Endocrine, *vol. 15, no. 1, 43–49, June 2001* 0969–711X/01/15:43–49/$11.75

Long-Term Therapy with Recombinant Human Growth Hormone (Saizen®) in Children with Idiopathic and Organic Growth Hormone Deficiency

Barry B. Bercu,[1] F. T. Murray,[2] S. D. Frasier,[3] C. Rudlin,[4] Louis S. O'Dea,[2] J. Brentzel,[2] B. Hanson,[2] and H. Landy[2]

[1]Division of Pediatric Endocrinology, Diabetes and Metabolism, Departments of Pediatrics and Pharmacology and Therapeutics, University of South Florida, Tampa and All Children's Hospital, St. Petersburg, FL; [2]Serono Laboratories, Norwell, MA; [3]Department of Pediatrics, University of California, Los Angeles; and [4]School of Medicine, Richmond, VA

In an open-label study, 69 children with organic or idiopathic growth hormone deficiency (GHD) were treated with recombinant human growth hormone (Saizen®) for an average of 64.4 mo, with treatment periods as long as 140.9 mo. Auxologic measurements, including height velocity, height standard deviation score, and bone age, were made on a regular basis. The data suggest that long-term treatment with Saizen in children with GHD results in a positive catch-up growth response and proportionate changes in bone age vs height age during treatment. In addition, long-term Saizen therapy was well tolerated, with the majority of adverse events related to common childhood disorders or existing baseline medical conditions and not to study treatment. There were no significant changes in laboratory safety data or vital signs, and no positive antibody tests for Saizen.

Key Words: Children; growth hormone; growth hormone deficiency; Saizen.

Introduction

Growth hormone deficiency (GHD) in children may be either congenital or acquired. Congenital GHD may be hypothalamic or pituitary in origin, while acquired GHD can arise as a result of tumors (principally craniopharyngiomas), trauma, ischemia, infection, surgery, or empty sella syndrome. Patients with idiopathic GHD generally show a better response to therapy than those with an organic cause *(1)*, partly because patients with organic GHD tend to begin treatment at a later age than those with idiopathic GHD.

Previous studies with recombinant human growth hormone (GH) (Saizen®; Serono, Norwell, MA) have demonstrated the efficacy and safety of this product in prepubertal GH-deficient children after 1 and 2 yr of GH treatment *(2,3)*. These studies showed significant improvements in auxologic parameters such as height velocity (HV), height standard deviation score (HSDS), and height velocity SDS (HVSDS), both in patients who had not previously been treated with GH and in patients who were switched to recombinant GH from pituitary-derived preparations.

This article presents efficacy and safety data from a group of GH-deficient children who received Saizen for an average of 64.4 mo and a maximum of 140.9 mo.

Results

Patient Demographics and Disposition

A total of 69 children (50 males, 19 females) from 21 centers in the United States were recruited into the study. Forty-eight children had idiopathic disease, and 21 had organic GHD. Table 1 summarizes the demographic characteristics of the patients at baseline.

Baseline HV data were available for 58 patients whose heights were measured between 123 and 392 d before the start of treatment (mean = 283 d) and on the first day of treatment. Table 2 presents summary statistics for these 58 patients for HV, standard height velocity (STDHV), and HVSDS.

Of the 69 patients enrolled in the study, 64 completed the originally scheduled 2 yr of treatment. Of the remaining patients, one was lost to follow-up, one withdrew at the patient's own request, one withdrew because of adverse events, and two withdrew because the investigator relocated. The mean duration of Saizen treatment was 64.4 mo (range: 1.2–140.9 mo).

Efficacy

Auxologic data, expressed as median values (with error bars extending to the 25th and 75th percentiles), are illustrated in Figs. 1–4. Figure 1 summarizes the annualized HV during Saizen treatment. Median HV was significantly different (p varying from 0.004 to <0.001) from that during the first 12-mo period for each subsequent period through-

Author to whom all correspondence and reprint requests should be addressed: Dr. Barry B. Bercu, All Children's Hospital, Department 6900, 801 Sixth Street South, St. Petersburg, FL 33701. E-mail: Bercub@allkids.org

Table 1
Patient Demographics (n = 69)

Age (yr)	9.5 ± 3.1 (4.1–14.9)[a]
Gender (males/females)	50/19 (72.5/27.5%)
Ethnic origin	
Caucasian	53 (76.8%)
African American	8 (11.6%)
Hispanic	2 (2.9%)
Asian	2 (2.9%)
American Indian	1 (1.4%)
Other	3 (4.3%)
Etiology of GHD	
Idiopathic	48 (69.6%)
Organic	21 (30.4%)
Height at enrollment (cm)	113.6 ± 16.0 (82.0–153.3)[a]
Weight at enrollment (kg)	23.1 ± 11.6 (10.3–78.5)[a]

[a]Mean ± SD (range).

Table 2
Baseline HV Data (n = 58)

Variable	Mean	SD	Median	Range
HV	3.68	1.52	3.64	0.34–8.09
STDHV	5.97	1.01	6.06	4.50–8.80
HVSDS	–2.85	2.40	–2.79	–8.64–3.67

out the study. Growth from baseline was 47.5 ± 8.5 cm (range: 27.2–62.6 cm) over 7 yr. Significant catch-up growth was present and progressive in each of the first 7 yr of treatment, and most subjects reached predicted height.

The median HSDS at the start of the study was –3.8, and this improved significantly to –3.3 ($p < 0.001$) during the first year after the start of GH therapy; this improvement was maintained throughout the study, resulting in a median value of –1.5 SDS after 7 yr of Saizen therapy (Fig. 2). Similarly, the median HVSDS at the start of the study was –2.8, and this improved significantly to 3.8 during the first year after the start of GH therapy (Fig. 3). Median HVSDS varied between 1.0 and 1.8 during yr 2-7.

Chronologic age and height age (HA) are presented in Fig. 4. The median chronologic and HAs at baseline were 9.7 yr (range: 4.1–14.9 yr) and 5.1 yr (range: 1.5–12.6 yr), respectively, and HA increased significantly, compared with baseline, at all time points to 96 mo.

Chronologic age and bone age (BA) are presented in Fig. 5. The median Tanner-Whitehouse and Greulich-Pyle BAs at baseline were 6.4 yr (range: 1.6–13.3 yr) and 5.5 yr (range: 0.5–12.5 yr), respectively, and BA was significantly increased, compared with baseline, at all time points from 24 to 108 mo. The ratio of change in BA from baseline to change in HA from baseline is shown in Fig. 6. When Tanner-Whitehouse BAs were used, this ratio did not differ significantly from unity in yr 1–5 but was significantly greater than unity in yr 6 and 7 ($p = 0.007$ for both years). When Greulich-Pyle BAs were used, the change in BA was significantly greater than the change in HA in yr 3-8 (p varying from 0.022 to <0.001).

Table 3 summarizes the mean and median changes in insulin-like growth factor-1 (IGF-1) concentrations during Saizen treatment**.** The mean IGF-1 concentration at baseline was 62.4 ± 44.8 ng/mL, and the mean increase for each patient from baseline to the last measurement taken while on treatment was 208.5 ± 195.5 ng/mL. IGF-1 increased from baseline to yr 7 by 344.1 ± 192 ng/mL (range: –32.3 to 579.6). In 13 patients, concentrations increased from below the normal range at baseline to within the normal range at the last visit, and in five other patients, concentrations increased from normal or low at baseline to above the normal range at the last visit. These findings are consistent with the known effects of GH on IGF-1 concentrations.

Safety

A total of 2111 adverse events were reported by 68 patients. These were most commonly events related to common childhood disorders, such as upper respiratory tract infection, headache, fever, and pharyngitis. Overall, 1874 (88.8%) of the adverse events were considered unrelated to study treatment, while another 213 (10.0%) had an unknown or unreported relationship, and only 24 (1.1%) were considered to be related to treatment. Nineteen of the events considered to be related to treatment were application site disorders; these were eight injection site reactions, seven cases of injection site pain, two cases of injection site burning, and one case each of injection site atrophy and injection site mass. The five other treatment-related events were three cases of hypoesthesia and one case each of abnormal glucose tolerance and hypothyroidism. Three patients withdrew from the study owing to adverse events. One patient withdrew at 34 mo because of a hyperglycemic reaction that was not considered serious; the relationship to Saizen was considered unknown. Two patients who had a history of brain tumors before starting GH treatment also withdrew from the study: one withdrew at 46.9 mo owing to decreased hearing, which was considered neither serious nor drug-related, and the discovery of an astrocytoma that was considered serious but not drug related; the other withdrew at 1.2 mo owing to a metastatic spinal neoplasm that was considered serious but not drug related.

There were no significant changes in laboratory safety data or vital signs during the course of 7 yr of treatment with GH. There were no significant consistent changes in thyroid function, as assessed by measurement of thyroxine, free thyroxine index, and thyroid-stimulating hormone. Eleven of 46 patients (24%) who were euthyroid at baseline developed hypothyroidism during the study and were treated with levothyroxine.

There were no positive antibody tests for Saizen for any patients at baseline or at the end of the study. One patient

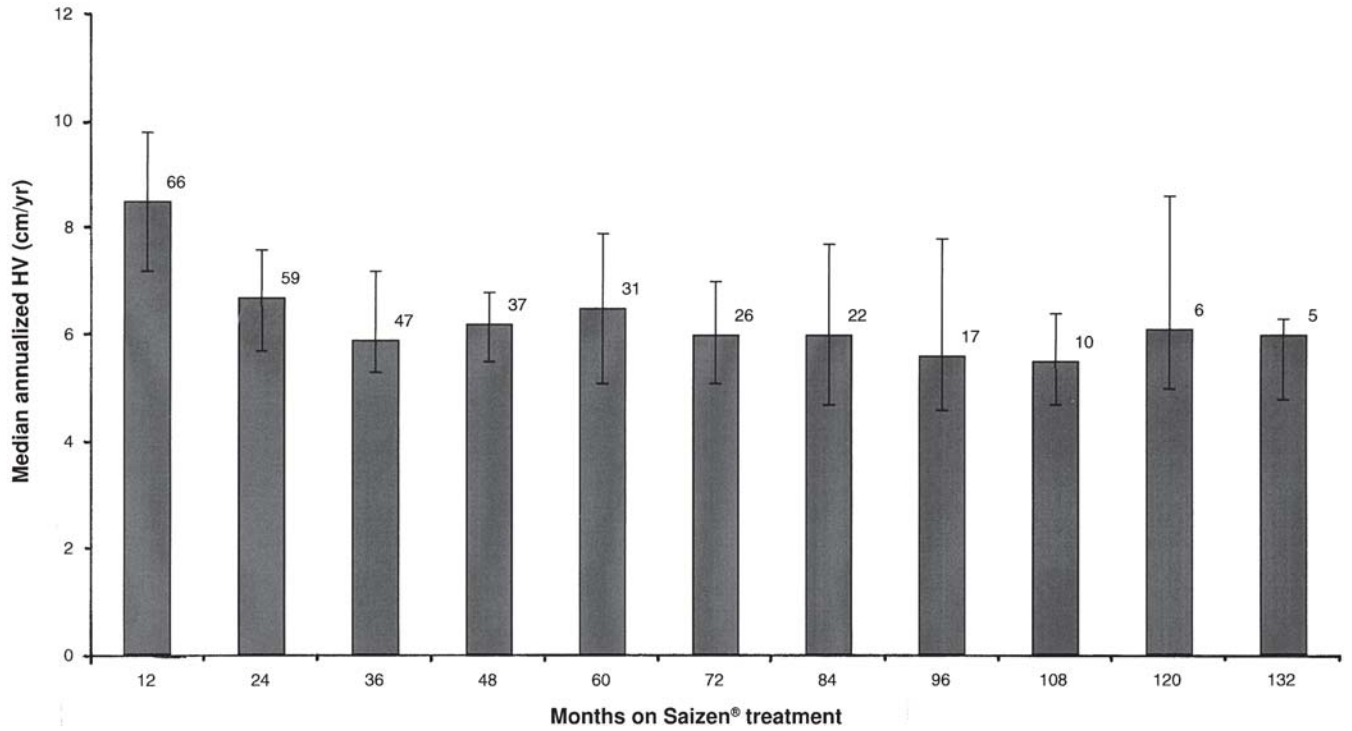

Fig. 1. Median annual HV during Saizen treatment. In this and subsequent figures, the numbers presented at each time point indicate the number of patients included at that time. The error bars extend to the 25th and 75th percentiles.

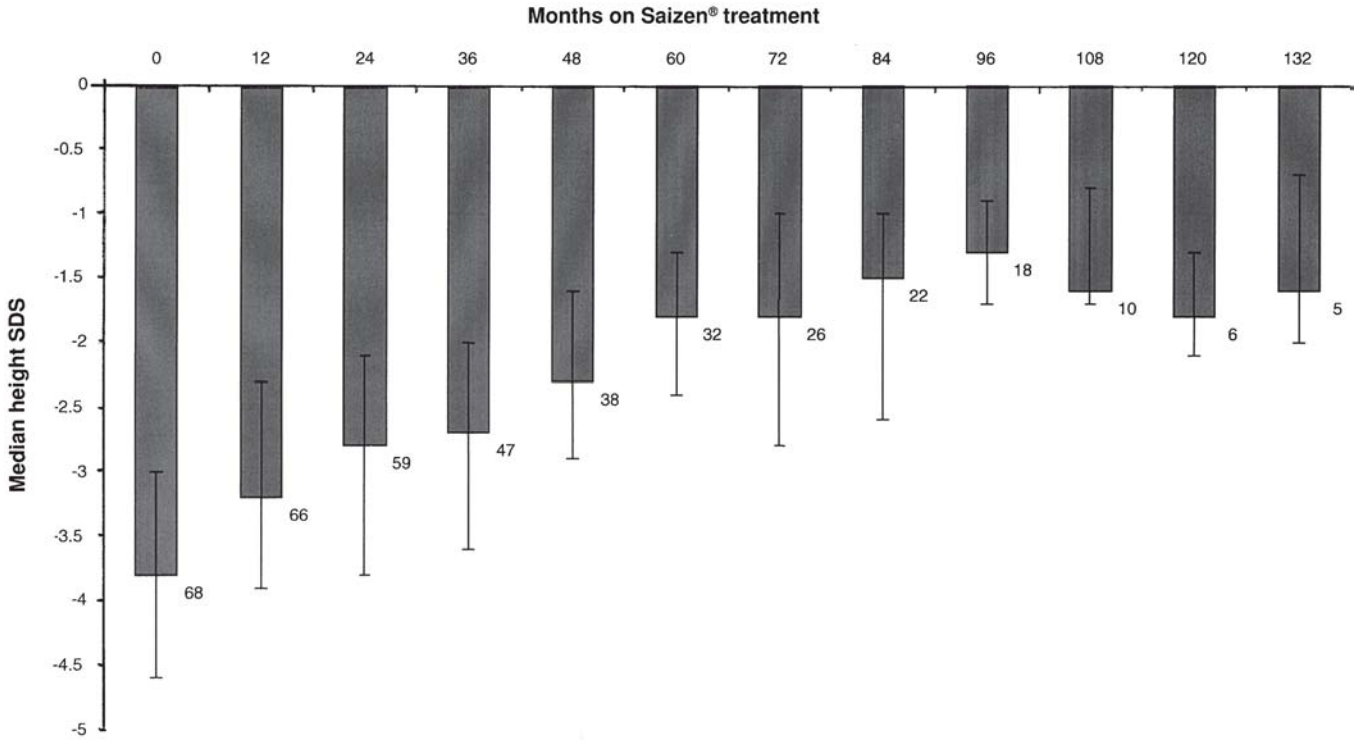

Fig. 2. Median HSDS.

had two positive host cell protein antibody tests at 72 and 75 mo, and another patient had several positive human GH antibody tests during the course of treatment, but these reverted back to a negative result by the end of treatment.

Discussion

The results of this long-term open study show that children with GHD, of either idiopathic or organic origin, show an excellent catch-up response to recombinant human GH

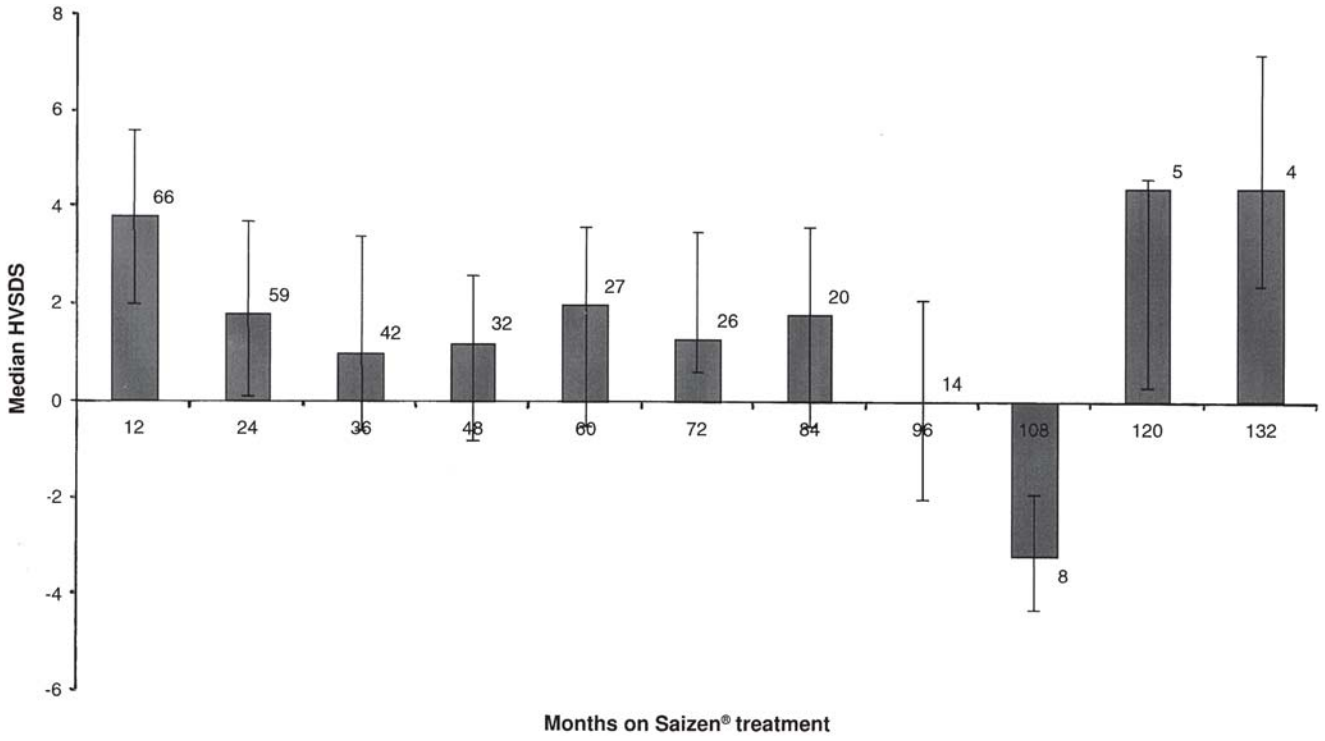

Fig. 3. Median HVSDS.

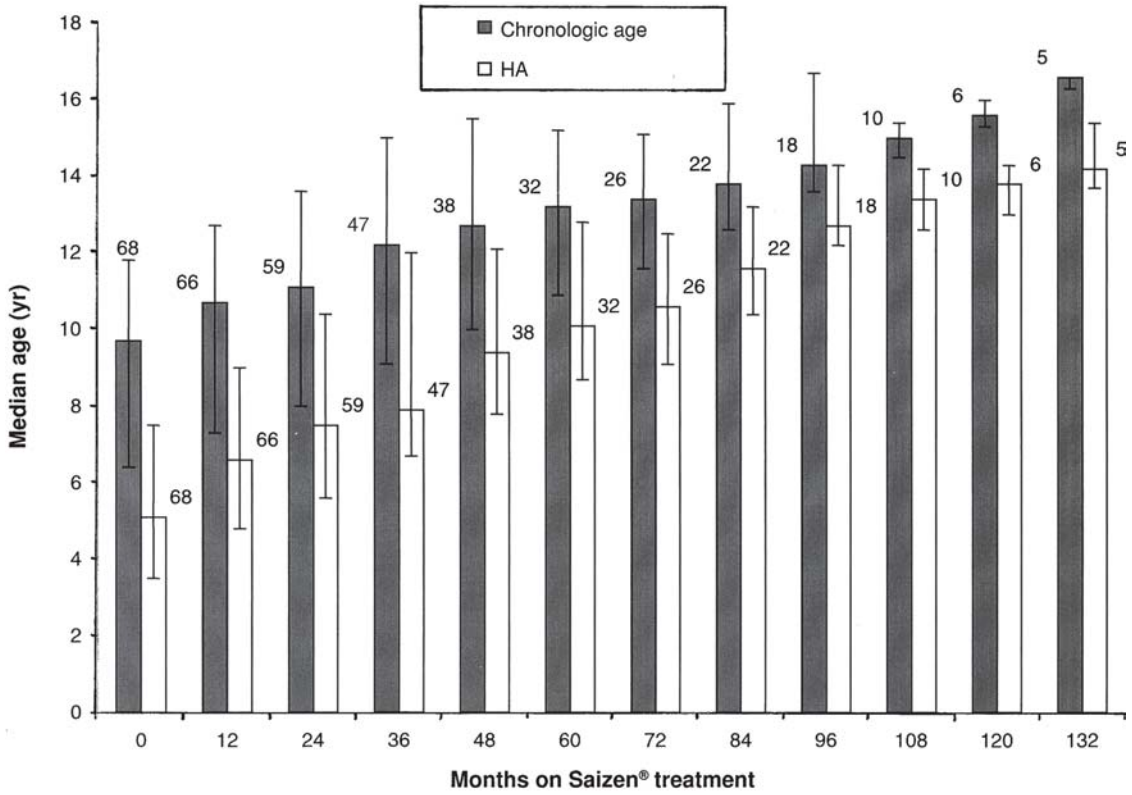

Fig. 4. Chronologic age and HA.

over 7 yr of treatment. Proportionate changes in BA vs HA were observed throughout GH treatment. These findings contrast with those published in 1997 by Coste et al. *(4)*, who concluded from their register-based study that GH therapy was "less favourable than initially assumed."

The height and growth parameters used in the present study are well-established measures of growth during GH treatment *(5)*. HV, HVSDS, and HSDS are usually adequate measures of the response to GH, particularly during the usual prepubertal age range. Beyond the ages of approx 9.5–10 yr,

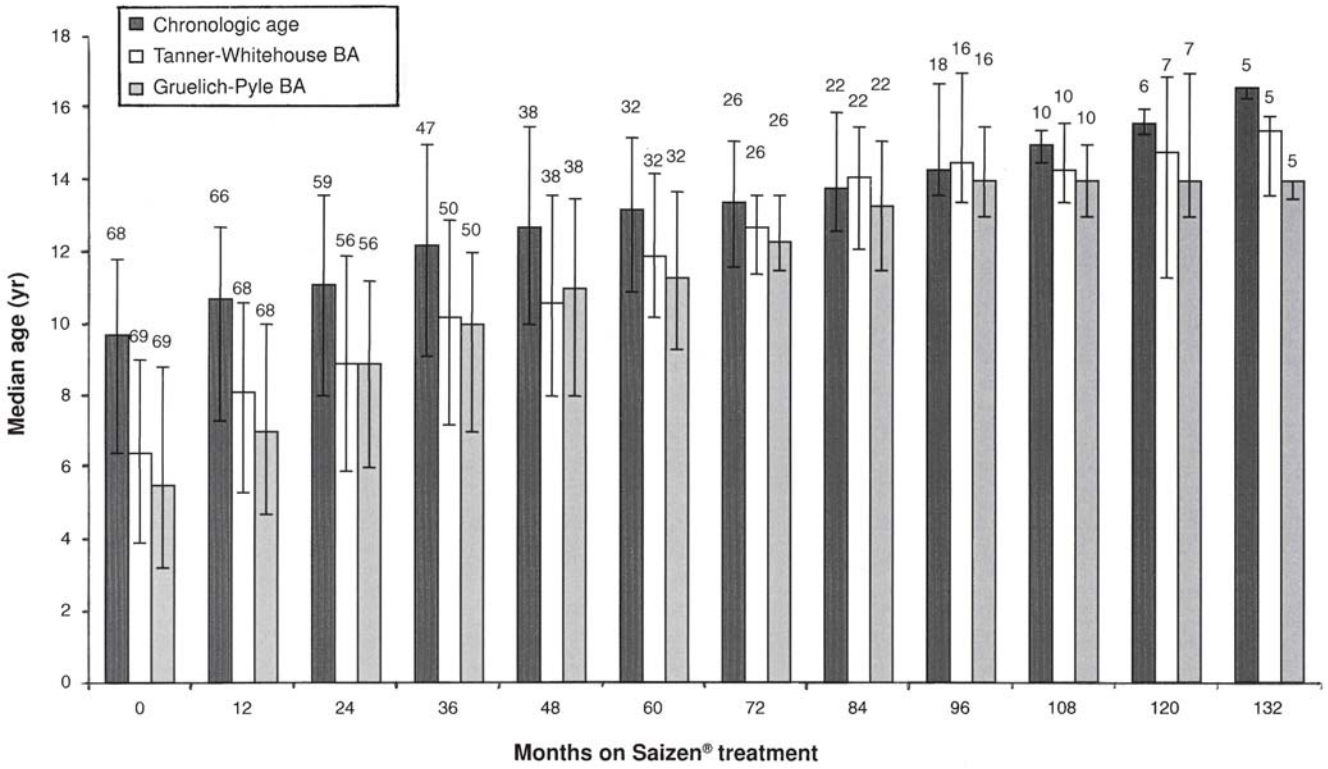

Fig. 5. Chronologic age and BA.

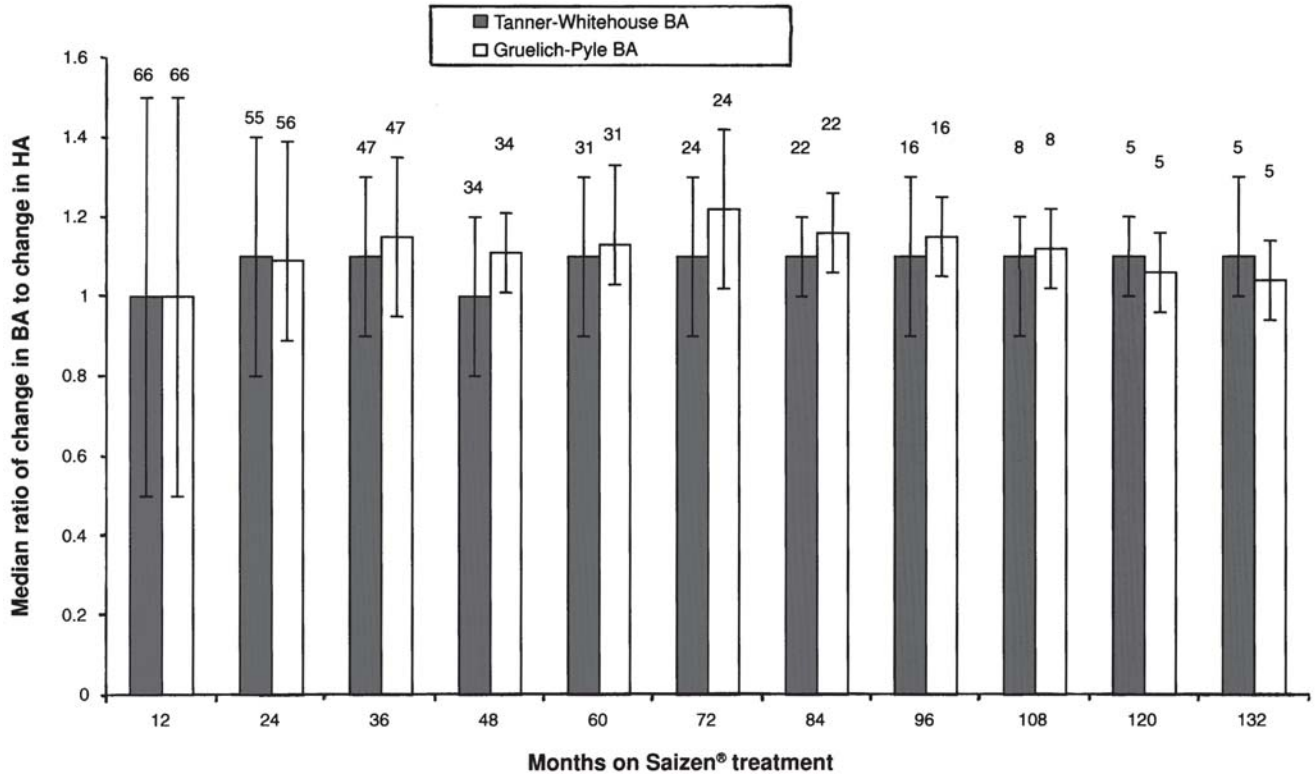

Fig. 6. Ratio of change in BA to change in HA.

the standard curves for height and HV are increasingly affected by the pubertal growth spurt. This may mask changes in HSDS in GH-treated children in whom puberty is delayed, and hence, HV may be a more appropriate measure of GH response in such children.

As in other studies of GH therapy in children with GHD *(4)*, the greatest improvements in HV, HSDS, and HVSDS were seen during the first year of treatment; thereafter the improvements tended to decline with time, but catch-up growth continued until final height or near final height was

Table 3
Serum IGF-1 Concentrations During Saizen Treatment by Annual Visit

		Value (ng/mL)			Change from baseline (ng/mL)		
Time point	n^a	Mean (SD)	Median	Range	Mean (SD)	Median	Range
Baseline[b]	69	62.4 (44.8)	49.7	7.9–274.3	—	—	—
12 mo	64	128.6 (82.1)	107.1	34.7–459.3	71.0 (69.1)	53.5	–41.6–361.2
24 mo	53	165.4 (97.6)	146.6	49.6–499.2	108.3 (93.1)	85.6	–34.5–474.5
36 m	40	171.5 (114.9)	155.0	13.0–510.0	120.4 (100.2)	105.1	–12.4–453.3
48 mo	32	192.0 (119.9)	170.0	30.0–590.0	137.2 (104.9)	123.9	3.4–536.6
60 mo	24	266.5 (179.0)	255.0	10.0–775.0	201.4 (154.1)	195.5	–14.8–721.6
72 mo	20	292.4 (144.4)	306.0	34.0–543.0	243.4 (128.1)	257.0	12.2–489.6
84 mo	16	397.3 (179.5)	461.0	57.0–633.0	344.1 (192.0)	429.3	–32.3–579.6
96 mo	14	353.7 (159.9)	384.0	72.0–581.0	311.5 (144.1)	355.4	52.8–500.1
108 mo	7	322.6 (232.1)	302.0	54.0–597.0	292.4 (223.6)	268.8	34.7–555.8
120 mo	4	482.8 (257.3)	541.0	124.0–725.0	444.6 (236.3)	514.7	104.8–644.1
132 mo	2	830.5 (67.2)	830.5	783.0–878.0	771.1 (97.6)	771.1	702.1–840.1
Last on treatment[c]	68	270.6 (202.9)	247.5	19.0–991.0	208.5 (195.5)	170.7	–34.5–891.4
Last posttreatment[d]	31	282.1 (199.8)	250.0	27.0–835.0	214.9 (184.6)	187.1	–39.6–793.8

[a] n = number of children.
[b] Last value prior to treatment.
[c] Last value obtained on treatment.
[d] Last value obtained posttreatment.

reached. Although the ratio between the change in BA and the change in HA was at times significantly greater than unity (during yr 6 and 7 for Tanner-Whitehouse BA, and yr 3-8 for Greulich-Pyle BA), the median value for this ratio was never greater than 1.1 (Tanner-Whitehouse) or 1.2 (Greulich-Pyle). This suggests that skeletal maturation was not occurring prematurely and that there were no disproportionate changes in either age variable. Thus, the final height potential of these 69 pediatric study participants was preserved during Saizen treatment.

The improvements in growth parameters observed in our study are more impressive when one considers that the dose of Saizen used (0.2 mg/[kg·wk]) was less than that now recommended (0.3-0.35 mg/[kg·wk] for prepubertal children and 0.5-0.6 mg/[kg·wk] for pubertal children). In addition, the infrequency of initial therapy (three times weekly during the first 2 yr) may have had a negative impact on HV. Indeed, the deceleration in HV observed after yr 1 may well have been caused by the low dose of Saizen and the low frequency of administration rather than owing to a characteristic of GH therapy, and results from other studies support this argument.

Long-term Saizen therapy was well tolerated, with the majority of adverse events considered unrelated to study treatment. The incidence of hypothyroidism (24%) is comparable with that reported in other studies with GH in children *(6–11)* and may be at least partly attributable to preexisting subtle abnormalities in hypothalamic-pituitary-thyroid function in children with GHD *(10)*.

In conclusion, our study showed that Saizen produces favorable growth responses in children with GHD during treatment for up to 140 mo, and is well tolerated.

Materials and Methods

Patients

All patients were at least 4 yr of age and prepubertal at the start of the study. Pretreatment growth velocity was <4.5 cm/yr and/or less than the 10th centile for age *(12, 13)*. Height was >3 SDS below the mean for age in patients with idiopathic GHD *(13,14)*. BA *(15,16)* was delayed more than 1 yr and/or 1 SDS below the mean for age in patients younger than 5 yr, or more than 2 yr and/or 2 SDS below the mean for age in older children. Height and BA criteria were not applied to patients with organic GHD. The peak serum GH concentration in response to at least two provocative tests was 8.0 ng/mL or less, as measured in the laboratory usually used at each center. Acceptable stimuli were insulin-induced hypoglycemia *(17)*, oral levodopa *(18)*, iv arginine hydrochloride *(19)*, oral clonidine hydrochloride *(20)*, and parenteral glucagon *(21)*.

All patients were studied under a common protocol approved by the human subject protection process at each participating institution. Written informed consent was obtained from each child's parent or legal guardian prior to enrollment in the study.

Methods

Prior to treatment, all patients underwent a 6- to 12-mo evaluation period during which baseline height and growth velocity were measured and pubertal status assessed. A complete clinical laboratory evaluation, including measurement of serum IGF-1 and thyroid function testing, was conducted 6 mo before and immediately before treatment began.

At the end of the pretreatment period, patients who fulfilled the entry criteria entered a 2-yr period of treatment

with Saizen. During this period, Saizen was administered subcutaneously at a dose of 0.6 IU/(kg·wk) (0.2 mg/[kg·wk]); the dosing frequency was three times weekly.

The initial treatment period was followed by an optional extended treatment period. The total weekly dose of Saizen was unchanged during this period, as was the route of administration. However, investigators were allowed to modify the dosing frequency if they saw fit; in most cases, dosing frequency increased to six or seven times per week. During both treatment periods, other medications that were considered necessary for the patient's welfare, and that would not interfere with the study medication or its evaluation, were permitted at the discretion of the investigator.

Height and weight were measured every 2 mo for the first year and every 3 mo thereafter. X-rays of the left wrist were taken yearly for determination of BA. All films were read by a central reader using both the Tanner-Whitehouse and Greulich-Pyle methods of measurement *(15,16)*. HV, HVSDS, and HSDS for chronologic age and BA were calculated yearly and compared with baseline values. Height and HVSDS were derived from the standard height tables of Prader et al. *(22)*. HV for each 12-mo period was calculated, and change in HV from the initial 12-mo period was calculated for baseline and for each annual visit. The HVSDS was calculated in a similar manner *(5,22)*. HVSDS was calculated for baseline and for each annual visit. Change from baseline was also determined for each annual visit. Pubertal status was assessed and recorded by investigators at each visit.

Safety was assessed by recording adverse events and vital signs, and by clinical laboratory testing every 3 mo during the early stages of the study and then every 6 mo in the latter stages, based on the extensive clinical experience gained with Saizen in this and other clinical trials. Serum IGF-1 measurements and thyroid function tests were conducted every 6–12 mo.

Statistical Methods

Changes in auxologic parameters from baseline were analyzed by Wilcoxon signed rank tests. All tests were two sided with a significance level of 0.05.

References

1. Milner, R. D. J., Russell-Fraser, T., Brook, C. G. D., Cotes, P. M., Farquhar, J. W., Parkin, J. M., Preece, M. A., Snodgrass, J. A. I., Mason, A. S., Tanner, J. M., and Vince, F. P. (1979). *Clin. Endocrinol.* **11**, 15–38.
2. Frasier, S. D., Rudlin, C. R., Zeisel, H. J., Lui, H. H., Long, P. C., Senior, B., Finegold, D. N., Bercu, B. B., Marks, J. F., and Redmond, J. P. (1992). *Am. J. Dis. Child.* **146**, 582–587.
3. Stubbe, P., Frasier, S. D., Stahnke, N., Cacciari, E., Job, J. C., Preece, M., Frisch, H., Zachmann, M., and Zeisel, H. J. (1992). *Horm. Res.* **37(Suppl. 2),** 28–36.
4. Coste, J., Letrait, M., Carel, J. C., Tresca, J. P., Chatelain, P., Rochiccioli, P., Chaussain, J. L., and Job, J. C. (1997). *BMJ* **315**, 708-713.
5. Frasier, S. D. (1983). *Endocr. Rev.* **4**, 155–170.
6. Sato, T., Suzuki, Y., Taketani, T., Ishiguro, K., Masuyama, T., Takata, I., Sano, M., Kawashima, H., Koizumi, S., and Nakajima, H. (1977). *J. Clin. Endocrinol. Metab.* **45**, 324–329.
7. Lippe, B. M., Van Herle, A. J., LaFranchi, S., Uller, R. P., Lavin, N., and Kaplan, S. A. (1975). *J. Clin. Endocrinol. Metab.* **40**, 612–618.
8. LaFranchi, S., Hanna, C. E., and Illingworth, D. R. (1985). *J. Pediatr.* **106**, 588–593.
9. Pirazzoli, P., Cacciari, E., Mandini, M., Sganga, T., Capelli, M., Cicognani, A., and Gualandi, S. (1992). *J. Pediatr.* **121**, 210–213.
10. Municchi, G., Malozowski, S., Nisula, B. C., Cristian, A., and Rose, S. (1992). *J. Pediatr.* **121**, 214–220.
11. Holcombe, J. H., Conforti, P. M., Wong, A. C., Thompson, R. G., and Draper, M. W. (1990). *Acta Paediatr. Scand. Suppl.* **367**, 44–48.
12. Tanner, J. M., Whitehouse, R. H., and Takaishi, M. (1966). Standards from birth to maturity for height, weight, height velocity, and weight velocity: British children. *Arch. Dis. Child.* **41**, 454–471.
13. Tanner, J. M. and Davies, P. S. (1985). Clinical longitudinal standards for height and height velocity for North American children. *J. Pediatr.* **107**, 317–329.
14. Hamill, P. V. V., Drizd, T. A., Johnson, C. L., Reed, R. B., Roche, A. F., and Moore, W. M. (1979). *Am. J. Clin. Nutr.* **32**, 607–629.
15. Greulich, W. W. and Pyle, S. I. (1959). *Radiographic atlas of skeletal development of the hand and wrist.* Stanford University Press: Stanford, CA.
16. Tanner, J. M., Whitehouse, R. H., Marshall, W. A., Healy, M. J. R., and Goldstein, H. (1975). *Assessment of skeletal maturity and prediction of adult height (TW2 method).* Academic: Orlando, FL.
17. Frasier, S. D. (1967). *J. Pediatr.* **71**, 625–638.
18. Root, A. W. and Russ, R. D. (1972). *J. Pediatr.* **81**, 808–813.
19. Parker, M. L., Hammond, J. M., and Daughaday, W. H. (1967). *J. Clin. Endocrinol. Metab.* **27**, 1129–1136.
20. Gil-Ad, I., Topper, E., and Laron, Z. (1979). *Lancet* **2**, 278,279.
21. Mitchell, M. L., Byrne, M. J., Sanchez, Y., and Sawin, C. T. (1970). *N. Engl. J. Med.* **282**, 539–541.
22. Prader, A., Largu, R. H., Molinari, L., and Issler, C. (1989). *Acta Paediatr.* **52**, 1–125.