

## ORIGINAL ARTICLE

# Control of growth hormone and IGF1 in patients with acromegaly in the UK: responses to medical treatment with somatostatin analogues and dopamine agonists

Trevor A. Howlett, Debbie Willis, Gillian Walker, John A. H. Wass, Peter J. Trainer and the UK Acromegaly Register Study Group (UKAR-3)\*

UK Acromegaly Register, Society for Endocrinology, Bristol, UK

## Abstract

**Objective** We investigated the control of GH and IGF1 in acromegaly in routine clinical practice in the UK on and off medical treatment.

**Design** The UK Acromegaly Register collected routine biochemical and clinical data on patients with acromegaly from 31 UK centres with GH data covering >30y.

**Patients** We identified 2572 patients. Somatostatin analogues (SMS) were used in 40.6% and dopamine agonists (DA) in 41.4%.

**Measurements** We identified 29,181 GH records linked to data on IGF1, surgery, radiotherapy and medical treatment and derived data on 9900 distinct Periods of Care including 4206 courses of medical treatment. We considered GH controlled when  $\leq 2 \mu\text{g/l}$ .

**Results** Control of GH and IGF1 improved over time, particularly on medical treatment. Control on medical treatment was better after prior surgery and/or radiotherapy. On long-term SMS, GH was controlled in 75%, IGF1 in 69% and both in 55%; on long-term DA, GH control was similar but IGF1 worse (77%/55%/45%). Responses to long-term treatment with octreotide LAR and lanreotide autogel were broadly similar, but we noted a failure to escalate SMS to maximal effective dose. Increasing precourse GH levels were associated with a decreasing proportion who achieved control, despite greater suppression from baseline.

**Conclusions** Control of acromegaly in the UK is improving, but 'safe' GH levels are still only achieved in 75% on long-term medical treatment, with GH and IGF1 both normalized in no more than 55% on SMS and 36% on cabergoline. It remains unclear whether the control of GH, but not IGF1, observed in

many patients is sufficient to restore long-term morbidity and mortality to normal.

(Received 24 September 2012; returned for revision 4 January 2013; finally revised 14 March 2013; accepted 14 March 2013)

## Introduction

Uncontrolled acromegaly is a well-established cause of increased morbidity and mortality with overall standardized mortality ratio (SMR) about 2 times greater than the background population.<sup>1</sup> Earlier studies in the UK found that morbidity and mortality were increased when latest GH levels were  $>5 \text{ mIU/l}$  (converted by then prevailing international standards to  $2.5 \mu\text{g/l}$ )<sup>2,3</sup> and subsequent analysis of the West Midlands pituitary database suggested that SMR was increased with latest GH levels  $>2 \mu\text{g/l}$ , but not correlated with increased IGF1 levels.<sup>4</sup> A meta-analysis of available studies in 2008 concluded that random GH  $<2.5 \mu\text{g/l}$  and normal serum IGF1 were each correlated with SMR close to expected levels while elevations of either parameter were associated with a rise in SMR (1.9 for GH  $>2.5 \mu\text{g/l}$ ; 2.5 for IGF1 elevation)<sup>5</sup> although the effect of GH is more consistent in the literature than that of IGF1.<sup>1</sup> Consistent with these findings, a series of successively more demanding consensus criteria have advocated both normal GH levels (currently defined as random GH  $<1 \mu\text{g/l}$  or GTT nadir  $<0.4 \mu\text{g/l}$ ) and normal IGF1 as necessary to define 'cure' of acromegaly<sup>6–9</sup>; however, although these criteria have also been widely adopted as the appropriate goal of treatment for acromegaly,<sup>10</sup> it remains unclear whether both are necessary to restore life expectancy to normal.

Pituitary surgery and radiotherapy have both been used as primary and secondary treatments for acromegaly for many years. The UK Acromegaly Register has previously shown wide variation in the outcomes of surgical treatment in the UK<sup>11</sup>; however, even in the best hands, pituitary surgery only achieves safe GH levels in 75–95% of microadenomas and 40%–68% of macroadenomas,<sup>8</sup> while our register data confirm that radiotherapy is only slowly effective over the course of years or decades<sup>12</sup> and overall only 60% patients are controlled 10–15 years after

Correspondence: Dr Trevor A Howlett, Dept of Diabetes and Endocrinology, Leicester Royal Infirmary, Leicester, LE1 5WW, UK.  
E-mail: Trevor.Howlett@uhl-tr.nhs.uk

\*Affiliations of individual authors and a full list of all investigators are given in Appendix.

radiotherapy.<sup>8</sup> Therefore, many patients require medical therapy to achieve GH and IGF1 targets, either following these primary ablative therapies or sometimes as primary medical therapy. Dopamine agonists (DA) were the first available medical treatment for acromegaly, with bromocriptine introduced in the 1970s<sup>13</sup> and cabergoline in the 1990s,<sup>14–16</sup> but the use of somatostatin analogues (SMS) became increasingly common with the introduction of octreotide in the 1980s, lanreotide in the 1990s and long-acting depot preparations of both drugs (octreotide LAR and lanreotide autogel) in the 1990s and 2000s.<sup>17</sup> In clinical trial situations on DA, control of GH has been reported in 0–100% (overall 48%) and control of IGF1 in 34% of patients on cabergoline,<sup>16</sup> and in a critical review of the largest trials of a variety of SMS preparations, 26–77% of patients achieved control of GH and 35–77% control of IGF1.<sup>17</sup> Higher initial GH values may also be associated with a lower response rate to SMS. In addition to this variability between studies, it is clear that patients included in such studies may represent a selected group of patients: patients were sometimes preselected as prior responders and thus sensitive to the class of drug under investigation, many studies were relatively short term, and because ‘study conditions’ typically show better results than uncontrolled clinical care, it remains unclear what degree of GH and IGF1 control is actually achieved long term in routine clinical practice.

We therefore studied GH and IGF1 responses to medical treatment with DA and SMS in a large unselected collaborative national register of patients with acromegaly in the UK, with patient, treatment and GH data extending over more than three decades.

## Methods

### *The register and database*

The UK Acromegaly Register was established in 1997 as a collaborative research and audit study between UK endocrinology centres and was adopted as a Society for Endocrinology (SfE) project in 2002 with data migrated to a new enhanced database in 2006. More details of the database are given in Appendix S1. The study was approved by the UK Multi-Centre Research Ethical Committee (MREC 03/5/76), given NHS R&D approval and subsequently adopted by UK Comprehensive Research Network (Project ID: 6687). Patients gave written, informed consent for storage of identifiable data and linkage with other UK data sources including death certification in the NHS Information Centre and cancer registry data.

The register has therefore collected real-life clinical and biochemical data (the GH and IGF1 values actually used in the routine clinical management of each patient and assayed in the routine clinical laboratories of participating centres) on a large number of patients with acromegaly throughout the UK over the course of many years. At the time of this analysis, we held data on over 2800 patients with acromegaly from 32 UK Centres with initial dates of diagnosis of acromegaly ranging from 1943 to 2011 and GH records dating from 1964 to 2011. Data entry

was undertaken by a wide variety of staff (endocrine nurses, research nurses and doctors; acknowledged in Appendix) in the different UK centres – typically with initial abstraction of the written case notes and subsequent intermittent data updates.

For this study, we analysed all growth hormone (GH) and insulin-like growth factor 1 (IGF1) records within the database in order to assess biochemical control of acromegaly, review trends over time and specifically to assess responses to medical treatment with somatostatin analogues (SMS) and dopamine agonists (DA).

### *Data export and analysis*

For analysis, we exported every record containing GH values and ran multiple linked database queries and Microsoft Excel subroutines to establish, add and analyse data on:

- A uniform ‘GH level for analysis’ and whether this GH was ‘controlled’: GH values in the database extended over several decades and many assays and laboratories and were reported in either mIU/l or  $\mu\text{g/l}$ . During the period under study, several international standards for GH were routinely used in centres in the UK with conversion factors from  $\mu\text{g/l}$  to mIU/l varying sequentially between  $2.0 \times$  and  $3.0 \times$ , the assays themselves progressed from polyclonal radioimmunoassay to monoclonal 2-site immunoassays, and the normal reporting of GH results in the UK was changed from mIU/l to  $\mu\text{g/l}$  in 2008. Retrospective conversion from mIU/l to  $\mu\text{g/l}$  using the conversion factor appropriate for the specific assay, date and standard utilized was impossible, and we therefore analysed GH in  $\mu\text{g/l}$ , converting all GH values in mIU/l to  $\mu\text{g/l}$  using a conversion factor of 2.5, and then considered GH to be ‘controlled’ if  $\leq 2 \mu\text{g/l}$  (or  $\leq 5 \text{ mIU/l}$ ). For GH ‘Profile’ records, we analysed the mean GH level, and for ‘Random’ and ‘Other’ records, we analysed the basal value. For ‘GTT’ records, we reviewed the nadir GH and considered GH controlled if nadir was  $\leq 0.4 \mu\text{g/l}$  (i.e. if GTT was normal on current consensus<sup>9</sup>), but assessed control on mean GH level if the nadir was above normal.
- IGF1 level either on the same date or within  $\pm 400$  days of the GH date on exactly the same treatment regime and with same surgery and radiotherapy status. Because of the multiple IGF1 assays and reference ranges employed, to assess ‘control’ we used the user-entered qualitative statement of whether each IGF1 value was normal or increased in that assay and age range.
- Whether both GH and IGF1 were controlled.
- Whether this record was obtained on treatment with each class of GH-lowering drug (SMS, DA or GH antagonist).
- An ‘Era’ for that GH sample, classified as ‘Pre-1990’, ‘1990s’ or ‘2000s’.
- Data on patient age, gender, use of pituitary surgery and radiotherapy and the size and extension of pituitary adenoma on imaging at diagnosis and at latest follow-up
- Summary data for each patient including the ever-use of each class of GH-lowering therapy alone and in combination, data of GH and IGF1 levels pretreatment, after surgery and at

latest follow-up (on and off treatment), data on tumour size and the Era of the first and last GH record on this patient.

- 'Period of Care' (POC) data – deriving and combining data from sequential GH records in the same patient on the same treatment regime (see Appendix S1 for details). For each POC, we recorded details of final drug and dose regime, counted GH records and calculated the mean GH level during the POC and the percentage of levels of GH, IGF1 and both which were 'controlled' during that POC. We also recorded the value of GH in the most recent preceding POC which had been obtained off medical treatment ('precourse GH') and from before any treatment ('pretreatment GH'). A simple descriptive POC description was automatically applied to aid grouping in analysis (e.g. 'post-TSS OffMedRx'). Each POC on medical treatment was regarded, and is subsequently described here, as a 'treatment course'.

Data were then analysed manually, initially via pivot table in Excel and subsequently with statistical analysis for any differences and trends that were noted. In view of the large number of potential data items and the very heterogeneous nature of our data, to avoid spurious statistical significance as a result of multiple comparisons, we did not perform statistical analysis for correlations or differences unless a possible difference or trend of potential clinical significance was apparent in pivot table analysis. More details of the processing algorithms are given in Appendix S1.

## Statistics

Where appropriate, mean values were compared by 2-tailed *t*-test using Microsoft Excel 2003 data-analysis add-in. Proportions of patients with different outcomes were compared by chi-squared test.

## Results

### GH records, patients and periods of care

We identified 29,181 GH records in 2572 patients with acromegaly and derived data on 9900 Periods of Care, of which 4206 were courses on medical treatment. The date of GH records was in the 2000s in 37%, in the 1990s in 41% and before 1990 in 22% (<5% before 1980). There were a mean of 11.3 GH records for each patient (range 1–93) with median period of observation from first to last GH of 7.1 years (range 0–43 years) representing a total of 23,107 patient-years of observation with 5,249 patient-years on medical treatment.

Of the patients, 49.7% were female and mean age was 47.4 years at diagnosis (range 4–90) and 58.0 years at the time of latest GH record. 70.0% had undergone pituitary surgery and 44.7% had some form of pituitary radiotherapy (38.1% conventional external beam radiotherapy, 3.8% stereotactic, 3.4% other radiotherapy including Yttrium).

In terms of medical treatment for acromegaly, 1549 patients (60.2%) had received some sort of medical therapy, 40.6% had

received SMS (34.9% as monotherapy), 41.4% DA (36.0% as monotherapy) and 3.7% a GH antagonist. 14.0% had received SMS and DA combined at some stage. SMS had been used in 17.8% of patients presurgery and 27.0% postsurgery, and DA in 21.7% and 24.1%, respectively.

### Trends in GH levels and control with time

We reviewed GH and IGF1 levels in each patient at latest follow-up and where available the latest GH levels both on and off medical treatment. Results are presented in Table 1 stratified by Era of the latest GH sample. Overall, mean levels of GH on treatment, and latest GH value whether on or off, appeared to be falling with time and percentages of cases showing control of GH, IGF1 and both GH and IGF1 increased with each Era, with both changes most marked in patients on medical treatment. The proportion of patients receiving medical treatment at latest follow-up also increased with time.

An alternative explanation for the fall in GH levels, and increase in the number achieving targets, with time would be whether changes in assay technology or international GH standards (and therefore the conversion value from mIU/l to  $\mu$ g/l) were sufficient in themselves to cause a downward drift of

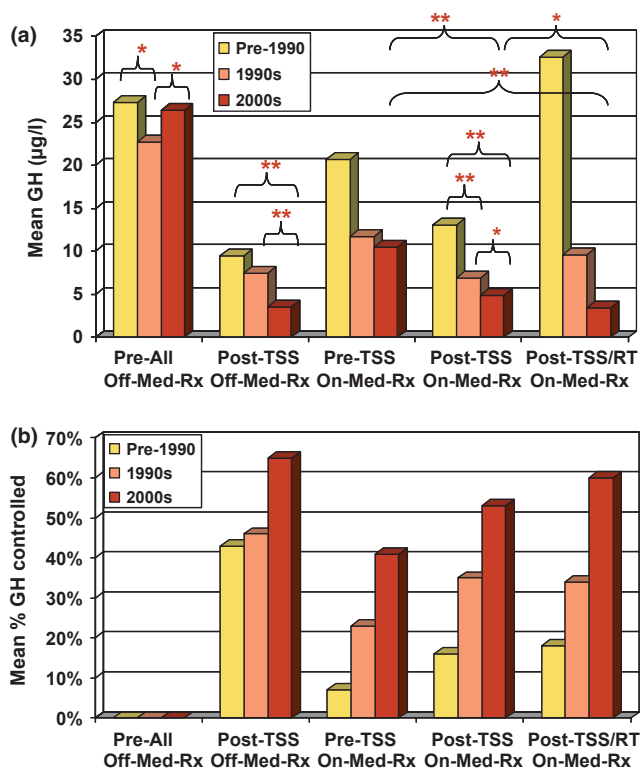
**Table 1.** GH levels and GH and IGF1 control in individual patients at latest value on and off medical treatment, stratified by last era of observation

	last era of observation		
	pre-1990	1990s	2000s
<b>All patients</b>			
Number of patients	149	631	1792
Mean of last GH – On or Off Rx	11.7	7.9	5.4
Mean of last GH value – On Rx	15.1	12.5	4.5
Mean of last GH value – Off Rx	15.4	7.6	10.6
<b>Latest values whether On or Off</b>			
Number of patients	149	631	1792
GH controlled	38%	56%	71%
IGF1 – no. of patients with value	22	465	1710
IGF1 controlled	64%	56%	59%
GH and IGF1 controlled	45%	41%	49%
On medical Rx at latest GH value	22%	32%	45%
<b>On medical treatment latest values</b>			
Number of patients	61	353	1135
GH controlled	21%	37%	61%
IGF1 – no. of patients with value	6	213	1015
IGF1 controlled	50%	44%	54%
GH and IGF1 controlled	33%	25%	41%
<b>Off medical treatment latest values</b>			
Number of patients	145	596	1671
GH controlled	35%	49%	51%
IGF1 – no. of patients with value	19	391	1484
IGF1 controlled	58%	53%	46%
GH and IGF1 controlled	42%	41%	37%

IGF1 data pre-1990 shaded because low numbers of samples make comparison unreliable.

absolute GH values reported with time. In an attempt to exclude such an effect, we examined mean GH levels and mean of percentage control of GH and IGF1 across all Periods of Care, stratified by Era and by a broad classification of prior treatment received (Fig. 1 and Table S2).

We found no evidence of systematic drift in GH levels obtained before all medical and surgery treatments with time (Period of Care: pre-1990s vs 1990s  $P < 0.05$  but 1990s vs 2000s  $P = 0.39$  and pre-1990s vs 2000s  $P = 0.84$ ). In contrast, GH levels recorded off medical treatment following pituitary surgery did fall with time – consistent with reported improved surgical outcomes (2000s vs 1990s and pre-1990s:  $P < 0.001$ ; 1990s vs pre-1990s:  $P = 0.08$ ). Even more marked falls with time were observed in GH values on medical treatment after surgery (Pre-1990s vs 1990s and vs 2000s:  $P < 0.001$ ; 1990s vs 2000s:  $P = 0.012$ ). In patients on medical treatment without prior surgery or radiotherapy, the mean GH levels were higher and the overall control of GH and IGF1 was lower than they were in patients on medical treatment after surgery and/or radiotherapy, although improvements in the degree of control were still observed over time (e.g. in 2000s: On Rx pre-TSS vs post-TSS or post-TSS+RT:  $P < 0.001$ ; post-TSS vs post-TSS+RT:  $P = 0.024$ ).



**Fig. 1** Mean GH levels (a) and percentage control of GH (b) in Periods of Care at different stages of clinical management, stratified by Treatment Status and Era. Med-Rx, Medical Treatment; TSS, Transphenoidal Surgery; RT, Radiotherapy. Asterisks show differences that are statistically significant (\*  $P < 0.05$ ) and highly significant (\*\*  $P < 0.01$ ).

### Comparison of control of acromegaly with somatostatin analogues vs dopamine agonists over time

We examined control of acromegaly in every available treatment course, and data for all nonantagonist regimes including SMS and DA are presented in Table 2. As expected, use of SMS increased and that of DA decreased with time. Mean percentage control of GH and IGF1 increased with time, but precourse GH levels also fell progressively through the 3 eras examined.

We compared the same parameters in more detail in all medical treatment courses during the 2000s and further stratified based on whether the course was the last course of medical treatment recorded for that patient ('LastRx') and whether that last course had a duration of at least 360 days ('LastRx>360d') (Fig. 2 and Table S3). For all treatment classes, the control of both GH and IGF1 was highest at LastRx>360d with control of GH achieved in around 75% on both SMS and DA although the percentage suppression achieved compared to precourse baseline GH was much greater with SMS. Control of IGF1 and of both GH and IGF1 appeared higher on SMS compared to DA, but control of both was achieved in no more than 55% of cases even at LastRx>360d. Notwithstanding the incomplete control of GH and IGF1,  $\geq 95\%$  of patients on long-term monotherapy with either SMS or DA achieved mean GH levels  $< 5 \mu\text{g/l}$ . Overall control achieved with DA and SMS combined was lower than with monotherapy (presumably reflecting prior nonresponse to one or both drug classes used alone), but overall suppression of GH compared to precourse levels was slightly greater.

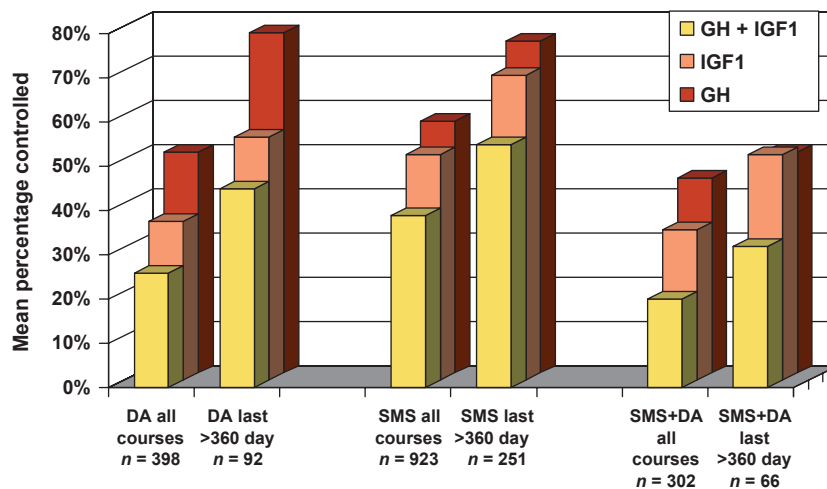
**Table 2.** Responses to SMS, DA and SMS+DA combined in all available treatment courses, stratified by Era of treatment

	Era of treatment course		
	pre-1990	1990s	2000s
<b>Dopamine agonist courses</b>			
Number treatment courses	587	742	398
Mean precourse GH ( $\mu\text{g/l}$ )	26.3	17.8	12.1
Mean of% GH controlled	13%	26%	50%
Mean of% IGF1 controlled		25%	36%
Mean of% GH+IGF1 controlled		12%	26%
<b>Somatostatin analogue courses</b>			
Number treatment courses	63	779	923
Mean precourse GH ( $\mu\text{g/l}$ )	33.7	20.3	16.3
Mean of % GH controlled	16%	36%	57%
Mean of % IGF1 controlled		40%	51%
Mean of % GH+IGF1 controlled		22%	39%
<b>SMS + DA combined courses</b>			
Number treatment courses	34	244	302
Mean precourse GH ( $\mu\text{g/l}$ )	31.6	28.4	24.1
Mean of % GH controlled	24%	29%	44%
Mean of % IGF1 controlled		29%	34%
Mean of % GH+IGF1 controlled		12%	20%

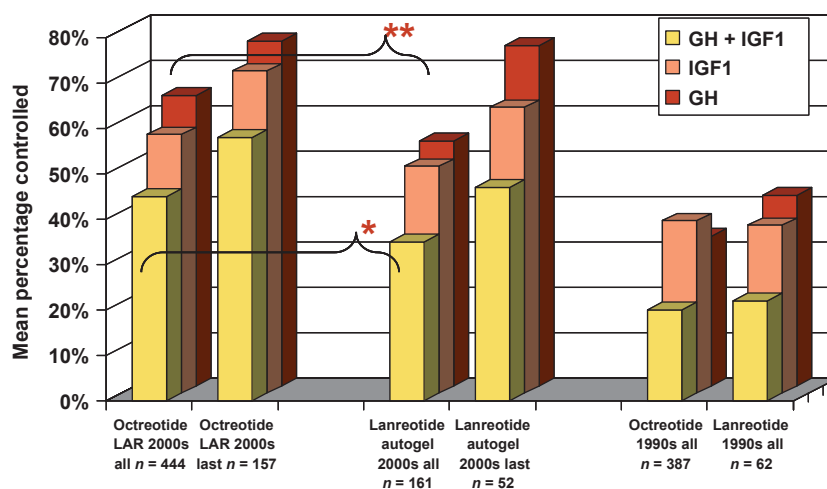
IGF1 responses pre-1990s are omitted due to the low proportion of treatment courses with IGF1 data available.

DA, dopamine agonists; SMS, somatostatin analogues.

**Fig. 2** Responses of GH and IGF1 to treatment with somatostatin analogues (SMS) and dopamine agonists (DA) in treatment courses during the 2000s. Bars show the mean percentage control of GH, IGF1 and both GH+IGF1 in all available treatment courses and at LastRx>360d.



**Fig. 3** Responses of GH and IGF1 during treatment courses with different types of somatostatin analogue in the 1990s and 2000s. Bars show the mean percentage control of GH, IGF1 and both GH+IGF1 in all available treatment courses and at LastRx>360d. Asterisks show differences that are statistically significant (\*  $P < 0.05$ ) and highly significant (\*\*  $P < 0.01$ )



### Comparison of somatostatin analogue types

Taking into account the times of introduction of different SMS drug types, we compared control of acromegaly between treatment courses where SMS type was recorded as 'octreotide LAR' or 'lanreotide autogel' in the 2000s and 'octreotide' and 'lanreotide' in the 1990s, and reviewed data from all courses and from LastRx>360d. Data are summarized in Figs 3 and 4 and Table S4. Control of both GH and IGF1 was higher on monthly SMS depots used in the 2000s than in courses on shorter-acting preparations in use in the 1990s, but precourse GH levels were also higher in the latter groups, suggesting greater biochemical severity of those patients treated in earlier decades. In LastRx>360d, there was no difference in GH control between octreotide LAR and lanreotide autogel (either in percentage of GH values controlled or in degree of suppression of GH from precourse baseline) ( $P = 0.90$ ) with mean percentage control of GH around 75%. In courses that did not fulfil these criteria, GH control appeared better on octreotide LAR ( $P < 0.01$ ). Mean percentage of IGF1 and both GH and IGF1 controlled appeared higher with octreotide LAR, but this was only statistically significant when considering control of both GH and IGF1 in all

treatment courses ( $P = 0.02$ ) and not in other cases (IGF1:  $P = 0.09$  all courses,  $P = 0.18$  last courses; GH and IGF1:  $P = 0.07$  last courses). Maximum control of both GH and IGF1 was achieved in no more than 58%.

Because octreotide LAR and lanreotide autogel were for the most part not used in the same patients, we compared basal precourse GH levels and other patient characteristics between courses of the two drugs (Table S5). Prior radiotherapy had been given to significantly fewer patients who received lanreotide autogel than in octreotide LAR courses (40% vs 59%;  $P < 0.01$ ). Precourse GH levels were not significantly different between preparations ( $P = 0.12$  for all courses;  $P = 0.18$  for last courses). There were no differences in proportion of cases with prior pituitary surgery or with pituitary macroadenoma.

We examined doses of lanreotide autogel and octreotide LAR in cases where this information had been entered in the database (Table S6). Apparent increasing effectiveness of GH control with increasing dose was seen up to doses of 90 mg of lanreotide autogel and 20 mg of octreotide LAR; on higher doses, the degree of GH control tended to worsen (probably reflecting the more severe or more resistant cases who required these higher doses). We noted that 40% of cases on lanreotide autogel were

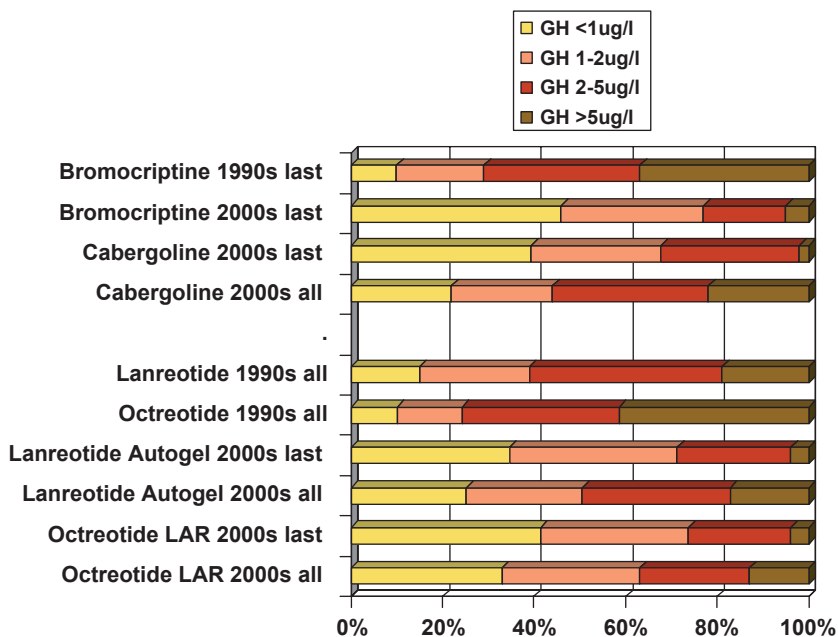


Fig. 4 Distribution of mean GH achieved during treatment courses with different types of dopamine agonist and somatostatin analogue in the 1990s and 2000s. Bars show the percentage distribution of GH levels in all available treatment courses or at LastRx>360d

on less than 90 mg at LastRx>360d, despite the fact that only 67%–76% had achieved control of GH on that dose; in contrast, only 16% of patients were on less than 20 mg octreotide LAR with 70% achieving GH control.

#### Comparison of dopamine agonists

The vast majority of DA treatment courses were with bromocriptine (978 courses) and cabergoline (355 courses); only nine courses were recorded on quinagolide and 54 as 'other dopamine agonist'. Control of acromegaly on bromocriptine and cabergoline in the 1990s and 2000s is presented in Fig. 4 and Table S7. Control achieved on bromocriptine in the 2000s at LastRx>360d (GH 79%, IGF1 68%) appeared slightly higher than that achieved with cabergoline (GH 73%, IGF1 45%), but responses to bromocriptine in the 1990s and pre-1990 were much less successful, suggesting that this reflects a group of DA responders who were found to be sensitive to bromocriptine in the 1990s and earlier, continuing with that treatment into the 2000s. Responses to cabergoline in the 1990s also appeared lower than in the 2000s. Mean percentage suppression of GH compared to precourse GH was inconsistent, and on inspection of the raw data, this was a result of a substantial number of patients in whom GH levels were higher during treatment with DA. Patients on bromocriptine in 2000s showed substantial suppression from baseline, supporting the view that these may be a selected group of DA responders (although many had also received radiotherapy in the past). In patients receiving DA in the long term in the 2000s (LastRx>360d), GH was suppressed to  $\leq 5 \mu g/l$  in 98% on cabergoline and 95% on bromocriptine.

There was substantial heterogeneity in dose and timing of DA therapy: bromocriptine doses recorded varied from 1 mg to 80 mg daily with mode of 7.5 mg, but most patients in the

range 10 mg–40 mg daily. Cabergoline dose ranged from 0.5 mg per week to 4 mg per day – with most common doses 0.5 mg twice weekly, 1 mg twice weekly and 0.5 mg daily. Doses were too heterogeneous to meaningfully stratify outcomes.

#### Analysis of treatment order

In order to establish overall trends in choice of first- and second-line medical treatments for acromegaly, we tracked the order of use of each class of GH-lowering drug (alone or in combination) in each patient (Table S8). As expected, before 1990, a majority of patients who had received medical therapy were treated with DA alone, with progressively greater usage of SMS in the 1990s and 2000s. In the 2000s, use of SMS alone was the most common treatment sequence but accounted for only 37% of treated patients with DA alone accounting for 17%; a substantial proportion of patients had received DA initially followed by SMS alone or in combination, but no single consistent treatment order strategy emerged from this analysis.

#### Relationship of responses to treatment with pretreatment and precourse GH levels

To examine the effect of pretreatment GH levels on the response to medical therapies, we stratified GH and IGF1 responses to DA and SMS by 'precourse GH' (Fig. 5 and Table S9) and by 'pretreatment GH' (Table S10). A clear and consistent reduction in the percentage control of GH and IGF1 achieved on medical treatment was seen with increasing pretreatment GH and the same effect was even more marked when stratified by precourse GH levels, despite the fact that greater percentage reductions in GH were being achieved with increasing precourse GH. Overall >50% control of GH was only achieved on SMS when precourse GH was  $\leq 10 \mu g/l$  and on DA when  $\leq 5 \mu g/l$ .

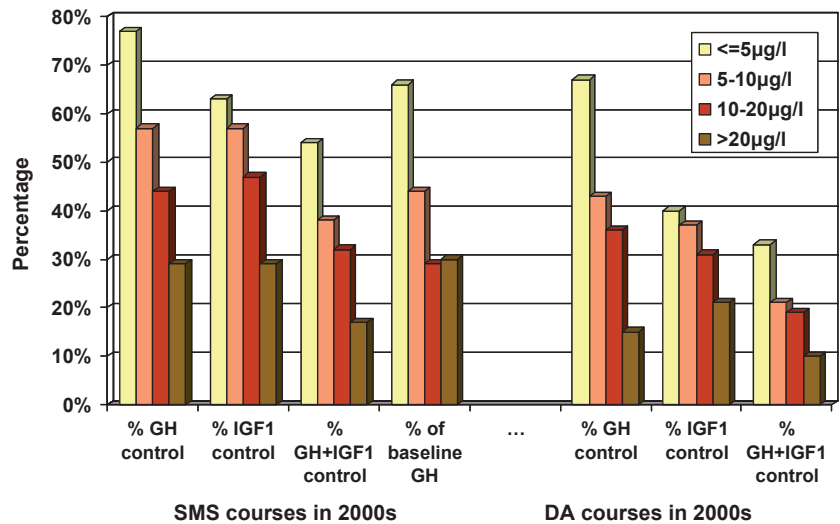


Fig. 5 Control of GH and IGF1 by dopamine agonists (DA) and somatostatin analogues (SMS) in 2000s, stratified by the precourse GH. Bars plot the mean percentage of each parameter controlled and (for SMS only) the degree of control achieved as a percentage of the precourse baseline GH off treatment for all recorded treatment courses during the 2000's

Comparison of control achieved between different centres

We attempted to compare control of acromegaly achieved between the 31 UK centres with GH data in this study. Wide variation in control achieved was observed and illustrated in Fig. 6 for courses of SMS in 2000s. Although the extremes of percentage control of GH during treatment are accounted for by centres with very small numbers of patients in the study, mean percentage of GH controlled varied from 35% to 88% even in centres with at least 10 cases in the study.

Discussion

The UK Acromegaly Register attempts to monitor uncontrolled, real-life management of acromegaly in endocrine centres around the UK in contrast to the often highly selected cases studied in controlled trials of medical treatment. We found evidence of overall improvement in GH levels and in the percentage control of biochemical parameters over time, probably reflecting both the improvement in surgical outcomes which was previously reported in this register<sup>11</sup> and the increasing use and/or efficacy of medical therapy in patients who had not achieved consensus targets. However, we were disappointed, but not entirely surprised, by the degree of control of GH and IGF1 actually achieved across all courses of medical therapy in the UK, with 'safe' GH levels being achieved in only around 75% of cases even in long-term medical treatment courses, and GH and IGF1 both normalized in no more than 55% on SMS and 36% on cabergoline. We used LastRx>360d course data to derive these percentage responses, hypothesizing that centres would be likely to give therapeutic trials of drugs to lower GH and IGF1 which might not be effective, but would not choose to continue a treatment in the long term unless they considered that a clinically useful effect had been achieved, and we suggest that the better control seen in these courses reflects optimization of therapy in individual patients by progressive changes in drug class, type and dosage.

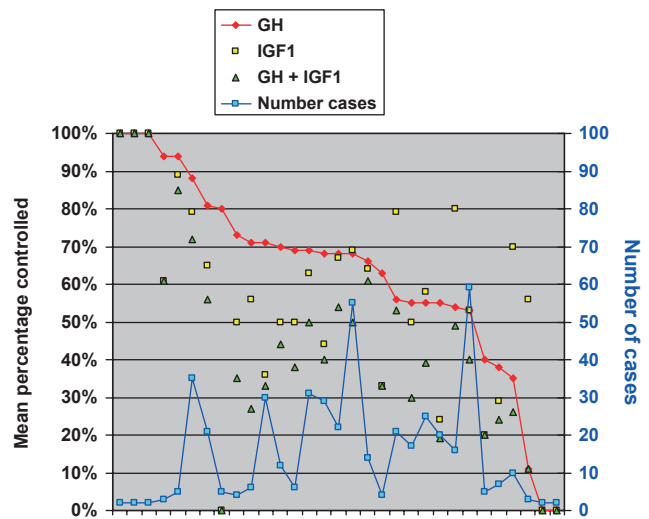


Fig. 6 Comparison of biochemical control of acromegaly in different UK centres and number of cases in each centre: Last Period of Care on SMS in 2000s. Mean percentage control achieved is shown for GH, IGF1 and both GH+IGF1 with centres arranged in descending order of percentage GH control (♦). Number of patients in each centre (□) is on the X axis.

Our study is the largest of the national registers currently attempting to study these issues<sup>18-20</sup> but all show broadly similar patterns of use of treatment modalities and of incomplete GH and IGF1 control at latest follow-up. None have attempted to study long-term control of GH and IGF1 throughout all courses of medical treatment as we have here; the German Register has recently reported that 65.2% of medically treated patients had control of IGF1 at latest follow-up, but did not study GH control.<sup>18</sup>

For bromocriptine in the 2000s (but not 1990s), our results are better than original unselected studies<sup>13</sup> but we suggest that this probably represents a selected group of DA responders continuing treatment in long term. For cabergoline, GH control in patients on long-term treatment was better than in meta-analysis of short-term studies,<sup>16</sup> but control of IGF1 was similar

and disappointing. Our results confirm the view of earlier meta-analyses that control of acromegaly with DA is most likely when basal GH and IGF1 are only modestly raised.<sup>16</sup>

For SMS, these real-life findings contrast with the consensus view that 70% patients on SMS have both GH levels below 2.5  $\mu\text{g/l}$  and normalized IGF1.<sup>8</sup> Our findings may also question the achievability of consensus guidelines for 'controlled' acromegaly which advocate strict control of GH to  $<1 \mu\text{g/l}$  and normalization of IGF1 as a goal of medical and/or surgical treatment of acromegaly<sup>9</sup> because by these criteria  $<40\%$  of treatment courses on either SMS or DA would have been consistently controlled even on long-term treatment (LastRx $>360\text{d}$ ).

If these goals are valid, then it appears that we are not achieving them in practice, so do these results give any guidance about how the admirable consensus targets for treatment might be achieved? Our data are consistent with our earlier report of improving surgical outcomes in acromegaly,<sup>11</sup> but also show that GH levels and percentage control of GH and IGF1 on medical treatment given after 'failed' surgery are better than those achieved in medical treatment courses given prior to surgery. Similarly, in patients on medical treatment, control was better in patients who had previously received pituitary radiotherapy than in those who had not. We suggest that both these factors probably reflect the powerful effect of precourse GH levels on the proportion of patients in whom GH and IGF1 can be controlled (despite the higher percentage reductions in GH from baseline observed in patients with higher GH values), but nonetheless this highlights the fact that surgery and radiotherapy may enhance the control achievable on medical therapy even if those interventions alone fail to achieve remission. The failure to achieve targets also does not mean that these courses of medical therapy are not worthwhile because substantial reductions in GH are being achieved, but does mean that additional ablative therapy needs to be considered where appropriate if adequate control of GH and IGF1 is to be obtained in the longer term.

Control achieved on modern SMS depot preparations in routine practice was better than earlier courses on short-acting SMS preparations or dopamine agonist drugs. Although this might in part represent greater efficacy, as well as greater convenience, of these modern SMS preparations, precourse GH levels were also higher in previous decades so it may also reflect the fact that relatively more severe cases were treated in earlier years. Equally, we show, in those patients where DA therapy has been continued in the long term, that percentage control of GH achieved is equivalent to that seen overall on SMS. In practice, we suggest that this represents patients who are proven to be sensitive to DA therapy continuing on this treatment in the long term, whereas nonresponders receive only a shorter trial of treatment. Overall, control of GH on DA only appears likely where the basal GH is relatively low ( $>50\%$  control was only seen in cases with basal GH  $\leq 5 \mu\text{g/l}$ ), and even in these cases, the control of IGF1 appears less satisfactory than on SMS.

It remains unclear whether failure to achieve the target of a normal IGF1 in a substantial proportion of medical treatment courses is important for long-term clinical outcomes. Previous UK studies have shown that patients achieving GH levels which

we have defined here as 'controlled' have mortality and morbidity no different from the background population.<sup>2-4</sup> Equally, elevated IGF1 is also known to correlate with increased SMR<sup>5</sup> although the significance of IGF1 is inconsistent between studies.<sup>1</sup> Longer-term follow-up studies, including future linking of data in this register to national morbidity and mortality statistics, are required to establish whether the control of GH, but not IGF1, achieved in very many of these patients on DA and a substantial minority of patients on SMS is 'good enough' to achieve long-term health outcomes. In the meantime, the fact that so many patients continued on long-term DA and/or SMS therapy in the UK in the 2000s with controlled GH but uncontrolled IGF1 presumably means that clinicians in many centres in the UK must either consider that control (or in some cases merely near-control) of GH alone is an adequate target, and/or remain unconvinced of the cost-effectiveness of escalating from DA to more expensive SMS therapy, or from SMS to very expensive GH antagonist therapy (the use of which is in any case currently not funded in a number of UK regions including in NHS Scotland and NHS Wales). Our data from the 1990s arguably pre-date widespread clinical reliance on IGF1 as a goal of therapy, but this cannot be argued for data from the 2000s. Very few patients in our register had received a GH antagonist, but we cannot be certain from our own data whether this represents an overall very low usage of this drug in the UK, or preferential inclusion of any patients on GH antagonists in the international register for that drug rather than our own register.

We confirm previous observations that both the currently available SMS analogues, octreotide LAR and lanreotide autogel, are able to achieve broadly equivalent control of GH levels in patients receiving long-term treatment.<sup>8,17</sup> This was not a controlled comparison, and evaluation of background patient characteristics showed that patients treated with these 2 drugs were not fully comparable – in particular, patients receiving lanreotide in our centres were less likely to have received previous radiotherapy. We also demonstrated an apparent failure to escalate doses of SMS appropriately in courses where GH and IGF1 targets were not achieved, an effect that was more marked in patients receiving lanreotide and that may therefore also contribute to the nonsignificant differences observed between the 2 drugs. This failure of escalation means that outcomes achieved were probably less good than the maximal achievable with optimal dosing. The data do not allow us to directly evaluate the reasons for this failure to increase doses, but we suspect that it represents a combination of therapeutic 'inertia' and optimism in the routine clinical setting, together with that fact that we have evaluated all of the available GH levels during every treatment course, whereas in the clinic only the most recent value(s) may have been considered (e.g. recent GH values with 3 below target and 1 above might be considered 'adequate' in clinic but would by definition represent only '75% GH control' in this study).

In conclusion, control of acromegaly in the UK has been imperfect as judged by current consensus guidelines for GH and IGF1 targets. Strategies for improving attainment of these targets might include more appropriate dose escalation of SMS, a change from DA to SMS therapy, increased use of GH

antagonist therapy where commissioners allow, use of newer SMS analogues, or proceeding to pituitary surgery in patients uncontrolled on primary medical therapy. Improving surgical techniques together with appropriate choice by the endocrinologist of an experienced surgeon may also continue to improve outcomes with time. All of these medical treatment therapies have consequences for medical treatment costs and the adverse effects of newer SMS analogues remain to be fully defined. Nevertheless, a recent comprehensive review suggested that total direct treatment costs are higher for patients with uncontrolled compared to controlled (GH <2.5 µg/l and normal IGF1) disease.<sup>21</sup> Increased use of pituitary radiotherapy would also be expected to increase the proportion of patients achieving a 'safe' GH, but it remains unclear whether this would be beneficial because, although patients in earlier studies with GH <5 mIU/l with normal SMR had frequently received pituitary radiotherapy as part of their treatment,<sup>2,3</sup> radiotherapy itself is associated with excess mortality, predominantly cerebrovascular mortality, in patients with acromegaly.<sup>4</sup> Whether newer radiotherapy techniques share the same problems remains to be evaluated. The UK Acromegaly Register will therefore continue to study this cohort of patients and attempt to correlate the effects of medical, surgical and radiotherapy treatments with long-term mortality, cancer and other health outcomes.

### Acknowledgements

We are grateful to Ipsen Ltd and to the Clinical Endocrinology Trust for their current generous support of the UK Acromegaly Register via unrestricted grant, and to the technical staff of the Society for Endocrinology for maintenance of the current database. Until 2009, the Register was also funded by Novartis Ltd.

### References

- Sherlock, M., Ayuk, J., Tomlinson, J.W. *et al.* (2010) Mortality in patients with pituitary disease. *Endocrine Reviews*, **31**, 301–342.
- Bates, A.S., Van't Hoff, W., Jones, J.M. *et al.* (1993) An audit of outcome of treatment in acromegaly. *The Quarterly journal of medicine*, **86**, 293–299.
- Orme, S.M., McNally, R.J., Cartwright, R.A. *et al.* (1998) Mortality and cancer incidence in acromegaly: a retrospective cohort study. United Kingdom Acromegaly Study Group. *Journal of Clinical Endocrinology and Metabolism*, **83**, 2730–2734.
- Ayuk, J., Clayton, R.N., Holder, G. *et al.* (2004) Growth hormone and pituitary radiotherapy, but not serum insulin-like growth factor-I concentrations, predict excess mortality in patients with acromegaly. *Journal of Clinical Endocrinology and Metabolism*, **89**, 1613–1617.
- Holdaway, I.M., Bolland, M.J. & Gamble, G.D. (2008) A meta-analysis of the effect of lowering serum levels of GH and IGF-I on mortality in acromegaly. *European Journal of Endocrinology*, **159**, 89–95.
- Giustina, A., Barkan, A., Casanueva, F.F. *et al.* (2000) Criteria for cure of acromegaly: a consensus statement. *Journal of Clinical Endocrinology and Metabolism*, **85**, 526–529.

- Melmed, S., Casanueva, F.F., Cavagnini, F. *et al.* (2002) Guidelines for acromegaly management. *Journal of Clinical Endocrinology and Metabolism*, **87**, 4054–4058.
- Melmed, S., Colao, A., Barkan, A. *et al.* (2009) Guidelines for acromegaly management: an update. *Journal of Clinical Endocrinology and Metabolism*, **94**, 1509–1517.
- Giustina, A., Chanson, P., Bronstein, M.D. *et al.* (2010) A consensus on criteria for cure of acromegaly. *Journal of Clinical Endocrinology and Metabolism*, **95**, 3141–3148.
- Giustina, A., Bronstein, M.D., Casanueva, F.F. *et al.* (2011) Current management practices for acromegaly: an international survey. *Pituitary*, **14**, 125–133.
- Bates, P.R., Carson, M.N., Trainer, P.J. *et al.*; UK National Acromegaly Register Study Group (UKAR-2). (2008) Wide variation in surgical outcomes for acromegaly in the UK. *Clinical Endocrinology*, **68**, 136–142.
- Jenkins, P.J., Bates, P., Carson, M.N. *et al.* (2006) Conventional pituitary irradiation is effective in lowering serum growth hormone and insulin-like growth factor-I in patients with acromegaly. *Journal of Clinical Endocrinology and Metabolism*, **91**, 1239–1245.
- Wass, J.A.H., Thorner, M.O., Morris, D.V. *et al.* (1977) Long-term treatment of acromegaly with bromocriptine. *British Medical Journal*, **1**, 875–878.
- Jackson, S.N., Fowler, J. & Howlett, T.A. (1997) Cabergoline treatment of acromegaly: a preliminary dose finding study. *Clinical Endocrinology*, **46**, 745–749.
- Abs, R., Verhelst, J., Maiter, D. *et al.* (1998) Cabergoline in the treatment of acromegaly: a study in 64 patients. *Journal of Clinical Endocrinology and Metabolism*, **83**, 374–378.
- Sandret, L., Maison, P. & Chanson, P. (2011) Place of cabergoline in acromegaly: a meta-analysis. *Journal of Clinical Endocrinology and Metabolism*, **96**, 1327–1335.
- Murray, R.D. & Melmed, S. (2008) A critical analysis of clinically available somatostatin analog formulations for therapy of acromegaly. *Journal of Clinical Endocrinology and Metabolism*, **93**, 2957–2968.
- Schoffl, C., Franz, H., Grussendorf, M. *et al.* (2012) Long-Term-Outcome in Patients with Acromegaly: analysis of 1344 Patients from the German Acromegaly Register. *European Journal of Endocrinology*, **168**, 39–47.
- Sesnilo, G., Gaztambide, S., Venegas, E. *et al.* (2013) Changes in acromegaly treatment over four decades in Spain: analysis of the Spanish Acromegaly Registry (REA). *Pituitary*, **16**, 115–121.
- Bex, M., Abs, R., T'Sjoen, G. *et al.* (2007) AcroBel—the Belgian registry on acromegaly: a survey of the 'real-life' outcome in 418 acromegalic subjects. *European Journal of Endocrinology*, **157**, 399–409.
- Ben-Shlomo, A., Sheppard, M.C., Stephens, J.M. *et al.* (2011) Clinical, quality of life, and economic value of acromegaly disease control. *Pituitary*, **14**, 284–294.

### Appendix

#### UK Acromegaly Register – Investigators and Data Entry Personnel

We thank all investigators and data entry personnel throughout the UK as well as the previous study coordinators and analysts without whom this study would have been impossible.

Centres are listed in alphabetical order of their geographical location – showing current\* and previous<sup>#</sup> principle investigators and data entry personnel in each centre:

**Aberdeen Royal Infirmary**

- J.S. Bevan\*
- A. Booth

**Belfast - Royal Victoria Hospital**

- A.B. Atkinson\*
- J. Quinn, N. Brown, A. Alexander

**Birmingham - QEH**

- J. Ayuk\*, P.M. Stewart<sup>#</sup>, M.C. Sheppard<sup>#</sup>
- N. Holden, L. Jablonski

**Bradford Hospitals NHS Trust**

- S.R. Peacey\*
- D. Wright, N. Ellis

**Brighton**

- A. Crown\*
- S. Canagon, S. Coombes, J. Morgan

**Bristol Royal Infirmary**

- K. Bradley\*, C. Dayan<sup>#</sup>, S. Lightman<sup>#</sup>
- M. Liu, J. Taheri, M. Hunt

**Cambridge - Addenbrookes**

- M. Gurnell\*, K. Chatterjee<sup>#</sup>
- A. Webb, A. Annamalai, N. Kandasamy, C. Holmes, E. Woods

**Cardiff – University Hospital Wales**

- A. Rees\*, M.F. Scanlon<sup>#</sup>
- J. Evans, A. Lansdown, L.N.R. Bondugulapati, T. Brown, S. Roberts

**Chester**

- F. Joseph\*
- K. Perkins, S. Edwards

**Dundee – Ninewells Hospital**

- G.P. Leese\*
- A. Booth,

**Edinburgh**

- B.R. Walker\*, A.W. Patrick<sup>#</sup>
- F. Gibb, M. Carson

**Exeter – Royal Devon and Exeter**

- B. Vaidya\*
- S. Revesz, L. Goss

**Glasgow – Western Infirmary**

- C. Perry\*, J.M.C. Connell<sup>#</sup>
- K. Campbell, D. Grant

**Hull**

- A. Wakil\*, S.L. Atkin<sup>#</sup>, B. Allan<sup>#</sup>
- C. Smith, C. Cleary

**Leeds – General Infirmary**

- S. Orme\*, R. Murray<sup>#</sup>
- S. Spink

**Leicester Royal Infirmary**

- T.A. Howlett\*

**Liverpool – Royal Liverpool Univ Hospital**

- J.P. Vora\*
- A. Hamilton, M. Chapman, P. Corlett, B. Morton, P. Whittingham

**London – St Bartholomew's Hospital**

- M. Druce\*, A. Grossman<sup>#</sup>, P. Jenkins<sup>#</sup>, J. Monson<sup>#</sup>
- K. Maher, L. Conrich, C. Gaygon, S. Owusu-Antwi, E. Stobie, E. Walker-Scott

**London – Kings College Hospital**

- S. Aylwin\*
- N. Gordon, J. Gilbert

**London - UCLH**

- G. Conway\*
- M. Band

**Manchester – Christie Hospital**

- P.J. Trainer\*, S. Shalet<sup>#</sup>
- M. Roberts, S. Hutton, L. Smethurst, C. Smith

**Manchester – Hope Hospital**

- T. Kearney\*
- L. Johnstone, S. Chapman, J. Cox

**Manchester – Royal Infirmary**

- J.R.E. Davis\*, F. Wu<sup>#</sup>, D. Ray<sup>#</sup>
- C. Gibson, T. Drowley

**Newcastle – Royal Victoria Infirmary**

- R.A. James\*
- M. Morris, J. Parker, J. Gebbie, P. Henderson, K. Johnstone, A. Murphy

**Norfolk and Norwich**

- F. Swords\*
- S. Gorrick

**Oxford**

- N. Karavitaki\*, J.A.H. Wass<sup>#</sup>
- A. Vincent, V. Thornton-Jones, V. Fazal-Sanderson, C. Cowshill, R. Smith

**Plymouth**

- D. Flanagan\*
- G. Twine

**Preston – Royal Preston Hospital**

- S.J. Howell\*, P.A. Vice<sup>#</sup>
- S. Wilson, S. Parkington

**Sheffield – Northern General Hospital**

- J. Newell-Price\*, R.J.M. Ross<sup>#</sup>
- V. Ibbotson, B. Roberts, A. Doane, R. Lynch, A. Murphy

**Stoke**

- R.N. Clayton\*
- M. Brown

**Watford**

- C. Johnston\*, M. Clements<sup>#</sup>
- E. Walker, S. Musaka

**York**

- P. Jennings\*
- E. Barry, N. Hudson

**Past Study Coordinator**

- Maggie Carson

**Past Study Analyst**

- Peter Bates

**Supporting Information**

Additional Supporting Information may be found in the online version of this article:

**Appendix S1.** Further details of the Register Database and Data-Processing Algorithms.

**Table S1.** Discrepancies in on-treatment flags in the GH export table.

**Table S2.** Summary of GH levels and control of GH and IGF1 in Periods of Care, stratified by Treatment Status and Era.

**Table S3.** Responses of GH and IGF1 to treatment with SMS and DA in treatment courses during the 2000s: (a) Percentages achieving biochemical control. (b) Distribution of GH levels.

**Table S4.** Responses of GH and IGF1 during treatment courses with different types of somatostatin analogue in the 1990s and 2000s: (a) Percentages achieving biochemical control, (b) Distribution of GH levels.

**Table S5.** Patient characteristics and pre-treatment GH levels in courses of lanreotide autogel compared to octreotide LAR.

**Table S6.** (a) Summary Dose Information for Lanreotide Autogel courses in the 2000s.

**Table S7.** Responses of GH and IGF1 during treatment courses with bromocriptine and cabergoline: (a) Percentages achieving biochemical control. (b) Distribution of GH levels.

**Table S8.** Sequence of use of different classes of GH-lowering drugs in individual patients analysed at the point of last period of care on medical treatment, and stratified by the era of that treatment course.

**Table S9.** Control of GH and IGF1 by DA and SMS in 1990s and 2000s, stratified by the mean GH level in the period of care off treatment prior to the current treatment course.

**Table S10.** Control of GH and IGF1 by DA and SMS in 1990s and 2000s, stratified by the mean GH level in the period of care before any medical, surgical or radiotherapy treatment.