OZGROW Annual Report 2011

Introduction

OZGROW Database

There are currently 1730 children receiving subsidised growth hormone (GH) treatment in Australia. The majority of these (850, 49.1%) are receiving GH under the Department of Health and Ageing's (DoHA) indication of Short Stature and Slow Growth indication. The other major indication is Biochemical GH Deficiency (357, 20.6%), while there are also 221 (12.8%) receiving GH for Turner Syndrome, 122 (7.1%) for Prader Willi Syndrome, 89 (5.1%) for an intracranial lesion or cranial radiation, and 31 (1.8%) for neonatal hypoglycaemia secondary to GH deficiency. Four patients (0.2%) are receiving GH under the new indication of Short Stature Homeobox (SHOX) gene disorders. In total, the OZGROW database contains records from 5808 individuals that date back to 1977.

OZGROW Activities 2011

Papers and publications

The following paper was published in Clinical Endocrinology,

Growth hormone treatment for Turner syndrome in Australia reveals that younger age and increased dose interact to improve response
Ian P. Hughes, Catherine S. Choong, Mark Harris, Geoffrey R. Ambler, Wayne S. Cutfield, Paul L. Hofman, Chris T. Cowell, George Werther, Andrew Cotterill and Peter S.W. Davies on behalf of the Australasian Paediatric Endocrine Group (APEG). *Clinical Endocrinology* (2011) 74, 473–480

A paper entitled,

Growth Hormone Regimens in Australia: Analysis of First Three Years of Treatment for Growth Hormone Deficiency and Idiopathic Short Stature.
Ian P Hughes, Mark Harris, Catherine S. Choong, Geoff Ambler, Wayne Cutfield, Paul Hofman, Chris T. Cowell, George Werther, Andrew Cotterill, and Peter SW Davies on behalf of the Australasian Paediatric Endocrine Group (APEG).

is in final revision after review for publication in Clinical Endocrinology.

Two posters, below, were accepted and presented on behalf of the OZGROW Subcommittee of APEG at the Endo2011 conference in Boston (June 4-7).

P1-752: Growth Hormone Treatment in Australia for Patients with Growth Hormone Deficiency and Short Stature and Slow Growth: Evaluation of the First three years
Ian Hughes, Catherine Choong, Peter Davies, and Andrew Cotterill

P1-752: Analysis of Growth Response to Treatment of Different Diagnostic Entities Comprising the "Short Stature and Slow Growth" Indication for GH Treatment in Australia.
Ian Hughes, Catherine Choong, Peter Davies, and Andrew Cotterill

An abstract has been submitted for presentation for the APEG/ESA Joint Scientific Meeting in Perth (28-31 August) entitled,

Adult Height Following Growth Hormone Treatment: Analysis of the OZGROW Database Suggests it is a Neglected Outcome Criterion for an Expensive Therapy.
Ian Hughes and Catherine Choong

A paper with primary authors Dr Steve Taggart and Dr Louise Conwell is being written in collaboration with Dr Hughes following analysis of the OZGROW database to investigate the incidence of post transplant lymphoproliferative disease (PTLD) in paediatric renal transplant recipients in Australia. An initial survey had suggested that incidence was influenced by whether or not the child had received GH treatment.

An OZGROW report commissioned by the Growth Hormone Advisory Committee (GHAC) was prepared to form part of a submission to the Pharmaceutical Benefits Advisory Committee (PBAC). Entitled, "OZGROW Briefing Note for the Pharmaceutical Benefits Advisory Committee (PBAC) and Growth Hormone Advisory Committee (GHAC)", it was prepared by Ian Hughes (OZGROW Research Fellow) and Catherine Choong (OZGROW Chair). It is included here as an Appendix.

Prader Willi Syndrome (PWS) Database
The OZGROW Research fellow, Dr Hughes, has worked closely with Dr Elly Scheermeyer, to establish a routine extraction protocol to obtain from the OZGROW database relevant information to populate the APEG-PWS database being established by Dr Scheermeyer.

APEG Merk Serono Research Grant 2011
A national collaboration of paediatric endocrinologists and scientists headed by Dr Ian Hughes (OZGROW) and Assoc. Prof. Maria Craig submitted a grant application to APEG and Merk Serono entitled, "Response to GH in Prader-Willi Syndrome: Results from OZGROW", which amounted to $15,000.

OZGROW Database Maintenance
Routine database maintenance has continued throughout 2011. Interrogations and manipulations of data occur on a daily basis for the various research projects underway as well as for specific requests from APEG members (eg GHAC) and DoHA.

Data transfer from the DoHA database to OZGROW is now routine although scrutinization of data and clarification of database fields continues which has resulted in a major audit of the DoHA database this year. Michelle Bradley, Assistant Director Special Access Pharmaceuticals Access and Systems Branch Pharmaceutical Benefits Division of DoHA, was OZGROWs main contact with DoHA and instrumental in establishing the data transfer protocols. Michelle has now moved to another position within the department and OZGROW would like to sincerely thank her for all her efforts over the last few years to facilitate this data transfer. We now look forward to working with Claire Paterson and Jacquie Maycock who have taken over the primary positions within the GH program.

The major structural problem remaining with respect to the OZGROW database and its link with the DoHA database is a consequence of a loss of data from certain fields when DoHA migrated data from their old database to the new one. This resulted in a loss of dose data prior to 2008 in the new DoHA database. However, the OZGROW database has retained this data and we are close to being able to link pre and post 2008 data within the OZGROW database. Unfortunately, it would seem to be a far greater challenge to permanently fix the problem within the new DoHA database.

Adverse Events

Long term safety monitoring was envisioned as a primary function for OZGROW when it was established. Reporting of adverse events to OZGROW is, however, not mandatory and the frequency of reporting, either via DoHA forms or directly to OZGROW is much lower than might be expected and geographically sporadic. In 2011 seven adverse events were reported to OZGROW, all from Western Australia. DoHA "encourages" reporting of adverse events but specifically only to the Advisory Committee on the Safety of Medicines of the Therapeutic Goods Administration (TGA). It is likely that clinicians inform the TGA believing, quite reasonably, that this information will automatically be incorporated into the DoHA and OZGROW databases. As discussed below, the goal of OZGROW is for the OZGROW database to become a designated clinical registry that operates electronically and links with other relevant registries and databases such as the TGA to prospectively facilitate audits for safety and efficacy.

Development of the OZGROW Database into a Clinical Registry

To further enhance the capacity of OZGROW as a prospective and comprehensive Clinical Registry, the OZGROW subcommittee has been reviewing the requirements and costs of transition to a Clinical Registry, in particular electronic data transfer, management, and archiving as well as ethical considerations. Transition to a Clinical Registry would facilitate, though is not specifically required, establishment of linkages with other registries (eg. Australasian Association of Cancer Registries (AACR)) which would enable a life-long monitoring of possible adverse effects of GH treatment as a child.

The OZGROW Subcommittee is currently discussing the benefits and requirement of developing international collaborations with our European and American colleagues to expand the application of OZGROW data for clinical benefit. One primary issue for future consideration is a review of the pretreament data and diagnostic information provided upon entry into the OZGROW Database as analyses about longer term safety and efficacy will require accurate precise pretreatment diagnoses.

Budget and Funding

Funding for OZGROW activity derives from the APEG council. The APEG Council allocated $64,081 in 2009 and $56,650 to OZGROW for the periods January to December in 2009 and 2010 respectively. A similar, though yet to be invoiced, amount has been allocated for 2011 with an additional $5000 provided for specific work undertaken for the Growth Hormone Advisory Committee. Funding will be outlined in greater detail at the upcoming Annual General Meeting. OZGROW benefits indirectly from contributions by Pharmaceutical Companies to APEG which

are then redirected to the OZGROW. In particular the OZGROW Subcommittee would like to acknowledge Pfizer, Novo Nordisk, Merck Serono, and SciGen who have generously contributed to funding OZGROW's continuing activities. In addition, SciGen, Pfizer, Novo Nordisk, Merck Serono, and Lilly supported conference attendance by the Ozgrow Research Fellow in Boston (Endo2011) and Perth (APEG- ESA 2011). The OZGROW Subcommittee acknowledges and sincerely appreciates pharmaceutical support which enables continuation and maintenance of the OZGROW Database and salary and conference attendance for an OZGROW Research Fellow. This funding is currently determined on a yearly basis. It is the view of the OZGROW Committee that substantive funding over a three or five year cycle will allow long term strategies to be put in place and implemented such as the transition of OZGROW to a clinical registry. Such a funding arrangement continues to be an important goal of the OZGROW subcommittee.

The OZGROW Database will be relocating from The Children's Nutrition Research Centre from January 2012. The OZGROW Subcommittee wishes to thank Professor Peter Davies for his strong support of the APEG-OZGROW Database since 2004 when it was relocated to Brisbane and the CNRC. The Database has been considerably improved from its association with Professor Davies's Team at the CNRC.

Finally the OZGROW Subcommittee wishes to acknowledge the APEG membership who demonstrate their continued interest and support of this clinical resource. The OZGROW Subcommittee continues to seek nominations for this important committee and invites members who are interested in undertaking research or who wish to ask clinically based questions that require, or would benefit from, interrogation of the OZGROW Database to contact the OZGROW Subcommittee Chair.

Appendix

OZGROW Briefing Note for the Pharmaceutical Benefits Advisory Committee (PBAC) and Growth Hormone Advisory Committee (GHAC)

Prepared by Ian Hughes (OZGROW Research Fellow)
and Catherine Choong (OZGROW Chair)

Diagnostic Subgroups within the Short Stature and Slow Growth Indication

The federal government's Department of Health and Ageing (DoHA) uses an eligibility criterion of a current height below the 1st centile and a growth velocity below the 25th centile as an indication for GH treatment subsidy. This indication is referred to as Short Stature and Slow Growing (SSSG) but contains within it a large variety of different diagnostic entities as defined by treating paediatric endocrinologists. The most common diagnosis within SSSG is idiopathic short stature (ISS) followed by growth hormone deficiency (GHD), although GHD also has its own indication category. Other diagnoses found in SSSG could also be classified under alternative indications such as renal disease, CNS malformations/neoplasia and cranial irradiation, hypoglycaemia, and Prader-Willi syndrome (PWS). SSSG also contains diagnoses of small for gestational age (SGA), familial short stature (FSS), Silver-Russel and Noonan syndromes, achondroplasia, hypochondroplasia, maturational delay, ademomatosis, small normal, mixed gonadal dysgenesis, rickets, low IGF1, asthma, chronic steroid treatment, thyroid disease, gastrointestinal disease, ADHD, GH receptor defect (Laron), thalasaemia, karyotypic abnormalities, chronic disease, Vater syndrome, male and female pseudointersex, and cerebral palsy.

The heterogeneity of the SSSG indication is exemplified by the significant differences with respect to both demographic variables and response to GH treatment as is shown in Table 1. The data in Table 1 is derived from extensive analyses performed on patients receiving GH at the end of 2007 but, with the exception of PWS patients being reclassified into their own indication category, is similar to that seen currently[1]. It can be seen that GHD and PWS patients respond significantly better and ISS and FSS patents significantly worse than the whole SSSG group. And this is despite GHD and PWS receiving a significantly lower mean GH dose over the first year of treatment. The nature of the differences in response across the diagnostic entities in SSSG can be seen in Table 2. For each year of GH treatment (first 3 years) the SSSG cohort was divided into tertiles based on response in terms of change in height SDS per year (ΔSDS/Yr). For example, for 1st year response, it can be seen that half of the GHD patients are found in the upper tertile of response with the other half equally distributed between the lower and middle tertiles. Conversely, for ISS, most patients fall within the lower tertile with numbers declining steadily through to the middle and upper tertiles. Such distinctions tend to disappear going into the second and third years of treatment.

[1] Current dose data will not available until later in 2011 due to database incompatibility issues.

Table 1. Baseline demographics and response data (medians) among diagnostic entities within SSSG (1st year data).

Diagnosis		ΔSDS	GV Z	Age (years) start GH	SDS Start GH	BMIZ Start	Mean Parental SDS	Birth Weight	Birth Length	Mean Dose $mg/m^2/wk$	Mean Dose (mg/kg/wk)	Peak Serum GH (µg/L)
GHD	N	116	115	116	116	109	68	64	46	116	116	59
	Median	0.77***	2.46**	6.18	-3.06	-0.20	-0.49	3.09*	48.0	4.43**	0.18**	4.0***
ISS	N	154	151	154	154	153	95	92	59	154	154	74
	Median	0.50**	1.91	8.20***	-2.99*	-0.47	-0.72	3.03	48.0	4.63	0.18	9.2***
SGA	N	31	31	31	31	30	19	19	10	31	31	13
	Median	0.66*	2.05	4.69**	-3.38*	-0.85**	-0.46	2.02***	42.5**	4.79	0.21**	7.9
FSS	N	56	56	56	56	56	35	33	23	56	56	31
	Median	0.46**	1.65	6.60	-2.85**	-0.15	-1.32***	2.90	49.0	4.57	0.19	6.9
PWS	N	20	20	20	20	16	9	7	6	20	20	6
	Median	1.01***	2.20	3.17***	-3.05	0.07	0.16**	2.50	47.3	4.11**	0.18	5.6
Other	N	147	143	147	147	142	73	75	58	147	147	48
	Median	0.54	1.51*	6.62	-3.22**	-0.27	-0.41*	2.96	47.8	4.63*	0.20**	10.5**
Total	N	524	516	524	524	506	299	290	202	524	524	231
	Median	0.57	1.82	6.60	-3.10	-0.33	-0.70	2.91	48.0	4.58	0.19	7.4

* - 0.01≤P<0.05 for Mann-Whitney U test comparing those with the diagnosis to all others within SSSG.
** - 0.001≤P<0.01 for Mann-Whitney U test comparing those with the diagnosis to all others within SSSG.
*** - P<0.001 for Mann-Whitney U test comparing those with the diagnosis to all others within SSSG.

Table 2. Frequency of specific diagnoses within the SSSG indication occurring in each ΔSDS tertile.

		ΔSDS/Yr Tertile				
Diagnosis	Year	Lower	Middle	Upper	Total	P
ISS	1st	64	55	35	154	**0.011**
	2nd	48	41	31	120	0.162
	3rd	29	31	34	94	0.814
SGA	1st	2	17	12	31	**0.004**
	2nd	6	11	9	26	0.490
	3rd	6	7	5	18	0.846
Russel-Silver	1st	6	8	5	19	0.618
	2nd	5	5	4	14	0.933
	3rd	7	3	4	14	0.395
Noonan	1st	5	3	2	13	0.489
	2nd	5	1	2	8	0.195
	3rd	3	1	2	6	0.607
FSS	1st	25	20	11	65	0.062
	2nd	14	22	11	46	0.133
	3rd	12	17	7	36	0.125
GHD	1st	31	27	58	117	**8.19×10^{-4}**
	2nd	22	28	43	93	**0.022**
	3rd	24	24	28	76	0.810
PWS	1st	0	4	16	20	**8.27×10^{-12}**
	2nd	2	5	9	16	0.098
	3rd	6	2	6	14	0.320

Peak Serum GH Levels within the SSSG Indication

Most patients within the SSSG indication have results recorded from one, two, or three GH stimulation tests. In Australia, subsidised GH treatment can be obtained through the indication of "Biochemical GH Deficiency" if serum GH concentration is less than 10mU/L (3.33µg/L) in response to two stimulation tests, one of which must be a pharmacological test. To assess the influence of serum GH levels of SSSG patients prior to commencing GH treatment the mean GH concentration recorded among the stimulation tests performed was noted for the 2007 SSSG cohort. An idea of the variation in these peak serum GH levels between different diagnoses within SSSG can be seen from Table 1. Not surprisingly, the GHD patients had the lowest median peak GH concentration at 4µg/L, just above that required for eligibility under the Biochemical GHD indication. A more detailed view of the distribution of peak serum GH concentrations is shown in Table 3 in which the frequency of patients from each diagnosis who fall into the categories <10U/L (3.33µg/L), 10-20U/L (3.33-6.67µg/L), and >20U/L are shown.

Table 3. Frequencies of SSSG Patients (2007 Cohort) Categorised by Mean Peak Serum GH prior to GH Treatment and Diagnostic Category.

Peak Serum GH (µg/L)	Total	GHD	ISS	SGA	Familial	PWS	Other
<3.33	38	24	3	0	3	1	7
3.33 to 6.67	75	27	18	5	16	1	8
>6.67	114	7	53	8	12	1	33

The total SSSG cohort, to January 2011, was also analysed with respect to the number of GH tests performed and the maximum peak GH recorded in those tests. Of 1368 SSSG

patients 880 (64%) were tested at least once for peak GH concentrations, 501 (37%) at least twice, eleven 3 or more times, and one patient was tested four times. Table 3A shows the proportions for each test that fall into the categories of <10U/L (3.33µg/L), 10-20U/L (3.33-6.67µg/L), and >20U/L. The last two columns of Table 3A show these frequencies for the maximum and minimum Peak serum GH values over at least two tests. The variation in these tests is evidenced by the fact that in only 2% of cases are both (or all) tests <10U/L but in 34% of cases at least one test is <10U/L.

Table 3A. Frequencies of SSSG Patients (Total Cohort to Jan. 2011) falling into Peak Serum Concentration categories for each GH test.

Peak Serum GH (µg/L)	1st Test	2nd Test	3rd Test	4th Test	Max GH >1 Tests	Min GH >1 Tests
n	880	501	11	1	501	501
<3.33	122 (14%)	96 (19%)	3	0	9 (2%)	168 (34%)
3.33 to 6.67	289 (33%)	165 (33%)	1	0	137 (27%)	202 (40%)
>6.67	469 (53%)	240 (48%)	7	1	355 (71%)	131 (26%)

Estimating the Effect of Increasing the Starting Dose to 7.5mg/m^2/week for the SSSG Indication.

As dose increases in the Australian cohort of SSSG patients only occur after 6 months of treatment on 4.5mg/m^2/week and only for patients considered poor responders it is difficult, using only Australian data, to predict the effect of an across-the-board dose increase to 7.5mg/m^2/week from treatment commencement. However, in 2005 Wit *et al.(1)* published a study in which ΔSDS response in ISS patients was measured over eight years of GH treatment. Two different doses were used, 0.24mg/kg/week and 0.37mg/kg/week. While mean dose for the Australian SSSG cohort increased from 4.58 to 4.76 to 5.10 in terms of mg/m^2/week in each year of treatment the dose in terms of mg/kg/week remained constant at 0.19. This meant that it would be reasonable to compare the 0.24mg/kg/week response curve of Wit et al.(1) to the "4.58" mg/m^2/week response curve from the Australian data. From Figure 1 it can be seen that the trajectories of the curves are similar, the only real difference being that the 0.24mg/kg/week group were shorter at treatment commencement and made slightly more improvement in the first year. The better first year response was probably as a consequence of the shorter starting height and slightly higher dose, although these were likely offset to some degree by the younger age at commencement of the Australian patients (6.6 years v. 9.4years) which is also a known factor in first year response.

As these trajectories were similar it is reasonable to assume that the Australian SSSG cohort would respond to a dose increase in a similar manner to that seen from Wit's 0.37mg/kg/week cohort. Based on this assumption two estimated responses to a dose of 7.5mg/m^2/week have been modelled. Both assume a constant dose (of 0.31 in terms of mg/kg/week) as, for the Australian cohort, an estimated dose of 7.5mg/m^2/week changed only marginally in terms of mg/kg/week from 0.31, 0.30, and 0.29 over the first three years of treatment. The first estimate, marked by the x's, is conservative and based only on proportionalities of dose differences (0.24 to 0.37mg/kg/week for Wit et al.'s(1) experiment and 0.19 to 0.31mg/kg/week for an Australian cohort) and response difference each year. Not surprisingly the Australian estimate tracks just below that of Wit et al.'s(1) group which has a slightly higher dose. The second estimate, marked by +'s, takes into consideration the younger starting age of the Australian cohort (6.6 years) as opposed to Wit et al.'s 0.37mg/kg/week cohort (10.0 years). This difference was based on regression models for response in the SSSG group that have been developed by OZGROW and will be published in the near future. The effect is most pronounced in the first and second years of treatment.

Attaining the 10th centile for adult height is a criterion for cessation of GH treatment in SSSG patients. Under the present dosing protocol for SSSG only 14% of girls and 8% of boys attain this cut-off and, for good responders, GH cessation usually occurs at a bone age of

13.5 (girls) or 15.5 years (boys). The median age of cessation at present is 14.9 years. If the 10th adult centile was attained by a greater proportion of patients this would mean, not only a better clinical outcome, but also an earlier mean age at cessation of treatment. If the current dose response curve on Figure 1 is extrapolated it is estimated that a final height difference of approximately 0.6 height SDs would be achieved between the 4.48mg/m^2/week cohort and a 7.75mg/m^2/week theoretical cohort. If this were the case it is estimated that 27% of girls and 23% of boys would attain the adult 10th centile cut-off. Thus under a 7.5mg/m^2/week protocol it could be expected that approximately a quarter of patients would cease treatment earlier than that defined by bone age.

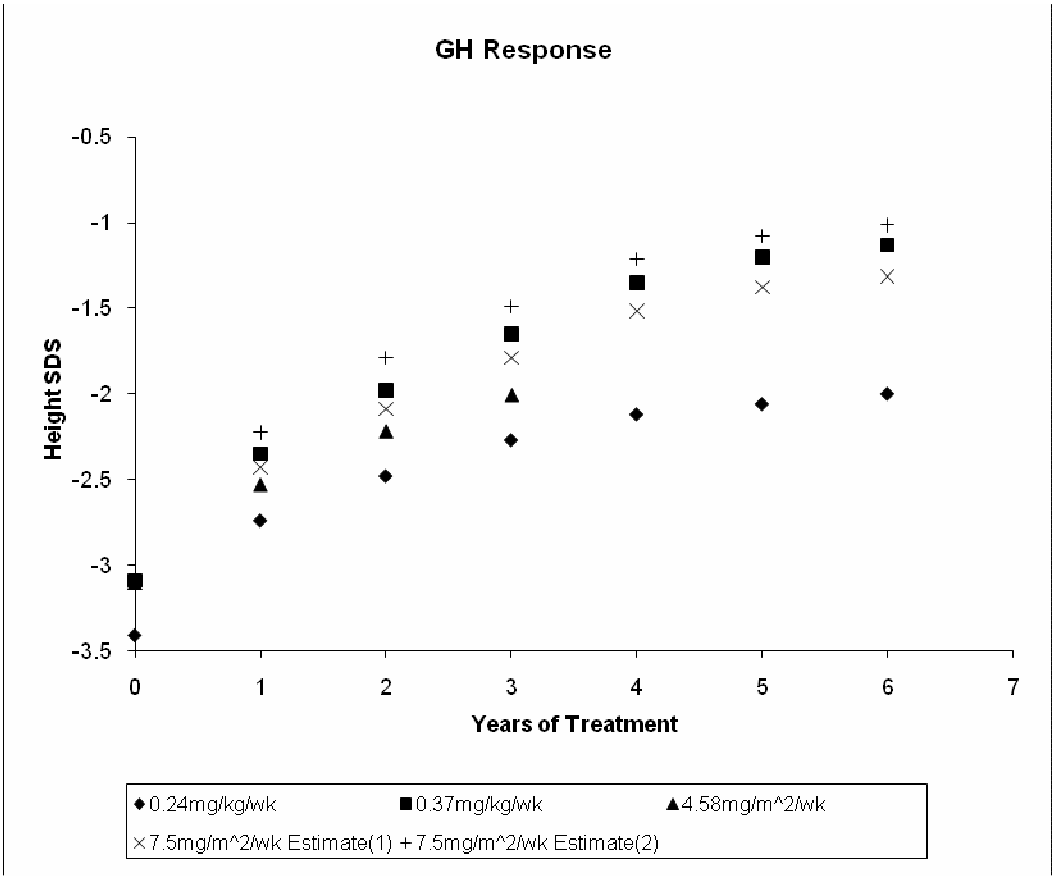

Figure 1. ISS response curves from Wit et al.(1), 0.24 and 0.37mg/kg/week, and from the Australian SSSG cohort, 4.8mg/m^2/week. Two estimated response curves have been constructed for the SSSG cohort receiving 7.5mg/m^2/week.

Effect of Starting Dose of 7.5mg/m^2/week on Identification of Non-Responders

Under the current dosing protocol the starting dose is 4.5mg/m^2/week which after 6 months can be increased if the patient fails to meet one or more of the response criteria as defined in the Guidelines for the Pharmaceutical Benefits Scheme- Growth hormone Program. The dose can be increased to 5.5 mg/m^2/week after 6 months at the starting dose and the dose reviewed again after 12 months with increases to 6.5, and 7.5 mg/m^2/week at 6 moth intervals if response criteria are not met. If after 6 months treatment at 7.5 mg/m^2/week the patient still does not meet response criteria GH treatment is terminated. Thus, a patient may be treated for 24 months with no or minimal response before GH treatment is ceased. If treatment commenced at 7.5 mg/m^2/week non-responders would be identified after 6 months of treatment and a decision to terminate treatment made, thus saving 18 months of fruitless GH treatment.

Summary

- The SSSG indication is a very heterogeneous group of patients as can be seen from the range of diagnoses that it includes, the peak serum GH levels measured prior to treatment, and diversity of demographic variables. Not surprisingly, there is a considerable range of responses to GH treatment seen in this group.

- Starting GH at a dose of 7.5 mg/m^2/week will be expected to result in better clinical outcomes for SSSG patients while the median period of treatment would also be reduced.

- Starting GH at a dose of 7.5 mg/m^2/week will lead to the identification of non-responding patients after 6 months of treatment rather than 24 months thus resulting in a more efficient use of resources.

Reference

1. Wit JM, Rekers-Mombarg LT, Cutler GB, Crowe B, Beck TJ, Roberts K, et al. Growth hormone (GH) treatment to final height in children with idiopathic short stature: evidence for a dose effect. J Pediatr. 2005 Jan;146(1):45-53.

2. Roberts CL, Lancaster PA. Australian national birthweight percentiles by gestational age. Med J Aust. 1999 Feb 1;170(3):114-8.

Addendum: Additional Requested Analyses from Dr Jan Fairchild (4/3/2011)

Chronological and Bone Ages of GHD and SSSG Patients at Commencement of GH Treatment.

Tables 1-8 detail the age at commencement of GH treatment for the current group of SSSG and GHD patients (as of January 2011) and a similar group who were current as of December 2007. For the 2011 cohort, only those commencing since December 2007 were used due to data prior to that date missing from the DoHA GETS database.

It should be noted that there is a considerable difference between the estimated median starting ages of the two cohorts. This probably reflects the different definitions used for "Starting Date" which arose from the different organisation of data in the DoHA database before and after December 2007. For the 2007 cohort the Starting Date was defined as the first visit date for which a GH dose was quoted. For the 2011 cohort GH dose was not recorded in relation to visits to a Growth Centre but in terms of application/reapplication periods. In this instance Start Date was defined as the "From Date" of the Initial Application period. Because of the loss of the "From Dates" data prior to December 2007 it was not possible to further investigate the discrepancy between the starting ages of the two cohorts.

The chronological age (CA) of a patient could be determined exactly for any starting date. However, it was rare that a Bone Age (BA) would be measured on the same date as the starting date. Thus the starting BA was defined as that recorded on the date closest to the starting date and no earlier or later than 6 months from it.

Specific CA and BA cut-offs for the current and proposed definitions of an "older child" are shown and the numbers and percentages for boys and girls from the GHD and SSSG indications are calculated.

Table 1. Cross Section of Median Chronological Ages (CA) at GH Commencement of Current (Jan. 2011) GHD and SSSG Patients (Those commencing since Dec. 2007).

Indication	Gender	Median CA Starting Age (Years)
GHD		6.51
SSSG		8.83
GHD	Female	5.53
GHD	Male	8.48
SSSG	Female	8.37
SSSG	Male	9.28

Table 2. Cross Section of Distribution of Chronological Ages (CA) at GH Commencement of Current (Jan. 2011) GHD and SSSH Patients (Those commencing since Dec. 2007). Specific cut-offs for males and females designated as "older" are shown.

Indication	Gender	n	CA (Years)					
			>=9	>=10	>=12.5	>=11	>=12	>=14.5
GHD	Female	61	19 (31%)	12 (20%)	3 (5%)			
	Male	107				38 (36%)	32 (30%)	11 (10%)
SSSG	Female	190	83 (44%)	65 (34%)	9 (5%)			
	Male	322				118 (37%)	86 (27%)	16 (5%)

Table 3. Cross Section of Median Bone Ages (BA) at GH Commencement of Current (Jan. 2011) GHD and SSSH Patients (Those commencing since Dec. 2007).

Indication	Gender	Median BA Starting Age (Years)
GHD		8.92
SSSG		8.29
GHD	Female	6.33
GHD	Male	10.75
SSSG	Female	8.17
SSSG	Male	8.38

Table 4. Cross Section of Distribution of Bone Ages (BA) at GH Commencement of Current (Jan. 2011) GHD and SSSH Patients (Those commencing since Dec. 2007). Specific cut-offs for males and females designated as "older" are shown.

Indication	Gender	n	BA (Years)					
			>=7	>=8	>=10.5	>=9	>=10	>=12.5
GHD	Female	16	6 (38%)	6 (38%)	3 (19%)			
	Male	46				26 (57%)	26 (57%)	15 (33%)
SSSG	Female	80	47 (59%)	41 (51%)	17 (21%)			
	Male	120				57 (48%)	49 (41%)	20 (17%)

Combining the thresholds of CA≥10 or BA≥8 for girls and CA≥12 or BA≥10 for boys the total number of children eligible as an "older child" is shown in Table 4A.

Table 4A. Specific cut-offs (years) for males and females designated as "older" for the combination of CA and BA for current (Jan. 2011) GHD and SSSH Patients (Those commencing since Dec. 2007)

Indication	Gender	n	BA>=8 or CA>=10	BA>=10 or CA>=12
GHD	Female	61	13 (21%)	
	Male	107		39 (36%)
SSSG	Female	190	72 (38%)	
	Male	322		96 (30%)

Table 5. Cross Section of Median Chronological Ages (CA) at GH Commencement of GHD and SSSH Patients Current as of Dec. 2007.

Indication	Gender	Median CA Starting Age (Years)
GHD		5.11
SSSG		6.60
GHD	Female	3.51
	Male	5.72
SSSG	Female	7.26
	Male	6.35

Table 6. Cross Section of Distribution of Chronological Ages (CA) at GH Commencement of GHD and SSSH Patients Current as of Dec. 2007. Specific cut-offs for males and females designated as "older" are shown.

Indication	Gender	n	CA (Years)					
			>=9	>=10	>=12.5	>=11	>=12	>=14.5
GHD	Female	63	9 (14%)	7 (11%)	2 (3%)			
	Male	123				24 (20%)	16 (13%)	6 (5%)
SSSG	Female	177	55 (31%)	44 (25%)	15 (8%)			
	Male	347				60 (17%)	40 (12%)	11 (3%)

Table 7. Cross Section of Median Bone Ages (BA) at GH Commencement of GHD and SSSH Patients Current as of Dec. 2007.

Indication	Gender	Median BA Starting Age (Years)
GHD		3
SSSG		4.5
GHD	Female	2
	Male	4
SSSG	Female	5.58
	Male	4.17

Table 8. Cross Section of Distribution of Bone Ages (BA) at GH Commencement of GHD and SSSH Patients Current as of Dec. 2007. Specific cut-offs for males and females designated as "older" are shown.

Indication	Gender		BA (Years)					
		Count	>=7	>=8	>=10.5	>=9	>=10	>=12.5
GHD	Female	49	7 (14%)	7 (14%)	5 (10%)			
	Male	93				16 (17%)	13 (14%)	4 (4%)
SSSG	Female	152	51 (34%)	34 (22%)	15 (10%)			
	Male	295				49 (17%)	36 (12%)	11 (4%)

Again, combining the thresholds of CA≥10 or BA≥8 for girls and CA≥12 or BA≥10 for boys the total number of children eligible as an "older child" is shown in Table 8A.

Table 8A. Specific cut-offs (years) for males and females designated as "older" for the combination of CA and BA for current (Jan. 2011) GHD and SSSH Patients (Those commencing since Dec. 2007).

Indication	Gender	Count	BA>=8 or CA >=10	BA>=10 or CA>12
GHD	Female	63	9(14%)	
	Male	123		18(15%)
SSSG	Female	177	50(28%)	
	Male	347		45(13%)

GH Dose Approved for the GHD and SSSG Indications at the 1st, 2nd, 3rd, 4th and 5th Reapplications.

Tables 9 and 10 show descriptive statistics for the GH dose approved at each reapplication for GHD and SSSG respectively for the 2011 cohort. While mean and standard deviation are shown it should be noted that all distributions were significantly different from being normally distributed (DiAgostino-Pearson Test). The tables also show statistics for the assessment period; that is, the period over which that dose rate was applied. The first reapplication dose was defined as the first GH dose received by a patient. In the database this was sometimes referred to as "Initial" but mostly as "Reapplication". It should be noted that the doses quoted are the maximum for each assessment period. The median assessment period is just over six months. The dose in mg/week is calculated with respect to the body surface area at the start of that period and thus the real dose, with respect to mg/m^2/week, declines during that period.

Table 9. GH Dose (mg/m^2/week) approved at each reapplication for the GHD indication. 2011 cohort.

GHD	Reapplication					Assessment Period (Days)
	1st	2nd	3rd	4th	5th	
Mean	5.17	5.23	5.38	5.48	5.60	205.2
Median	4.68	4.7	4.84	4.91	5.19	188
SD	1.15	1.20	1.21	1.26	1.23	89.0
1st Q	4.49	4.48	4.52	4.57	4.64	175
3rd Q	5.89	5.91	6.2	6.54	6.69	210
IQR	1.4	1.44	1.68	1.97	2.05	35

Table 10. GH Dose (mg/m^2/week) approved at each reapplication for the SSSG indication. 2011 cohort.

SSSG	Reapplication					Assessment Period (Days)
	1st	2nd	3rd	4th	5th	
Mean	5.72	5.84	6.05	6.21	6.39	213.6
Median	5	5.48	6	6.25	6.56	189
SD	1.29	1.26	1.26	1.19	1.15	88.9
1st Q	4.61	4.66	4.82	5	5.31	175
3rd Q	7.26	7.21	7.39	7.43	7.48	215
IQR	2.65	2.55	2.58	2.43	2.17	40

SSSG Patients Who Have a Birth Weight Less Than the 3rd centile for Gestational Age

All SSSG patients in the OZGROW database as of January 2011, including current and ceased recipients of GH, were assessed. Of 1049 babies who had both birthweight and gestation recorded, 229 (21.8%) had birthweights less than the 3rd centile for gestational age as defined by Roberts and Lancaster (1999)(2) for Australian, non-indigenous, singletons. Of the 1349 who had OZGROW Diagnosis Codes recorded 122 (9.0%) were diagnosed by the paediatric endocrinologist as Small for Gestational Age.