituitary adenoma. Surgery represents the first option but rate of long time success is almost 50% thus the patients need other therapies. Apart from radiation, medical therapy panel includes previously used long-acting formulas of first-generation somatostatin analogues like ocreotide or lanreotide and, moreover, pasireotide LAR which is a recently introduced second-generation analogue. Non-responders to prior medication, proved a good response to this as pointed by C2305 extension trial or PAOLA study. The rate of overresponse to pasireotide may be explained by a different receptor target: mostly on somatostatin receptor type 5 opposite to type 2 as it acts first-generation compounds. The tolerance of pasireotide LAR is good; the safety profile includes the awareness of hyperglycaemia risk. The cross-road that follows the lack of acromegaly control after a patient was treated with somatostatin analogue of first generation is currently more complex since pasireotide LAR became a feasible option.

Key words: acromegaly, pasireotide LAR, pituitary gland, tumour, glycaemia.

Résumé

De nouvelles perspectives pour la thérapie médicale de seconde ligne dans l'acromégalie

L'acromégalie est un trouble complexe causé par un excès de l'hormone de croissance, principalement dû à un adénome hypophysaire. La chirurgie représente la première option, mais le taux de réussite à long terme est d'environ 50% et les patients ont besoin d'autres thérapies. A part la radiation, le panneau de la thérapie médicale inclut des formules à action prolongée précédemment utilisées d'analogues de la somatostatine de première génération comme l'ocréotide ou le lanréotide et, de plus, le pasiréotide LAR qui est un analogue de deuxième génération récemment introduit. Les non-répondeurs aux médicaments antérieurs, se sont montres etre une bonne réponse à cela comme indiqué par l›essai d›extension C2305 ou l›étude PAOLA. Le taux de l'extra-réponse au pasiréotide peut être expliqué par une cible différente du récepteur: principalement sur le récepteur de la somatostatine de type 5 opposé au type 2, car il agit sur les composés de première génération. La tolérance du pasiréotide LAR est bonne; le profil de sécurité comprend la prise de conscience du risque d'hyperglycémie. Le carrefour qui suit le manque de contrôle de l'acromégalie après

Corresponding author: Andra Cocolos
Address: Aviatorilor Ave 34-38, Bucharest, sector 1, postal code 011684, Romania
Email: andra_buruiana@yahoo.com

Abbreviations
EMA = European Medicines Agency
FDA = Food and Drug Administration
GH = Growth Hormone
IGF1 = Insulin-like Growth Factor
OGTT = Oral Glucose Tolerance Test
SSTR = Somatostatin Receptor

qu'un patient a été traité avec un analogue de la somatostatine de première génération est actuellement plus complexe puisque le pasiréotide LAR est devenu une option réalisable.

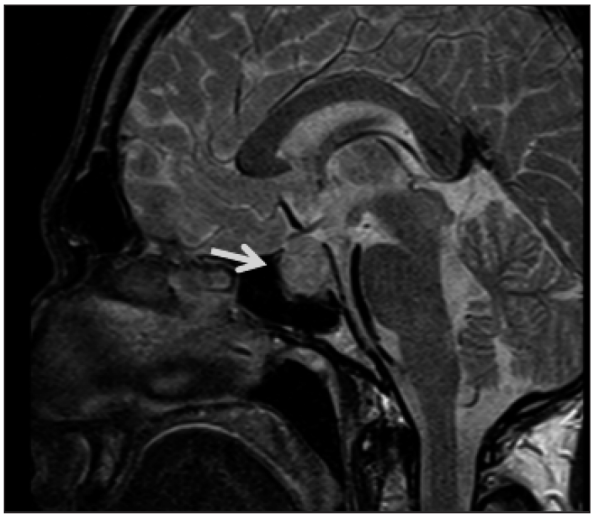
Mots-clés: acromégalie, LAR pasiréotide, glande pituitaire, tumeur, glycémie.

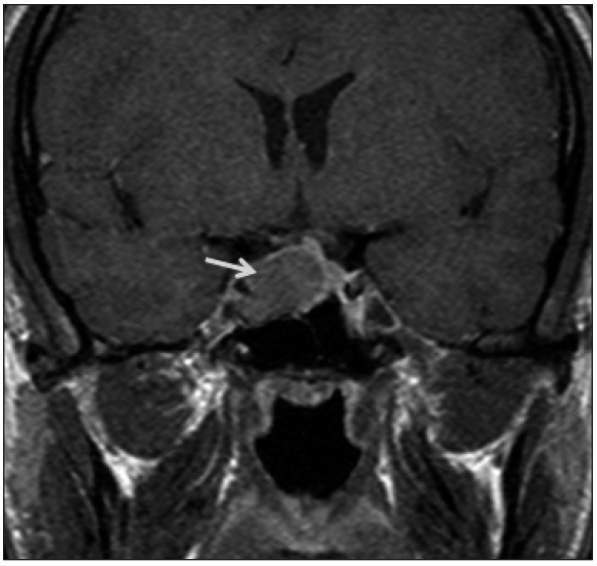
Introduction

Acromegaly, a complex condition, caused in 95% of cases by a GH (Growth Hormone) secretor pituitary adenoma, includes metabolic, cardiovascular, and bone anomalies, as well as pituitary tumour-related syndrome due to large hypophyseal masses[1-3]. This particular complication impairs the growth and final height, and also adequate puberty-associated sexualisation, if the onset is early in life[4,5]. First-line therapy, as well as most of the pituitary secretor and non-secretor adenomas, except for prolactinomas, is pituitary surgery, but the rate of persistence or recurrence is relatively high[6-8].

Unsuccessful surgery or impossibility of performing it due to cardiovascular comorbidities and increased anaesthetic risk makes the patient a candidate to medical therapy and/or associated pituitary irradiation[9,10]. Modern medicine brings in frontline a vast panel of medical approaches from three different types of somatostatin analogues to GH receptor blockers to less efficient adjuvant option of dopamine agonists, as cabergoline or bromocriptine, which are all already approved medication in daily practice[11,12].

These drugs may be offered to the acromegalic patients as single therapy or in combination, and due to long-time history of the condition, inter-changes of the products or different regimes may actually be used in the same patient through life span[13,14]. The most recent medication for acromegaly is pasireotide LAR, a second-generation somatostatin analogue, which is also available since 2017 for Romanian population, based on a specific country protocol[15,16]. Pasireotide has been offered as an alternative medication in Cushing's disease but under a different dosage





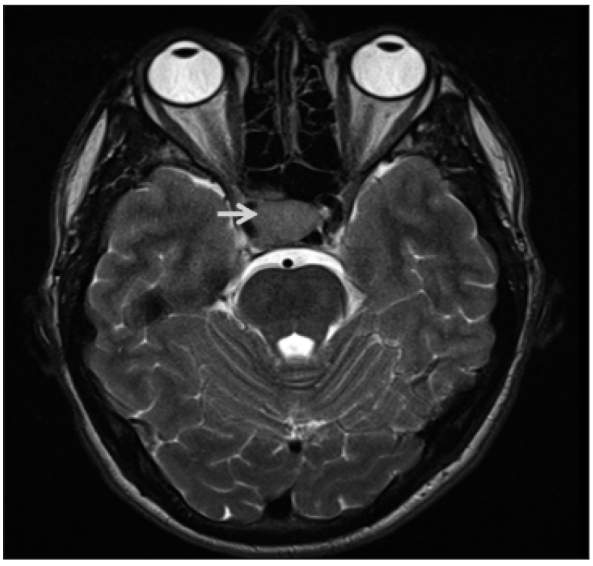


Figure 1. Computed-tomography of a 27-year old male patient with a large macroadenoma (different planes)

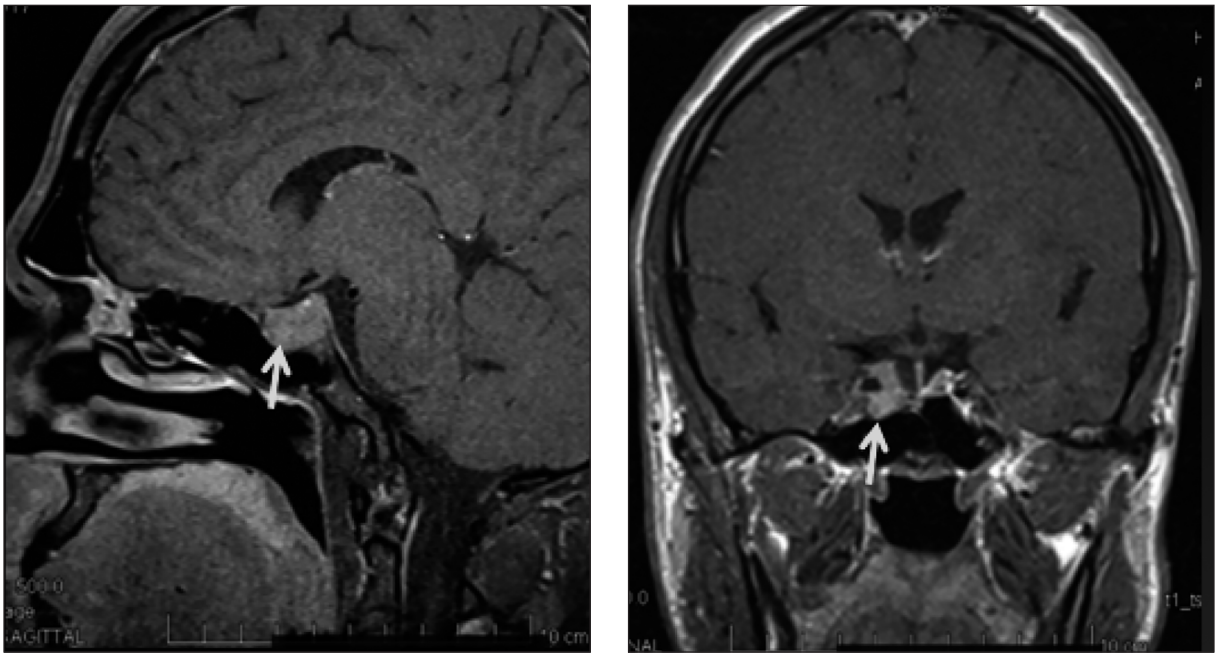


Figure 2. Post-operatory aspect after hypophysectomy of a large Growth-Hormone secreting macroadenoma in a 27-year old male (different sections)

and route of administration from acromegaly, since last 3 years[16-18].

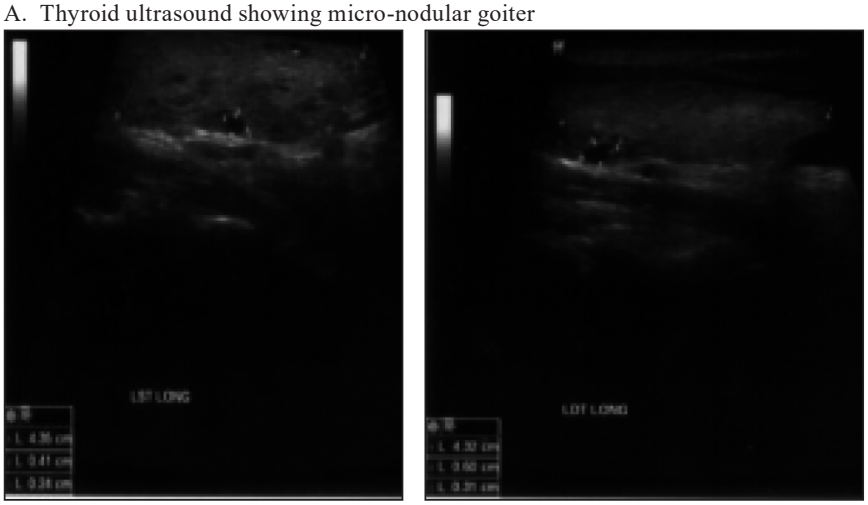
Our purpose is to introduce a brief narrative review regarding the most recent medication for acromegaly: pasireotide LAR, starting from a case who was non-responsive to first-line medication treatment. The cross-roads of second line medical therapy in this particular situation include a second-generation somatostatin analogue, as an alternative to prior already known options of therapy included in acromegaly's management.

This is a review of 60 papers related to keywords like "acromegaly" and "pasireotide". The main, but not exclusive, tool of research is PubMed database. The previously unpublished case is introduced from a typical endocrine type of presentation, providing the hormonal and imagery panel of investigations, in addition to personal medical background. The patient has been evaluated in different centres of endocrinology and consented for anonymously use of his medical data when he was evaluated at " C.I. Parhon" National Institute of Endocrinology from Bucharest, Romania.

From case report to literature review

This is a 24-year-old male non-smoking patient, without family medical background, accusing persistent headache of non-specific pattern for almost three years, without any investigations or specific therapy. At age of 27 years, a computed tomography scan was performed, that identified a pituitary mass of 1.9 by 1.3 by 1.2 cm, with extension outside the sellar area, respectively to right cavernous sinus invasion, surrounding more than a half of intra-cavernous path of internal carotid artery (Figure 1). Hypophysectomy was performed soon after the detection of macro-adenoma, but large remnants were found after the procedure (Figure 2). Some improvement of the headache was registered after surgery; he also developed transitory diabetes insipidus. The patient was referred to an endocrine check-up, which confirmed acromegaly based on lack of GH suppression during OGTT (Oral Glucose Tolerance Test) and high IGF1 (Insulin-like Growth Hormone) (Table 1). The patient did not associate pituitary deficiency or visual field amputation due to hypophyseal mass, neither other significant complications of acromegaly, except for a small goiter, and a 0.3 cm ileum polyp at colonoscopy, with hyperplasia of mucosa at histopathological exam (Figure 3). Further irradiation therapy was added: gamma knife (18 Gy on iso-dose of 50%). Two years later, the patient presented for an endocrine re-assessment and acromegaly was still active (Table 1). Magnetic Resonance Imaging (MRI) showed a pituitary mass of 1.7 by 1.5 cm, with right cavernous sinus invasion. Therapy with first-generation somatostatin analogue octreotide LAR (20 mg every 28 days) was started, in association with twice weekly cabergoline of 1 mg. After three months, IGF1 decreased to 783 ng/mL, with normal levels being considered between 117 and 329 ng/mL. An escalade to weekly 2 mg of

A. Thyroid ultrasound showing micro-nodular goiter



B. Normal visual field

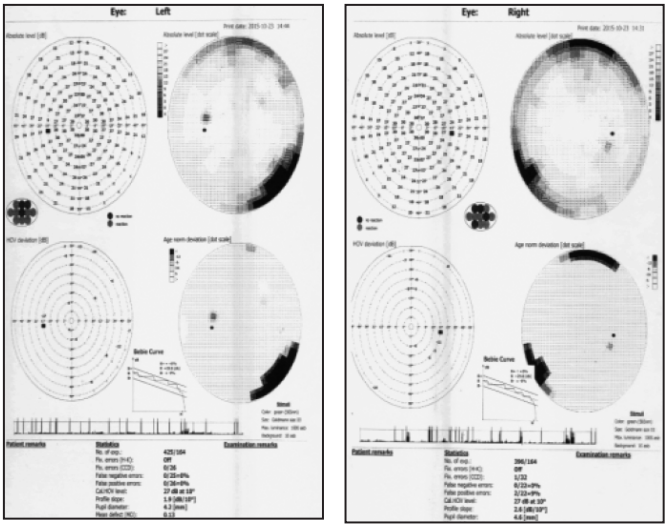


Figure 3. Assessment of potential complications related to GH excess and/or GH producing tumour

cabergoline was done at that moment. At the end of the first 6 months, the assays revealed a still uncontrolled disease, so a higher dose of Octreotid LAR (30 mg every 28 days), in addition to 3 mg per week of cabergoline, was offered to the patient for another 6 months (Table 1). The evaluation after one year of octreotid LAR and cabergoline therapy showed partial control of acromegaly (Table 1).

Cross-road with pasireotide LAR indication for acromegaly

We used as *intro* the previous case, since the lack of adequate response after first-generation somatostatin analogues may represent a potential scenario in clinical every day practice, also mentioning that surgery has rather disappointing results in cases with cavernous sinuous invasion as in the case presented[19-21]. The potential therapeutic options are: switch to lanreotide (a long-active formula of first-generation, also), association of a GH-blocker drug pegvisomant, re-surgery or switching to pasireotide LAR instead of octreotide LAR. This cross-road will be further discussed (Figure 4).

Active acromegaly after pituitary surgery

Besides sinus cavernous involvement, which is considered by some authors (but not all) the best predictor of persistent disease after hypophysectomy, other factors have been taken into consideration, like surgeon's skills, the volume of the pituitary mass, high pre-operative levels of GH and IGF1[22-24]. Diri H *et al.* revealed on a total resection rate of 50% that poor long-term prognosis is related to female sex and a pre-operative level of IGF1 higher than 850 ng/mL[25]. Nishioka H *et al.* identified on a series of 150 acromegalic patients, cavernous invasion on 36.7% of them, and this was associated with the most important factor of unfavourable outcome, with remission

Table 1. The panel of specific investigations in a young male adult with acromegaly during different moments of therapy

Investigations performed 3 months after pituitary surgery					
OGTT	0'	30'	60'	90'	120'
GH (ng/mL)*	5.5	4.8	3.8	3	3.2
Glycaemia (mg/dL)	97	105	188	184	120
IGF1 (ng/mL)	1248 ng/mL (normal levels: 90-262)				
Investigations performed 2 years after pituitary surgery + gamma knife therapy					
GH (ng/mL)*	6.6	6.7	9.3	7.6	6.4
Glycaemia (mg/dL)	65	135	151	130	80
Mean GH/24-hours** (ng/mL)	7.4				
IGF1 (ng/mL)	804 (normal levels: 93-250)				
Evaluation after 6 months of Octreotide LAR 20 mg/28 days + Cabergoline					
GH (ng/mL)*	3.1	3	2.9	2.4	2.4
Glycaemia (mg/dL)	80	123	151	116	82
Mean GH/24-hours** (ng/mL)	2.7				
IGF1 (ng/mL)	710 (normal levels: 84-250)				
Evaluation after another 6 months of Octreotide LAR 30 mg/28 days + Cabergoline					
GH (ng/mL)*	3.2	3.3	3.2	3.1	2.8
Glycaemia (mg/dL)	80	125	114	97	80
Mean GH/24-hours** (ng/mL)	3.1				
IGF1 (ng/mL)	617 (normal levels: 84-250)				

OGTT=Oral glucose Tolerance Test (performed with oral 75 g of glucose), IGF1=Insulin-like Growth Factor
*normal levels to infirm acromegaly: < 1 ng/mL; **normal mean of GH/24 hours: <2.5 ng/mL

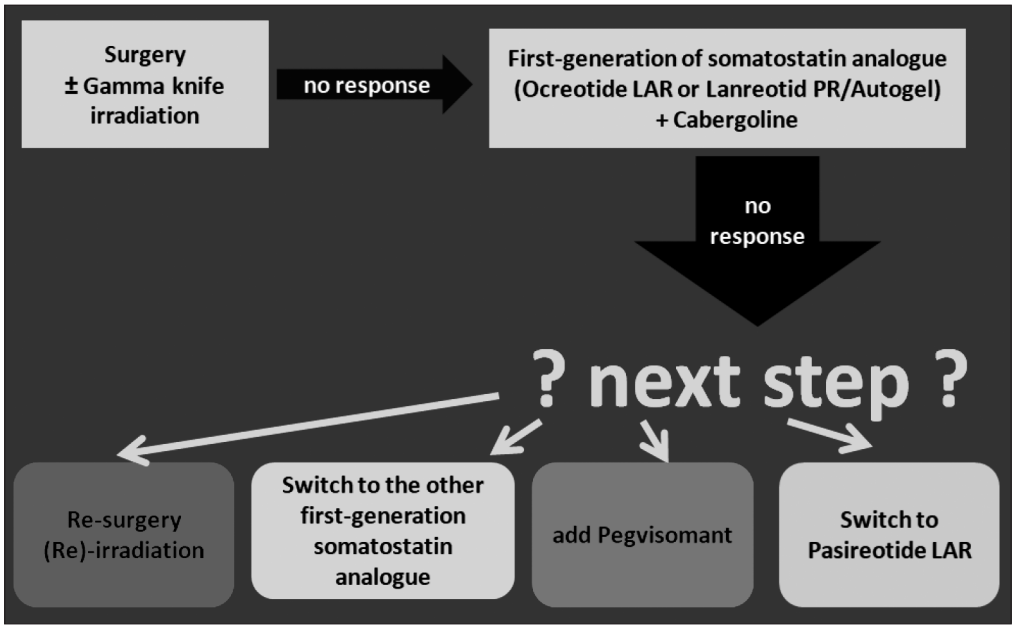


Figure 4. The cross-road after first line medical therapy failed to control acromegalic disease

in 69% of cases[26]. The authors highlighted the importance not only of direct visualization, but also of histological check-up of invasion at that level[26].

Long-acting formulas of first-generation somatostatin analogues

The persistent or recurrent acromegaly after surgery or the impossibility of hypophysectomy, as well as the time necessary to achieve disease control through irradiation, represent the frame of initiating medical therapy. Protocols available in Romania include, as initial choice of medical therapy, the first-generation somatostatin analogue: octreotid LAR (with possibility of progressive dose increase, from 20 to 30 or 40 mg every 28 days) or lanreotid PR (30 mg every 7 to 21 days, depending on the case) or Autogel 120 mg per months[16]. They are generally efficient and well tolerated with a good adherence rate[27-29]. As side effects, the main focus is on glycaemia profile. [30,31]. Among the factors that have been found in correlation with lack of response or partial control of the disease under octreotid or lanreotid, we mention young age at diagnosis of acromegaly, with or without genetic alterations, such as AIP mutations, negative gsp mutation, as well as male sex, low-expression of adherence molecule E-cadherin and increased expression of beta-arrestin, etc[32-34]. However, there are patients resistant to first-generation of somatostatins, who become responders to second-generation, and this is explained by the configuration of somatostatin receptor into the tumour [35].

Pasireotide LA in clinical trials

There are four large clinical trials that represent the first step in understanding the pasireotide use in acromegaly, according to evidence based medicine: C2305 study and its extension, C2402 (also names as an acronym PAOLA) study and its recent extension[15,36-39]. Earlier, cells line observations and pre-clinical studies exposed different components of somatostatin receptors in corticotropinomas, respectively somatotropinomas, which were later translated into clinical practice as the next logical step[40-42]. Clinical approach confirmed that, while first-generation of somatostatin analogues as octreotide or lanreotide have the highest affinity to SSTR2 (Somatostatin Receptor), pasireotide has the following descending affinities: SSTR5>2>3>1[15,43,44]. Opposite to octreotide, pasireotide has 40 times higher affinity on SSTR5, 20 times higher on SSTR1, and 5 times higher on SSTR3 and 2.5 times lower on SSTR2; opposite to lanreotide it has 106 times higher affinity on SSTR5[15,43,44].

The long-acting formula of the somatostatin multireceptor ligand was approved for acromegaly since 2014 by both FDA (Food and Drug Administration) and EMA (European Medicines Agency)[15,45,46]. Recommended doses are 40 or 60 mg per month, with the alternative of temporary switch to 20 mg per month[15,45,46]. C2305 study had a prospective, randomized multicenter, interventional design[36]. Out of 358 subjects with active acromegaly and free of other specific medical treatment exposure, they were treated of either pasireotide LAR 40 mg or octreotide LAR 20 mg for a year[36]. Dose titration of either drug was allowed to pasireotide LAR 60 mg or octreotide LAR 30 mg[36]. Control disease was 31% versus 19% (p=0.007) with second-generation versus first-generation somatostatin[36]. C2305 extension study is also a randomised, large, multicenter one-year trial[37]. Mainly, the non-responders from core-study were switched to the other drug and the responders continued for another year [37]. The non-switched groups revealed an additional percent of 27%, respectively 5% patients who achieved control after another year of pasireotide LAR, respectively octreotide LAR[37]. The primary outpoint was the response in those patients who changed the medication compared with first year and the results highlighted a percent of 17.3%, respectively 0% of controlled acromegaly in cross-over groups from octreotide to pasireotide, respectively from pasireotide to octreotide[37]. PAOLA study is a multicenter, randomised study of phase 3, who included 198 adult acromegalic patients, non-controlled under octreotide LAR 30 mg or lanreotide 120 mg per month (called "active control"), who received either active control, either pasireotide LAR (40 mg or 60 mg), while a subgroup continued the first-generation medication[38]. After 6 months, the achievement of GH and IGF1 suggestive for acromegaly control was done on 15%, 20%, respectively 0% of patients under lower dose, higher dose of pasireotide, respectively active control[38].

Pasireotide LAR in daily practice

Pasireotide LAR has a rate of response up to 80% and it associates a particular profile, meaning that evaluation after the first three months of therapy is predictive for the following rate of response[15]. The drug has similar rate of adverse effects with already known first-generation octreotide and lanreotide, except for glucose tolerance[15,36,38]. For instance, in C2305 study, the rate of adverse events caused by glucose profile anomalies was of 57% versus 21% under pasireotide LAR versus octreotide LAR[36]. In C2402 study, the percentage of patients developing the same type of disturbances was 21%, if the patients were treated with 40 mg of pasireotide LAR, respectively of 31% under 60 mg pasireotide LAR per month[38]. Other potential side effects are diarrhoea,

QT interval changes on electrocardiogram, etc[47-49]. Also, some authors suggested transitory inhibition of the other pituitary non-GH lines by pasireotide, which seems irrelevant in most of the cases, opposite to pituitary insufficiency caused by large masses themselves or following pituitary surgery[50-52]. Practical points of understanding the over response to pasireotide opposite to first-generation of somatostatin analogues are the tumor combination of SSTR[53-55]. Despite the guideline recommendation that surgery remains the first option in a newly diagnosed case of acromegaly, the molecular approach based on medical therapy is heterogeneous and a better understanding of immunohistochemistry configuration immediately after pituitary surgery is very useful in deciding the further management. Almost half of the patients become candidates for further management due to functional disease; patient's option and cost-effective analysis should be taken into consideration, too[56,57].

Discussion

There are some limits of current use of pasireotide LAR for acromegaly in Romania. The first one, it is already discussed above: the use of pasireotide LAR as first line medication, as in subjects from C2305 study, which is not possible for the moment, unless the patients have been pre-exposed to octreotide or lanreotide and found non-responsives[36,58,59]. The second aspect, is related to the fact that for the moment the association with pegvisomant is not allowed in our country, opposite to other studies as recently published PAPE study[60].

Conclusion

In acromegalic patients, who were treated with somatostatin analogues of first generation and did not achieve disease control, the clinician has to establish the second-line therapy and currently this cross-road includes a new feasible option – pasireotide LAR.

Conflict of interest: AG, MC, AV have been speakers for Novartis; however, the present paper is independent of any pharmaceutical company and it entirely represents the authors' opinion.

Founding resources: none

Acknowledgment: we thank the medical teams that initially followed-up the patient and referred him to us.

Compliance with Ethics Requirements:

„The authors declare no conflict of interest regarding this article"

„The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from the patient included in the study"

References

1. Katznelson L, Laws ER Jr, Melmed S, et al. Endocrine Society Acromegaly: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab.* 2014;99(11):3933-51.
2. Valea A, Carsote M, Morar A, et al. Metabolic approach in patients with active acromegaly: a cross-sectional study of 60 cases. *Current Health Sciences Journal.* 2015;41(Suppl. 1): 47-53.
3. Carsote M, Ghemigian A, Ghervan C, Valea A. Acromegaly: focus on facial, oral, and dental anomalies. *Medicine in evolution.* 2016;XXII(2):241-247.
4. Hannah-Shmouni F, Trivellin G, Stratakis CA. Genetics of gigantism and acromegaly. *Growth Horm IGF Res.* 2016;30-31:37-41.
5. Paun D, Carsote M, Valea A, Ghemigian A. Hypogonadism hypogonadotropic on young females without genetic syndromes. *Current Health Sciences Journal.* 2016;42(S5):43-45.
6. Ghemigian A, Carsote M, Ghervan C, et al. Long-term follow-up after transcranial hypophysectomy in macroprolactinomas. *Journal of Surgical Sciences.* 2016;3(1):44-50.
7. Carsote M, Albu SE, Ghemigian A, Georgescu C, Valea A. Surgical approach in pituitary tumours: the role of endocrine profile. *Journal of Surgical Sciences.* 2015;2(4):176-182.
8. Valea A, Ghervan C, Carsote M, Albu SE, Georgescu CE. Different surgical options in Cushing's disease. *Journal of Surgical Sciences.* 2016;3(1):39-43.
9. Kimmell KT, Weil RJ, Marko NF. Multi-modal management of acromegaly: a value perspective. *Pituitary.* 2015;18(5):658-65.
10. Valea A, Carsote M, Terzea D, Ghemigian A. Timing of surgical approach on patients with somatotropinoma and differentiated thyroid cancer. *Journal of Surgical Sciences.* 2016;3(3):148-152.
11. Giustina A, Chanson P, Kleinberg D, et al. Acromegaly Consensus Group. Expert consensus document: A consensus on the medical treatment of acromegaly. *Nat Rev Endocrinol.* 2014;10(4):243-8.
12. Biermasz NR. New medical therapies on the horizon: oral octreotide. *Pituitary.* 2017;20(1):149-153.
13. Donoho DA, Bose N, Zada G, Carmichael JD. Management of aggressive growth hormone secreting pituitary adenomas. *Pituitary.* 2017;20(1):169-178.
14. Gheorghisan-Galateanu AA, Valea A, Carsote M. Acromegaly profile on menopausal women after 36 months of medical therapy with somatostatin analogues. *Medicine in evolution.* 2016;XXII(3):361-366.
15. Cuevas-Ramos D, Fleseriu M. Pasireotide: a novel treatment for patients with acromegaly. *Drug Des Devel Ther.* 2016;10:227-39.
16. www.cnas.ro
17. https://ec.europa.eu/health/documents/community-register/2016/20161118136298/anx_136298_ro.pdf

18. Valea A, Morar A, Pop D, Carsote M, Ghemigian A, Dumitrache C. Infertility as the onset of Cushing's disease: is pasireotide a treatment option? *Ars Medica Tomitana*. 2015;3(21):128-131.
19. Kim EH, Oh MC, Chang JH et al. Postoperative gamma knife radiosurgery for cavernous sinus-invading growth hormone-secreting pituitary adenomas. *World Neurosurg.* 2017; S1878-8750(17)31966-6.
20. Almeida JP, Ruiz-Treviño AS, Liang B, et al. Reoperation for growth hormone-secreting pituitary adenomas: report on an endonasal endoscopic series with a systematic review and meta-analysis of the literature. *J Neurosurg.* 2017:1-13.
21. Kim JH, Hur KY, Lee JH, et al. Outcome of endoscopic transsphenoidal surgery for acromegaly. *World Neurosurg.* 2017;104:272-278.
22. Babu H, Ortega A, Nuno M, et al. Long-term endocrine outcomes following endoscopic endonasal transsphenoidal surgery for acromegaly and associated prognostic factors. *Neurosurgery.* 2017;81(2):357-366.
23. Briceno V, Zaidi HA, Doucette JA, et al. Efficacy of transsphenoidal surgery in achieving biochemical cure of growth hormone-secreting pituitary adenomas among patients with cavernous sinus invasion: a systematic review and meta-analysis. *Neurol Res.* 2017;39(5):387-398.
24. Anthony JR, Alwahab UA, Kanakiya NK, et al. Significant elevation of growth hormone level impacts surgical outcomes in acromegaly. *Endocr Pract.* 2015;21(9):1001-9.
25. Diri H, Ozaslan E, Kurtsoy A, et al. Prognostic factors obtained from long-term follow-up of pituitary adenomas and other sellar tumors. *Turk Neurosurg.* 2014;24(5):679-87.
26. Nishioka H, Fukuhara N, Horiguchi K, Yamada S. Aggressive transsphenoidal resection of tumors invading the cavernous sinus in patients with acromegaly: predictive factors, strategies, and outcomes. *J Neurosurg.* 2014;121(3):505-10.
27. Gurel MH, Han Y, Stevens AL, Furtado A, Cox D. Treatment adherence and persistence with long-acting somatostatin analog therapy for the treatment of acromegaly: a retrospective analysis. *BMC Pharmacol Toxicol.* 2017;18(1):22.
28. Dal J, Høyer KL, Pedersen SB, et al. Growth hormone and insulin signaling in acromegaly: impact of surgery versus somatostatin analog treatment. *J Clin Endocrinol Metab.* 2016;101(10):3716-3723.
29. Cuny T, Barlier A, Feelders R, et al. Medical therapies in pituitary adenomas: Current rationale for the use and future perspectives. *Ann Endocrinol (Paris).* 2015;76(1):43-58.
30. Valea A, Carsote M, C.Ghervan, C.Georgescu. Glycemic profile in patients with acromegaly treated with somatostatin analogue. *Journal of Medicine and Life*. 2015;8(Special Issue):79-83.
31. Valea A, Ghervan C, Carsote M, Morar A, et al. Effects of combination therapy: somatostatin analogues and dopamine agonists on GH and IGF1 levels in acromegaly. *Clujul Medical*. 2015;88(3):310-313.
32. Nishioka H, Fukuhara N, Yamaguchi-Okada M, Takeshita A, Takeuchi Y, Yamada S. Pitfalls in early biochemical evaluation after transsphenoidal surgery in patients with acromegaly. *Endocr J.* 2017;64(11):1073-1078.
33. Christiansen ASM, Trolle C, Alvarson E, Bæk A, Dal J, Otto Lunde Jørgensen J. Biochemical assessment of disease control in acromegaly: reappraisal of the glucose suppression test in somatostatin analogue (SA) treated patients. *Endocrine.* 2017;56(3):589-594.
34. Gatto F, Biermasz NR, Feelders RA, et al. Low beta-arrestin expression correlates with the responsiveness to long-term somatostatin analog treatment in acromegaly. *Eur J Endocrinol.* 2016;174(5):651-62.
35. Bronstein MD. Acromegaly: molecular expression of somatostatin receptor subtypes and treatment outcome. *Front Horm Res.* 2006;35:129-34.
36. Colao A, Bronstein MD, Freda P, et al. Pasireotide C2305 Study Group. Pasireotide versus octreotide in acromegaly: a head-to-head superiority study. *J Clin Endocrinol Metab.* 2014;99(3):791-9.
37. Bronstein MD, Fleseriu M, Neggers S, et al. Pasireotide C2305 Study Group. Switching patients with acromegaly from octreotide to pasireotide improves biochemical control: crossover extension to a randomized, double-blind, Phase III study. *BMC Endocr Disord.* 2016;16:16.
38. Gadelha MR, Bronstein MD, Brue T, et al. Pasireotide C2402 Study Group. Pasireotide versus continued treatment with octreotide or lanreotide in patients with inadequately controlled acromegaly (PAOLA): a randomised, phase 3 trial. *Lancet Diabetes Endocrinol.* 2014 ;2(11):875-84.
39. Gadelha M, Bronstein M, Brue T, et al. Long-acting pasireotide provides clinical benefit in patients with acromegaly: results from a 30-month analysis of the phase 3 Paola Study. *ENDO* 2017. Sun432 abstract.
40. Lewis I, Bauer W, Albert R, et al. A novel somatostatin mimic with broad somatotropin release inhibitory factor receptor binding and superior therapeutic potential. *J Med Chem.* 2003;46(12):2334-44.
41. Murasawa S, Kageyama K, Sugiyama A, et al. Inhibitory effects of SOM230 on adrenocorticotropic hormone production and corticotroph tumor cell proliferation in vitro and in vivo. *Mol Cell* Endocrinol. 2014; 25;394(1-2):37-46.
42. Feelders RA, de Herder WW, Neggers SJ, van der Lely AJ, Hofland LJ. Pasireotide, a multi-somatostatin receptor ligand with potential efficacy for treatment of pituitary and neuroendocrine tumors. *Drugs Today* (Barc). 2013;49(2):89-103.
43. Shenouda M, Maldonado M, Wang Y, et al. An open-label dose-escalation study of once-daily and twice-daily pasireotide in healthy volunteers: safety, tolerability, and effects on glucose, insulin, and glucagon levels. *Am J Ther.* 2014;21(3):164-73.
44. Cuevas-Ramos D, Fleseriu M. Somatostatin receptor ligands and resistance to treatment in pituitary adenomas. *J Mol Endocrinol.* 2014;52(3):R223-40.
45. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/002052/WC500128059.pdf
46. https://www.pharma.us.novartis.com/sites/www.pharma.us.novartis.com/files/signifor_lar.pdf
47. Ben-Shlomo A, Liu NA, Melmed S. Somatostatin and dopamine receptor regulation of pituitary somatotroph adenomas. *Pituitary.* 2017;20(1):93-99.
48. Paragliola RM, Corsello SM, Salvatori R. Somatostatin receptor ligands in acromegaly: clinical response and factors predicting resistance. *Pituitary.* 2017;20(1):109-115.
49. Maffezzoni F, Frara S, Doga M, Mazziotti G, Giustina A. New medical therapies of acromegaly. *Growth Horm IGF Res.* 2016;30-31:58-63.
50. Maffezzoni F, Formenti AM, Mazziotti G, Frara S, Giustina A. Current and future medical treatments for patients with acromegaly. *Expert Opin Pharmacother.* 2016;17(12):1631-42.
51. Sun L, Coy DH. Somatostatin and its Analogs. *Curr Drug Targets*. 2016;17(5):529-37.
52. Valea A, Marcusan A, Carsote M, Ghemigian A, Ghervan C, Dumitrache C. From headache to Rathke's cleft followed by diabetes insipidus with panhypopituitarism. *Ars Medica Tomitana* – 2015;3(21);137-140.
53. Shimon I, Saeger W, Wildemberg LE, Gadelha MR. Somatotropinomas inadequately controlled with octreotide

may over-respond to pasireotide: the importance of dose adjustment to achieve long-term biochemical control. *Hormones* (Athens). 2017;16(1):84-91.
54. Shanik MH, Cao PD, Ludlam WH. Historical response rates of somatostain analogues in the treatment of acromegaly: a systematic review. *Endocr Pract.* 2016;22(3):350-6.
55. Frara S, Maffezzoni F, Mazziotti G, Giustina A. The modern criteria for medical management of acromegaly. *Prog Mol Biol Transl Sci.* 2016;138:63-83.
56. Wildemberg LE, Gadelha MR. Pasireotide for the treatment of acromegaly. *Expert Opin Pharmacother.* 2016;17(4):579-88.
57. Zhang JJ, Nellesen D, Ludlam WH, Neary MP. Budget impact of pasireotide LAR for the treatment of acromegaly, a rare endocrine disorder. *J Med Econ.* 2016;19(4):374-85.
58. Iacovazzo D, Carlsen E, Lugli F, et al. Factors predicting pasireotide responsiveness in somatotroph pituitary adenomas resistant to first-generation somatostatin analogues: an immunohistochemical study. *Eur J Endocrinol.* 2016;174(2):241-50.
59. McKeage K. Pasireotide in acromegaly: a review. *Drugs.* 2015;75(9):1039-48.
60. Muhammad A, van der Lely AJ, Delhanty PJD, et al. Efficacy and safety of switching to pasireotide in acromegaly patients controlled with pegvisomant and first-generation somatostatin analogues (PAPE study). *J Clin Endocrinol Metab.* 2017.