An Auxology-based Growth Hormone Program: Update on the Australian Experience

George A. Werther\textsuperscript{1}, Mei Wang\textsuperscript{2} and Christopher T. Cowell\textsuperscript{2}

\textsuperscript{1}Centre for Hormone Research, Royal Children’s Hospital, Parkville, Victoria and
\textsuperscript{2}Institute of Endocrinology and Diabetes, The Children’s Hospital, Westmead, New South Wales, Australia

ABSTRACT

In 1988, new guidelines for growth hormone (GH) usage emphasizing auxological criteria were adopted in Australia. Currently, 1,250 children with the following diagnoses are being treated: idiopathic GH deficiency (IGHD), 23.4\%; malignancy-related GHD, 7.9\%; Turner’s syndrome, 12.1\%; nonendocrine disorders, 22.2\%; idiopathic short stature, 26.0\%; endocrine disorders, 3.2\%; unknown, 5.3\%. At onset of GH therapy, mean age remained lowest in patients with IGHD (8.6 years); mean height SDS was unchanged over time in all groups (-2.8 to -3.3); mean GH doses were lowest for patients with idiopathic and malignancy-related GHD (0.15-0.16 mg/kg/week) and highest for the Turner’s syndrome group (0.22 mg/kg/week). Children with GHD demonstrated the best final height outcome (mean final height SDS -1.0 ± 1.1 for boys and -1.4 ± 1.2 for girls; improvements of 2.0 SDS for both genders). Mean final height SDS for the other etiologies were similar: -2 in malignancy-related GHD (no improvement), -2.3 in nonendocrine disorders (improvement of 0.7), -1.8 in idiopathic short stature (improvement of 1.1), and -2.3 for Turner’s syndrome (improvement of 0.9). In 1993-94, when more stringent entry and exit criteria were introduced, patient numbers and expenditure were halved and have remained unchanged (US$ 9-10M per year). The use of auxology-based criteria continues to make possible rational, effective, and economical use of GH therapy in short children in Australia.

KEY WORDS

growth hormone, auxology, database, short stature, Turner’s syndrome

INTRODUCTION

Since 1988, the federally funded and administered growth hormone (GH) program in Australia has been based primarily on auxological criteria, rather than a clinical diagnosis of GH deficiency (GHD), as previously reported at the ninth National Cooperative Growth Study (NCGS) Annual Meeting in 1995\textsuperscript{1}. This report provides an update on our experience since that time. Our rationale for using auxological diagnostic criteria was based on factors such as the difficulty in making a definitive diagnosis of GHD, the appropriateness of various physiological and pharmacological GH stimulation tests, the minimum response to stimulation, and variations in GH assays. These issues have been grappled with in recent reports, and attempts have been made to develop alternative means of diagnosing GHD, such as the measurement of serum levels of circulating insulin-like growth factor (IGF)-I and IGF-binding protein (IGFBP)-3\textsuperscript{24}. However, there remains no consensus on the diagnosis of GHD. Furthermore, there are numerous reports of medium-term and long-term growth responses to GH in individuals with a variety of short-stature conditions that are not associated with classic GHD\textsuperscript{57}.

HISTORY AND CRITERIA OF THE AUSTRALIAN GH PROGRAM

The use of GH in Australia is regulated by an expert national government committee. In 1988, for the reasons previously described, the guidelines for
prescribing GH were revised to use exclusively auxological criteria. Essentially, the existing auxological components of the guidelines were maintained; to be eligible for GH therapy, children had to be below the 3rd percentile for height (this was reduced to the 1st percentile in 1993) and below the 25th percentile for growth velocity over 12 months on the basis of skeletal age. GH secretory status does not affect eligibility, except in children with acquired GHD who are growing slowly but are above the 1st height percentile: they are eligible on the basis of slow growth plus GHD. Children with Turner’s syndrome and renal failure have specific eligibility criteria; children with maturational delay are specifically excluded on the basis of a good prognosis for normal height without GH therapy, in the presence of a significant bone age delay. The response criteria for GH therapy were based on the child achieving and maintaining a growth velocity above the 50th percentile for skeletal age, although these criteria were recently broadened to include alternative responses, such as increased height standard deviation score (SDS) and maintenance of midparental height SDS.

In 1990, body surface area replaced body weight for dosage calculation, thus reducing the very large doses previously administered to obese adolescents. Cessation of therapy was mandatory at a skeletal age of 15 years for girls and 17 years for boys, but was reduced to 13.5 years and 15.5 years, respectively, in 1993.

**ANALYSIS OF BASELINE DATA AND GH TREATMENT OUTCOMES**

More than 4,617 Australian children (2,625 males and 1,992 females) have been treated with GH therapy since 1988. Currently, 1,250 children are being treated in the following diagnostic categories: idiopathic GHD (peak GH serum concentration <5 µg/l using a variety of assays), 23.4%; malignancy-related GHD (including craniopharyngioma), 7.9%; Turner’s syndrome, 12.1%; non-endocrine disorders (including syndromes, intrauterine growth restriction [IUGR], chronic disease, and skeletal disorders), 22.2%; idiopathic short stature (height below the 1st percentile and growth velocity below the 25th percentile for bone age; peak GH serum concentration >5 µg/l and other causes of short stature excluded), 26.0%; endocrine disorders (includes children with precocious puberty and short stature, and congenital adrenal hyperplasia and short stature), 3.2%; unknown, 5.3% (Fig. 1).

![Fig. 1: Pie chart showing the spectrum of diagnostic categories in the current Australian national growth hormone database, OZGROW.](image-url)
As shown in Table 1, over three time periods (1987-1992, 1993-1996, and 1997-2002), the mean age at the start of GH therapy was lowest and remained unchanged over time in patients with idiopathic GHD (most recently, 8.6 years). In patients with malignancy-related GHD or idiopathic short stature, the mean age remained consistently higher (10.8 and 10.0 years, respectively, for the most recent time period). There was a trend over time for patients with nonendocrine disorders and patients with Turner’s syndrome to start GH therapy at a younger age (mean 10.3 and 10.6 years, respectively, for 1987-1992, and 8.8 and 9.2 years for 1997-2002). Increasing recognition and awareness of the value of GH therapy in these latter diagnostic groups may explain the earlier age of onset of GH therapy over time, while the age of diagnosis of GHD, whether idiopathic or associated with malignancy, has predictably not changed over time. The mean height SDS at the beginning of treatment has remained similar over time for most diagnoses (-2.8 to -3.3), except for malignancy-related GHD, which has decreased from -2.0 in 1987-1992 to -1.7 in 1997-2002. The later onset of GHD and shorter history of GH therapy in this group may account for its lesser degree of short stature.

The rate of testing for GHD has remained fairly consistent, with 34% of patients tested in 1989 and 27% tested in 2002. Testing was mainly performed when there was a clinical indication of GHD or known pituitary hormone deficiency. Of those tested, 30% were found to be GH-deficient.

Mean doses at the start of GH therapy were lowest for patients with idiopathic GHD deficiency and malignancy-related GHD in both sexes (0.15-0.16 mg/kg/week). Average initial GH doses were 0.17 mg/kg/week for patients with idiopathic short stature and 0.18 mg/kg/week for those with nonendocrine disorders. Patients with Turner’s syndrome had the highest mean dose, 0.22 mg/kg/week. In a subgroup of 751 patients followed to final height, similar patterns in mean GH starting dose emerged, but with greater differences among the groups: idiopathic GHD, 0.15 mg/kg/week; malignancy-related GHD, 0.18 mg/kg/week; nonendocrine disorders, 0.22 mg/kg/week; idiopathic short stature, 0.23 mg/kg/week; Turner’s syndrome, 0.3 mg/kg/week. These differences reflect the doses recommended in Australia, based on the knowledge that in true idiopathic GHD, lower GH doses are required, while in non-GH-deficient children, including those with Turner’s syndrome, higher GH doses are necessary to achieve adequate growth velocity. Nevertheless, these doses are generally lower than those currently reported by NCGS and the Kabi International Growth Study (KIGS).

### Table 1

Baseline data in OZGROW, the Australian national growth hormone database, for the major diagnostic groups over the three time periods

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Growth hormone deficiency (GHD)</td>
<td>8.5</td>
<td>-3.1</td>
<td>8.6</td>
<td>-2.7</td>
<td>5.45</td>
<td>-2.7</td>
</tr>
<tr>
<td>Malignancy-related GHD</td>
<td>10.9</td>
<td>-2.0</td>
<td>11.2</td>
<td>-2.1</td>
<td>10.8</td>
<td>-1.7</td>
</tr>
<tr>
<td>Nonendocrine disorders</td>
<td>10.3</td>
<td>-3.3</td>
<td>9.4</td>
<td>-3.2</td>
<td>8.8</td>
<td>-3.1</td>
</tr>
<tr>
<td>Idiopathic short stature</td>
<td>10.8</td>
<td>-2.8</td>
<td>9.6</td>
<td>-3.0</td>
<td>10.0</td>
<td>-3.0</td>
</tr>
<tr>
<td>Turner’s syndrome</td>
<td>10.6</td>
<td>-1.6</td>
<td>9.7</td>
<td>-1.5</td>
<td>9.2</td>
<td>-1.6</td>
</tr>
</tbody>
</table>

VOLUME 16, SUPPLEMENT 3, 2003
FINAL HEIGHT

Final height was determined in a group of patients who had been treated with GH for at least 12 months. Final adult height was defined by a growth velocity of <1 cm/year and bone age >17 years for boys and >15 years for girls. Final height data was collected from 751 patients. At final height, the best outcome occurred in patients with idiopathic GHD, with a mean height SDS of -1.0 ± 1.1 for boys and -1.4 ± 1.2 for girls (both improvements of 2.0 SDS). In boys, the remaining groups had mean height SD scores of -2 in malignancy-related GHD (no improvement), -2.3 in nonendocrine disorders (an improvement of 0.9), and -1.8 in idiopathic short stature (an improvement of 1.1). In girls, the mean final height SDS was -2.0 for patients with malignancy-related GHD (no improvement), -2.9 for those with nonendocrine disorders (an improvement of 0.7), -1.8 for patients with familial short stature (an improvement of 1.0), and -2.3 for Turner’s syndrome (an improvement of 0.9).

These findings are comparable to recently published final height data from two other major international GH databases, KIGS and NCGS. In particular, for Australian patients with idiopathic GHD, the gain of 2.0 SDS is higher than that of patients in a recent NCGS report, who showed a mean gain of 1.5 SDS, and slightly better than that of patients in a recent KIGS report, who had a mean gain of 1.7 SDS. In patients with idiopathic/familial short stature, the gain of 1.1 SDS is greater than the mean gain reported from a recent meta-analysis of 10 controlled trials (mean gain of 0.84 SDS) and 28 uncontrolled trials (mean gain of 0.56 SDS). For patients with Turner’s syndrome, the gain of 0.9 SDS (5-6 cm) is similar to that reported in several other studies. It is possible that the reason for our overall better outcome in various diagnostic groups compared with the results reported from other databases, despite our use of lower doses of GH, is because of our stringent requirement for commencement height less than the 15th percentile. Thus, Australian children are generally shorter at the onset of their GH therapy. Most studies have recognized the degree of short stature at onset as an indicator of response to GH. In the case of Turner’s syndrome, in which our outcomes are similar to others, our criteria are similar to those in other databases, namely height below the 95th percentile. Another contributing factor to our outcomes might be the rigorous monitoring of responsiveness and compliance through the Australian central committee system.

PATTERN OF GH USAGE AND EXPENDITURE OVER TIME

The audit-based changes in entry and exit criteria implemented in 1993 have contributed to a reduction in GH expenditures in Australia from A$31M (US$16M) per year during 1990-91 to A$16M (US$8M) annually in 1994-95. Since then, GH usage has been remarkably constant in Australia, with annual patient accrual remaining around 200-250 per year. With a similar number exiting annually, the number of children receiving GH therapy has remained consistent at approximately 1,250 in a total Australian population of 19 million for the last 3-4 years. Expenditure has also remained consistent, at around A$18-20M (US$9-10M) annually over this period.

Apart from the tightening of the guidelines, prescribing practices have become more conservative since the early 1990s, with increasing recognition among clinicians that GH is not a panacea for short stature, particularly in early adolescents with maturational delay, as well as in specific conditions such as skeletal dysplasias. In the case of maturational delay, our guidelines exclude this diagnosis from eligibility for GH therapy unless the final height prognosis is 'poor' - clearly a somewhat loose condition. Data from our own audits, together with findings from other studies, has led to more conservative GH prescribing practices in this and other diagnostic groups. Furthermore, the cost of GH has fallen as more companies have entered the market. There are five GH preparations currently available in Australia, although four companies essentially hold the market. The current unit cost of GH in Australia is around A$50 (US$25) per milligram, similar to the unit cost in North America.
GROWTH HORMONE USE IN AUSTRALIA RELATIVE TO OTHER NATIONS

Australia has been considered more liberal than other nations with respect to GH treatment for short children, but, as we reported in 1995, the use of GH in Australia was at that time in the midrange internationally. Although current comparative figures are not available, it is likely that Australia still remains in the midrange internationally for GH usage. We believe that our auditing and guideline-revision processes, which provide a rational basis for eligibility, have enabled us to achieve judicious and effective use of GH in short children.

CONCLUSIONS

The use of auxology-based criteria, together with a comprehensive national database*, continues to make possible the rational, effective, and economical use of GH in short children in Australia. Outcomes for major treatment groups compare favorably with those from other international databases, where GH secretory status, rather than auxology, remains the primary criterion for eligibility. The identification of children with idiopathic GHD remains important, not only because awareness of the associated pathology and other hormonal deficiencies is important to successful treatment, but also because children in this group require lower doses of GH compared with other children receiving GH therapy, and long-term treatment is most effective in this group with respect to final height outcomes.

ACKNOWLEDGEMENTS

We gratefully acknowledge the support and provision of data from Vincent O'Sullivan in the Commonwealth Department of Health and Aged Care, Canberra, Australia, as well as our Australian paediatric endocrine colleagues.

REFERENCES


* Further details about OZGROW, the Australian national database supporting this program, have been previously reported.

VOLUME 16, SUPPLEMENT 3, 2003
