Pharmacokinetics and Efficacy of a long-acting human growth hormone with Fc fusion protein

Su Jin Kim[1],Sung-Yoon Cho[2], Kim Jin-sup[2], Huh Rimm[2], Yang A-ram[2], Dong-Kyu Jin[2]

[1]Departmnet of Pediatrics, Myongji Hospital, Seonam University College of MedicineGoyang, Korea

[2]Department of Pediatrics,Samsung Medical Center, SungKyunKwan University School of Medicine, Korea

Background

Recombinant human growth hormone (rhGH) therapy requires daily subcutaneous (s.c.) injections, this inconvenient treatment regimen results to poor compliance of the patient. Thus, to improve patient compliance, long-acting rhGH products including various protein fusion techniques have been in development during past 15 years.

Methods

To reduce the dosing frequency, we generated a chimeric protein of rhGH and the Fc-domain of immunoglobulin G (IgG) (rhGH-Fc). The pharmacokinetics and pharmacodynamics of SC-injected rhGH-Fc were assessed in male Sprague Dawley rats and hypophysectomized rats, respectively.

Results

A single SC injection of rhGH-Fc at a dose of 0.2 mg/kg slowly reached a Cmax of 16.80 ng/mL and remained for 7 days with a half-life of 51.1 hr. Conversely, a single SC injection of rhGH 0.2 mg/kg rapidly reached a Cmax of 46.88 ng/ml and declined with a half-life of 0.55 hr to baseline values in 4 hr. In the efficacy study, the SC-injected rhGH-Fc induced rapid weight gain and tibial width growth at a dose of 240 μg/animal. The effect of two injections of rhGH-Fc separated by one week was comparable to that of the same dose of 14 daily injections of rhGH. .

	rhGH 0.2 mg/kg	rhGH-Fc 0.2 mg/kg	rhGH-Fc 1.0 mg/kg
Half-life (hr)	0.55 ± 0.12	51.12 ± 3.12*	47.76 ± 4.32*
C_{max} (ng/mL)	46.88 ± 5.93	16.80 ± 0.72	330.32 ± 29.07*†
AUC_{0-14d} (day*ng/mL)	2.79 ± 0.36	39.57 ± 1.51*	538.72 ± 53.73*†
T_{max}(hr)	0.85 ± 0.06	14.40 ± 3.92*	8.00 ± 0.00*

Table 1. Pharmacokinetic parameters of rhGH and rhGH-Fc in rats. Data are shown as mean ± SEM.

: p<0.05, vs. rhGH 0.2 mg/kg,

†: p<0.05, vs. rhGH-Fc 0.2 mg/kg

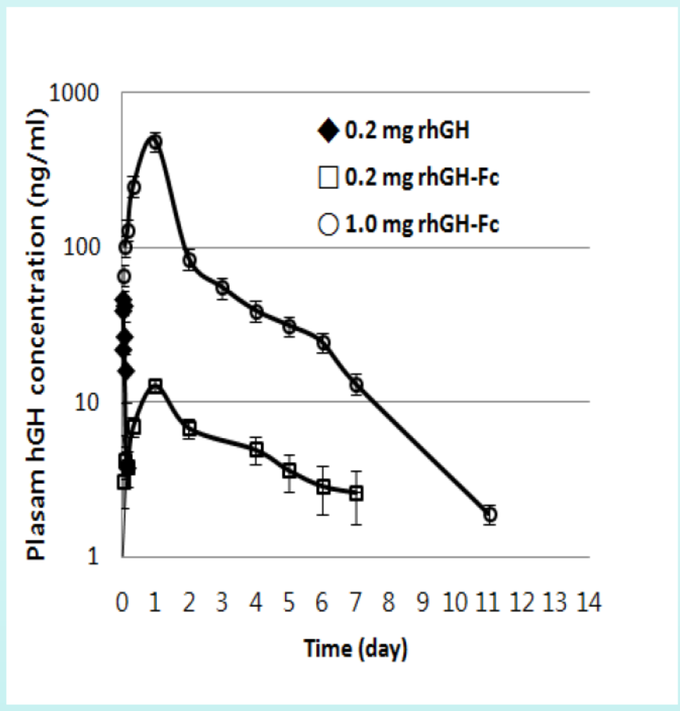

Figure 1. Results of pharmacokinetic studies in rats after SC administration of 0.2 mg rhGH (◆), 0.2 mg rhGH-Fc (□), 1.0 mg rhGH-Fc (○).

	Daily rhGH 15 μg	rhGH-Fc 240 μg	rhGH-Fc 480 μg	Vehicle
Body weight gain (g)	20.27 ± 0.45*†	19.02 ± 0.82*†	25.13 ± 0.79*	2.51 ± 0.97
Width of tibial growth plate (μm)	299.04 ± 6.42*	283.34 ± 6.38*†	319.04 ± 7.87*	190.29 ± 5.4

Table 2.Efficacy of rhGH and rhGH-Fc in Hpx rats,

***: p<0.05, vs. Vehicle, †: p<0.05, vs. rhGH-Fc 480 μg/animal**

Conclusion

The rhGH-Fc is a novel candidate for long-acting rhGH therapy with more convenient weekly administration, as it reduces glomerular filtration and receptor-mediated clearance while allowing for the rapid reversal of potential adverse events.

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SU JIN KIM

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