CLINICAL STUDY

The efficacy and safety of lanreotide Autogel in patients with acromegaly previously treated with octreotide LAR

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Abstract

Objective: Lanreotide Autogel is a sustained-release aqueous gel formulation supplied in a prefilled syringe, with injection volume <0.5 ml. The aim of this study was to establish the efficacy and safety of Autogel in patients with acromegaly previously treated with octreotide LAR.

Design: A 28-week, open, multicentre study.

Patients: Twelve patients with acromegaly, treated with 20 mg octreotide LAR for >4 months, with serum GH levels <10.0 mU/l.

Methods: Autogel (90 mg) was given every 28 days during weeks 0–12. At week 16 the dose was titrated based on GH levels at weeks 8 and 12. If GH levels were <2.0, 2.0–5.0, or >5.0 mU/l, Autogel was reduced to 60 mg, maintained at 90 mg, or increased to 120 mg respectively, for the next three injections. GH and IGF-I levels were reassessed at weeks 24 and 28.

Results: Ten patients completed the study. Five remained on 90 mg Autogel throughout the study; in two patients the dose was reduced to 60 mg from week 16; in three patients it was increased to 120 mg. Mean GH levels were: baseline, 3.0 ± 1.7 mU/l; week 12, 3.5 ± 1.8 mU/l; week 28, 3.3 ± 1.6 mU/l (NS). Mean IGF-I levels were: baseline, 212 ± 70 µg/l; week 12, 185 ± 91 µg/l; week 28: 154 ± 61 µg/l ($P = 0.027$). Six patients at baseline and eight at week 28 had normalised GH and IGF-I levels. Three patients reported adverse events: musculoskeletal pain ($n = 2$) and injection-site symptoms ($n = 1$).

Conclusions: Lanreotide Autogel is effective and well tolerated in patients with acromegaly. This study in a small group of patients with well-controlled acromegaly suggests that the majority of patients switched from 20 mg LAR to 90 mg Autogel will have equivalent or better disease control.

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Introduction

The introduction of long-acting somatostatin analogues has transformed the treatment of acromegaly, enabling effective symptom and disease control for patients in whom surgery and/or radiotherapy have not effected a cure. Slow-release preparations have further improved control and efficacy (1) and these agents are now the medical therapy of choice in this situation (2, 3). Somatostatin analogues also provide effective primary medical therapy for a proportion of patients with *de-novo* acromegaly, in whom there results normalisation of GH and IGF-I levels, together with substantial tumour shrinkage (4, 5).

Native somatostatin-14 has a plasma half-life of only approximately 2.5 min (6, 7). The synthetic somatostatin analogues, lanreotide and octreotide, have longer plasma half-lives of 90 and 110 min respectively (8, 9). However, multiple daily injections or continuous

subcutaneous infusion of these drugs remains a necessity and this detracts from patient acceptability.

Depot formulations of these peptides, octreotide LAR (LAR) and lanreotide LA, have been developed by incorporation of the somatostatin analogue into a biodegradable polylactide–polyglycolide co-polymer. These preparations result in extended drug release following intramuscular injection and provide effective plasma drug levels and growth hormone suppression for approximately 28 and 14 days following a single intramuscular injection of octreotide LAR and lanreotide LA respectively (1, 10, 11).

Recently, a new formulation of lanreotide has become available, Autogel. This is a viscous aqueous gel, composed solely of water and lanreotide. Intramuscular injection results in a pharmacokinetic profile very close to first-order kinetics, with plasma lanreotide concentrations being maintained above the therapeutic level of 1 µg/l for at least 28 days after injection

(Beaufour Ipsen, Paris, France, unpublished observations). However the pharmacokinetics of Autogel are not different if given by intramuscular or deep subcutaneous injection (Ipsen Limited, unpublished observations). Autogel is presented in a sterile, prefilled syringe in doses of 60, 90 and 120 mg, with an injection volume of 0.2–0.4 ml. Elimination of the need for reconstitution with vehicle increases the ease of use of the drug and minimises wastage compared with microparticle preparations. Deep subcutaneous administration may also lead to increased treatment acceptance compared with intramuscular depot preparations.

Biochemical control of acromegaly has been reported to be equivalent with Autogel and lanreotide LA. In a study of 107 patients previously treated with 30 mg lanreotide LA every 14, 10 or 7 days, Autogel was commenced at doses of 60, 90 or 120 mg respectively, every 28 days (12). After three injections of Autogel, disease control (as assessed by plasma lanreotide, growth hormone (GH), insulin-like growth factor-I (IGF-I) levels and symptoms) was not different to that achieved with lanreotide LA. The relative efficacy of lanreotide Autogel and octreotide LAR, and the effect of switching from LAR to Autogel have not yet been investigated.

The aims of this study were to establish the efficacy and safety of lanreotide Autogel in patients with acromegaly previously treated with octreotide LAR, to investigate whether switching from LAR to Autogel would have any impact on biochemical or symptomatic disease control, and to establish clinically equivalent doses.

Subjects and methods

This was a phase 3, open-label, multicentre study performed at three specialist UK centres, in patients with acromegaly stably treated with 20 mg octreotide LAR. Treatment was switched to lanreotide Autogel at week 0 and disease control with Autogel therapy was compared with the patients' baseline control on LAR.

An independent ethics committee approved the study protocol and documentation at each site. The study was performed in accordance with the Declaration of Helsinki and the principles of Good Clinical and Laboratory Practices (GCP, GLP). All patients gave written informed consent before entering the study.

Patients

For inclusion, patients (aged over 18 years) with acromegaly were required to have been treated with 20 mg LAR for at least 4 months. Mean baseline serum GH level on octreotide LAR had to be ≤ 10.0 mU/l. Patients were excluded if they had undergone pituitary surgery within 6 months or radiotherapy within 1 year of the start of the study, or if either of these interventions were thought to be required during the 28-week

study period. Patients were excluded if they were being treated with a dopamine agonist or a somatostatin analogue other than octreotide LAR (20 mg). Female patients of childbearing age were excluded if they were pregnant, lactating, or were not taking adequate contraception.

Twelve patients were recruited. Two patients withdrew before week 12, one due to symptoms that may have been related to GH control (see adverse events), and one due to recurrent depression, thought to be unrelated to Autogel treatment. Ten patients completed the study and represent the per-protocol population (Tables 1 and 2). All results reflect data collected from this population. This was a group of patients with well-controlled acromegaly (baseline serum GH 3.0 ± 1.7 mU/l; IGF-I 212 ± 70.1 μ g/l). However, requirement for somatostatin analogue therapy was demonstrated by mean serum GH and IGF-I levels of 8.0 ± 3.7 mU/l and 453 ± 145 μ g/l respectively, following withdrawal from, or prior to commencement of therapy, at a mean of 44 ± 23 months before the study.

Study design

Patient eligibility was confirmed by a screening visit 4 weeks before the study commenced at week 0. This included an assessment of mean serum GH and IGF-I levels. The study was then conducted in two stages (Fig. 1).

Stage 1 (weeks 0–12) Baseline serum GH and IGF-I levels were measured at week 0, 28 days after the final injection of octreotide LAR. Patients were given 90 mg Autogel, by deep subcutaneous injection. This injection was repeated at weeks 4, 8 and 12. Serum GH, IGF-I and lanreotide measurements were repeated before Autogel injection at weeks 8 and 12.

Stage 2 (weeks 16–28) The dose of Autogel was titrated at week 16 based on serum GH concentrations obtained at weeks 8 and 12. If at both of these assessments mean serum GH level was <2.0 , 2.0 – 5.0 or

Table 1 Patient characteristics (per protocol population).

	Value	Range
Number of patients (n)	10	–
Age (years) (mean $\pm$ s.d.)	55.8 ± 9.1	41.8–72.8
Gender (male:female)	6:4	
Duration of previous LAR treatment (months) (mean $\pm$ s.d.)	32.8 ± 15.7	9–55
Previous pituitary surgery (n)	7	
Previous pituitary radiotherapy (n)	5	
Baseline GH (mU/l) (mean $\pm$ s.d.)	3.0 ± 1.7	0.5–5.8
Baseline IGF-I (μ g/l) (mean $\pm$ s.d.)	212 ± 70.1	108–336
Mean GH off somatostatin analogue therapy (mU/l) (mean $\pm$ s.d.)	8.0 ± 3.7	2.0–16.4
Mean IGF-I off somatostatin analogue therapy (μ g/l) (mean $\pm$ s.d.)	485 ± 105	354–625

Table 2 Baseline characteristics of individual patients, including details of previous treatment and GH/IGF-I levels before, or during a break from, somatostatin analogue therapy.

Centre and Patient no.	Surgery (year)	Radiotherapy (year)	Primary pharmacotherapy (year)	Mean GH concentration off somatostatin analogue therapy (mU/l)	IGF-I concentration off somatostatin analogue therapy ($\mu\text{g/l}$)	Interval between initial GH/IGF-I assessment and study start (months)
1.001	1996	No	No	7.2	603	31
1.002	No	1989	No	8.7	465	52
1.003	1995	No	No	6.2	435	44
1.004	1994	No	No	6.4	366	46
1.005	No	No	Octreotide LAR '97	9.8	618	47
2.003	1998 & 1999	1999	No	6.5	549	14
2.004	No	2000	No	8.7	404	9
3.001	1992	1992	No	7.8	432	77
3.002	1995	1995	No	16.4	625	81
3.003	1997	No	No	2.0	353	34
Mean				8.0 ± 3.7	485 ± 105	43.5 ± 23.4

>5.0 mU/l, the Autogel dose was reduced to 60 mg, maintained at 90 mg or increased to 120 mg every 28 days respectively. Serum IGF-I values were not used to guide the dose titration. This adjusted dose was given at week 16 and repeated at weeks 20 and 24. Mean serum GH, IGF-I and lanreotide measurements were repeated at weeks 24 and 28.

Treatment

Lanreotide Autogel was supplied in prefilled syringes with injection volumes of 0.2, 0.3 and 0.4 ml for the 60, 90 and 120 mg doses respectively. The syringes are fitted with a 2 cm needle of external diameter 1.2 mm (1.4 mm for the 120 mg dose). All injections were given in the upper external quadrant of the buttock, perpendicular to, and without pinching the skin, and the needle was inserted to its full length. The syringes were stored in a refrigerator until use, but were brought to room temperature at least 30 min before injection.

Sampling procedures and hormone assays

Blood was collected at each specified time point of the biochemical assessment into tubes containing clot activator. Each sample was allowed to coagulate and was then centrifuged at 3000 r.p.m. for 15 min. The supernatant was transferred into two separate plain tubes for analysis of GH and IGF-I concentrations. The samples were then stored at -20°C until the assays were performed. The remaining serum was frozen at -20°C for later determination of lanreotide levels.

Prior to each GH/IGF-I assessment patients were asked to fast from 2200 h the previous day, but were allowed a light breakfast after the first blood sample had been taken. Nine blood samples were taken at 30-min intervals for 4 h and the mean GH level determined from these. IGF-I concentration was determined from the first fasting sample.

GH was measured using the Immulite® method (EURO/DPC Ltd, Glyn Rhonwy, Llanberis, UK). This is an automated, solid-phase, two-site chemiluminescent,

Figure 1 Schematic representation of study design. After a screening visit (week -4), patients received 90 mg Autogel every 28 days from weeks 0 to 12. Based on mean GH levels at weeks 8 and 12, the Autogel dose was adjusted up to 120 mg, down to 60 mg, or maintained at 90 mg. This dose was given at weeks 16, 20 and 24. GH and IGF-I measurements were repeated at weeks 24 and 28.

immunometric assay. It has a detection range of 0.13–104 mU/l and a sensitivity of 0.008 mU/ml. The data sheet reports an intra-assay coefficient of variation (CV) of 5.3–6.5% and an inter-assay CV of 5.5–6.2%.

IGF-I levels were determined using an immunoradiometric assay (IMRA) (Nicolas Institute Diagnostics, Nimegen, The Netherlands). It has a detection range of 80–3000 µg/l and sensitivity of 6 µg/l. The reference range for men and women aged 40–54 years is 75–306 µg/l and in those aged 55 years or over, 48–225 µg/l. The data sheet reports an intra-assay CV of 3.3–4.6% and an inter-assay CV of 9.3–15.8%. Both assays were performed by a central laboratory (Chandos Clinical Research, London, UK).

Lanreotide levels were measured using a validated Ipsen RIA and were performed at Ipsen Pharma central laboratory (Pharmacokinetic Service, Barcelona, Spain). This assay has a lower detection limit of 0.08 µg/l. The intra-assay CV was 5% and the inter-assay CV was <13%.

Data analysis

Paired comparisons of GH and IGF-I levels at week 28 and those at baseline were made using a paired *t*-test. Comparisons of the relative proportions of patients achieving normalised GH and IGF-I levels were made using Fisher's exact test.

Results

Efficacy of lanreotide Autogel

Mean serum GH level for the whole group at baseline, 28 days after the final injection of LAR, was 3.0 ± 1.7 mU/l (mean $\pm$ s.d.). This increased to 3.9 ± 1.9 mU/l at week 8, but declined to 3.5 ± 1.8 mU/l by week 12. By week 28, the group's mean serum GH level declined to levels similar to baseline: 3.3 ± 1.6 mU/l (Fig. 2, Table 3). There were no statistically significant differences in mean GH levels from baseline at any time point. Individual patients' mean GH levels are shown in Fig. 3.

Figure 2 Mean serum levels of GH (mU/l) (■) and IGF-I (µg/l) (▲) (mean $\pm$ s.d.) for the per protocol population ($n = 10$) treated with lanreotide Autogel. There were no statistically significant differences in mean GH levels at any time point from baseline. Mean IGF-I levels were lower at week 28 than at baseline ($P = 0.027$).

Mean serum IGF-I concentration at baseline was 212 ± 70 µg/l. From week 0 to week 28 this progressively declined for the group, evident at all time points. Mean serum IGF-I concentration at the study endpoint (week 28) was statistically significantly lower than that at baseline: 154 ± 61 vs 212 ± 70 µg/l ($P = 0.027$). Individual patients' IGF-I levels are shown in Fig. 4.

At baseline, nine patients had mean serum GH concentrations <5.0 mU/l and seven patients had a normalised age-adjusted IGF-I concentration. Nine patients fulfilled each of these criteria at the study endpoint. At baseline, 60% of patients had both a mean serum GH level <5.0 mU/l and a normalised age-adjusted IGF-I level. This proportion rose to 80% at the study endpoint ($P = 0.003$).

Lanreotide levels

Trough serum lanreotide levels rose gradually from 1.9 ± 0.5 µg/l at week 8 to 3.3 ± 1.0 µg/l at study endpoint (Table 3). A steady state in lanreotide levels was not reached by week 28 for the group as a whole.

Lanreotide Autogel dose titration

When the Autogel dose was titrated at week 16, the largest number of patients (five out of ten) had achieved GH levels within the target range and thus remained on 90 mg Autogel every 28 days. In two patients, the dose was reduced to 60 mg due to mean serum GH levels <2.0 mU/l, and in three patients an increase to 120 mg Autogel was required in order to achieve optimal GH control.

GH, IGF-I and lanreotide levels were analysed separately according to the Autogel dose after titration, in the second stage of the study (Table 4, Fig. 5). Serum lanreotide levels changed little between week 12 and study endpoint in patients in whom the dose of Autogel was reduced to 60 mg. These patients ($n = 2$) had very low mean baseline GH levels that showed little change throughout the observation period. In the group who remained on 90 mg Autogel ($n = 5$), serum lanreotide levels rose between weeks 12 and 28 (2.3 ± 0.7 and 3.1 ± 0.9 µg/l respectively) and a steady state was not achieved. However, the change between weeks 24 and 28 was small (0.4 µg/l). Mean serum GH levels in this group also showed little change during the course of the study. In the group in whom the Autogel dose was increased to 120 mg at week 16, mean serum lanreotide levels more than doubled between week 12 and week 28. The early rise in serum GH levels was the most pronounced in this group, but mean GH levels were similar to baseline by week 28. Serum IGF-I levels reduced progressively in all groups.

Adverse events

Two patients withdrew from the study before week 12, one due to symptoms possibly relating to GH control.

Table 3 Serum GH, IGF-I and lanreotide levels (mean±s.d.) for the per protocol population ($n = 10$) during the course of the study.

Week no.	GH (mU/l)	Number of patients with GH <5.0 mU/l (n)	IGF-I (μ g/l)	Number of patients with normalised age-adjusted IGF-I (n)	Number of patients with normalised age-adjusted IGF-I and GH <5.0 mU/l (n)	Trough lanreotide (μ g/l)
0	3.0±1.7	9	212±70	7	6	Not detectable
8	3.9±1.9	7	196±86	8	6	1.9±0.5
12	3.5±1.8	7	185±91	8	6	2.3±0.7
24	3.1±1.6	9	179±66	9	8	2.8±1.0
28	3.3±1.6	9	154±61*	9	8	3.3±1.0

* $P = 0.027$ for comparison of mean IGF-I level at week 28 and week 0 (paired t -test). **Figure 3** Mean serum GH levels in individual patients ($n = 10$) treated with lanreotide Autogel. Based on GH levels at weeks 8 and 12, the treatment dose was adjusted from week 16 up to 120 mg (---), down to 60 mg (···), or maintained at 90 mg (—). **Figure 4** Serum IGF-I levels in individual patients ($n = 10$) treated with lanreotide Autogel. Based on GH levels at weeks 8 and 12, the treatment dose was adjusted from week 16 up to 120 mg (---), down to 60 mg (···) or maintained at 90 mg (—).**Table 4** Subgroup analysis of serum GH, IGF-I and lanreotide levels (mean±s.d.) in the per protocol population ($n = 10$) according to the titrated dose of Autogel at week 16.

Dose	No. of patients	Week no.	GH (mU/l)	IGF-I (μ g/l)	Lanreotide (μ g/l)
60 mg	2	0	0.8	197	Not detectable
		12	1.2	145	2.3
		28	1.2	118	2.3
90 g	5	0	3.0±1.6	221±83	Not detectable
		12	3.1±1.0	194±127	2.3±0.7
		28	3.2±1.3	164±77	3.1±0.9
120 mg	3	0	4.4±0.4	209±88	Not detectable
		12	5.5±0.5	195±46	2.1±1.0
		28	4.8±1.1	163±44	4.4±0.6

Figure 5 Serum lanreotide levels in patients treated with 90 mg lanreotide Autogel from weeks 0 to 12 and either 60 (■), 90 (◆) or 120 (▲) mg in weeks 16–24. The Autogel dose was titrated at week 16 based on GH levels assessed at weeks 8 and 12. Data points represent means $\pm$ S.D.: 90 mg ($n = 5$), 120 mg ($n = 3$), 60 mg ($n = 2$, mean alone shown).

This patient complained of headaches from week 2, sweating and snoring from week 4, and digital enlargement from week 6, which led to his withdrawal at week 12. Mean serum GH levels at screening, and at weeks 0, 8 and 12 were 6.1, 4.7, 6.3 and 7.8 mU/l respectively, although the data for week 12 were not available at the time of withdrawal. Four other patients reported adverse events: respiratory arrest during hip replacement surgery, considered to be unrelated to the Autogel treatment ($n = 1$); pain and swelling at the site of Autogel injection ($n = 1$); joint pain ($n = 1$); and intermittent back pain ($n = 1$). These events were all classified as mild to moderate. No gastrointestinal adverse events were reported.

Discussion

The efficacy of lanreotide Autogel in patients with acromegaly has previously been compared only with that of its microparticle formulation, lanreotide LA (12, 13). In the first of these two sequential studies a fixed dose of Autogel was given, the starting dose being derived from the prior frequency of injection of LA (12). Patients receiving lanreotide LA (30 mg) every 14, 10 and 7 days were treated with 60, 90 and 120 mg Autogel every 28 days, respectively. After three monthly injections of Autogel, control of GH and IGF-I levels, and symptoms were found to be equivalent to those obtained with LA. Patients from this study were then enrolled into a subsequent study (13). The dose of Autogel was titrated at baseline according to GH and IGF-I levels at the end of the previous study. Titration was repeated at 4 and 8 months. In the year that the study covered, control of GH and IGF-I levels, and symptoms were all significantly improved with lanreotide Autogel compared with LA.

However the obvious questions remaining thus far unanswered relate to the relative efficacy of lanreotide

Autogel and octreotide LAR, the clinically equivalent doses of these two products, and the effect of switching from LAR to Autogel. In the present study ten patients with acromegaly were switched at baseline from treatment with octreotide LAR (20 mg) to lanreotide Autogel, which was given every 28 days for 24 weeks, including a dose titration step. Control of GH and IGF-I levels with Autogel was compared with levels at baseline with LAR. Disease control with Autogel was at least equivalent to that obtained with LAR (20 mg).

This was a group of patients with well-controlled acromegaly: baseline mean serum GH level 3.0 ± 1.7 mU/l and IGF-I level 212 ± 70 µg/l, on LAR therapy. Furthermore, at baseline, seven of the ten patients, had a normalised age- and sex-adjusted serum IGF-I level, and nine had a mean serum GH level < 5.0 mU/l, on LAR. Overall mean GH levels for the whole group were similar at study endpoint and baseline. Mean IGF-I levels declined throughout the course of the study and were statistically significantly lower at endpoint compared with baseline.

The proportion of patients achieving a mean serum GH level < 5.0 mU/l was used as a marker of disease control as the achievement of a post-treatment GH level below this limit appears to reduce the overall mortality rate in acromegaly to a level similar to the general population (14). A greater proportion of patients achieved both a GH level of < 5.0 mU/l and a normalised age-adjusted IGF-I level at study endpoint than at baseline.

The initial rise in GH levels observed at week 8 of the study was not unexpected and is likely to relate to a nadir in somatostatin analogue levels being reached at this time, in much the same way as was observed (and directly measured) previously (12). This relates to serum octreotide levels declining whilst lanreotide concentrations had yet to rise to a steady state. These changes may have led to the withdrawal of one patient from the study at week 12 due to the return of his symptoms of acromegaly. However the rise in serum GH levels in this patient was not great and did not exceed 10 mU/l at any time. Serum IGF-I levels in the whole group did not reflect this transient rise in GH concentration. Such discordance between GH and IGF-I levels has been well reported previously (15–17).

It appears that mean serum lanreotide levels did not reach a steady state for the whole group during the course of the study, though in six of the ten patients a steady state was achieved. Whilst it would be logical to assume that this was a result of only three injections of the titrated Autogel dose being given, this may not be the case. Even in the group who remained on 90 mg Autogel for the entire 28 weeks, a steady state may not have been achieved, although the change in mean serum lanreotide levels between weeks 24 and 28 was small. Thus it appears that at least 6 months may be required for steady state to be reached with Autogel treatment in some patients.

When Autogel dose titration was undertaken at week 16, seven of the ten patients either remained on the initial 90 mg dose, or received a reduced dose of 60 mg. Thus it seems that the majority of patients treated with 20 mg LAR every 4 weeks will be well controlled with lanreotide 90 mg Autogel every 4 weeks. The remaining three patients required an increased dose of 120 mg in order to gain optimal biochemical control. This group, which had higher baseline serum GH levels, was principally responsible for the rise in mean GH levels at week 8 that was seen for the entire study group.

Serum IGF-I levels fell progressively, irrespective of the titrated Autogel dose, suggesting that the significant reduction in mean serum IGF-I levels in the whole group did not simply occur as a result of upwards titration of the Autogel dose. It could be argued that other factors contributed to the observed decline in IGF-I in this study. These include the effect of prior radiotherapy, or a protracted effect of prior octreotide LAR therapy. The former is unlikely, since the decline in IGF-I was seen in all patients, including the five (50%) who had not had prior radiotherapy. IGF-I concentration has been shown to decline progressively with prolonged somatostatin analogue therapy (17). This is also, however, an unlikely explanation for the IGF-I decline in this study, since levels continued to decline to week 28, far beyond the therapeutic effect of octreotide LAR, which was stopped at week 0.

One aim of this study was to establish whether switching from LAR to Autogel would compromise control of biochemical markers and symptoms of acromegaly. The study was not designed to show relative efficacy in terms of GH/IGF-I control with Autogel compared with LAR. In a study of only ten patients, it is clearly difficult to observe statistically significant differences in markers of disease control. Since this group of patients had well-controlled acromegaly prior to Autogel treatment, the scope for detecting further improvement in biochemical disease control may have been limited.

Lanreotide Autogel was well tolerated in this study with no reported gastrointestinal adverse events. In previous studies gastrointestinal adverse effects were reported with an equal, or reduced frequency with Autogel in comparison with lanreotide LA (12). The lack of gastrointestinal adverse events in the present study may relate to a degree of tolerance in these patients, since they had received longstanding somatostatin analogue therapy. However, taking into account the results from previous studies, the reduced 'burst effect' of Autogel, resulting in lower peak lanreotide levels immediately after injection may also be contributory (12). The local injection site reaction in one patient is consistent with the observations from previous large studies where injection site adverse events were reported to occur with a frequency of <7% (12).

In conclusion, switching from octreotide LAR to lanreotide Autogel, with active dose titration, in this small group of patients with well-controlled acromegaly resulted in equal control of serum GH levels and improved control of serum IGF-I levels. Autogel was well tolerated and there are no safety concerns associated with switching from LAR. Although disease control had been achieved using the slow-release microparticle preparation, there may be advantages in the newer aqueous gel preparation, especially in its ease of use and patient acceptability.

References

- 1 Lancranjan I, Bruns C, Grass P, Jaquet P, Jervell J, Kendall-Taylor P *et al.* Sandostatin LAR: a promising therapeutic tool in the management of acromegalic patients. *Metabolism* 1996 **45** (Suppl 1) 67–71.
- 2 Amato G, Mazziotti G, Rotondi M, Lorio S, Doga M, Sorvillo F *et al.* Long-term effects of lanreotide SR and octreotide LAR on tumour shrinkage and GH hypersecretion in patients with previously untreated acromegaly. *Clinical Endocrinology* 2002 **56** 65–71.
- 3 Freda P. Somatostatin analogues in acromegaly. *Journal of Clinical Endocrinology and Metabolism* 2002 **87** 3013–3018.
- 4 Ferone D, Colao A, Van-de-Lely A & Lamberts S. Pharmacotherapy or surgery as primary treatment for acromegaly? *Drugs and Ageing* 2000 **17** 81–92.
- 5 Bevan J, Atkin S, Atkinson A, Bouloux P, Hanna F, Harris P *et al.* Primary medical therapy for acromegaly: an open, prospective, multi-center study of the effects of subcutaneous and intramuscular slow-release octreotide on growth hormone, insulin-like growth factor-I, and tumor size. *Journal of Clinical Endocrinology and Metabolism* 2002 **87** 4554–4563.
- 6 Sheppard M, Shapiro B, Pimstone B, Kronheim S, Berelowitz M & Gregory M. Metabolic clearance and plasma half-disappearance time of exogenous somatostatin in man. *Journal of Clinical Endocrinology and Metabolism* 1979 **48** 50–53.
- 7 Skamene A & Patel Y. Infusion of graded concentrations of somatostatin in man: pharmacokinetics and differential inhibitory effects on pituitary and islet hormones. *Clinical Endocrinology* 1984 **20** 555–564.
- 8 Nicholls J, Wynick D, Domin L, Sandler L & Bloom S. Pharmacokinetics of the long-acting somatostatin analogue octreotide (SMS 201–995) in acromegaly. *Clinical Endocrinology* 1990 **32** 545–550.
- 9 Kuhn J, Basin C, Mollard M, deRouge B, Baudoin C, Obach R *et al.* Pharmacokinetic study and effects on growth hormone secretion in healthy volunteers of the new somatostatin analogue BIM 23014. *European Journal of Clinical Endocrinology* 1993 **45** 73–77.
- 10 Heron I, Thomas F, Dero M, Gancel A, Ruiz J, Schatz B *et al.* Pharmacokinetics and efficacy of a long-acting formulation of the new somatostatin analogue BIM 23014 in patients with acromegaly. *Journal of Clinical Endocrinology and Metabolism* 1993 **76** 721–727.
- 11 Grass P, Marbach P, Bruns C & Lancranjan I. Sandostatin LAR (microencapsulated octreotide acetate) in acromegaly: pharmacokinetic and pharmacodynamic relationships. *Metabolism* 1996 **45** (Suppl 1) 27–30.
- 12 Caron P, Beckers A, Cullen DR, Goth MI, Gutt B, Laurberg P *et al.* Efficacy of the new long-acting formulation of lanreotide (lanreotide Autogel) in the management of acromegaly. *Journal of Clinical Endocrinology and Metabolism* 2002 **87** 99–104.
- 13 Caron P 2002 One-year treatment with titrated doses of lanreotide Autogel in patients with acromegaly. *Proceedings of the Endocrine Society, 84th Annual Meeting, San Francisco, CA, USA.* OR13-6.

- 14 Orme S, McNally R, Cartwright R & Belchetz P. Mortality and cancer incidence in acromegaly: a retrospective cohort study. *Journal of Clinical Endocrinology and Metabolism* 1998 **83** 2730–2734.
- 15 Bates A, Evans A, Jones P & Clayton R. Assessment of GH status in acromegaly using serum growth hormone, serum insulin-like growth factor-1 and urinary growth hormone secretion. *Clinical Endocrinology* 1995 **42** 417–423.
- 16 Biermasz NR, van den Oever NC, Frolich M, Arias AM, Smit JW, Romijn JA *et al.* Sandostatin LAR in acromegaly: 6-week injection interval suppresses GH secretion as effectively as a 4-week interval. *Clinical Endocrinology* 2003 **58** 288–295.
- 17 Cozzi R, Attanasio R, Montini M, Pagani G, Lasio G, Lodrini S *et al.* Four-year treatment with octreotide-long-acting repeatable in 110 acromegalic patients: predictive value of short-term results? *Journal of Clinical Endocrinology and Metabolism* 2003 **88** 3090–3098.

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