Study to determine the optimum serum IGF-I range in patients with acromegaly treated with Pegvisomant

VJ Moyes, WM Drake

5.1 Introduction

Pegvisomant, a GH receptor antagonist, is a highly effective treatment for acromegaly with clinical and biochemical response rates of up to 97% reported (van der Lely, Hutson et al. 2001). Monitoring of treatment can be difficult; the similarity of pegvisomant to GH dictates that, for many assays, serum GH levels cannot be used to guide treatment (Veldhuis, Bidlingmaier et al. 2001) leaving serum IGF-I as the sole marker of disease activity. There are a number of problems with this (unavoidable) approach. First, IGF-I has a wide normal reference range and, without knowledge of an individual patient's GH/IGF-I physiology prior to the development of acromegaly, it is not clear where, within that reference range, GH activity is at its most "normal." Second, variations in IGF-I assay quality are well recognised (Pokrajac, Wark et al. 2007) and many do not take account of the known gender difference in IGF-I generation for a given excess GH stimulus (Parkinson, Ryder et al. 2001). Third, as discussed earlier in this thesis, there is a known 30% discordance rate between GH and IGF-I for unknown reasons. Characteristic physiological and metabolic changes occur in relation to both GH deficiency and excess. For example, active acromegaly is associated with increased lean body mass, decreased fat mass, redued C-reactive protein (CRP) levels, sodium and water retention and accelerated lipolysis. In contrast, untreated severe adult-onset GHD is characterised by decreased muscle mass, visceral adiposity, elevated CRP, a reduction in totally body sodium and fasting hyperlipidaemia. The aim of this study, therefore, was to document changes in GH-dependent metabolic parameters with pegvisomant treatment, in order to determine where within the reference range of IGF-I 'optimum' biochemical control of acromegaly lies (thereby acting as a guide for pegvisomant treatment) and to explore whether it is possible that a state of 'functional/pharmacological' GHD may be induced by excessive pegvisomant dosing in this condition.

5.1.1 Aim of this section

- To induce a metabolic syndrome similar to GH deficiency with the use of supra-physiological doses of pegvisomant to allow the identification of an 'optimum' range of serum IGF-I to guide pegvisomant dosing.

5.2 Study Design

This clinical trial was approved by a central ethics committee (Reference 07/H0703/126) and by the Medicines Healthcare Regulatory Agency (EudraCT No: 2007-003741-33).

A cohort of 10 patients currently receiving pegvisomant treatment for active acromegaly was prospectively recruited; 1 patient subsequently withdrew from the study due to personal reasons. All patients were already taking pegvisomant for acromegaly that was refractory to other treatment (i.e previous non curative surgery, radiotherapy or failure to achieve remission with somatostatin analogues). The following inclusion and exclusion criteria were applied:

5.2.1 Inclusion criteria:

- Active acromegaly on pegvisomant monotherapy at a stable dose with a normal age-adjusted serum IGF-I for at least 3 months
- Over 18 years of age
- Willing to provide informed consent

5.2.2 Exclusion criteria:

- Unwilling or unable to provide informed consent
- Other conditions known to alter IGF-I levels (severe hepatic disease, severe renal disease, malnutrition, ethanol and drug abuse)
- Abnormal liver enzymes
- Pregnancy/lactation

All had achieved biochemical control of acromegaly, as evidenced by a normal serum IGF-I level on their maintenance dose of pegvisomant. All study participants provided informed, written consent.

5.2.3 Clinical Assessment

The following markers of GH activity were taken at baseline whilst on their maintenance dose of pegvisomant:

- Body Composition: DXA % Body fat and waist: hip ratio
- Glycaemic control and insulin resistance: fasting insulin and glucose and **HOMA2 IR analysis**
- Cardiovascular risk: Lipoprotein (a), fibrinogen, CRP
- Quality of life: AcroQoL, EuroQoL, AGHDA questionnaires (Appendix)

All patients then followed a dose titration of pegvisomant, with monitoring of serum IGF-I levels on a 2 weekly basis, aiming for just below the lower limit of the age adjusted reference range. Once target IGF-I was achieved, the dose of pegvisomant was continued for a 12 week period and the above measurements were reassessed at the end of the trial period.

5.2.4 Statistical model

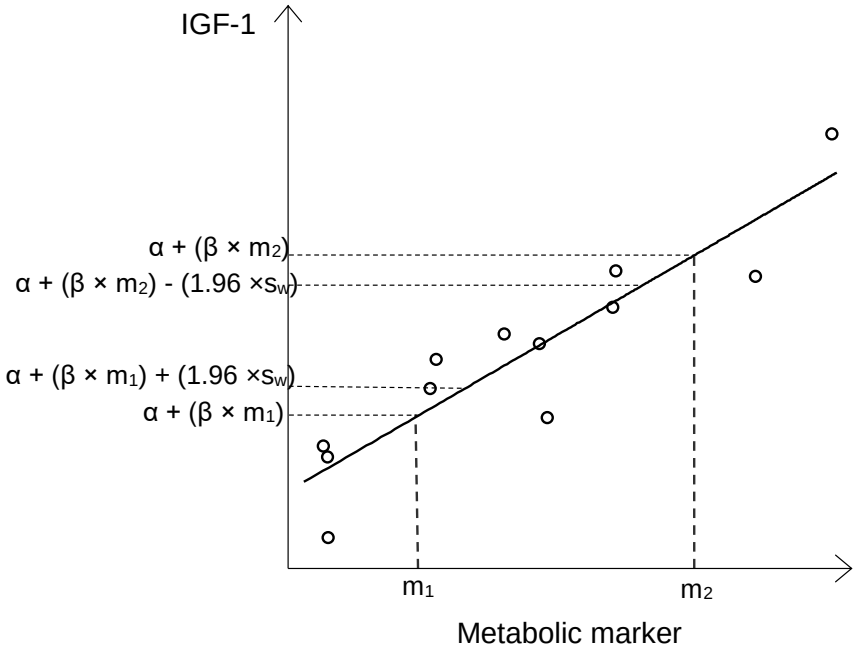
The proposed statistical model to identify the optimal IGF-I range from the distribution of results of the physiological markers of GH activity was as follows: perform a regression of IGF-I against physiological marker to form regression line IGF-1 = $\alpha + \beta \times M$, where α is the value of IGF-1 at M=0 and β is the slope of the line. The range of IGF-I values that correspond to the 'safe' range of the metabolic marker are: $\alpha + \beta \times m_1$ and $\alpha + \beta \times m_2$. The range can then be narrowed by adding and subtracting 1.96 times the within-person standard deviation of paired measurements of IGF-1from the same sample from the lower and upper intervals of the range (figure 5.1). The proposed model requires a full set of data of IGF-I levels with paired physiological markers taken at baseline and with a subnormal IGF-I induced by over treatment with pegvisomant.

In order to investigate for differences in the physiological markers between baseline and after 12 weeks at an increased dose of pegvisomant, non-parametric tests were performed due to the small sample size. Results are reported as median (range) due to the small sample size. Statistical significance was accepted at a p value <0.05. Analysis was performed using SPSS (version 11.01; SPSS Inc, Chicago, IL) for Windows XP (Microsoft Corp).

Figure 0.1 Statistical model to identify the range of IGF-I which corresponds to normalisation of physiological markers of GH activity

This graph demonstrates the proposed model for calculation of the optimal range of IGF-I in pegvisomant treatment. A regression line of IGF-I against physiological marker; IGF-1 = $\alpha + \beta \times M$, where α is the value of IGF-1 at M=0 and β is the slope of the line. The range of IGF-I values that correspond to the 'safe' range of the physiological marker are: $\alpha + \beta \times m_1$ and $\alpha + \beta \times m_2$. To further narrow the 'safe' range, add and subtract 1.96 times the within-person standard deviation of paired measurements of IGF-1from the same sample from the lower and upper intervals of the range.

Figure 5.1 Statistical model to identify the range of IGF-I which corresponds to normalisation of physiological markers of GH activity



5.3 Pegvisomant Dose Titration

All patients followed the dosing regimen shown below with the aim of achieving an IGF-I just below the normal reference range. The section in italics was included as an amendment to the original protocol to allow an increase of the maximum dose to 50mg od; this is the maximum daily dose used in the original pegvisomant publications. Response to an increased pegvisomant dose was assessed by IGF-I measured two weeks post increase and subsequent changes were made as per protocol. Weekly doses were calculated as an equivalent daily dose (weekly dose divided by 7) and the above protocol was followed accordingly. Any increases in dose were administered as a single weekly dose, for example an additional dose of 10mg per day was administered as additional 70mg per week in addition to the usual maintenance dose.

Table 5.0.1 Pegvisomant Dosing regime

This table summarises the pegvisomant dosing schedule used in this study. The target for treatment was a serum IGF-I level below the normal reference range. IGF-I levels were rechecked two weeks after an increase in dose and further increases made as necessary. The doses in italics were an amendment to the original protocol in view of the difficulty experienced in achieving target IGF-I.

Table 5.1 Pegvisomant Dosing regime

Dose of pegvisomant		Increase by	Dose
5 mg od		5 mg	10mg
10mg	IGF-I below median	5mg	15 mg od
	IGF-I above median	10mg	20 mg od
15 mg od	IGF-I below median	5mg	20 mg od
	IGF-I above median	10mg	25 mg od
20 mg od	IGF-I below median	10mg	30 mg od
	IGF-I above median	15mg	35 mg od
25 mg od	IGF-I below median	10mg	35 mg od
	IGF-I above median	15mg	40 mg od
30 mg od	IGF-I below median	10mg	40 mg od
	IGF-I above median	15mg	45 mg od
35mg od	*IGF-I below median*	*10mg*	*45mg*
	IGF-I above median	*15mg*	*50mg*
40mg od	*IGF-I below median*	*10mg*	*50mg*
	IGF-I above median	*10mg*	*50mg*

5.4 Results

5.4.1 Patient Cohort

10 patients with active acromegaly treated with pegvisomant for acromegaly and refractory to standard medical treatments (in accordance with clinical guidelines) were originally recruited. The cohort consisted of five male and five female patients aged between 32 and 74 years of age; one female patient subsequently withdrew from the study for personal reasons. All nine of the cohort had received prior pituitary surgery and/or external pituitary irradiation and/or medical therapy (Table 5.2). All had been treated with a stable dose of pegvisomant for a minimum of 3 months and had a normal age-adjusted serum IGF-I level prior to commencement of the study.

Table 5.0.2 Cohort Details

This table summarises the clinical details for the study cohort including diagnostic clinical and biochemical data and previous treatment received for acromegaly. The IGF-I levels taken prior to commencing pegvisomant as part of their clinical care is also stated; this demonstrates the severity of their GH excess despite previous treatment with surgery, radiotherapy and medical treatments.

IGF-I levels are reported as % upper limit of normal; this allows direct comparison of results measured on different assays.

Key: Diag: diagnosis, TSS: trans-sphenoidal surgery, RT: external beam radiotherapy, RS: radiosurgery, DA: dopamine agonists, SA: somatostatin analogs, %ULN: IGF-I level reported as % upper limit of normal reference range, * data not available, IGF-I Pre Pegv: IGF-I level taken prior to commencing pegvisomant.

Table 5.2 Cohort Details

Pt	Age M/F	IGF-I Diag ng/ml (%ULN)	Mean GH Diag miu/l	Tumour size at diagnosis	Previous Treatment					Pre-Pegv IGF-I ng/ml (%ULN)
					TSS	RT	RS	DA	SA	
1	74 F	*not available	200	“enlarged fossa”	N	N	Y	Y	Y	452 (226%)
2	48 M	86.8 (139.5%)	43.1	Macro	Y x2	Y	Y	Y	Y	478 (189.7%)
3	59 F	120 (187.5%)	26.3	Macro	Y	Y	N	Y	Y	416 (184.8%)
4	64 M	1022 (454.2%)	130.4	macro	Y	Y	N	N	Y	703 (312.4%)
5	56 M	1205 (535.5%)	71.4	macro	Y	Y	Fail	Y	Y	556 (247%)
6	69 M	* not available	106.3	Macro	Y	Y	Y	Y	Y	365 on SA (182.5%)
7	48 F	* not available	88.0	Macro	Y	Y	N	Y	Y	407 (161.5%)
8	46 M	988 (392%)	199	Macro	Y	N	N	Y	Y	678 (269%)
9	32 F	1001 (280.4%)	197	Macro	Y	Y	N	Y	Y	732 (204%)

5.4.2 Response to Pegvisomant dose titration

Pegvisomant doses were increased as detailed in section 5.3 with the aim of achieving a serum IGF-I just below the normal age-adjusted reference range. The summary of the dosing schedule and IGF-I levels for all nine subjects are shown in table 5.3. IGF-I levels were converted to standard deviation scores using *N – mean / SD* using age and gender related normative data for the assay used; these data are shown in table 5.4. At baseline IGF-I SDS were median 2.08 (range -0.77 to 3.55) and on the maximum trial dose IGF-I SDS were median -1.43 (range -3.09 to 0.20) (Figure 5.2). One of the cohort had a high IGF-I SDS of 3.55; at the time of recruitment he satisfied inclusion criteria with a stable IGF-I level but was unexpectedly found to have a high IGF-I at his initial visit. In view of the limited number of patients on pegvisomant, he was included in the study.

There is no prior intellectual knowledge regarding the use of supra-physiological doses of pegvisomant; all previous clinical trials used clinically effective doses only aiming for normalisation of IGF-I rather than mild GH deficiency. Although reductions in IGF-I were seen in all patients (figure 5.2) with a decrease in IGF-I of median 54.7% (range 26.6-66.4%) (Table 5.3), only three patients achieved a target IGF-I of below the age and gender defined normal reference range (table 5.3). Of the six patients who failed to achieve the target IGF-I, four were on the maximum dose of pegvisomant (50mg). Due to a limitation of time caused by a prolonged titration phase, two patients were unable to increase to the maximum 50mg and completed the study on 40mg per day. The three patients who achieved a sub-normal IGF-I were all female; two were post menopausal and thus oestrogen deficient.

The inability to achieve target IGF-I in the whole cohort prevented completion of the full statistical analysis as per the original protocol; from the data available it was not possible to determine the optimal range of IGF-I for monitoring of pegvisomant using

the proposed statistical model. The data does however provide interesting information regarding the unexpected difficulty in inducing a subnormal serum IGF-I even with very high doses of pegvisomant.

Table 5.0.3 Summary of IGF-I levels at baseline and following increased doses of pegvisomant

This table summarises the IGF-I levels taken at baseline on the usual maintenance pegvisomant dose and subsequent changes to IGF-I (numbered 1 to 5) in response to the increased pegvisomant doses (numbered 1 to 5) for the study cohort of 9 subjects. Doses of pegvisomant were increased aiming for a target IGF-I level of below the lower limit of age and gender defined reference range as shown in italics.

Dose of pegvisomant is reported as mg per day (mg per week stated in brackets for those patients on a weekly dose). A maximum dose of pegvisomant of 50mg per day was stipulated based on data from previous clinical trials. The lowest IGF-I level achieved is shown in bold; six out of the nine patients failed to achieve target IGF-I despite the use of high dose pegvisomant.

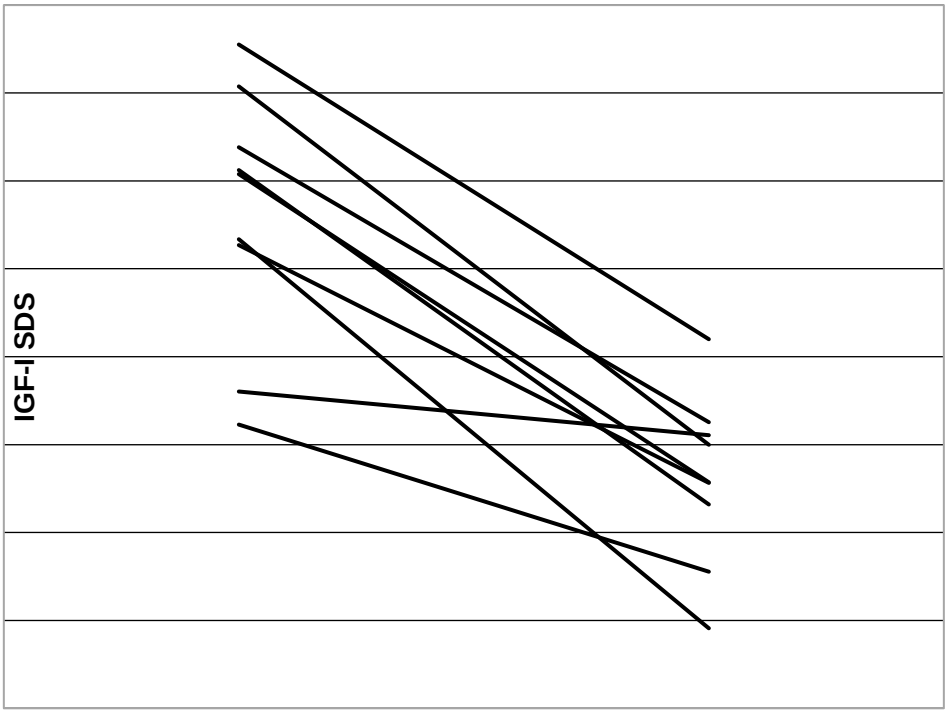
Table 5.3 Summary of IGF-I levels at baseline and following increased doses of pegvisomant

Pt	Baseline dose mg/day (mg/wk)	Baseline IGF-I	*Target IGF-I*	Dose (1)	IGF-I (1)	Dose (2)	IGF-I (2)	Dose (3)	IGF-I (3)	Dose (4)	IGF-I (4)	Dose (5)	IGF-I (5)	Trial dose	Weight kg	Target IGF-I achieved
1	10	90	*69*	15	140	20	115	25	102	30	87	35	**66**	35	59	Yes
2	15	250	*94*	15	214	25	147	30	147	35	118	40	**105**	40	92	No
3	10	182	*81*	20	104	25	**64**							25	65	Yes
4	8.6 (60)	250	*81*	15 (105)	174	25 (175)	123	35 (245)	106	40 (280)	**91**			40	101	No
5	20	285	*81*	35	241	50	**158**							50	105	No
6	20	223	*69*	35	149	50	**123**							50	95	No
7	10	130	*94*	15	104	20	**68**							20	68	Yes
8	14.3 (100)	248	*94*	20 (140)	227	30 (210)	228	40 (280)	175	50 (350)	**95**			50	86	No
9	30	243	*109*	45	188	50	**129**							50	82	No

Figure 5.2 Difference in IGF-I levels between baseline and trial end

This graph demonstrates the fall in serum IGF-I in response to the increased dose of pegvisomant. IGF-I levels are reported as standard deviation scores; -2 to +2 are considered normal. Each line represents an individual patient's IGF-I results at baseline and on the trial dose of pegvisomant. The aim was to increase the dose to lower the IGF-I level to below the normal reference range; although all IGF-I levels decreased in response to the increased dose only three patients achieved a level below the normal reference range.

Figure 5.2 Difference in IGF-I levels between Baseline and Trial end



5.4.3 Change in IGF-I

Although the majority of patients failed to achieve target IGF-I, all subjects experienced a reduction in IGF-I in response to the increased dose of between 26.7 and 66.4%. Figure 5.3 demonstrates the plot of change in IGF-I against change in pegvisomant dose for the cohort; it is apparent that although there appears to be a linear relationship, there are a number of outliers which suggests that an individual patient's biochemical response to pegvisomant is multi-factorial. To investigate this further, a regression analysis was performed to investigate the individual and cumulative effects of pegvisomant dose, gender and body weight on ΔIGF-I. Results are shown in table 5.4; none of the factors were found to have a statistically significant effect on ΔIGF-I.

Figure 5.3 Plot of ΔIGF-I against ΔPegvisomant Dose

This graph represents the plot of ΔIGF-I against ΔPegvisomant Dose for the cohort studied. Only three out of the nine patients studied achieved a target sub-normal IGF-I which suggests there is some variability in response to pegvisomant. This variability is further demonstrated in this plot; although the relationship of ΔIGF-I against ΔPegvisomant Dose is mostly linear, a number of outliers are present.

Figure 5.3 Plot of ΔIGF-I against ΔPegvisomant Dose

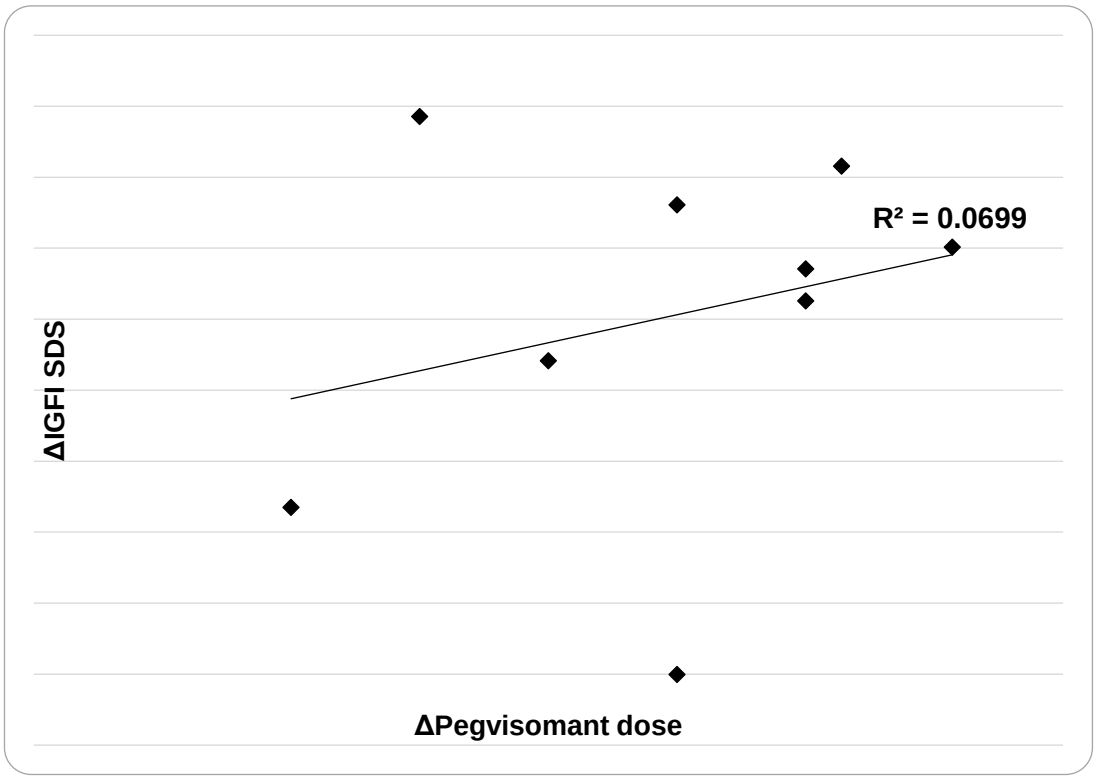


Table 5.0.4 Factors affecting IGF-I response to Increased Dose Pegvisomant

A linear regression model of ΔIGF-I SDS against change in dose, body weight, gender and maintenance pegvisomant dose was performed to investigate the individual and cumulative effects on ΔIGF-I SDS; none were found to have a statistically significant effect on ΔIGF-I.

	ΔIGF-I	
	β-Coeff	*p value*
Change in Pegvisomant Dose	-0.453	*0.561*
Maintenance Pegvisomant Dose	-0.81	*0.902*
Gender	-0.576	*0.680*
Body weight	0.377	*0.749*
R Squared	0.388	

5.4.4 Effect of Pegvisomant on Physiological Markers of GH activity

Characteristic physiological changes are expected in relation to GH activity levels; the most directly measurable relate to changes in body composition, insulin resistance, markers of cardiovascular risk and quality of life. These were assessed at baseline on the patient's maintenance pegvisomant dose and at the end of the trial period on the increased dose.

Fasting plasma glucose at baseline was median 5.0mmol/l (range 4.5-6.5) and at trial end median 4.9mmol/l (3.9-7.5); no statistically significant difference was detected (p= 0.373) using non parametric tests in view of the small sample size (Table 5.5). Repeat testing with removal of the outlier (figure 5.4a) confirmed no statistically significant difference (p=0.091). Fasting insulin levels were median 7.5miu/l (range 2.0-26.0) at baseline and 4.2miu/l (2.0-9.0) at the end of the trial; again no statistically significant difference detected (p=0.069) (figure 5.4b). There was also no significant difference in HOMA2-IR Insulin resistance scores; median 1.1 (0.4-3.5) at baseline and median 0.6 (0.4-1.3) on increased dose pegvisomant (p=0.075) (figure 5.4c).

Assessment of body composition revealed a significant difference in percentage body fat as measured by DXA; median 25.4% (19.4-36.5) at baseline and 26.5% (18.6.0-37.6) final result, p=0.036 (figure 5.5a). No difference was detected with waist:hip ratio however; median 0.87 (0.83-1.03) at baseline compared to 0.90 (0.83-0.98) on high dose pegvisomant (p=0.528) (figure 5.5b). Cardiovascular risk factors were assessed; a significant response to pegvisomant was seen with fibrinogen, baseline median 3.13g/l (2.31-3.92) compared to 2.86g/l (1.99-3.45) at trial end (p=0.012) (figure 5.6b). There was however no detectable difference with lipoprotein A; median 135mg/l (24-806) at baseline and 82mg/l (24-679) at trial end (p=0.345) (figure 5.6a).

No statistically significant differences were detected in the quality of life assessments. The Adult Growth Hormone Deficiency Assessment (AGHDA) score was median 3 (range 0-23) at baseline and median 5 (2 to 23) at trial end; this was not statistically significant p=0.102 (figure 5.7a).

AcroQol; a specific acromegaly related questionnaire of physical and psychological wellbeing, also showed no statistically significant difference between baseline (median 86.4, range 29.5 to 109.1) and trial end (median 80.7, range 15.9-98.9) p=0.173 (figure 5.7b). The visual analog scale of EuroQoL, a non disease specific QoL questionnaire, also demonstrated no statistically significant difference; median 75 (50-95) at baseline and median 80(50-95) on high dose pegvisomant, p=0.344 (table 5.5, figure 5.7c).

The aim of the study was to induce 'functional/pharmacological' GHD; due to the inability to achieve target IGF-I in the majority of the cohort, it was not possible to perform the statistical analyses initially planned due to the overlap of results. Figure 5.8 uses fasting plasma glucose as an example to demonstrate this overlap of results; it is not possible to calculate the difference between mean + and - 1.96SD for the two sets of results. Similar plots were evident for all markers of GH activity assessed.

Table 5.0.5 Response of Physiological Markers of GH to Increased Pegvisomant Dose

This table summarises the results taken at baseline on maintenance pegvisomant dose in comparison to measurements taken after 3 months of overtreatment, with a serum IGF-I below or close to the lower limit of the normal reference range. Measurements were made of characteristic markers of GH activity; body composition, insulin resistance, cardiovascular risk and quality of life scores. Non-parametric tests (Wilcoxon signed rank) were performed in view of the small sample size; significance is taken at $p \leq 0.05$.

	Baseline Median (Range)	Final Median (Range)	*p value*
Fasting Plasma Glucose	5.0 (4.5-6.5)	4.9 (3.9-7.9)	*0.373*
Fasting Insulin	7.5 (2.0-26.0)	4.2 (2.0-9.0)	*0.069*
HOMA2-IR	1.1 (0.4-3.5)	0.6 (0.4-1.3)	*0.075*
Fibrinogen	3.13 (2.31-3.92)	2.86 (1.99-3.45)	*0.012*
Lipoprotein A	135 (24-806)	82 (24-679)	*0.345*
% Body Fat	25.4 (19.4-36.5)	25.4 (21.0-37.2)	*0.028*
Waist:Hip Ratio	0.87 (0.83-1.03)	0.91 (0.86-0.97)	*0.398*
AGHDA (Max 25)	3 (0-23)	6 (2-23)	*0.194*
ACROQOL (Max 110)	84.1 (29.5-109.1)	78.4 (15.9-98.9)	*0.310*
EUROQOL	75 (50-95)	76 (50-95)	*0.465*

Figure 5.4 Change in Fasting Plasma Glucose in Response to Increased Pegvisomant Dosing

This graph represents the changes in fasting glucose in relation to a change in GH activity caused by the increase in pegvisomant dose. Each line corresponds to an individual patient's data; the baseline level was taken on the maintenance dose pegvisomant and the final level was taken on the increased pegvisomant dose used for the trial period. No statistically significant difference was seen with any parameter in this cohort; this is likely to reflect a combination of the difficulty in achieving the target sub-normal IGF-I levels and the modest numbers of patients available to recruit into such studies, even in tertiary centres.

One outlier is noted for the fasting glucose measurements; levels increased from 5.6mmol/l to 7.9mmol/l in this patient. Repeat analysis of the results excluding the outlier confirmed a lack of a statistically significance (p=0.091).

Figure 5.4 Fasting Plasma Glucose in Response to Increased dose of Pegvisomant

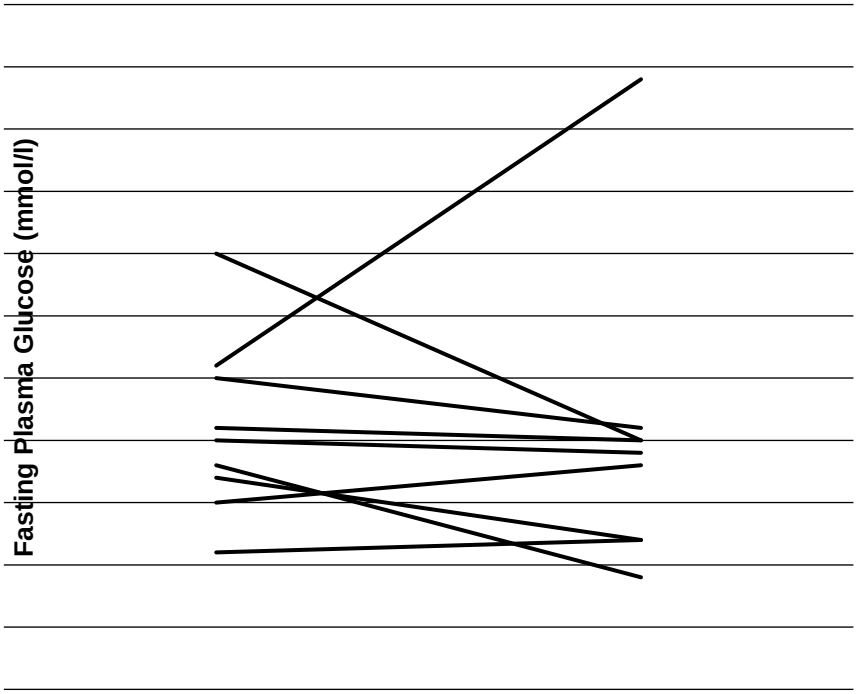


Figure 5.5 Change in Fasting Insulin levels in Response to Increased dose of Pegvisomant

This graph represents the changes in fasting insulin in relation to a change in GH activity caused by the increase in pegvisomant dose. Each line corresponds to an individual patient's data; the baseline level was taken on the maintenance dose pegvisomant and the final level was taken on the increased pegvisomant dose used for the trial period. No statistically significant difference was seen with any parameter in this cohort; this is likely to reflect a combination of the difficulty in achieving the target sub-normal IGF-I levels and the modest numbers of patients available to recruit into such studies, even in tertiary centres.

Figure 5.5

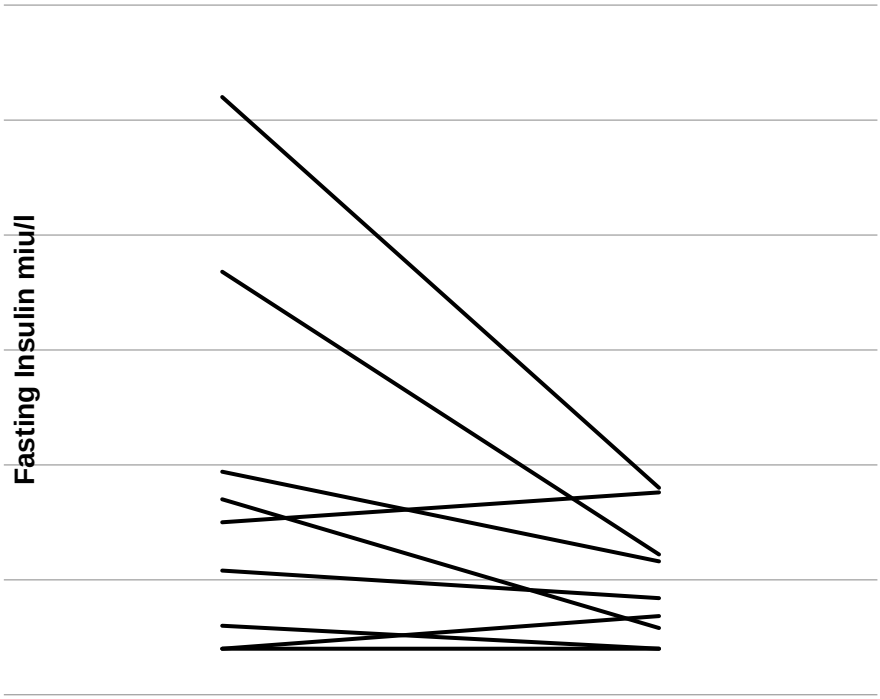


Figure 5.6 HOMA2-IR insulin resistance

This graph represents the changes in HOMA2 insulin resistance in relation to a change in GH activity caused by the increase in pegvisomant dose. Each line corresponds to an individual patient's data; the baseline level was taken on the maintenance dose pegvisomant and the final level was taken on the increased pegvisomant dose used for the trial period. No statistically significant difference was seen with any parameter in this cohort; this is likely to reflect a combination of the difficulty in achieving the target sub-normal IGF-I levels and the modest numbers of patients available to recruit into such studies, even in tertiary centres.

Figure 5.6

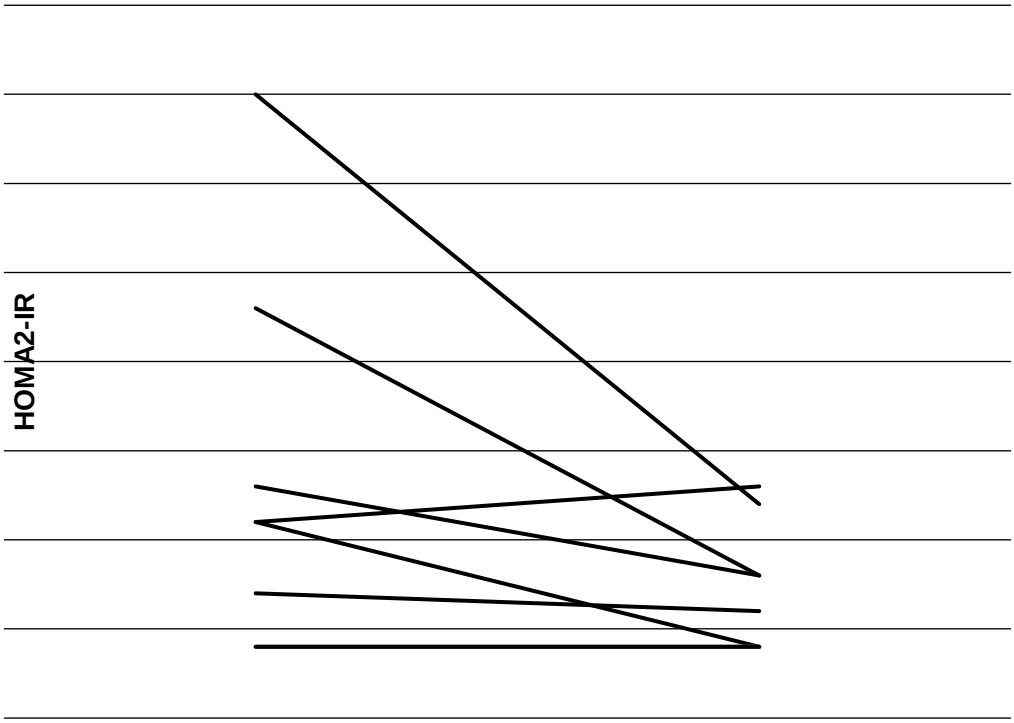


Figure 5.7 Change In Body Composition In Response To Increased Dose Pegvisomant

The following graph reflects the changes in body composition in response to the increased pegvisomant dose. %body fat was measured for each patient at baseline on their usual maintenance pegvisomant dose and again after 12 weeks on the increased trial dose; each line on the graph corresponds to an individual patient's data.

A statistically significant difference was detected for %body fat

Figure 5.7 Change in %Body Fat in Response to Increased Dose Pegvisomant

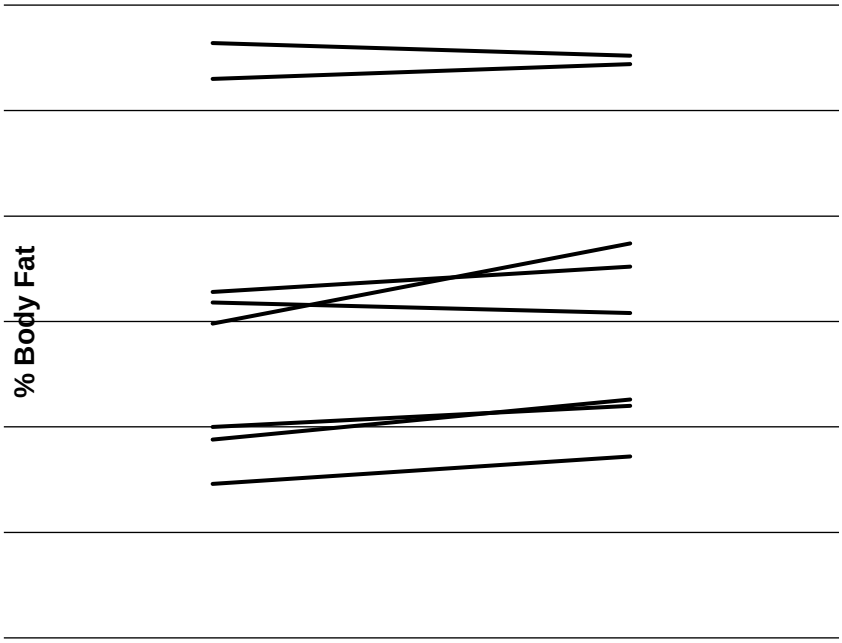


Figure 5.8 Change in Waist Hip Ratio in Response to Increased Dose Pegvisomant

The following graph reflects the changes waist:hip ratio in response to the increased pegvisomant dose; this was measured for each patient at baseline on their usual maintenance pegvisomant dose and again after 12 weeks on the increased trial dose; each line on the graph corresponds to an individual patient's data.

No statistically significant difference was detected.

Figure 5.8

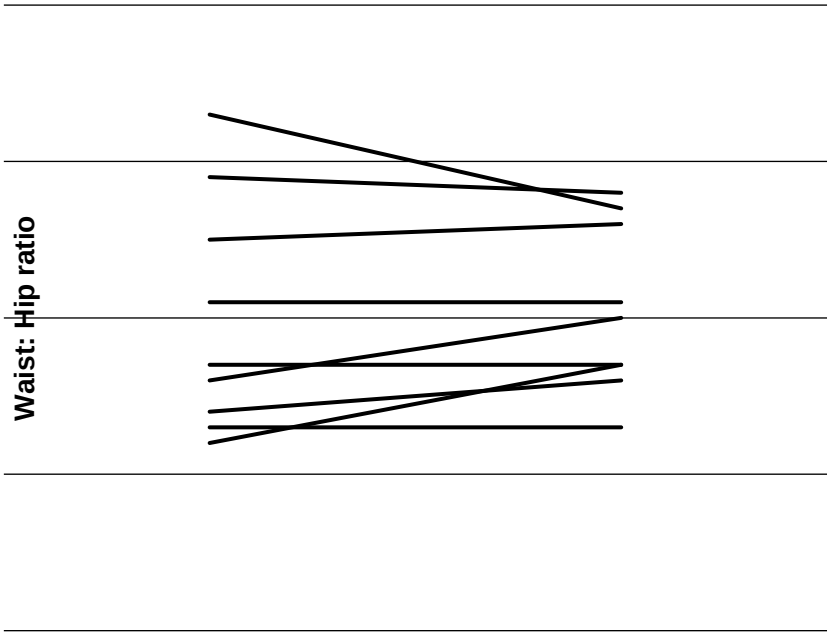


Figure 5.9 Change in Lipoprotein A levels in Response To Increased Dose Pegvisomant

The following graph reflects the changes in the cardiovascular risk marker lipoprotein A in response to the increased pegvisomant dose. These were measured for each patient at baseline on maintenance dose pegvisomant and again after 12 weeks on the increased trial dose; each line on the graph corresponds to an individual patient's data. No statistically significant difference was detected for lipoprotein a.

Figure 5.9 Change in Lipoprotein A levels in Response To Increased Dose Pegvisomant

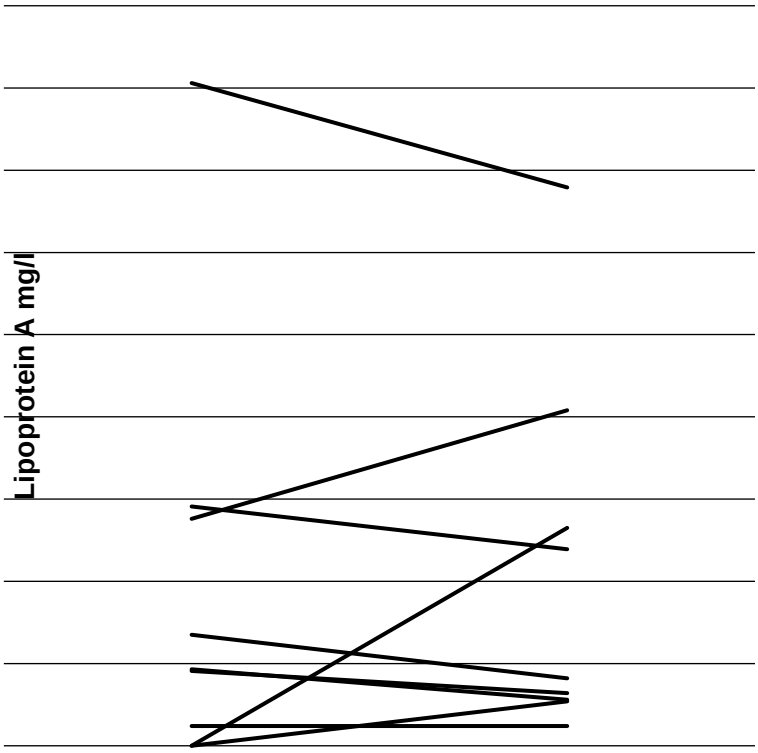


Figure 5.10 Change in Fibrinogen levels in Response To Increased Dose Pegvisomant

The following graph reflects the changes in the cardiovascular risk marker fibrinogen in response to the increased pegvisomant dose. These were measured for each patient at baseline on maintenance dose pegvisomant and again after 12 weeks on the increased trial dose; each line on the graph corresponds to an individual patient's data. A statistically significant difference was detected for fibrinogen.

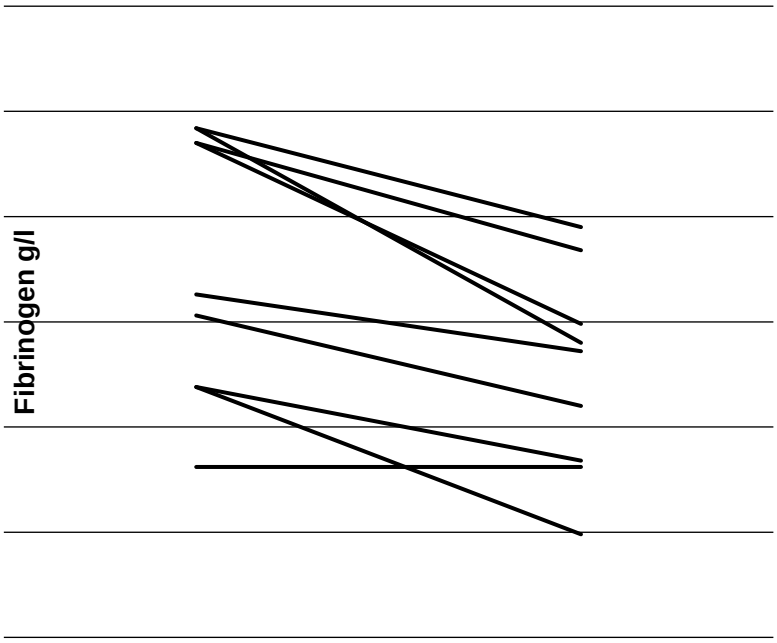


Figure 5.11 Changes in Adult Growth Hormone Deficiency Assessment (AGHDA) In Response To Increased Dose Pegvisomant

The following graph reflects the change in the AGHDA quality of life questionnaire score in response to the increased pegvisomant dose and consequent reduction in GH activity. These were measured for each patient at baseline on maintenance dose pegvisomant and again after 12 weeks on the increased trial dose; each line on the graph corresponds to an individual patient's data.

No statistically significant difference was detected between baseline and on the trial dose of pegvisomant.

Figure 5.11 Changes in Adult Growth Hormone Deficiency Assessment (AGHDA) In Response To Increased Dose Pegvisomant

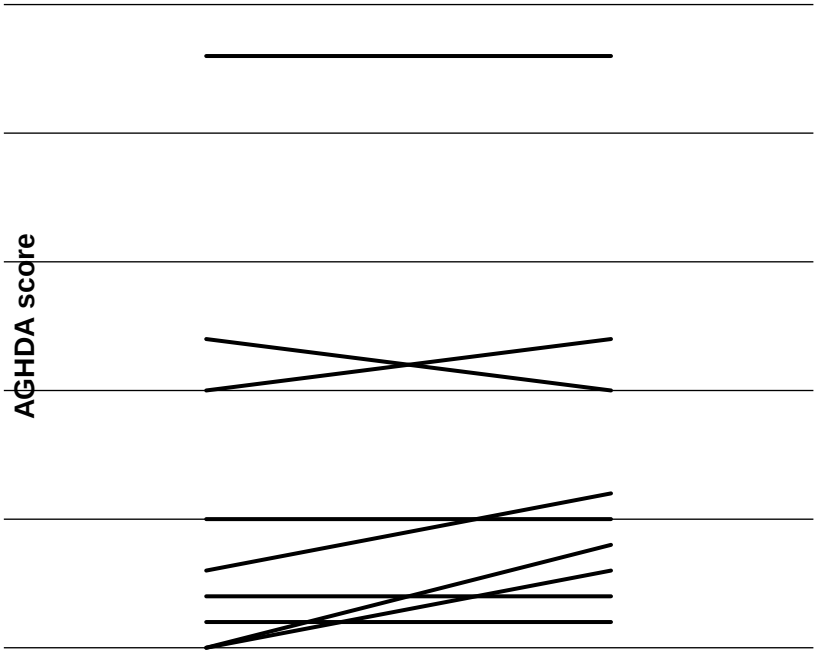


Figure 5.12 Changes in AcroQoL In Response To Increased Dose Pegvisomant

The following graph reflects the change in the AcroQoL quality of life questionnaire score in response to the increased pegvisomant dose and consequent reduction in GH activity. These were measured for each patient at baseline on maintenance dose pegvisomant and again after 12 weeks on the increased trial dose; each line on the graph corresponds to an individual patient's data.

No statistically significant difference was detected between baseline and on the trial dose of pegvisomant.

Figure 5.12

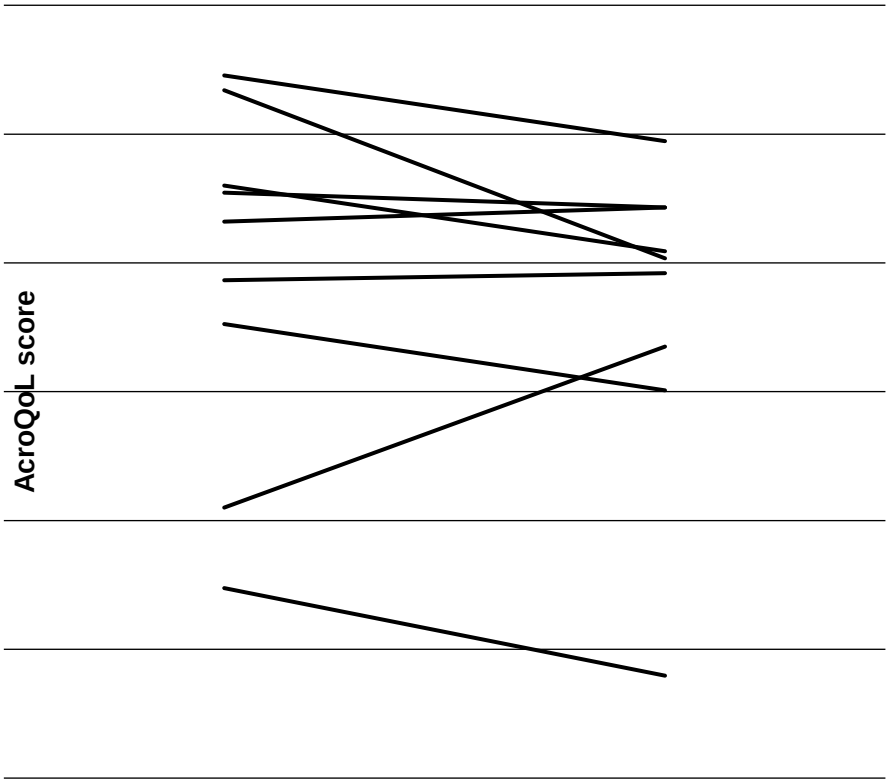


Figure 5.13 Change in EuroQoL Visual Analogue score In Response To Increased Dose Pegvisomant

The following graph reflects the change in the EuroQoL quality of life questionnaire score in response to the increased pegvisomant dose and consequent reduction in GH activity. These were measured for each patient at baseline on maintenance dose pegvisomant and again after 12 weeks on the increased trial dose; each line on the graph corresponds to an individual patient's data.

No statistically significant difference was detected between baseline and on the trial dose of pegvisomant.

Figure 5.13

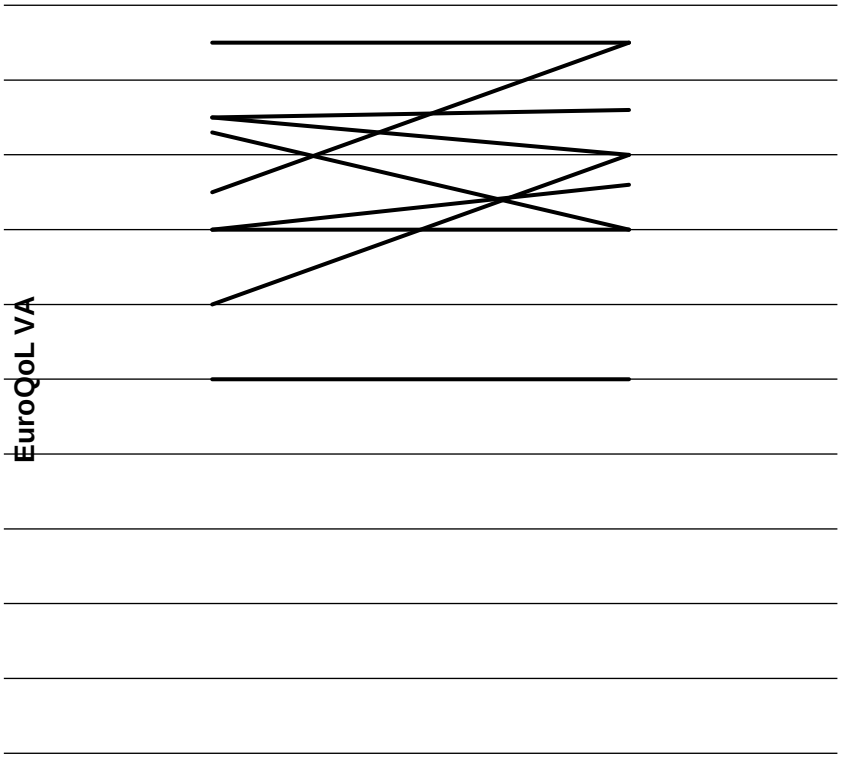
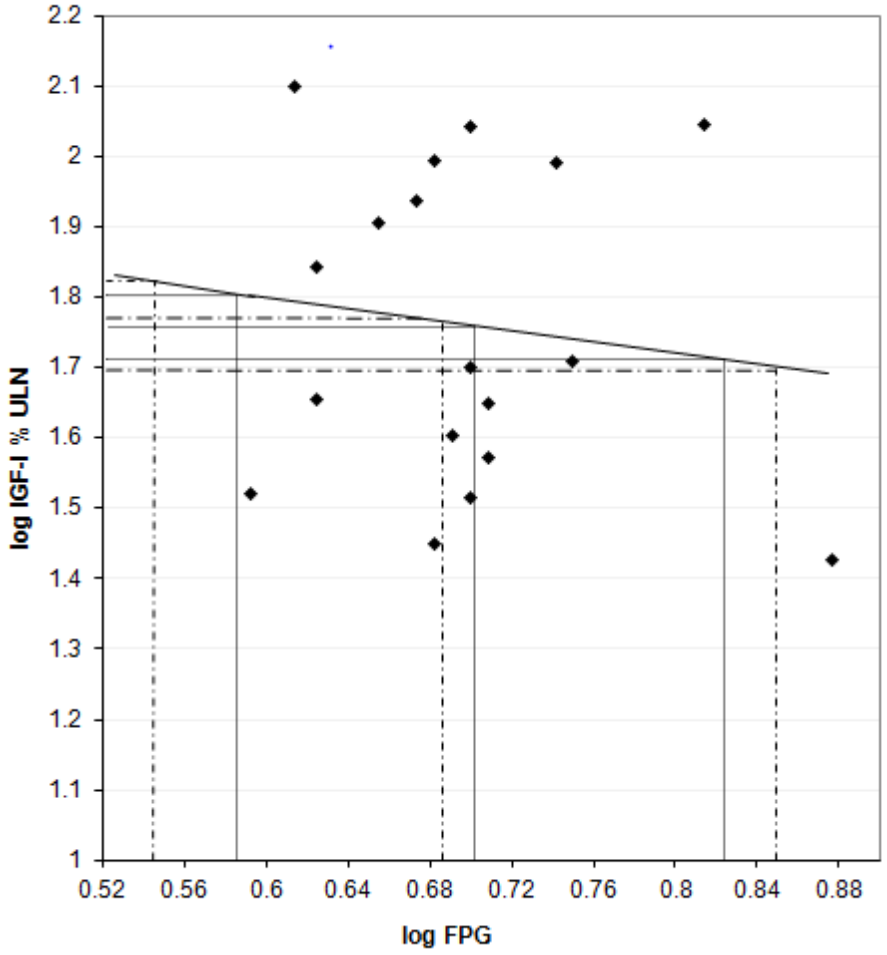


Figure 5.14 Plot of the Results for Fasting plasma glucose against IGF-I

This graph shows the plot of the log [fasting plasma glucose] results taken at the start of the trial on maintenance pegvisomant dose and at the end of the trial on an increased dose against log [IGF-I %ULN] . Log transformation was necessary to form a straight line relationship and the regression line is shown. The dotted lines(⋯⋯) demonstrate the mean +/- 1.96x SD for baseline FPG results. The dashed lines(- - -) demonstrate the mean +/- 1.96x SD for the final FPG results.

The intention of the study was to render patients mildly GH deficient in order to investigate the effect on metabolic markers such as FPG to try to narrow the range of IGF-I as a guide for treatment, by calculating the difference between mean +/- 1.96 x standard deviation on the samples at baseline and at trial end. Unexpectedly even in spite of maximal doses of pegvisomant the majority of the cohort failed to lower their IGF-I levels sufficiently, thereby resulting in a significant overlap in metabolic marker results such as FPG. This overlap of results prevents the calculation of the “safe range” of IGF-I.

Figure 5.14 Plot of the Results for Fasting plasma glucose against IGF-I



5.5 Discussion

Pegvisomant is well established as a medical therapy for patients with acromegaly whose disease is refractory to conventional therapies, but its clinical use is made difficult by the lack of a robust method for monitoring treatment. Although serum IGF-I serves as a marker of GH activity, variability in the assay and known discordance between GH and IGF-I levels limit its reliability. The original purpose of this study was to investigate, using biological parameters relevant to the GH/IGF-I system, whether there is an 'optimum part of the age-adjusted IGF-I reference range within which clinicians can be confident that patients are not either over- or under-treated.

The main conclusion of this study was the unexpected finding that even with maximal increases in pegvisomant dose it was difficult to reduce serum IGF-I to levels below the reference range. This observation hampered the planned statistical analyses but did provide an interesting insight into the pharmacological properties of pegvisomant.

Summary of Results

Response to Pegvisomant Dose Titration

The cohort of nine patients underwent a scheduled dose titration whereby doses were increased by 2 to 4.6 fold. Only three patients achieved a target IGF-I of below the age-related reference range, all of whom were female and two of whom were postmenopausal, suggesting that this observation is unlikely to be an oestrogen effect. Previous data suggests that increased body mass is associated with increased pegvisomant clearance; to test this hypothesis a regression analysis of ΔIGF-I was performed to investigate the effects of body weight, gender and pegvisomant dose. None of these factors were found to have a significant effect on ΔIGF-I.

It should be noted that although six patients failed to achieve the target IGF-I of below the normal reference range, all patients achieved a reduction in serum IGF-I of between 26.7 and 66.4%. Those who failed to reach the target range had higher starting values and so had further to fall; it is possible that further increases in pegvisomant doses may have been able to achieve the desired subnormal serum IGF-I, but a lack of safety data regarding the use of higher daily doses constrained the protocol design. It should also be noted that although all patients prior to enrolment had serum IGF-I levels within the normal range, values at commencement of the dose titration protocol were actually above the normal reference range for three patients. Although they subsequently achieved between 44 - 63% reductions in IGF-I, they required a far larger drop in order to achieve target IGF-I.

Effect of Pegvisomant on Physiological Markers of GH activity

Due to the lack of overt 'pharmacological' GH deficiency (arbitrarily defined as a subnormal serum IGF-I) in the majority of the cohort, the original statistical analyses of these results were not possible. All measures assessed are known to be markers of GH activity with distinct patterns in relation to both GH excess and deficiency. Non-parametric testing confirmed that there was not a statistically significant difference between baseline and final results for the majority of the physiological markers – presumably due, at least in part, to this difficulty in achieving a sufficiently low serum IGF-I.

On review of individual results, some marked improvements in metabolic markers occurred in response to the reduction in IGF-I. Patient no 6's fasting insulin level decreased from 26miu/l to 9miu/l with a reduction in fasting glucose from 6.5 to 5mmol/l as a result of reducing serum IGF-I from the upper limit of normal to the level

of the median for his age related reference range. This emphasises the point that a clearer target for treatment is needed in order to minimise risk of excess GH; prior to the study he was considered to be on a satisfactory dose of pegvisomant but these results suggest it is entirely plausible that values of serum IGF-I that lie within a population reference may represent marginal GH excess for an individual patient.

Such exuberant responses were not universal throughout the cohort for each measure however, thus accounting for the lack of statistical significance. The quality of life questionnaires in particular demonstrated a variety of responses which emphasise the potential for bias. It is not possible to remove the influence of an individual's personality when using these quality of life scores. For example one patient scored 23/25 on AGHDA questionnaires both at baseline and at the end of the study; no change was evident despite the IGF-I level decreasing from above the median to a level of GHD (IGF-I 64ng/ml).

Critique of Work

The unexpected difficulty in achieving the target IGF-I is a major drawback of this study; as such the proposed statistical analyses were not possible. The protocol was written using all available pharmacological data from the original pegvisomant trials; however the previous studies had not intended to cause GH deficiency and therefore the relevant information regarding high dose pegvisomant was not available. The study was also limited by the lack of safety and pharmacokinetic data above 50mg; without such data it was not possible to obtain the necessary approval to use higher doses for the purpose of a study.

In order to fully answer the study question of identifying the optimum serum IGF-I range with pegvisomant use, a number of requirements exist. This study design largely focused on improving the accuracy of the lower end of the normal IGF-I

reference range by inducing pharmacological GH deficiency. Ideally the baseline investigations would occur at a time of GH excess followed by a period of mild GH deficiency in order to narrow the IGF-I range from the top and the bottom. This however is not possible in view of the ethical implications of withholding necessary treatment for GH excess with the potential for causing significant morbidity. This study was also restricted by the limitations on pegvisomant dose; it is possible that with further increases in dose all patients may have achieved target IGF-I although the lack of safety and pharmacokinetic data in humans above 50mg per day precludes this. A larger cohort would also have been preferable although cohort size would always be limited by the comparatively small number of patients on pegvisomant.

Other limitations of this work include the reproducibility of some measures. Waist hip ratio in particular is subject to error even when performed by the same investigator. Quality of life questionnaires are subject to influence by an individual's personality and judgement of their own symptoms; a more stoic individual tends to score lower marks than a person with depression and yet there is no method for correcting for this when analysing results. The duration of this study also influenced results, particularly as the dose titration phase took considerably longer than expected, there was up to 22 weeks between baseline and final assessments which had potential implications for the results. One outlier is evident in the fasting plasma glucose levels; results increased from 5.6 to 7.9mmol/l despite the reduction in GH activity; this suggests that lifestyle factors perhaps influenced by the duration of the study affected this individual's insulin resistance.

Consideration of these data in the context of the Published Literature

No previous studies have sought to answer the question of identifying the optimal serum IGF-I for acromegalic patients treated with pegvisomant. Furthermore no previous studies have aimed to induce GH deficiency with pegvisomant or have used such high doses for an extended period of time.

There is a report of an accidental pegvisomant overdose; 80mg daily was taken for seven days instead of 80mg per week. The only symptom reported was slight increase in fatigue and the serum IGF-I decreased from 940ng/m to 153ng/ml (this measurement was taken after 4 weeks on the increased dose) (Pegvisomant Investigator's Brochure).

Future work

The experience gained from this study has given a further insight into the properties of pegvisomant that encourage further investigation. In order to further investigate the optimum IGF-I range ideally further studies would be undertaken using higher pegvisomant doses and in particular to perform more detailed pharmacokinetic studies of high dose pegvisomant. Previous data assumes a linear dose response relationship but this is based primarily on doses of 10-20mg per day.

It would also be preferable to perform the study prospectively with the baseline data taken prior to the commencement of pegvisomant, when IGF-I levels for the whole cohort were high. This would allow a more robust analysis of the data with a clearer identification of the optimum IGF-I range rather than focusing primarily on the lower end of the normal reference range. The feasibility of such a study would however be limited by ethical considerations and the necessary time to recruit patients at a time of GH excess prior to commencement of pegvisomant.

The variability in achieving target IGF-I highlights the need for further studies into variability in pegvisomant responsiveness; factors such as heterogeneity in the GH receptor and variation in serum pegvisomant levels, in particular pegvisomant clearance in relation to body mass would be of interest.

Summary and Conclusion

Although the difficulty in achieving the target serum IGF-I in the cohort and to therefore perform the necessary statistical analyses was disappointing, this study has instead revealed the unpredicted difficulty in achieving sub-normal IGF-I levels with pegvisomant. Such information is of interest to the clinician; it does provide some reassurance that it is surprisingly difficult to over-treat a patient with pegvisomant. It has also highlighted the variability that is seen with pegvisomant levels and raises questions over what is underlying this variability in response.