KIGS marks 20 years of outstanding achievement

Stockholm June 2007. Since 1987, KIGS – Pfizer International Growth Database – has enrolled over 62,000 patients from more than 50 countries, and has become a major source of insight into growth disorders and their treatment with recombinant human growth hormone (GH).

Almost 20 years to the day since the survey was initiated, it was fitting that many of the key investigators should meet on June 25–26 in Stockholm – the city where the KIGS concept was developed – to review the contribution that KIGS has made to the practice of medicine. Spanning 2 days of intensive presentations arranged in four symposia, the meeting attracted some 300 delegates, including many of those involved in the initial conception and planning of the survey over 20 years ago.

The meeting was opened by Dr Patrick Wilton (Pfizer, New York, NY, USA) and Margaretha Lindell (Pfizer, Stockholm, Sweden), who have been involved with KIGS from the very beginning. KIGS data have been instrumental in increasing awareness and understanding of diseases of short stature and their treatment in children, they explained.

In this short overnight report we cannot hope to cover everything, but we hope that you agree with us that we have captured some of the highlights from a wonderful event. Be sure that we will be following up with more news in the weeks to come.

Overview from Stockholm

- Prediction models based on KIGS have become important tools for physicians throughout the world
- The achievement of near-adult height in idiopathic GH deficiency has been aided by insights from a large number of patients enrolled in KIGS
- Similarly, we have gained considerable understanding about Turner syndrome and its treatment with GH from the large number of patients in KIGS
- Finally, KIGS has made a great contribution to the safety information regarding GH treatment
Lessons from history

After a historical overview by Professor Michael Ranke (Tübingen, Germany), co-chairs Professor Juan Jorge Heinrich (Buenos Aires, Argentina) and Professor Angel Ferrandez-Longas (Zaragosa, Spain) opened the symposium KIGS – lessons from history, which reviewed the development of our understanding of growth and growth disorders over the last 20 years. The first speaker, Dr Mitchell Geffner (Los Angeles, CA, USA), described the rapid evolution that has taken place in the treatment of growth disorders.

Near-adult height in children with IGHD
Professor Edward Reiter (Massachusetts, MA, USA) presented a key talk on the achievement of near-adult height in children with idiopathic GH deficiency (IGHD). Among patients for whom the cause of GH deficiency is unknown, most have isolated GH deficiency (70%), he said, while only 30% have multiple pituitary hormone deficiencies.

An important finding clearly seen in KIGS data, is that the longer the duration of GH treatment before puberty, the greater the height gain over baseline (Figure 1). Prepubertal height gain is strongly predictive of total height gain, as is growth during the first year of treatment, highlighting the importance of early diagnosis and appropriate clinical interpretation.

Overall, said Professor Reiter, KIGS data have confirmed that GH treatment increases final height (Ranke et al. 2007). Important predictors of outcome include:

• height at start of GH treatment (the taller the better)
• age at start of treatment (the younger the better, allowing maximum duration of prepubertal treatment)
• the stature of the parents (the taller the better)
• first-year responsiveness to GH (the greater the better)
• degree of GH deficiency (the greater the severity of deficiency the better).

Near-adult height in patients with Turner syndrome
Following a presentation on puberty by Dr Toshiaki Tanaka (Tokyo, Japan), Professor Ranke presented findings from KIGS on near-adult height in patients with Turner syndrome.

Slow childhood growth and a delayed and blunted adolescent growth spurt are characteristic of Turner syndrome, leading to adult heights that are typically approximately 20 cm below the mean for females of their respective ethnic group. A diagnosis of Turner syndrome should be considered in any girl.

Figure 1. KIGS data show that the longer the duration of GH treatment in patients with idiopathic GH deficiency (IGHD) the greater the height gain over baseline. NAH, near-adult height.
with unexplained growth retardation, regardless of the presence or absence of dysmorphic features (Rosenfeld 2007). Of the 5500 or so patients with Turner syndrome included in KIGS, more than 1000 have been treated with GH to adult height. Importantly, early introduction of GH therapy permits the greatest gain in height.

A range of factors influencing height and height gain in these patients has been analysed using multiple regression analysis (Ranke & Lindberg 2007). Near adult height was found to be positively and significantly (p < 0.01) related to:

• mid-parental height
• height at start of GH treatment
• responsiveness during the first year on GH
• mean weekly GH dose
• age at start of puberty.

All parameters were significant with a probability level of p < 0.01 (Ranke & Lindberg 2007).

Safety profile of GH therapy

Over 20 years of use in children has shown that recombinant GH has a favourable safety profile, reported Dr Wilton. The KIGS protocol makes it mandatory to report all adverse events, regardless of whether they are thought to be GH related. As a result, a substantial body of safety data has been gathered within KIGS.

One of the most important safety concerns about GH treatment in children is the development of de novo neoplasms. In an analysis of 51 813 children in KIGS, representing 152 882 treatment-years, there were 22 cases of de novo neoplasms, explained Dr Wilton. This compares with 19.9 expected cases. Of these cases, eight were neoplasms of the CNS, two were non-Hodgkin lymphomas, two were embryonic cell carcinomas and three were leukaemias. The standardized incidence ratio for developing a de novo tumour in KIGS is 1.1, indicating that there is no significant increased risk compared with children not receiving GH therapy.

Some studies have shown that GH replacement therapy in survivors of childhood cancer may increase the risk of development of second neoplasms. In KIGS, 3008 patients have been treated for a malignant neoplasm, and 38 (1.3%) of these developed a second neoplasm, explained Dr Wilton. The most common form of second neoplasm was meningioma; in all cases, patients had received irradiation therapy for their primary tumour.

“These data indicate that there may be an increased risk of second neoplasms in GH-treated children,” said Dr Wilton. It is important to remember, however, that this risk should be weighed against the potential benefits of GH therapy.

KIGS 20-year book available now

In celebration of 20 years of KIGS, Pfizer has published a comprehensive book ‘Growth hormone therapy in pediatrics: 20 years of KIGS’, edited by Professors Michael Ranke, David Price and Edward Reiter. This publication charts the progress made in the field of childhood growth disorders and the contribution of KIGS to this area.

Meet-the-Professor

In parallel interactive sessions, the audience had the chance to question the experts. Discussing rare syndromes and disorders associated with CNS or pituitary malformations was Professor Feyza Darendeliler (Istanbul, Turkey) in a session chaired by Professor Thomas Hertel (Odense, Denmark), while Dr Anita Hokken-Koelega (Rotterdam, The Netherlands) chaired a session where Professor Otto Mehls (Heidelberg, Germany) addressed issues relating to children with impaired growth as a result of chronic kidney disease. Endocrine problems in children treated for craniopharyngioma and brain tumours were discussed by Professor Stephen Shalet (Manchester, UK) and Professor Helmuth Dörr (Erlangen, Germany).
GH treatment strategies

Symposium 2, which focussed on GH treatment strategies, was chaired by Professor Ciril Kržišnik (Ljubljana, Slovenia). After an update on diagnosing GH deficiency by Professor Maïthé Tauber (Toulouse, France) and a comparison of country practices by Professor Christopher Kelnar (Edinburgh, UK), Professor Ranke presented the latest information on the computerized growth prediction models that have evolved from analysis of the KIGS data.

**Prediction models**

Prediction models developed using data from KIGS have been used by physicians throughout the world. Their clinical utility arises from the facts that the KIGS prediction models are based on parameters that are easily accessible to each clinician, are available before treatment, and can be determined with a relatively high degree of accuracy, said Professor Ranke.

Importantly, they also contain key information on treatment (dose, frequency of injections) as variables.

The KIGS prediction models will continue to evolve. The objective is to calculate the most likely response to a chosen treatment, predicting as much of the variability of the response as possible with the lowest error.

We are convinced, concluded Professor Ranke, that such models will guide us towards a more informed approach to GH treatment that will help to optimize and individualize outcomes in terms of efficacy, safety and cost.

**Plenary lectures**

Two plenary lectures were presented during the meeting. Chaired by Professor David Dunger (Cambridge, UK), the first was Genetic variation and GH responsiveness, by Professor Peter Clayton (Manchester, UK). The second, chaired by Professor Jan Martin Wit (Leiden, The Netherlands) and entitled New approaches to therapy, was presented by Professor Ron Rosenfeld (Palo Alto, CA, USA). These, together with the workshop reports from symposium 3, GH treatment outcome beyond growth, chaired by Professor Kenji Fujieda (Hokkaido, Japan) and Professor Berthold Hauffa (Essen, Germany), will be reported in our follow-up newsletter.

During the first 20 years of KIGS the role of GH in areas other than statural growth has become better understood. The symposium reflected this wider appreciation for the actions of GH through presentations on metabolism by Professor Roberto Lanes (Caracas, Venezuela) and on brain activity by Professor Peter Gluckman (Auckland, New Zealand). Future transition strategies for patients with childhood-onset GH deficiency were discussed by Professor John Monson (London, UK).

**KIGS: planning the future**

The final session was devoted to symposium 4: KIGS – planning the future, chaired by Professors Ieuan Hughes (Cambridge, UK) and Paul Czernichow (Paris, France). The symposium began with a review of GH dosing strategies from Professor Pierre Chatelain (Lyon, France). Professor Wayne Cutfield (Auckland, New Zealand) presented the value of KIGS alongside conventional clinical trials as a source of evidence-based medicine.

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**References**

