The Era of Personalized Treatment in Acromegaly

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Acromegaly is characterized by chronic hypersecretion of growth hormone (GH) almost always by a pituitary somatotroph adenoma leading to elevated IGF-1 levels (1). Recent data suggests an increased prevalence of acromegaly (71 - 87.8 cases/$10^{6)}$ and incidence (9.6 - 11.7 new cases/10^6/year) compared to previously reported (2). Acromegaly is diagnosed usually 6 - 10 years after the estimated onset of symptoms [1,3]. Comorbidities of acromegaly could be from cardiovascular system (hypertension, left ventricular hypertrophy, cardiomyopathy, congestive heart failure, arrhythmias, coronary atherosclerosis), respiratory system (obstructive sleep apnea, upper respiratory tract obstruction), reproductive system (decreased libido, erectile dysfunction), metabolic disorders (diabetes, abnormal glucose tolerance), pituitary gland disorders (hyperprolactinemia, pituitary insufficiency), thyroid disorders, osteoarthritis, bone growth disorders, intestinal neoplasms and organs swelling [4]. Acromegaly is a disorder with increased late morbidity and mortality if not treated. Mortality in acromegaly has been decreased over time, while recent data suggests that cardiovascular complications are no longer the first cause of death, as opposed to malignancies [5,6].

Surgery is usually the mainstay of therapy [4]; most patients are cured by a trans-sphenoidal removal of the adenoma. After disease remission the annual follow-up includes assessment of insulin-like growth factor 1 (IGF - 1), a random value of GH and oral glucose tolerance test (OGTT). When there are clinical or biochemical signs of recurrence, assessment with magnetic resonance imaging (MRI) should be considered. In cases of persistent disease (incomplete surgical removal), surgical debulking or poor surgical candidate, medical therapy should be administered. Drugs include mostly somatostatin analogs (SSAs), dopamine agonists (DA) in mild disease and pegvisomant [4].

First-generation somatostatin analogs (SSAs) (octreotide or lanreotide)

Are the first-line medical therapy used in acromegaly [4]. Response rates vary considerably in the literature [7]. Normal levels of IGF - 1 are achieved by SSAs treatment in 17 - 35% of patients and tumor size decreases > 50% in 59% of patients. Partial response is considered the reduction of GH and IGF - 1 by 50% compared to basal levels and/or tumor size by 20%. Both IGF - 1 and GH are important parameters, since IGF - 1 reflects the activity of disease and GH reflects the activity and viability of tumor [8]. Colao, *et al.* suggested a beneficial effect of dose escalation of octreotide long-acting repeatable (LAR) as first-line therapy in patients with acromegaly [9]. On the other hand, Somarcol study (an observational multicenter study), showed a beneficial outcome with the administration of lanreotide auto gel 120 mg at extended dosing intervals (more than 4 weeks) at least for 6 months providing IGF - 1 control in more than 90% of patients with acromegaly, with good levels of treatment satisfaction and compliance [10].

Regarding the preoperative role SSAs therapy, the only valid recommendation for pre-treatment with SSA might be the invasive macro- or giant adenomas, without a clear benefit for the entire group of GH-secreting pituitary adenoma [11].

Long- acting pasireotide, a 2nd generation SSAs, has higher affinity for somatostatin receptor 1 (SSTR1), -2,-3 and -5 (highest affinity for SSTR5) [12]. Pasireotide has proven its effectiveness not only in non-treated patients but also in patients with no biochemical response in first-generation SSAs. Pasireotide decreases GH and IGF-1 and improves clinical signs and has been associated with a signifi-

cant decrease of tumor size. Pasireotide is safe as first-generation SSAs except for the higher prevalence and severity of hyperglycemia [13,14]. According to PAOLA study, a prospective, randomized, phase III, 24 - week, multicenter study, pasireotide provided superior efficacy compared with continued treatment with octreotide or lanreotide, and could become a novel therapeutic option in patients with acromegaly, who had inadequate response at first-generation SSAs [14,15]. Furthermore, an ongoing observational study in patients with uncontrolled acromegaly and being treated with long-acting pasireotide (ACRONIS) has showed by first interim analysis at six months, a significant biochemical improvement [16].

The role of SSA was also reflected by the reduction in mortality caused by the disease as it has recently been shown [17].

Cabergoline, a dopamine agonist, DA, is more effective in patients with mild to moderate increase in GH and IGF - 1 [4,18]. It is well tolerated, and the most common side effects are weakness, dizziness and nausea; echocardiogram should be recommended to check valvolopathy [18].

Pegvisomant (PEG), a GH receptor antagonist, does not target the adenoma but blocks the peripheral synthesis of IGF - 1 [19,20]. It is well tolerated, and the most common side effects are cutaneous rashes, skin reaction at site and elevated levels of transaminases [20]. Therefore, systemic monitoring of tumor size and hepatotoxicity is required. The first meta-analysis evaluating the effect of PEG on a complete panel of glucose metabolism parameters has showed that PEG can induce significant decrease in fasting plasma glucose (FPG), glycosylated hemoglobin A1c (HbA1c), fasting plasma insulin and homeostatic model assessment of insulin resistance (HOMA-IR) and consequently improve glucose metabolism. Of note, PEG effect on glucose metabolism seems to be independent from disease control and therefore should be considered in patients with severe metabolic impairment as opposed to SSA treatment which reduces insulin levels, increases after load glucose and, increases HbA1c levels without affecting FPG [21].

In case of partial clinical and biochemical response to maximal doses of the aforementioned drugs, their combination should be considered. Another option includes an alternative drug monotherapy. Radiation either stereotactic or conventional might be used in cases with no response or intolerance to medication or at any point after incomplete surgical removal [4].

Predictors of therapeutic response to SSAs of first generation are young age, male sex, increased levels of GH, sparsely granulated adenoma, high signal intensity on T2 - weighted MRI (marker for granulation pattern), or aggressivity of pituitary adenoma as assessed by Knops criteria [22,23]. Interestingly, sparsely granulated adenomas had a higher T2 intensity than densely or intermediately granulated adenomas [24,25]. Other predictors of therapeutic response to SSAs are negative octreotide scan, high expression of ki-67, low expression or absence of SSTR2, low ratio SSTR2/SSTR5, high expression of somatostatin receptor 5 coupled transmembrane domain 4 (functional variant SSTR5TMD4), SSTR5 mutation, low aryl hydrocarbon receptor-interacting protein (AIP) expression, decreased expression of tumor-suppressor gene ZAC1 after SSAs administration, low E-cadherin and low Raf Kinase Inhibitory Protein (RKIP) [23]. The antiproliferative effect of SSAs depends on tissue SSTR expression pattern, agonist binding profile and SSTR effector coupling [26]. However, the variable expression of SST receptors may explain the lack of correlation between low levels of SSTR and response to treatment [27]. According to The Molecular Registry of Pituitary Adenomas (REMAH study), somatotropinomas are heterogeneous tumors with a high variable molecular expression of genes associated to SSAs response [28]. E-cadherin expression is associated with the response to SSAs in patients with acromegaly; a poor response is associated with absence of E-cadherin (E-cadherin⁻) in somatotropinomas [29]. More specifically, at 3 months of treatment, the median decrease in percent of IGF-1 for adenomas E-cadherin⁻ was 4.1% and for E-cadherin⁺ 44.2%. At 6 months of treatment, the median decrease of IGF-1 for E-cadherin⁻ adenomas was 8.9% and for E-cadherin⁺ a 49.8%. E-cadherin⁻ adenomas displayed lower SSTR1 and D4 dopamine receptor expression levels [28,29].

The relationship between receptor profiling and response to treatment is not simple due to variety of receptor expression [30]. Despite the fact that pasireotide LAR demonstrated superior efficacy over octreotide LAR in terms of biochemical control and tumor volume, the presence of receptors in the tumor, particularly SSTR2, is not sufficient to predict response. Proteins such as AIP, ZAC, β-arrestin, or fila-

min could explain some pure responses [23,31]. Heterogeneity in measuring techniques and differences across studies in treatments and criteria used should be taken in consideration [23,32-38].

Summarizing, SSAs, DA and PEG are our medical choices. The SSAs of first-generation treatment is the first choice and the majority of patients respond to them. In case of partial response to the above mentioned treatments, a combination of them or higher dose of SSAs is suggested. Alternative monotherapy either with pegvisomant or pasireotide in case of no response should be also considered [4]. Nowadays, in patient with no response to monotherapy with first-generation SSAs, combination therapy either SSA (1st or 2nd generation) and/or pegvisomant and/or cabergoline is suggested to improve the therapeutic response and may allow a decrease in dose of the individual drug [39]. Monitoring is recommended for the side effects from each medical choice. PAPE study, a 24 - week prospective study, showed efficacy and safety of switching to pasireotide LAR monotherapy or in combination with pegvisomant in patients controlled with combination therapy of first-generation SSAs and pegvisomant [40]. An extension, open-label 48 - week study, revealed a further benefit of this latter treatment [41]. On the other hand, the efficacy of pasireotide LAR as first-line treatment in patients with resistant acromegaly was suggested by an Italian cohort in a large and single center [42].

To note, data collected in national registry studies highlight that patients receiving medical therapy, either as first-line treatment or following surgery or radiotherapy, are not adequately controlled in real-world clinical practice [43-46]. A single center study highlights the role of GH in morbidity and mortality in acromegaly. The decrease of GH concentration significantly reduces vascular morbidity, which was considered the predominant cause of death for patients with acromegaly. Assessment of total exposure to GH emerged as a new parameter reflecting disease severity [47]. The above results highlight the importance of achieving control of GH levels early, to minimize the exposure of various tissues to supra-physiological doses of GH and thereby reduce mortality and morbidity.

Hence, approved treatments related to SSAs are: octreotide LAR, which is administered IM every four weeks; lanreotide autogel, which is administered subcutaneously every 4 weeks, and pasireotide LAR, which is administered IM every four weeks. Octreotide capsules are under completion of phase III trials [48] and octreotide implants are under phase II trials [49]. Factor CAM2029, an octreotide binding in a liquid mold with affinity for SSTR2and5 subcutaneously administered is under investigation [50-52]. Under phase II trials is also factor PTR - 3173 (Somatropin), a ligand to somatostatin receptor with high selectivity for GH suppression and affinity for SSTR2,4,5, administered IM every 4 weeks [53]. Moreover, the only approved treatment not related to SSAs is pegvisomant, a GH receptor antagonist administered subcutaneously. Under investigation are also other factors non related to SSAs such as: ATL1103, a subcutaneously administered oligonucleotide for the GH receptor [54]; dopastatin (BIM - 23A760/BIM - 065) [55], a D2R chimeric receptor that binds to D2 and SSTR2,-5 is more potent and without intermediate metabolites but its efficacy decreases over time [56]; temozolamide, an alkylating agent [22]; botulinum toxin molecule [57], a chimeric molecule that binds to cells expressing GHRH receptors to induce GH inhibition.

In conclusion, patients with acromegaly deal with increased morbidity and mortality if not adequately controlled. New prognostic markers in response to treatment are recognized and employed for therapeutic decisions aiming to a personalized treatment. It is expected that new pharmaceutical agents will be more efficient and safer.

Bibliography

1. Melmed S. "Medical progress: Acromegaly". *The New England Journal of Medicine* 355 (2006): 2558-2573.

2. Broder MS., *et al.* "Incidence and Prevalence of Acromegaly in The United States: A Claims-Based Analysis". *Endocrine Practice* 22 (2016): 1327-1335.

3. Schneider HJ., *et al.* "A novel approach to the detection of acromegaly: accuracy of diagnosis by automatic face classification". *The Journal of Clinical Endocrinology and Metabolism* 96 (2011): 2074-2080.

4. Katznelson L., *et al.* "Acromegaly: an endocrine society clinical practice guideline". *The Journal of Clinical Endocrinology and Metabolism* 99(2014): 3933-3951.

5. Dal J., *et al.* "Cancer Incidence in Patients with Acromegaly: A Cohort Study and Meta-Analysis of the Literature". *The Journal of Clinical Endocrinology and Metabolism* 103 (2018): 2182-2188.

6. Maione L., *et al.* "French Acromegaly Registry Group. Changes in the management and comorbidities of acromegaly over three decades: the French Acromegaly Registry". *European Journal of Endocrinology* 176 (2017): 645-655.

7. Colao A., *et al.* "Interpreting biochemical control response rates with first-generation somatostatin analogues in acromegaly". *Pituitary* 19 (2016): 235-247.

8. Oldfield EH., *et al.* "Correlation between GH and IGF-1 during treatment for acromegaly". *Journal of Neurosurgery* 126 (2017): 1959-1966.

9. Colao A., *et al.* "Beneficial effect of dose escalation of octreotide-LAR as first-line therapy in patients with acromegaly". *European Journal of Endocrinology* 157 (2007): 579-587.

10. Álvarez Escolá C., *et al.* "Observational, multicentre study to evaluate the effectiveness in routine clinical practice of Lanreotide Autogel 120 mg at extended dosing intervals (> 4 weeks) for the treatment of acromegaly: SOMACROL study". *Endocrine Abstracts* (2018) 56 GP11.

11. Lv L., *et al.* "Presurgical treatment with somatostatin analogues in growth hormone-secreting pituitary adenomas: A long-term single-centre experience". *Clinical Neurology and Neurosurgery* 167 (2018): 24-30.

12. Hofland LJ and Lamberts SW. "The pathophysiological consequences of somatostatin receptor internalization and resistance". *Endocrine Reviews* 24 (2003): 28-47.

13. Colao A., *et al.* "Pasireotide C2305 Study Group. Pasireotide versus octreotide in acromegaly: a head-to-head superiority study". *The Journal of Clinical Endocrinology and Metabolism* 99 (2014): 791-799.

14. Gadelha M., *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 Endocrinology* 2(2014): 875-884.

15. Gadelha MR., *et al.* "Long-Acting Pasireotide Provides Clinical Benefit in Patients with Acromegaly: Results from a 30-Month Analysis of the Phase 3 Paola Study, SUN 432". *Endocrine Reviews* 38.3 (2017).

16. Schöfl C., *et al.* "European observational study in patients with uncontrolled acromegaly who are being treated with long acting pasireotide: first interim analysis". *Endocrine Abstracts* (2018) 56 GP8.

17. Postma MR., *et al.* "Postoperative use of somatostatin analogs and mortality in patients with acromegaly". *Endocrine Abstracts* (2018).

18. Sandret L. *et al.* "Place of cabergoline in acromegaly: a meta-analysis". *The Journal of Clinical Endocrinology and Metabolism* 96 (2011): 1327-35.

19. Freda P., *et al.* "Long-term treatment with pegvisomant as monotherapy in patients with acromegaly: experience from ACROSTUDY". *Endocrine Practice* 21 (2015): 264-274.

20. van der Lely AJ., *et al.* "Long-term treatment of acromegaly with pegvisomant, a growth hormone receptor antagonist". *Lancet* 358 (2001): 1754-1759.

21. Cozzolino A., *et al.* "Somatostatin Analogs and Glucose Metabolism in Acromegaly: A Meta-analysis of Prospective Interventional Studies." *The Journal of Clinical Endocrinology and Metabolism (*2018).

22. Chatzellis E., *et al.* "Aggressive pituitary tumours". *Neuroendocrinology* 101 (2015): 87-104.

23. Gadelha M., *et al.* "Novel pathway for somatostatin analogs in patients with acromegaly". *Trends Endocrinology Metabolism* 24 (2013): 238-246.

24. Mete O and Lopes MB. "Overview of the 2017 WHO Classification of Pituitary Tumors". *Endocrine Pathology* 28 (2017): 228-243.

25. Potorac I., *et al.* "Pituitary MRI characteristics in 297 acromegaly patients based on T2-weighted sequences". *Endocrine-Related Cancer* 22(2015): 169-177.

26. Fougner SL., *et al.* "The clinical response to somatostatin analogues in acromegaly correlates to the somatostatin receptor subtype 2a protein expression of the adenoma". *Clinical Endocrinolog*y 68 (2008): 458-465.

27. Puig-Domingo M., *et al.* "Molecular profiling for assistance to pharmacological treatment of acromegaly ECE 2018.

28. Luque RM., *et al.* "The Molecular Registry of Pituitary Adenomas (REMAH): A bet of Spanish Endocrinology for the future of individualized medicine and translational research". *Endocrinología y Nutrición* 63 (2016): 274-284.

29. Cano DA., *et al.* "E-cadherin expression is associated with the response to somatostatin analogues in patients with acromegaly". *Endocrine Abstracts* (2018): 56 GP196.

30. Neto LV., *et al.* "Expression Analysis of Dopamine Receptor Subtypes in Normal Human Pituitaries, Non-functioning Pituitary Adenomas and Somatotropinomas, and the Association between Dopamine and Somatostatin Receptors with Clinical Response to Octreotide-LAR in Acromegaly". *The Journal of Clinical Endocrinology and Metabolism* 94 (2009): 1931-1937.

31. Gatto F., *et al.* "Low beta-arrestin expression correlates with the responsiveness to long-term somatostatin analogy treatment in acromegaly". *European Journal of Endocrinology* 174 (2016): 651-662.

32. Wenjuan Liu., *et al.* "Expression of Somatostatin Receptor 2 in Somatotropinoma Correlated with the Short-Term Efficacy of Somatostatin Analogues". *International Journal of Endocrinology (*2017).

33. Gonzalez B., *et al.* "Cytoplasmic expression of SSTR2 and 5 by immunohistochemistry and by RT/PC". *Endocrinol Nutrition* 61 (2014): 523-530.

34. Wildemberg LE., *et al.* "Low somatostatin receptor subtype 2, but not dopamine receptor subtype 2 expression predicts the lack of biochemical response of somatotropinomas to treatment with somatostatin analogy". *Journal of Endocrinological* 36 (2013): 38-43.

35. Takei M., *et al.* "Immunohistochemical detection of somatostatin receptor (SSTR) subtypes 2A and 5 in pituitary adenoma from acromegalic patients: good correlation with preoperative response to octreotide". *Endocrine Pathology* 18 (2007): 208-216.

36. Casar-Borota O., *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". *The Journal of Clinical Endocrinology and Metabolism* 98 (2013): E1730-9.

37. Park C., *et al.* "Somatostatin (SRIF) receptor subtype 2 and 5 gene expression in growth hormone-secreting pituitary adenomas: the relationship with endogenous srif activity and response to octreotide". *Endocrine Journal* 51 (2004): 227-236.

38. Ibáñez-Costa A., *et al.* "Octreotide and pareptide (dis)similarly inhibit pituitary tumor cells in vitro". *Journal of Endocrinology* 231 (2016): 135-145.

39. Lim DS, Fleseriu M. "The role of combination medical therapy in the treatment of acromegaly". *Pituitary* 20(2017):136-148.

40. Muhammad A., *et al.* "Efficacy and Safety of Switching to Pasireotide in Patients with Acromegaly Controlled with Pegvisomant and First-Generation Somatostatin Analogues (PAPE Study)". *The Journal of Clinical Endocrinology and Metabolism* 103 (2018): 586-595.

41. Coopmans EC., *et al.* "Efficacy and safety of switching to pasireotide LAR monotherapy or in combination with pegvisomant in acromegaly patients controlled with combination therapy of somatostatin analogues and pegvisomant (PAPE study): a prospective, open-label 48-week study". *Endocrine Abstracts* (2018): 56 GP4.

42. Chiloiro S., *et al.* "Efficacy of pasireotide lar in first line somatostatin analogue resistant acromegaly patients: experience from a large and single centre Italian cohort". *Endocrine Abstracts* (2018) 56 P875.

43. Mestron A., *et al.* "Epidemiology, clinical characteristics, outcome, morbidity and mortality in acromegaly based on the Spanish Acromegaly Registry (Registro Espanol de Acromegalia, REA)". *European Journal of Endocrinology* 151 (2004): 439-446.

44. Bex M., *et al.* "AcroBel--the Belgian registry on acromegaly: a survey of the 'real-life' outcome in 418 acromegalic subjects". *European Journal of Endocrinology* 157 (2007): 399-409.

45. Christof Schöfl., *et al.* "Long-term outcome in patients with acromegaly: analysis of 1344 patients from the German Acromegaly Register". *European Journal of Endocrinology* 168 (2013): 39-47.

46. Howlett TA., *et al.* "Control of growth hormone and IGF1 in patients with acromegaly in the UK: responses to medical treatment with somatostatin analogues and dopamine agonists". *Clinical Endocrinology* 79 (2013): 689-699.

47. Varadhan L., *et al.* "The role of cumulative growth hormone exposure in determining mortality and morbidity in acromegaly: a single centre study". *Pituitary* 19 (2016): 251-261.

48. Melmed S., *et al.* "Safety and efficacy of oral octreotide in acromegaly: results of a multicentre phase III trial". *The Journal of Clinical Endocrinology and Metabolism* 100 (2015): 1699-1708.

49. Long-term Safety and Efficacy Study of Octreotide Implant in Patients with Acromegaly. ClinicalTrials.gov.

50. Chieffo C., *et al.* "Efficacy and safety of an octreotide implant in the treatment of patients with acromegaly". *The Journal of Clinical Endocrinology and Metabolism* 98 (2013): 4047-4054.

51. Gadelha MR., *et al.* "A subcutaneous octreotide hydrogel implant for the treatment of acromegaly". *Endocrine Practice* 18 (2012): 870-881.

52. Phase II Study of Subcutaneous Inj. Depot of Octreotide in Patients with Acromegaly and Neuroendocrine Tumours (NETs). Clinical-Trials.gov.

53. Shimon I., *et al.* "PTR-3173 (somatoprim), a novel somatostatin analog with affinity for somatostatin receptors 2, 4 and 5 is a potent inhibitor of human GH secretion". *Journal of Endocrinol Investigation* 27 (2004): 721-727.

54. Trainer PJ., *et al.* "A randomised, open-label, parallel group phase 2 study of antisense oligonucleotide therapy in acromegaly". *European Journal of Endocrinology* 179 (2018): 97-108.

55. Jaquet P., *et al.* "BIM-23A760, a chimeric molecule directed towards somatostatin and dopamine receptors, vs universal somatostatin receptors ligands in GH-secreting pituitary adenomas partial responders to octreotide". *Journal of Endocrinol Investigation* 28 (2005): 21-27.

56. Jaquet P., *et al.* "Efficacy of chimeric molecules directed towards multiple somatostatin and dopamine receptors on inhibition of GH and prolactin secretion from GH-secreting pituitary adenomas classified as partially responsive to somatostatin analogy therapy". *European Journal of Endocrinology* 153 (2005): 135-141.

57. Somm E., *et al.* "A botulinum toxin-derived targeted secretion inhibitor downregulates the GH/IGF1 axis". *Journal of Clinical Investigation* 122 (2012): 3295-3306.

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