Recombinant Growth Hormone Therapy For Prepubertal Children With Idiopathic Short Stature In Korea: A Phase III Randomized Trial

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Background

1) Idiopathic Short Stature (ISS)

ISS is defined as a height more than two standard deviations (SD) below the age-, sex-, and population-matched mean, despite a normal or increased response to growth hormone (GH) on the GH stimulation test.

2) GH therapy

Studies evaluating GH therapy in children with ISS for 4–7 years revealed an increase in adult height of 3–6cm and a safety profile similar to other GH indications. There was significant variability in individual growth responses, including no measurable increase in height standard deviation scores (Ht SDSs) in some patients.

Objectives

This study evaluated the efficacy and safety of Growtropin®-II (recombinant human GH) in Korean patients with ISS.

Methods

Study Design: 1-year, open-label, multicenter, phase III randomized trial of Growtropin®-II in Korean patients with ISS.

Materials and Subjects

- The rhGH (Growtropin®-II, DA-3002) was provided by Dong-A ST Ltd. (Korea)
- In total, 70 prepubertal, GH-naive subjects (39 males, 31 females) between 4 and 12 years of age were included.
- **Inclusion criteria**: prepubertal children (tanner stage I); older than 4 years of age with a bone age (BA) of < 11 years (girl) or < 13 years (boys), and a disparity of 3 years or less between BA and chronological age (CA); height below the 3% for a Korean population of the same CA and sex; one or more peak GH levels of 10ng/ml or above, confirmed by GH stimulation testing.
- **Exclusion criteria**: currently receiving a drug that may affect the action of GH; congenital or chronic disease; medical history that may affect growth retardation except for ISS.

Intervention

- Children were given subcutaneous injections of rhGH at a dose of 1.11 IU. (0.37mg)/kg/week, divided into six to seven doses per week, for 52 weeks.
- Treatment group (n=36) received rhGH from week 0 to week 52.
- Control group (n=34) were observed without treatment from week 0 to week 26 and received the rhGH from week 27 to week 52.

Outcome Measures

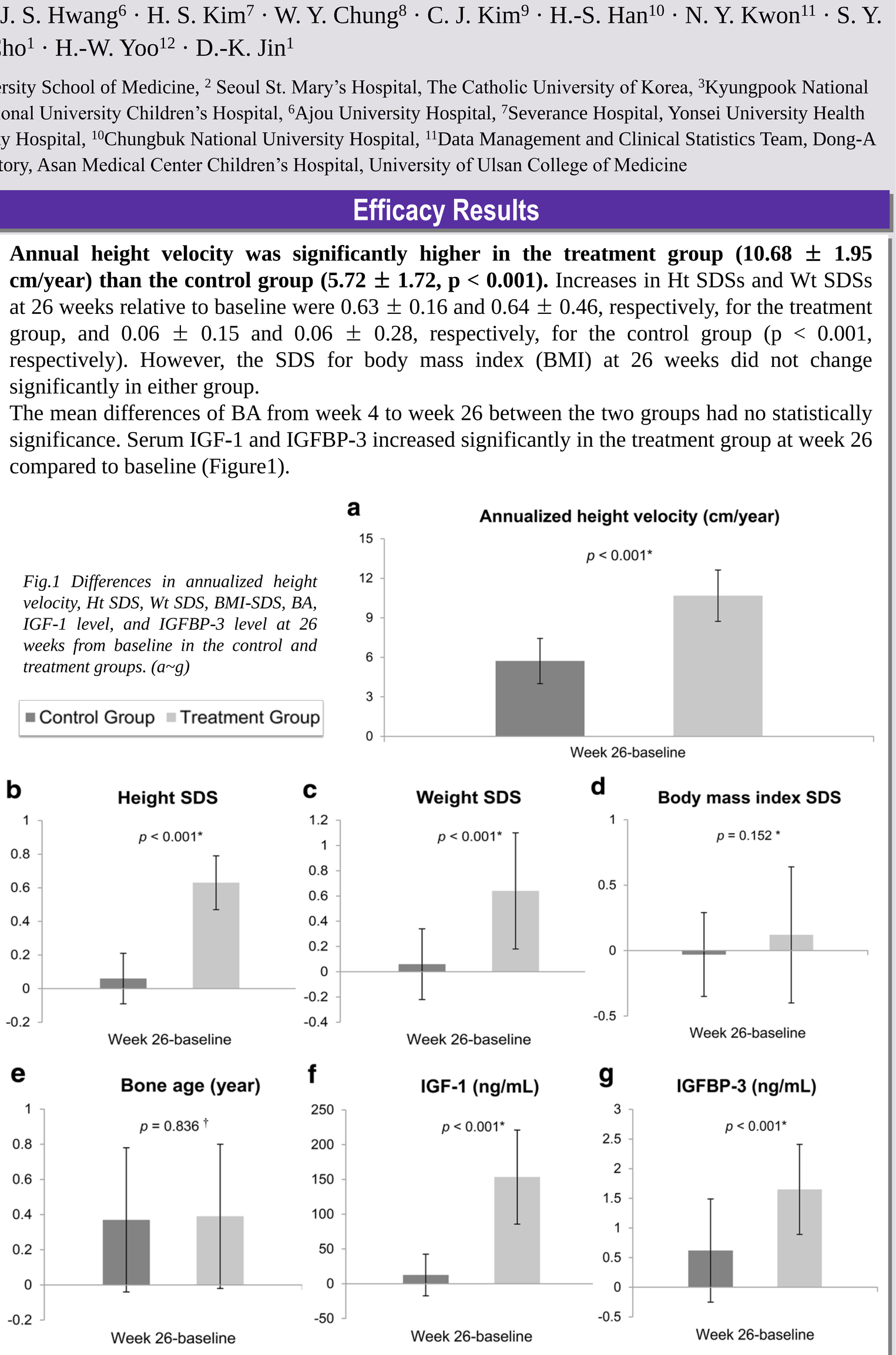
- The primary efficacy endpoint was the difference in annual height velocity at week 26 between the treatment and control groups.
- Secondary efficacy endpoints were the differences in Ht SDS, BA, Serum insulin-like growth factor (IGF-1) and IGF binding protein-3 (IGFBP-3) between the two groups at week 26.

Efficacy Results

Annual height velocity was significantly higher in the treatment group (10.68 ± 1.95 cm/year) than the control group (5.72 ± 1.72, p < 0.001). Increases in Ht SDSs and Wt SDSs at 26 weeks relative to baseline were 0.63 ± 0.16 and 0.64 ± 0.46, respectively, for the treatment group, and 0.06 ± 0.15 and 0.06 ± 0.28, respectively, for the control group (p < 0.001, respectively). However, the SDS for body mass index (BMI) at 26 weeks did not change significantly in either group.

The mean differences of BA from week 4 to week 26 between the two groups had no statistically significance. Serum IGF-1 and IGFBP-3 increased significantly in the treatment group at week 26 compared to baseline (Figure1).

Fig.1 Differences in annualized height velocity, Ht SDS, Wt SDS, BMI-SDS, BA, IGF-1 level, and IGFBP-3 level at 26 weeks from baseline in the control and treatment groups. (a~g)



Also, the pretreatment height velocity did not differ significantly between the two groups. The subjects had no history of GH therapy before this study, and there was no significant group difference in demographic information or baseline characteristics.

Safety Results

Growtropin®-II was well tolerated and safe over 1 year of treatment.

There was no statistically difference in adverse drug reaction (ADR) incidence. One ADR, a mild rash occurred in the treatment group. Three serious adverse events (SAEs) were reported. However, none of these events was related to the drug and all three subjects recovered without sequelae. No serious ADRs were reported and there was no withdrawal due to adverse events. As for the clinical laboratory findings regarding blood chemistry and thyroid function, most of the parameters, except phosphorus level, did not show statistically significant within-group changes and were classified as changes from 'outside the normal range' to 'normal'.

Conclusions

One-year GH treatment for prepubertal children with ISS demonstrated increased annualized velocity, height and weight SDSs, and IGF-1 and IGFBP-3 levels, with a favorable safety profile. Further evaluations are needed to determine the optimal dose, final adult height, and long-term effects of ISS treatment.