Linear Growth and Final Height in Patients with Systemic Juvenile Idiopathic Arthritis Treated with Longterm Glucocorticoids

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ABSTRACT. ***Objective.*** To assess linear growth and final height in patients given glucocorticoids during childhood for systemic juvenile idiopathic arthritis (JIA).

Methods. Heights throughout followup for JIA and final height were recorded in 24 patients. Height data were expressed as the height standard deviation score for chronological age (HSDS/CA). Final height was compared to reference values for the French population and to target height.

Results. During glucocorticoid therapy, mean loss of HSDS/CA was –2.7 ± 1.5 and was positively correlated with prednisone therapy duration ($p < 0.01$). After prednisone discontinuation, 17 patients (70%) had catch-up growth and 7 (30%) continued to experience slow linear growth. Mean final height was –2.0 ± 1.8 HSDS and was correlated with mean height at prednisone discontinuation ($p < 0.0001$). Mean final height was significantly greater in the patients with catch-up growth at prednisone discontinuation (–1.5 ± 1.6 vs –3.6 ± 1.2 HSDS), and 87% of patients had a final height below their target height.

Conclusion. These data suggest that chronic inflammation and prednisone therapy may adversely affect growth in patients with JIA, and that final height may be closely dependent both on the severity of growth retardation during the active phase of the disease and on linear growth after remission. Thus treatments like growth hormone presently under investigation to improve final height may be most effective when given early after disease onset and/or at remission. (J Rheumatol 2002;29:1296–300)

Key Indexing Terms:
JUVENILE IDIOPATHIC ARTHRITIS GLUCOCORTICOID THERAPY
GROWTH GROWTH HORMONE FINAL HEIGHT

Growth retardation is often a major problem in patients with childhood arthritides and can result in a short final stature, especially when the disease is severe. Factors involved in the pathogenesis of growth retardation in patients with childhood arthritides include chronic inflammation, undernutrition, and longterm glucocorticoid therapy. Moreover, subtle abnormalities in the growth hormone (GH)–insulin-like growth factor-1 (IGF-1) axis have been reported in patients with childhood arthritides and growth retardation[1–5].

Although growth retardation is often described as a severe complication of childhood arthritides, few data are available on linear growth during the active phase of the disease and on final height. Such data are of considerable interest because several studies[6-9] have shown a beneficial effect of GH on growth velocity in these children. We describe linear growth patterns during and after glucocorticoid therapy in patients who had arthritis during childhood that we retrospectively identified according to the International League Against Rheumatism (ILAR) criteria[10]. We evaluated the influence of disease activity and glucocorticoid treatment on final height.

MATERIALS AND METHODS

Patients. Patients followed for juvenile idiopathic arthritis (JIA) from 1966 to 1998 in one pediatric rheumatology unit were studied retrospectively. To be included, the patients had to be adults at the time of the study and to have a history during childhood of systemic JIA meeting ILAR criteria and treated during at least the first 2 years with daily oral prednisone in a mean dosage of 0.2 mg/kg or more. Twenty-four patients (15 female, 9 male) met these inclusion criteria, i.e., arthritis of at least 6 weeks' duration with or preceded by daily fever of at least 2 weeks' duration, accompanied by a minimum of one of the following symptoms: evanescent erythematous rash, lymphadenopathy, hepato/splenomegaly, or serositis. Table 1 reports their individual characteristics. Mean followup was 13.6 ± 5.0 years (range 6.2 to 24.2). Mean age at disease onset was 3.4 ± 2.4 years (range 0.1 to 10.5). All patients were prepubertal at disease onset. Mean age at prednisone initiation was 3.5 ± 2.3 years and mean duration of prednisone therapy was 6.5 ± 3.6 years (range 2 to 15). In 6 patients (Patients 1, 5, 7, 14, 18, 19), prednisone therapy was interrupted during the followup because of remission of the disease, then restarted after relapse. Prednisone therapy was interrupted for a mean duration of 2.4 years (range 0.75 to 6.6).

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Table 1. Individual data of the patients.

Patient	Sex	CA at Diagnosis, yrs	Glucocorticoid Therapy Duration, yrs	HSDS/CA at Diagnosis	HSDS/CA at End of Glucocorticoids	Loss of HSDS/CA	Final HSDS	Change in HSDS/CA After Glucocorticoid Discontinuation	Target Height (HSDS)	Δ Target Height – Final Height (HSDS)	Final Height, m
1	F	0.1	5.4	–1.2	–2.2	–1.0	–1.8	0.4	NA	NA	1.52
2	F	0.5	3.6	1.6	–0.8	–2.4	–0.6	0.2	0.2	–0.8	1.60
3	F	0.8	5.1	0.3	–2.5	–2.8	–0.6	1.9	–0.6	0.0	1.60
4	F	1.0	3.0	2.8	–1.6	–4.4	–0.7	0.9	–0.3	–0.4	1.59
5	F	1.8	15.0	NA	–5.9	–7.5	–5.2	0.7	–1.9	–3.4	1.34
6	F	2.0	6.2	0.0	–2.1	–2.1	0.1	2.2	–0.6	0.7	1.64
7	F	2.0	5.1	–1.4	–3.8	–3.5	–4.7	–0.9	–0.8	–3.8	1.36
8	F	2.8	4.4	1.4	–0.9	–2.3	0.3	1.2	1.0	–0.7	1.65
9	F	3.0	8.8	NA	–2.9	–3.2	–3.2	–0.4	–2.0	–1.2	1.45
10	F	3.3	4.3	–1.4	–3.0	–1.5	–3.4	–0.4	–0.9	–2.5	1.44
11	F	4.0	12.8	NA	–3.2	–3.6	–2.7	0.5	1.7	–4.4	1.48
12	F	4.0	6.6	–1.1	–4.5	–3.4	–2.9	1.6	–1.3	–1.6	1.47
13	F	4.3	8.5	0.0	–5.1	–5.1	–4.5	0.6	–0.2	–4.3	1.38
14	F	4.5	11.0	–0.6	–1.9	–1.3	–1.5	0.4	–1.3	–0.2	1.55
15	F	7.0	2.0	–2.2	–3.0	–0.8	–3.6	–0.6	–0.2	–3.4	1.43
16	M	1.2	4.5	0.7	–2.6	–3.3	–2.0	0.6	–0.2	–1.8	1.62
17	M	1.7	4.2	–1.3	–4.5	–3.2	–4.9	–1.2	–0.7	–4.2	1.45
18	M	3.0	7.6	1.4	–0.3	–1.7	0.9	1.2	1.2	–0.3	1.80
19	M	3.6	3.0	0.9	–0.8	–2.1	0.6	1.4	–0.7	1.3	1.78
20	M	4.0	4.8	–1.0	–2.1	–1.1	–1.3	0.8	0.8	–2.1	1.67
21	M	4.2	13.6	–0.6	–2.8	–2.5	–1.8	1.0	–0.5	–1.3	1.64
22	M	4.3	9.2	NA	–2.9	–2.7	–4.2	–1.3	–0.5	–3.7	1.49
23	M	7.2	3.2	0.7	–0.5	–1.2	–1.1	–0.6	–0.2	–0.8	1.68
24	M	10.5	4.8	0.3	–2.1	–2.4	–1.3	0.8	0.6	–1.8	1.67
Mean ± SD		3.4 ± 2.4	6.5 ± 3.6	–0.03 ± 1.3	–2.6 ± 1.4	–2.7 ± 1.5	–2.0 ± 1.8	0.45 ± 1	–0.3 ± 0.9	–1.7 ± 1.6	

Other antirheumatic drugs given during or after prednisone therapy included nonsteroidal antiinflammatory agents (n = 24), chlorambucil (n = 11), D-penicillamine (n = 10), gold salts (n = 7), and methotrexate (n = 4). Five patients received intraarticular glucocorticoid injections.

At the end of followup, 7 patients had achieved a full recovery with no residual abnormalities, 14 had recovered with residual joint abnormalities, 2 had active arthritis requiring antiinflammatory medications, and one had died in an accident unrelated to the joint disease.

Methods. The height measurements recorded at regular intervals in the medical charts were used to evaluate linear growth. During the followup, patients were measured using a wall mounted scale. Final height (n = 11) and heights of the parents (n = 10) were obtained from the medical charts or reported by the patients contacted at the time of the study by phone or mail. In these cases, parents (n = 14) and adult patients (n = 13) were measured by their local physician.

Height data were expressed as the height standard deviation score for chronological age (HSDS/CA) and were compared with reference values for the French population[11]. The target height was calculated from the mean parental height plus or minus 6.5 cm for boys and girls, respectively, and was expressed as the HSDS using the same reference values[11]. Catch-up growth was defined as a greater than normal growth velocity sufficient to return the child to his target growth curve when it was complete or sufficient to improve HSDS when it was partial.

The active phase of the disease was defined as the period during which patients had been receiving steroid therapy. Disease activity was assessed based on erythrocyte sedimentation rates (ESR, mm/h) obtained yearly throughout followup. The mean prednisone dose per year was calculated and reported in mg/kg body weight/day.

Statistical analysis. Data are reported as means ± SD. Differences across mean values obtained at different times during followup were tested using paired ANOVA. Differences between the groups with and without catch-up growth were tested using the nonparametric Mann-Whitney test. Correlations between variables were evaluated by linear regression analysis. P values < 0.05 were considered statistically significant.

RESULTS

Linear growth during the active phase of the disease treated with prednisone. Table 1 reports heights in individual patients throughout followup. At diagnosis, mean HSDS/CA was –0.03 ± 1.3 (–1.4 to 1.4 HSDS/CA, except in 2 patients whose HSDS/CA values were –2.2 and +2.8, respectively), which did not differ significantly from the mean target height, which was –0.3 ± 0.9 HSDS (–2 to 1.7 HSDS). During followup, mean HSDS/CA decreased significantly to –1.0 ± 1.4 (n = 19, $p < 0.001$), –1.6 ± 1.4 (n = 19, $p = 0.01$), –2.1 ± 1.0 (n = 20, $p = 0.05$), and –2.4 ± 1.2 (n = 19, $p = 0.04$) at the end of the first, second, third, and fourth years of the disease, respectively. Mean HSDS/CA at the end of the fourth year was significantly different from mean HSDS/CA at diagnosis ($p < 0.0001$) and from mean target height ($p < 0.0001$). HSDS/CA did not change significantly after the fourth year of followup. At prednisone discontinuation, mean HSDS/CA was –2.6 ± 1.4 (–5.9 to –0.3 HSDS/CA). Mean loss of HSDS/CA during the entire period taking prednisone was –2.7 ± 1.5 (–7.5 to –0.8). We found a strong positive correlation between mean loss of HSDS/CA during prednisone therapy and duration of prednisone therapy ($r^2 = 0.2$, $p < 0.01$, data not shown).

Changes in mean ESR values and mean prednisone dosages are reported in Table 2. The mean prednisone dosage was decreased from 1 ± 0.5 mg/kg/day (n = 23) during the first year to 0.5 ± 0.4 mg/kg/day during the third year and to 0.3 ± 0.3 mg/kg/day during the fifth year of the disease, when 66% of the patients were still undergoing prednisone therapy.

Growth after prednisone discontinuation. Prednisone therapy was discontinued at a mean age of 11.6 ± 4.6 years (range 4.8 to 20.7). Pubertal growth was not evaluated because the medical charts did not contain data on age at puberty onset or on the clinical progression of puberty. In females, mean age at menarche was 14.3 ± 1.2 years (range 12.6 to 16.1).

After prednisone discontinuation, the mean HSDS/CA gain was 0.45 ± 1 overall (Table 1). Seventeen (70%) patients had partial catch-up growth (only Patients 3 and 19 had complete catch-up growth), with a mean HSDS/CA gain of 1 ± 0.6 (range 0.2 to 2.2), whereas 7 (30%) patients had a mean HSDS/CA loss of –0.8 ± 0.4 (range –1.3 to –0.4). Mean final height was significantly greater in the 17 patients with partial catch-up growth (–1.5 ± 1.6 HSDS) than in the 7 other patients (–3.6 ± 1.2 HSDS) (p = 0.01). Table 3 reports the main characteristics of the patients with and without partial catch-up growth. We found no significant differences in age at JIA diagnosis, age at prednisone therapy discontinuation, or prednisone therapy duration. One significant difference was shorter stature at diagnosis in the patients without catch-up growth than in those with partial catch-up growth. Moreover, patients with partial catch-up growth grew slightly above their target height channel before the onset of the disease, whereas the patients without catch-up growth grew below their target height channel.

Final height. Final height was reported at a mean age of 25 ± 5.4 years. Mean final height was –2.0 ± 1.8 HSDS (–5.2 to 1.7) (Table 1) and was strongly correlated with mean HSDS/CA at prednisone discontinuation ($p < 0.0001$, $r^2 = 0.76$) (Figure 1). Ten (41%) patients had a decrease in final height > 2 SD, and 21 (87%) had a final height below their target height. The mean difference between final height and target height was –1.7 ± 1.6 HSDS. In males, mean final height was –1.7 ± 1.9 HSDS (range –4.9 to 0.9), i.e., 1.64 m (range 1.45 to 1.80), with a mean difference between final height and target height of –1.6 ± 1.7 HSDS (range –4.2 to 1.3). In females, mean final height was –2.3 ± 1 HSDS (range –5.2 to 0.3), i.e., 1.5 ± 0.1 m (range 1.34 to 1.65), with a mean difference between final height and target height of –1.9 ± 1.7 HSDS (range –4.4 to 0.7).

DISCUSSION

For a long time, growth retardation in children with chronic arthritides has been a matter of concern for pediatric rheumatologists. Previous studies dealt with patients referred as juvenile chronic arthritis (JCA, European League Against Rheumatism) or as juvenile rheumatoid arthritis

Table 2. Changes in ESR and prednisone dosages during followup.

	Time Since Disease Onset, yrs					
	1	2	3	4	5	6
ESR*	66 ± 26 (20)	54 ± 31 (22)	46 ± 27 (21)	45 ± 28 (20)	45 ± 28 (20)	35 ± 25 (16)
Prednisone dosage, mean for the year, mg/kg/day*	1 ± 0.5 (23)	0.7 ± 0.6 (22)	0.5 ± 0.4 (21)	0.4 ± 0.4 (18)	0.3 ± 0.3 (14)	0.3 ± 0.2 (8)
No. (%) of patients taking prednisone	24 (100)	24 (100)	22 (92)	19 (79)	16 (66)	10 (40)

* Data in parentheses are numbers of patients for whom a value was available at the relevant time point.

Table 3. Main characteristics of patients with (n = 17) or without (n = 7) catch-up growth after discontinuation of prednisone.

	Catch-up Growth	No Catch-up Growth	p
Age at diagnosis, yrs	3.0 ± 2.4	4.0 ± 2.2	NS
Duration of prednisone therapy, yrs	7.0 ± 3.8	5.2 ± 2.7	NS
Age at prednisone discontinuation, yrs	11.5 ± 4.9	11.8 ± 3.8	NS
HSDS/CA at diagnosis	0.3 ± 1.1	–1.1 ± 1	0.01
HSDS/CA at diagnosis – target HSDS	0.57 ± 1	–0.56 ± 1	0.04
HSDS/CA at prednisone discontinuation	–2.4 ± 1.5	–2.9 ± 1.2	NS
Final HSDS	–1.5 ± 1.6	–3.6 ± 1.2	0.01
Target HSDS	–0.1 ± 0.9	–0.7 ± 0.6	NS

HSDS: height standard deviation score; HSDS/CA: height standard deviation score for chronological age.

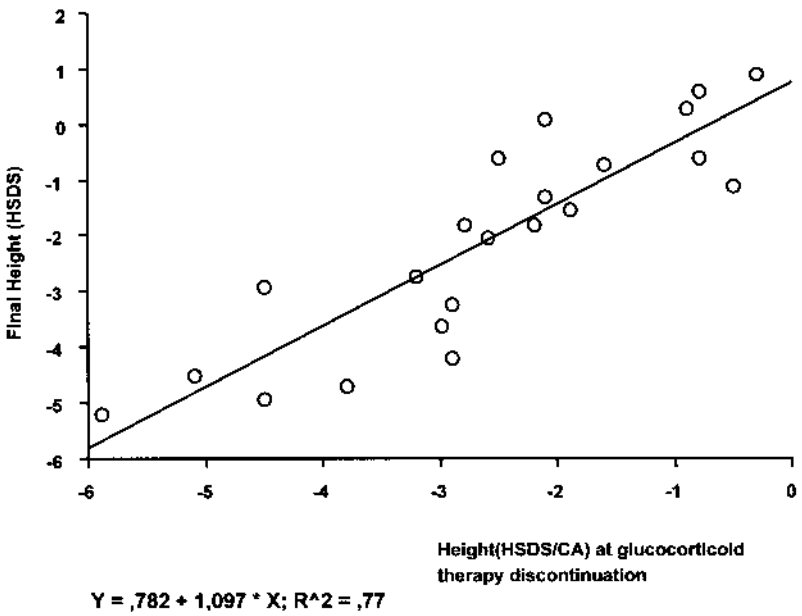

Figure 1. Correlation between final height standard deviation score for chronological age (HSDS/CA) and HSDS/CA at discontinuation of glucocorticoid therapy.

(JRA, American College of Rheumatology). Since these classifications were not exactly the same and were not universally embraced, a new classification of 7 homogenous categories was proposed denoting juvenile idiopathic arthritis (JIA) and known as the ILAR criteria[10]. In this new classification, the systemic category comprised the presence of arthritis for a duration of at least 6 weeks and we adopted this characteristic for our patients.

We retrospectively studied linear growth from the diagnosis in early childhood until adulthood in 24 patients with systemic JIA. Slowing in linear growth occurred early after disease onset. A significant drop in height velocity of more than 2 SD occurred during the first 4 years of the disease and the loss in linear growth was correlated with duration of prednisone therapy. Our findings are consistent with earlier studies[12-14] reporting that linear growth retardation during the active phase of childhood chronic arthritides was mainly dependent on disease severity and duration, but was worsened by high dose glucocorticoid therapy. In our patients, severe chronic inflammation was attested by high ESR values for longer than 2 years. Moreover, it has been established that glucocorticoid therapy slows growth[15,16] when the dosage is at least 0.25 mg/kg/day prednisone-equivalent[17,18]. The mean glucocorticoid dosages in our patients during the first years of the disease were far higher, suggesting that glucocorticoid therapy also contributed to the linear growth retardation. Thus, the combined effects of severe chronic inflammation and longterm high dose glucocorticoid therapy may explain why linear growth retardation was more severe in our patients than in previous studies[19,20].

In our patients, mean final height was strongly correlated with mean height at prednisone discontinuation, suggesting that the loss of linear growth during the active phase of the disease may govern the loss of final height. However, final height also depended on height velocity after prednisone discontinuation. It has been reported that many children with Still's disease, particularly the younger ones, experience partial catch-up growth when their disease becomes inactive, and that catch-up growth is less common in patients with longer disease durations[12]. In our study, most patients (17/24) had partial catch-up growth after prednisone discontinuation, whereas a minority (7/24) continued to exhibit slow linear growth. Mean height at prednisone discontinuation was similar in these 2 groups, and mean final height was significantly greater in the patients with partial catch-up growth. At the time of diagnosis, the patients with partial catch-up growth were taller than the patients without catch-up growth, and they grew above their target height channel. These data suggest that in these patients, catch-up growth may partially depend on their genetic potential for growth. Persistent disease activity after prednisone discontinuation and/or bone lesions ascribable to longterm glucocorticoid therapy were not recorded in our study; these factors may have played a role in the further linear growth loss seen in some patients after prednisone discontinuation. Delayed onset of puberty and reduced duration and magnitude of the pubertal growth spurt are known to occur in patients with chronic diseases[19,21,22]. This can explain the irreversible loss of height observed during puberty in these patients and their short adult height. Given that mean age at prednisone discontinuation was 11 years, pubertal growth was probably involved in the extent of

catch-up growth. Unfortunately, puberty could not be assessed accurately in this retrospective study, but the delay in menarche in the females suggests delayed puberty.

Finally, our data suggest that 2 periods exerted a critical influence on final height: the active phase of the disease, characterized by a significant loss of linear growth, and the period following prednisone discontinuation, during which partial catch-up growth occurred in most, but not all, patients. Final height varied markedly across patients, but 40% of the patients had a final HSDS under –2 SD and more than 80% had a final height below their target height. Few studies have reported final height in children with a history of chronic arthritides. In a study of 65 patients with JCA, Zak, *et al*[23] found that final HSDS was under –2 SD in 11% of patients, all of whom had had polyarticular disease treated with glucocorticoid therapy, and that polyarticular or systemic disease was associated with a final height less than the target height. Their data suggest that polyarticular or systemic JCA treated with glucocorticoids is associated with an increased risk of reduced final height, and consequently may be a good indication for GH therapy.

Several studies have shown benefits of short term GH treatment in growth retarded children with JCA[7-9]. Linear growth returned to normal during GH treatment, so that further loss was prevented, but no catch-up growth occurred[9]. Further, a negative correlation has been reported between height velocity during GH therapy and disease activity as assessed by C-reactive protein levels[24]. These data and the pattern of growth in our patients with systemic JIA suggest strategies for increasing the efficacy of GH therapy in children with JIA. Using GH earlier may be useful in preventing the linear growth retardation that occurs during the first years of the disease. During puberty and/or after remission of the inflammatory process, GH therapy may improve the pubertal growth spurt and catch-up growth. The good correlation in our study between final height and height at prednisone discontinuation suggests that treatments capable of increasing linear growth during the active phase of the disease may improve final height. Further clinical trials in larger numbers of patients treated with GH for longer periods are needed to assess the effects of GH treatment in JIA and to define the strategy that produces the best response. Moreover, accurate evaluation of the benefits of GH therapy in patients with JIA requires comparisons of final height with and without longterm GH administration.

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