INVITED COMMENTARY

Somatostatin analogs in the treatment of acromegaly: the choice is now possible

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Introduction

There is now a consensus on the need for medical treatment with a somatostatin analog for acromegalic patients when surgery has failed or is contraindicated, or while waiting for the effects of pituitary irradiation. Extensive experience has been accumulated with octreotide, the first available somatostatin analog, which must be injected s.c. three times daily (1). Two long-lasting forms of somatostatin analogs, octreotide LAR (long-acting release) (2) and lanreotide PR (prolonged release) (3) are now available. Both depot formulations consist of active compounds encapsulated within microspheres of a biodegradable poly lactide-poly glycolide copolymer. After i.m. injection, both formulations result in a biphasic drug release. However, the pharmacokinetic profiles of the two formulations are quantitatively different. With the need for only one (octreotide LAR) or two to three monthly injections (lanreotide PR), these analogs markedly improve the quality of life of patients requiring long-term medical therapy. After the initial trials testing each of these prolonged-release forms and with regard to the experience accumulated by numerous clinicians, the questions which now arise are the following: (i) Do, nowadays, all acromegalic patients who require medical treatment for their disease, need to be treated with long-acting forms of somatostatin analogs, instead of short-acting octreotide? In other words, have long-acting forms of somatostatin analogs been proven to be at least as effective and as well tolerated as short-acting octreotide? (ii) Are the two available long-acting forms of somatostatin analogs comparable in terms of therapeutic efficacy? (iii) Finally, how will these two somatostatin analogs compare with pegvisomant, the new growth hormone (GH) receptor antagonist, whose efficacy and tolerance have been very recently published?

Long-acting somatostatin analogs vs short-acting somatostatin analogs

GH levels decrease in 50–80% of patients treated with octreotide s.c. three times daily (4–6). Up to 50% of acromegalic patients may be considered as ‘cured’ (GH plasma levels $<2 \mu g/l$ (20–30%) and/or normal insulin-like growth factor-I (IGF-I) (20–60%) with this treatment) (4–6). Similar results are obtained with lanreotide 30 mg administered i.m. for 10 or 14 days (GH plasma levels $<2 \mu g/l$ (30–70%) and/or normal IGF-I (40–70%)) (6–8). The multicenter study from Belgium and Italy published in this issue of European Journal of Endocrinology (9) confirms these data by showing that 45% (30 out of 66) and 45% (29 out of 66) of patients attained GH levels $<2.5 \mu g/l$ or normal age-adjusted IGF-I levels respectively. Even though this study was not randomized for the two forms of treatment, it demonstrates that both s.c. octreotide and PR lanreotide (in conditions of increasing frequency of lanreotide PR injections to once every 10 days in 29% and to once every week in 16% of patients) seemed equally effective when the same patients were successively treated by either form of treatment. It must be pointed out that a similar small number of patients (five) who were not controlled by one form of treatment were well controlled by the other.

Similar results are obtained with octreotide LAR, which may be administered i.m. every month at a dose of 20–30 mg (GH plasma levels $<2 \mu g/l$ (50–60%) and/or normal IGF-I (60–90%)) (2, 5, 6).

The variation in the efficacy figures obtained from one study to another may appear surprising. In fact, this is probably explained by the variation in the method of IGF-I measurement, and by the differences in the inclusion criteria of each study. Indeed, in some studies assessing the efficacy of the long-acting forms of somatostatin analog, patients were included only if they were previously responsive to octreotide, while in others, patients were entered blindly, without knowing if they were or were not responsive to octreotide.

The long-term tolerability of lanreotide PR is good, as shown by the low (9%) discontinuation rate reported in the study of Verhelst et al. (9), mainly due to gastrointestinal symptoms and pain at the injection site. In a large multicenter French study involving 116 patients we have previously shown that a large proportion of patients completed the 12 month treatment period (74%), and the remaining dropped out because of adverse events (7%), lack of efficacy (12%), and personal or treatment-unrelated reasons (7%) (8). However, about three-quarters of the patients complained of adverse effects in this study, a rate very
comparable with that observed in the study by Verhelst et al. (9). In the American multicenter trial of octreotide therapy in acromegaly, comparable rates of adverse events were elicited by enquiry (68 of 103 patients) during the first month of the study (10). In contrast, the number of patients self-reporting side-effects is generally lower in studies evaluating the effects of somatostatin analogs, whether they involve lanreotide PR (46% in the study by Giusti et al. (7)) or octreotide (37% in the study by Vance & Harris (4)). In all these long-term studies using octreotide or lanreotide, the incidence of side-effects tended to fall with time. Pain at the injection site is probably one of the major side-effects of both long-acting somatostatin analog treatments, as shown by the high number of patients (20–30%) complaining of this side-effect as compared with the small percentage of patients complaining of pain after s.c. injection of octreotide (7.5%) (7–12).

Either as short-acting or as long-acting forms, somatostatin analogs do not produce clinically relevant modifications in glucose tolerance of normal individuals or in glucose control in diabetic patients. Whether treatment with long-acting somatostatin analogs is or is not associated with a reduced incidence of new gallstones is difficult to assess for two reasons. First, because numerous papers do not provide data about the true incidence of new gallstones (i.e. after exclusion of patients with gallstones at enrollment) as they did not perform ultrasonographic studies before somatostatin analog treatment and only give gallstones prevalence rates at the end of the study. Secondly, because there is a wide difference in prevalence and incidence of gallstones according to the country in which the study has been conducted, emphasizing the importance of ethnic origin and nutritional habits. Nevertheless, when compared with the incidence observed in prospective gallbladder ultrasonography studies of patients treated with octreotide, which ranged between 9.5% of English, 19% of French, 23.5% of American, 27.7% of Italian and 55% of Chinese acromegalic patients (6), biliary tolerability of lanreotide PR treatment may be better, as only 3–12% of Italian, Belgian or French acromegalic patients developed new gallstones (8, 9).

Finally, what is not doubtful from clinical trials and overall from clinical practice is that patients largely prefer long-acting forms, even at the price of a painful injection, due to the major advantage of the reduced number of injections.

**Octreotide LAR vs lanreotide PR**

Very few studies have compared the efficacy and tolerability of the two long-acting somatostatin analogs octreotide LAR and lanreotide PR. In two studies, the sample size of the patients was small (n = 10 and 12), but their results were in favor of octreotide LAR (13, 14). In a larger multicenter study involving 125 patients switched from lanreotide PR, we have recently shown that the GH concentrations were significantly lower after three injections of 20 mg octreotide LAR as compared with those found at the last evaluation on lanreotide PR (11). The percentages of patients with GH profile mean levels ≤2.5 μg/l and ≤1 μg/l slightly increased after the change of the treatment. Furthermore, the percentage of patients with a normal age-adjusted IGF-I level increased from 48 to 65%. However, it must be pointed out that in this study the patients were on two or three monthly injections (as recommended by the manufacturer) and thus were not potentially on the maximal therapeutic regimen, if one considers that up to 16% of patients may require four injections per month, as shown in the study reported by Verhelst et al. (9). In conclusion, differences in efficacy between the two long-acting analogs, if they exist, are probably small if comparison is made between once monthly injection of octreotide LAR (at doses of 10, 20 or 30 mg) and two to four monthly injections of 30 mg lanreotide PR. In the absence of true double-blind randomized studies allowing comparison of tolerance between the two long-acting forms, it is only possible to consider the reported incidence of side-effects with both formulations, which seems very comparable.

**Somatostatin analogs vs GH receptor antagonists**

Recently, the GH receptor antagonist pegvisomant has been reported to be effective in the treatment of acromegaly (15). A significant and dose-dependent reduction in IGF-I levels was observed (−26.7%, −50.1% and −62.5% with 10, 15 or 20 mg pegvisomant respectively). At the end of the study, normal age-adjusted IGF-I levels were obtained in 54, 81 and 89% of patients treated with 10, 15 or 20 mg pegvisomant respectively. Obviously, a significant increase in mean GH levels was observed in patients treated with 15 or 20 mg pegvisomant. Rare gastrointestinal symptoms and local skin reactions at the site of injection were reported. In one patient, hepatic cytolysis was observed. At the first glance, this type of treatment appears to be superior to treatment with somatostatin analogs. However, it must be pointed out that patients were treated during a short period of time (3 months in this study) and that data on sustained effects with prolonged treatment are not yet available in a large group of patients. There also remains some concern about the course of tumoral remnants during this type of treatment, particularly for long-lasting periods as required by medical management of acromegaly. To allow strict comparisons between somatostatin analogs and GH receptor antagonists to be made, it is urgent to design well-conducted, double-blind randomized trials. Indeed, with regards to the very high costs of these
different treatments, strong data about efficacy, tolerability and quality of life are mandatory.

References