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EDITORIAL

Somatostatin analog withdrawal in patients with acromegaly: an elusive goal?

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The depot somatostatin analogs (SA) Octreotide LAR and Lanreotide autogel are currently the mainstay of the pharmacological therapy of acromegaly. These analogs are capable of achieving biochemical control (GH levels <2.5 ng/mL and IGF-1 normalization) in 30–60 % of the patients and importantly, most patients report a significant improvement in clinical symptoms of the disease [1–3]. Primary pharmacological therapy of acromegaly with these agents is increasingly being used in patients with inoperable tumors or with medical contraindications for surgery [1–3]. Furthermore, in some cases SA are used as primary treatment simply because of patient's preference. Perhaps the major disadvantage of SA therapy in acromegaly is the need to continue it indefinitely. Although long-term therapy with SA is safe and well tolerated, it does represent a significant economic burden [4]. Well-controlled patients can have their dose down titrated by increasing the injection interval, a strategy that can reduce costs significantly, while increasing convenience [5–7]. Although increasing the injection interval to every 6, 8, or more weeks is off-label in the US, it is a common practice in Europe and in Latin America [5–7]. In some patients increasing the injection interval is medically necessary in order to avoid GH deficiency.

The possibility of stopping SA after several years of successful therapy is tempting for obvious reasons. In this issue of *Endocrine* Vilar and colleagues from four Brazilian centers report a study in which octreotide LAR was withheld in 20 patients with acromegaly (four on primary treatment) who had been adequately controlled for at least 2 years [8]. They carefully followed these subjects with serial IGF-1 measurements and defined recurrence as the rise of IGF-1 to above 1.2× the upper limit of normal (ULN). Within 9 months of octreotide LAR discontinuation, 16 of the 20 patients recurred and were started back on the SA; the four remaining patients (one on primary treatment) continued to be on remission after 12–18 months follow up [8]. The only distinctive feature of the patients who remained on remission was having a lower IGF-1 at the moment of drug discontinuation [8].

Earlier attempts to discontinue SA therapy in patients with acromegaly have been made with rather disappointing results as over 80 % of the subjects relapse within a year of drug discontinuation [9–11]. The majority of these studies were not specifically designed to assess the feasibility of drug withdrawal, used varying definitions of biochemical recurrence and included patients receiving standard monthly doses of either octreotide LAR or lanreotide [10, 11]. Attempting drug withdrawal in patients who have required 20 or 30 mg of octreotide LAR every four weeks to maintain their GH and IGF-1 levels under control is probably a futile endeavor. In contrast, patients who over time have required a progressive reduction in dose (which in actual reality means increasing the injection interval) are the logical candidates to attempt drug withdrawal, as they had already proved to be exquisitely sensitive to the SA. In support of this concept, in a more recent prospective study, octreotide LAR was stopped in 12 patients with acromegaly who had been very well controlled on 20 mg injected every 8 or more weeks; 40 % of them remain in remission after over 3 years of follow up [12]. Of the 20 subjects included in Vilar's study, 12 were being injected every 4 weeks and 6 every 6 weeks, so it is no surprise that the

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injection interval did not turn out to be a predictive factor of successful discontinuation [8]. Furthermore, the 4 patients who remained in remission had very low baseline IGF-1 values (below 0.6 × ULN), almost in the GH deficiency range, and were probably receiving inappropriately high doses of the SA [8].

Most patients in whom octreotide discontinuation has been attempted in the context of a prospective study had been on secondary therapy after failed pituitary surgery [8, 12]. However, one of the four patients who successfully came off octreotide in Vilar's study was on primary treatment [8]. The other published prospective study evaluating the feasibility of SA withdrawal included one primarily treated patient, who has remained in remission for over 3 years after stopping octreotide [12]. This low probability of a successful drug discontinuation is in concordance with what we know about the effects of SA on GH-secreting tumors. Morphological changes in tumors pre-treated with octreotide include acidophilia, interstitial fibrosis, and a moderate reduction in cytoplasmic volume, yet no necrosis is found [13]. Studies carried out in primary cultures of somatotrophinomas do suggest that octreotide exposure results in activation of the caspase pathway; however, the induction of apoptosis in vivo has not been clearly demonstrated [14]. Thus, the available data indicate that the anti-proliferative effect of SA is more cytostatic than cytocidal. This is in contrasts to what occurs with prolactinomas treated with dopamine agonists whereby a cytocidal effect has been demonstrated and the likelihood of successfully coming off the medication after long-term treatment can be as high as 50 % [15].

Although discontinuing SA in patients with acromegaly is probably an elusive goal, increasing the injection interval is a feasible strategy and should be tried in selected patients since not only can result in important cost savings, but also can improve quality of life.

Conflict of interest Moisés Mercado is lecturer and consultant for Novartis, Oncology and Sanofi/Ipsen, México.

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