Clinical Pediatric Endocrinology

Vol.33 / No.1
January 2024
pp 1–11

Review

GH therapy in children with juvenile idiopathic arthritis: a four-decade review

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Highlights

- JIA may cause growth failure, from slight implications to severe growth delay.
- Bone formation and prepubescent growth seem to be significantly increased during rhGH treatment.
- Despite therapy, target height remains challenging to achieve in many children.

Abstract. Chronic inflammatory conditions, such as juvenile idiopathic arthritis, are associated with growth failure. Growth failure appears to be correlated with both the effects of inflammation and negative effects of glucocorticoids (used as therapeutic option) on the growth hormone axis and locally on the growth plate and bone metabolism. In the last decade, the introduction of biologics has changed the disease course regarding consequences and outcomes. Anyway in some cases, treatment with biologics has failed in restoring normal growth in patients with juvenile idiopathic arthritis; in contrast, several studies have reported improved height velocity and growth rate in patients with juvenile idiopathic arthritis treated with growth hormone. This study aimed to evaluate the impact of growth hormone treatment on the growth and pubertal development in juvenile idiopathic arthritis patients through a narrative review of the literature over the last four decades.

Key words: rhGH, juvenile idiopathic arthritis (JIA), growth failure, short stature in JIA

Received: June 29, 2023 Accepted: November 12, 2023 Advanced Epub: December 2, 2023
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Introduction

Juvenile idiopathic arthritis (JIA) is a chronic inflammatory joint disease of unknown etiology that begins before 16 yr of age and lasts for more than 6 wk (1–4). Environmental and genetic factors play a crucial role in disease pathogenesis (2, 4, 5). JIA has an annual incidence and prevalence of 2–20 cases per 100,000 people per year and 16–250 per 100,000, respectively, in developed countries (2, 6). According to the current International League of Associations for Rheumatology (ILAR) JIA classification, seven subtypes of JIA can be defined: systemic JIA (sJIA), oligoarticular JIA (oJIA), rheumatoid factor (RF)-positive and-negative polyarticular JIA (pJIA), psoriatic arthritis (PsA), enthesitis-related arthritis (ErA), and undifferentiated arthritis (2, 7). Each disease subgroup differs according to age at onset, modality of presentation, clinical signs and symptoms, genetic background, severity, possible complications, and prognosis (2). Similar to other chronic inflammatory conditions, JIA appears to be associated with growth failure, ranging from a slight decrease in height to severe short stature (2). Still has described systemic JIA in 1897 and was the first to note a general growth arrest when the disease began in early childhood (8). In 1956, Ansell and Bywaters wrote about growth retardation in 119 children with JIA, noting that disease activity and the use of glucocorticoids (GCs) could be the main causes of growth impairment (9). Even in the absence of GC treatment, growth retardation was observed, underlying the correlation between disease subtype, disease duration and severity, and growth development. A longitudinal study has revealed that patients with systemic JIA lost 0.55 of height standard deviation score (HSDS), and those with polyarticular JIA lost 0.7 of HSDS during the observation period (10). More recently, in patients with systemic JIA followed up for > 9 yr, Liem and Rosenberg have reported a mean decrease in HSDS from + 0.4 to 1.8 (11). A reduced final height could be one of the permanent consequences of the disease, affecting approximately 10.4% of pJIA patients and 41% of patients with the systemic form (12). Growth delay is correlated with both the deleterious effects of inflammatory cytokines and negative effects of glucocorticoids (GCs) on the GH axis and locally on the growth plate and bone metabolism (**Fig. 1**) (3, 13, 14). In the last decade, the therapeutic strategies for the treatment of JIA have changed significantly. The introduction of biological drugs has changed the course of the disease regarding consequences and outcomes.

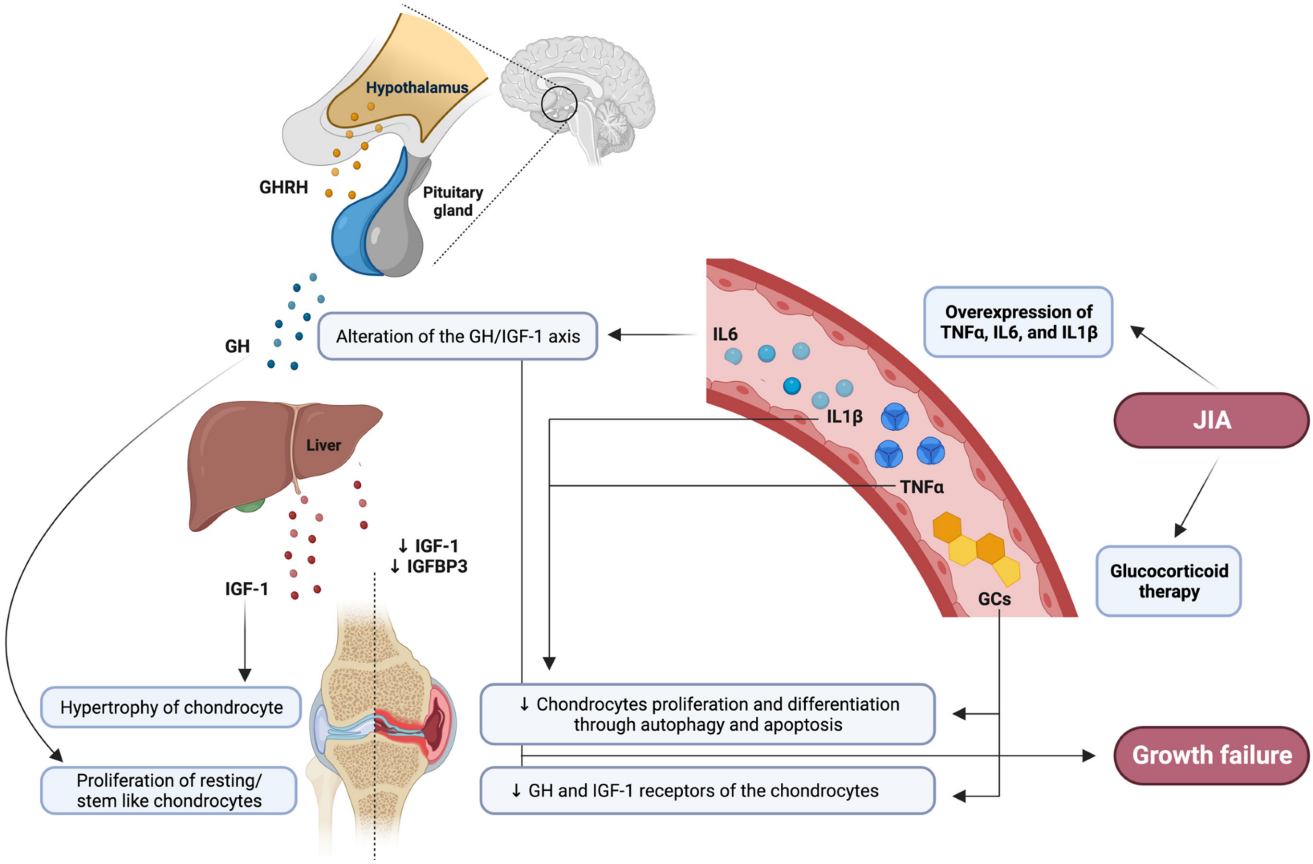

Fig. 1. Juvenile idiopathic arthritis (JIA) and growth delay. JIA may be accountable for growth failure and short stature due to chronic inflammation and use of prolonged glucocorticoid therapies. Owing to its effects on the growth plate, a correct treatment strategy with recombinant human GH (rhGH) can often result in a partial recovery of final height.

doi: 10.1297/cpe.33.2023-0036

Moreover, biologics that improve inflammation control have reduced the use of GCs in routine management. Several studies have found an improved growth in patients with JIA using cytokine antagonists (15, 16). However, there have been recent reports in the medical literature of cases in which treatment with biologics failed to restore normal growth velocity in patients with JIA, particularly in those with sJIA or those who required more than one biologic to control the disease (3, 17). In contrast, several studies have reported improved height velocity and growth rates in JIA patients treated with recombinant human GH (rhGH) (12, 18–20). This study aimed to evaluate the impact of rhGH treatment on growth and pubertal development in patients with JIA through a narrative review of the literature over the last four decades.

Hypothalamus–pituitary–GH/IGF1 axis and physiological bone growth

GH is a peptide secreted by cells of the anterior pituitary gland under the control of GHRH. It plays a critical role in the regulation of cell growth, development, and metabolism in multiple target tissues. The GH axis is a major regulator of longitudinal bone growth (21, 22). The effects of GH are mostly mediated by the IGF1 that is produced in the liver upon GH stimulation. Moreover, while GH intervenes only during postnatal growth, IGF1 works both during embryonic and postnatal growth (22). One of the most common abnormalities in patients with chronic inflammatory diseases and growth delay is low serum IGF1 (21, 23, 24). The original somatomedin hypothesis states that GH has only an indirect effect on the growth plate by stimulating the production of IGF1 from the liver, which in turn exerts its effects on the growth plate (21, 25). However, several studies have demonstrated both the direct and indirect effects of GH on the growth plate. In 2004, Wang *et al*. have determined that GH can directly stimulate the proliferation of resting/stem-like chondrocytes and indirectly lead to the hypertrophy of chondrocytes through IGF1 (21, 26). Further, Parker *et al*. have shown that GH receptors could be detected in the chondrocytes of all zones of the growth plate. Regarding the indirect effect, GH can stimulate the local production of IGF1 acting on the chondrocytes of the proliferative zone (21, 27). Thus, locally produced IGF1 in growth plate chondrocytes via autocrine/paracrine mechanisms is crucial for the normal regulation of longitudinal bone growth (21, 28).

Chronic illness and malnutrition and nutritional effects on growth

Inflammatory chronic diseases are often associated with so-called "rheumatoid cachexia" (29). This term refers to a condition characterized by decreased lean body mass, increased catabolism, and decreased energy expenditure. The association between malnutrition and chronic inflammatory diseases is associated with an increase in fibroblast growth factor-21 (FGF-21) due to brief periods of fasting and hepatic GH resistance, which results in elevated levels of GH in the bloodstream. By stimulating the activity of leptin receptor overlapping transcript-like 1 (LEPROTL1) and leptin receptor overlapping transcript (LEPROT), FGF-21 inhibits GH receptor binding in growth plate chondrocytes (30).

Systemic and local effects of pro-inflammatory cytokines on growth mechanisms

In children with chronic inflammatory diseases, several factors, such as constant pro-inflammatory cytokine exposure and extensive use of glucocorticoid therapy, contribute to growth impairment. These factors can interfere with normal growth at local and systemic levels. Systemic effects of pro-inflammatory cytokines have been reported in transgenic mice overexpressing tumor necrosis factor α (TNFα) and interleukin (IL)-6; both models show growth retardation (21, 31, 32). IL-6-overexpressing mice exhibit a defective growth phenotype with a size reduction of 50–70% compared to normal non-transgenic littermates. Growth retardation in mice was associated with decreased levels of IGF1 and IGF1-binding protein 3 (IGFBP3), but with a normal distribution of GH pituitary cells and GH production (21, 31, 33). This finding is consistent with the fact that, in patients with JIA, high circulating levels of IL-6 are negatively correlated with IGF1 and IGFBP3 levels (21, 34). IL-6 systemically suppress growth by altering the GH/IGF1 axis; however, other pro-inflammatory cytokines, such as TNFα, have direct effects on the growth plate chondrocytes (35). In 2004, Martensson *et al*., using a model of cultured fetal rat metatarsal bones, have demonstrated that TNFα can suppress longitudinal bone growth through direct actions on the growth plate cartilage, including decreased chondrocyte proliferation and increased apoptosis (14). This finding manifested only when the model was exposed to a high concentration (100 ng/mL) of TNFα (14). Later, in 2006, MacRae *et al*. have found that TNFα can reduce proteoglycan synthesis and the number of cells, as well as mRNA expression of aggrecan, type II collagen and type X collagen (36). It is crucial to point out that TNFα is physiologically produced throughout the growth plate and that it plays a critical role in the normal regulation of bone growth; on the contrary, the negative effects of TNFα take place only at very high concentrations. Additionally, for IL-1β, the same effects on the growth plate have been reported (14). Moreover, TNFα and IL-1β were reported to have a synergistic effect in decreasing longitudinal growth (14) (**Table 1**).

Systemic and local effects of glucocorticoid therapy on growth mechanisms

Patients with chronic inflammatory disease often

doi: 10.1297/cpe.33.2023-0036

Table 1. Cytokine effects on growth plate cells in juvenile idiopathic arthritis (31, 36, 73, 74).

Cytokine	Growth plate cell	Effects
IL-6	Chondroblasts	• Reduces the formation of cartilaginous nodules by inhibiting the early differentiation of chondrocyte precursors
	Chondrocytes	• Through JAK/STAT signaling, inhibits the production of aggrecan and type II and X collagen. • Chondrocyte turnover in the growth plate is reduced in patients with sJIA; this effect is mediated by IL-6 inflammation.
	Osteoblasts	• Decreased osteoblastic activity results in impaired ossification, osteopenia, and an inadequate mineral apposition rate
	Osteoclasts	• Increases osteoclastogenesis with augmented bone reabsorption and osteopenia
IL-1 and TNF-α	Chondroblasts and chondrocytes	• Reduce the rate of endochondral ossification and the extent of the proliferating zone of growth cartilage, thereby inhibiting chondrocyte proliferation and inducing apoptosis in proliferative cells (likely through the downregulation of the *SOX9* gene) • Murine models showed compromised cartilage synthesis of collagen types II and X, aggrecan, and proteoglycan due to the overexpression of proteases, such as stromelysins and collagenases • Disrupt chondrocyte differentiation and hypertrophy, impairing their critical function in longitudinal bone growth

IL, interleukin; TNF, tumor necrosis factor.

require long-term treatment with high-dose systemic steroids for long periods. GCs exert numerous effects on growth. GCs, especially at high doses, can inhibit the pulsatile release of GH and expression of GH and IGF-1 receptors by chondrocytes at the growth plate level and impair IGF-1 signaling at the growth plate through the phosphoinositide 3-kinase (PI3K) pathway (37). Further, GCs can inhibit chondrocyte proliferation and differentiation by stimulating autophagy and apoptosis (38, 39). After GC discontinuation, during the remission, it is possible to observe a phenomenon called "catch-up growth". This phenomenon results from reduced chondrocyte senescence at the growth plate level. Decreased cell proliferation during GC treatment preserved the proliferative capacity of chondrocytes, resulting in a greater proliferative potential at the end of the treatment (38). This accelerated growth rate, beyond the normal growth rate for age, has been observed in various growth-retarding conditions, such as Cushing's syndrome and celiac disease, but may not be completed after discontinuation of GC if inflammation is still ongoing (40). It is crucial to point out that a significantly short stature or deviation from the target height has been reported only in children treated with systemic GCs for > 1 yr (41). Simon *et al.* have retrospectively analyzed the linear growth patterns during and after GCs therapy in 24 prepubertal patients with sJIA treated for at least the first 2–7 yr with daily oral prednisone at a mean dosage of ≥ 0.2 mg/kg (12). A significant drop in height velocity and HSDS lower than −2 SD occurred during the first 4 yr of the disease in 40% of patients and was correlated with the duration of prednisone therapy and with the severity of growth retardation during the active phase of the disease. Moreover, 70% of patients had a catch-up growth, and 30% continued to show slow linear growth after prednisone discontinuation. The mean final height was below the target height in 80% of patients and was significantly correlated with mean height at prednisone discontinuation. Steroid treatment seems to have a dual role: it can delay or improve the growth of patients with JIA. Its positive effect on growth in the short term is correlated with aggressive control of inflammation. Early aggressive treatment could increase linear growth during the active phase of the disease and thus improve final height (42, 43). However, the potentially beneficial outcomes of steroid therapy should be weighed against the potential for enduring complications, including secondary osteoporosis, non-traumatic osteonecrosis, myopathy, hyperglycemia, dyslipidemia, weight gain, Cushingoid features, and hypertension. Moreover, glucocorticoids are considered as independent risk factors for adverse gastrointestinal events, including gastritis, peptic ulcer formation, and gastrointestinal bleeding. Additionally, glucocorticoids are responsible for neuropsychiatric symptoms, such as minor mood changes, depression, euphoria, mood lability, irritability, akathisia, and anxiety, as well as cognitive impairments, such as attention, concentration, and memory deficits. Psychosis, dementia, and delirium rarely occur (44).

Puberty in patients with chronic inflammatory disease

Puberty is a critical transitional life process in which a complex series of hormonal and neurological changes result in the physical development of sexually mature adults (45). The mechanisms governing the timing of puberty are currently a rich field of research, but are not completely understood. However, both

doi: 10.1297/cpe.33.2023-0036

exogenous and endogenous factors (nutrition, genes, inflammatory status, endocrine disruptor agents, and societal changes) can influence pubertal neuroendocrine events (46). In patients with JIA or other chronic inflammatory conditions, the most frequent pubertal abnormality is delayed puberty, followed by slow clinical progression of puberty, isolated delayed menarche, and decreased duration and intensity of pubertal growth (47, 48). Delayed puberty is often considered a normal variant or expected cause of an underlying chronic disease. Pubertal delay is associated with a decrease in the duration and intensity of the pubertal growth spurt, resulting in a loss of height, which partially explains why chronically ill patients are usually shorter than healthy individuals (49). However, the pathogenesis of the pubertal abnormalities in these patients remains unclear. A persistent inflammatory state and GCs treatment are the main factors responsible for the impaired regulation of GH and gonadotropin secretion through multiple mechanisms (48).

Recombinant GH (rhGH) therapy in children with juvenile idiopathic arthritis

The effects of recombinant GH (rhGH) therapy in children with chronic arthritis remain controversial. To the best of our knowledge, the first study evaluating the use of rhGH in JIA patients was conducted in 1979, when 20 children with chronic rheumatoid arthritis and growth failure were treated at a dose of 7.5–17 IU/m^2/d (mean, 0.17 mg/kg/d), with reported increased growth velocity rate in more than half of them from 1.9 (0–3.3) cm/yr to 6.2 (3.6–12) cm/yr over up to 7 mo, with similar improvements during a second year of treatment (**Table 2**) (50). However, the growth velocity decreased in six patients after drug discontinuation (50). In 1991, six children with JIA, previously on corticosteroid therapy for a mean of 8.4 yr, were treated with low doses of prednisolone and daily rhGH injections at 0.07–0.2 IU/kg/d for a time lasting 0.5–3 yr (51). The mean pretreatment growth velocity rate increased by 2.8 (0.3–5.7) to 6.7 (2.8–12.4) cm/yr after 1 yr of treatment, with no side effects reported (51). After 3 yr, another study has revealed that rhGH at a dosage of 12 IU/m^2/d (0.15 mg/kg/d) or 24 IU/m^2/d (0.3 mg/kg/d) significantly increased the height velocity during 1 yr of treatment in patients with juvenile chronic arthritis (JCA), especially in those with polyarticular disease, even if the final effect on adult height remained uncertain (52). In 1997, a crucial study evaluated the effects of rhGH treatment for 1 yr in 18 prepubertal children with juvenile rheumatoid arthritis and growth delay (53). In the affected patients, IGF-1, IGFBP-3, and osteocalcin levels were significantly lower, and insulin levels were significantly higher than those in the controls. In addition, height increase and mean levels of IGF-1, osteocalcin, and insulin increased significantly after 1 yr of treatment (53). The study has determined that IGF-1 levels are reduced in children with active diseases and that rhGH therapy can rectify IGF-1 deficiency within a few days; however, its effect is adversely influenced by inflammation (53). In 1998, the efficacy of rhGH therapy on growth delay was evaluated on 14 sJIA patients, highlighting increased IGF-I and IGFBP3 levels in blood and higher mean growth velocity in treated patients than controls from 1.9 to 5.4 cm/yr after 12 mo of treatment. However, both induced hyperinsulinemia and increased insulin resistance were

Table 2. Results achieved in the increase of growth velocity and improvement of height standard deviation score after recombinant human GH therapy in patients with juvenile idiopathic arthritis previously treated with systemic glucocorticoids

Study	Patients N. (age baseline in yr)	Prednisone equivalent dose (yr of disease duration)	rhGH dosage mg/kg/wk (yr of treatment)	Baseline GV (cm/yr)	GV gain (cm/yr)	Baseline HSDS	HSDS gain
Butenandt *et al.*, 1979 (50)	20 (13)	0.17 mg/kg/d (8.2)	0.1–0.2 (1–2)	2.7	6.2 at 1 yr	.	.
Svantesson *et al.*, 1991 (51)	6 (13.7)	≤ 5 mg/d (9.2)	0.16–0.46 (0.5–3)	2.8	6.7 at 1 yr	–3.4	.
Davies *et al.*, 1994 (52)	10 (9.2) 10 (10.6)	5–11 mg/d (6.2–7)	0.15 (1) 0.3 (1)	2.4 2.0	4.5 at 1 yr 6.1 at 1 yr	–3.0 –3.4	. .
Touati *et al.*, 1998 (19)	15 (9.8)	0.38 mg/kg/d (6.5)	0.46 (1)	1.9	5.4 at 1 yr	–4.3	–4.3 at 1 yr
Simon *et al.*, 2003 (57)	13 (12.4)	0.39 mg/kg/d (8.2)	0.46 (3)	2.1	6.0 at 1 yr 5.0 at 2 yr 4.1 at 3 yr	–4.6	–4.5 at 1 yr –4.5 at 2 yr –4.3 at 3 yr
Bechtold *et al.*, 2003 (65)	18 (10.1)	0.2 mg/kg/d (6.3)	0.2–0.33 (4)	2.4	4.7 at 4 ar	–3.3	–2.3 at 4 yr
Simon *et al.*, 2007 (58)	15 (1.5–11)	≥ 0.2 mg/kg/d (1–1.25)	0.46 (3)	2.7	6.1 at 1 yr 6.0 at 2 yr 6.5 at 3 yr	–1.1	–1 at 1 yr –0.9 at 2 yr –0.4 at 3 yr
Bechtold *et al.*, 2007 (60)	31 (10.5)	4.7 mg/kg/d (3.9)	0.33 (6.7)	–2.15 SD	–	–3.2	–1.67 at 6.7 yr
Bechtold *et al.*, 2012 (67)	39 (9.6)	0.16 mg/kg/d (4.3)	0.33 (6.3)	–	–	–3.3	–1.67 at 7 yr
David *et al.*, 2017 (1)	53 (10.1)	0.4 mg/kg/d (9–14.4)	0.39 (4.7–7.9)	–	–	–2.9	–1.7 at 8.6 yr

rhGH, recombinant human GH; GV, growth velocity; HSDS, height standard deviation.

doi: 10.1297/cpe.33.2023-0036

observed; subsequently, decreased glucose tolerance and increased glycated hemoglobin levels were reported during treatment. However, glucocorticoids further induced insulin resistance, and this point should be better clarified (19). Growth velocity returned to pretreatment values 1 yr after the drug was discontinued, whereas after 2 yr, HSDS was even lower than the pretreatment values (19). Simon and Bechtold have studied rhGH therapy in patients with JCA/JIA for a long time, with relevant discoveries and evidence (12, 54–65). In 1999, 14 children with JCA and growth delay were treated with rhGH at 1.4 IU/kg/wk for 1 yr, with a follow-up of a second year after the drug was discontinued (54, 55). Baseline GH, IGF-1, and IGFBP-3 in the blood were found to be lower than the normal limit; however, they were elevated after rhGH treatment. In addition, all patients showed an increase in height velocity after treatment from 1.9 to 5.4 cm/yr, and their mean lean body mass increased by 12% and mean fat mass fell by 20% compared with baseline, with reported decreased glucose tolerance and increased glycated hemoglobin levels, confirming the evidence that has been reported in literature the previous year (54). However, after discontinuation of rhGH therapy, height velocity decreased to pretreatment values and weight and fat mass increased markedly (54, 55). Moreover, Simon *et al*. have reported that bone formation significantly increased during treatment and that multiple factors, such as chronic inflammation and undernutrition, may contribute to growth failure in JCA patients (54, 55). In 2001, 13 of the 14 previously enrolled patients were treated again with rhGH at the same dosage (0.07 mg/kg/d) for another 3 yr (12, 56). Increased growth velocity rate was reported, from 2.1 to 6.0 cm/yr in the first year; however, with less efficacy in the following period, the final HSDS did not change significantly (–4.6 SDS at baseline vs –4.3 SDS at discontinuation) (12, 56). However, the conclusions were that rhGH treatment had significantly improved body composition, increased lean mass by 33%, and prevented further bone loss, increasing lumbar bone mineral density by 36.6% (56). This was one of the first evidence that JIA children on long corticosteroid therapy could remain as short as adults, even after prompt rhGH treatment (12, 56, 57). Linear growth and final height were retrospectively evaluated in 24 patients with JIA receiving corticosteroid therapy. In these patients, a significant loss of height of ≥ 2 SDS during the first years of the disease was noted, correlating positively with the duration of prednisone therapy. After discontinuation of steroid treatment, 70% of patients achieved catch-up growth, even if up to 30% reported a persistent loss of height (12, 56). However, the mean final height was strongly correlated with the mean height at discontinuation of corticosteroid therapy (56). A group of 18 children with pJIA was treated with rhGH at 0.2–0.33 mg/kg/wk for 4 yr, and the mean improvement in height gain was 1 SD (from –3.3 to –2.3 HSDS), with reported beneficial effects in children with severe forms of JIA (65). In 2004, Bechtold *et al*. have studied the acquisition of bone mass and changes in bone mineral density (BMD) in 11 patients over a 4-yr period of rhGH treatment compared to healthy children (61). Before treatment, all patients had low BMD; however, after 4 yr of GH treatment at 0.036–0.047 mg/kg/d, it increased significantly from –2.97 to –2.83 SD (61). Compared to pretreatment values, bone formation and resorption markers increased significantly during treatment. Bechtold *et al*. have shown an increase in bone turnover and stabilization of BMD after rhGH therapy in patients with JIA (61). The following year, they conducted a controlled study on 17 patients with JIA receiving the same rhGH dosage (0.036–0.047 mg/kg/d) for a mean of 3.8 yr, to evaluate their forearm muscle, fat area, bone mass, density, and geometry compared with untreated controls (59). In 2007, a 3-yr randomized controlled study was conducted, enrolling 30 JIA patients with a growth delay on corticosteroid therapy for 12–15 mo (58). Such children were treated with daily injections of rhGH at high doses (0.07 mg/kg/d) or no therapy (58). A larger mean increase in HSDS was observed in treated patients (+0.37 +/– 1.5 SDS) than controls (–0.96 +/– 1.2 SDS), whereas mean height velocity returned to normal within the first year of treatment and remained normal after the drug was discontinued. Normalized height velocity and increased HSDS in rhGH-treated patients compared with controls were demonstrated in this study, although significant changes in growth velocity did not differ between the groups at the end of the study (58). Interestingly, up to 85% of treated patients reached their adjusted mid-parental height compared to 22% of controls, suggesting a beneficial role for rhGH on final height in adult age (58, 66). In addition, a greater increase in mean lean mass was evident in treated patients, whereas fat mass and bone mineralization were not significantly different between the two groups (58). However, the study was not blinded; only patients with systemic or polyarticular forms were included, and those with other severe growth-affecting conditions or diabetes mellitus were excluded (66). Nevertheless, rhGH therapy may often only restore linear growth and avoid height loss, which typically results from the natural progression of the disease (62). Bechtold *et al*. have conducted a randomized controlled study to evaluate the efficacy of rhGH therapy in patients with glucocorticoid-dependent JIA (60). In this study, 31 children with both polyarticular and systemic JIA and growth delay were treated with rhGH at 0.33 mg/kg per wk for a mean of 6.7 yr. The study has demonstrated a better mean final height in treated children (–1.6 SDS) than in untreated controls (–3.4 SDS) (60). Children receiving rhGH therapy most frequently reached a final height within their target height (11/13) compared to untreated patients (4/18) (60). In 2009, Simon and Bechtold have investigated the effects of rhGH treatment on growth in children with JIA and concluded that rhGH therapy may reduce growth delay in affected patients, often resulting in an adult height that is similar to the

doi: 10.1297/cpe.33.2023-0036

genetically determined target height (64). Additional studies have indicated that rhGH therapy may boost growth rate, height, BMD, and bone mass (63). A recent study has evaluated growth outcomes in 53 JIA patients with a long history of glucocorticoid use; patients were treated with rhGH and enrolled in three prospective clinical trials between 1997 and 2002. The mean rhGH was 0.056 mg/kg/d for a median duration of 6.5 yr (minimum, 4.7 yr). Thus, although large patient variability was noted, the authors conclude that long-term rhGH therapy significantly improved growth in JIA patients (HSDS raised from –2.9 to –1.7 in adult age), but not sufficiently to achieve the genetic growth target. In addition, the most influential factors were age, height at rhGH initiation, and mean C-reactive protein levels during follow-up, and the outcome was worse in patients with severe inflammation (1, 4).

Delayed puberty in JIA: efficacy of rhGH therapy on pubertal growth

Delayed puberty is not commonly observed in patients with JIA and is often accompanied by a compromised pubertal growth spurt, resulting in impaired final adult height (4). A study by Bechtold *et al.* has aimed to compare pubertal growth in 34 JIA children treated with rhGH at 0.33 mg/kg/wk and 29 untreated JIA patients. In children who received treatment, the overall pubertal growth was 1.5 times higher than that in untreated patients, resulting in a significantly increased final height (**Table 3**) (67). Specifically, the mean total pubertal growth in GH-treated JIA patients was 21.1 cm (boys, 23.2 cm; girls, 19.8 cm), compared to 13.8 cm in controls (boys, 15.0 cm; girls, 12.5 cm), even if lower than that of healthy children (20–35 cm) (67). Treated JIA patients gained a mean of +1.16 HSDS throughout puberty and had a considerably greater ultimate height than controls. Hence, adult height was significantly higher in those who underwent GH treatment than in controls (–1.67 SDS vs –3.20 SDS) (67, 68). Growth response during puberty, evaluated as total pubertal growth, and differences in goal height at the beginning of puberty were significant predictors of ultimate height. According to Bechtold *et al.*, the age at onset of puberty was the most influential factor for total pubertal growth, and rhGH therapy should be started early to minimize the height deficit at the onset of puberty (67). In addition, for every 1-yr increase in age at puberty, height growth was decreased by 2.3 cm in the rhGH-treated group and by 4.2 cm in the control group throughout puberty, indicating that rhGH may partially counterbalance the unfavorable impact of pubertal delay on ultimate height (67). This is strongly consistent with the recommendation to reduce the height deficit in patients with a short JIA before puberty. A promising therapeutic strategy may consist in delaying pubertal onset with a gonadotropin-releasing hormone analog and promoting growth with high dose of rhGH (0.05 mg/kg/d) when the inflammatory state is lowered, as described in an intriguing study published in 2018 with a long-term follow-up of five extremely short children wit sJIA (69). A key factor that could make this strategy successful is the use of rhGH in the on-biological phase, once inflammation is controlled and high glucocorticoid doses are no longer required (69). In fact, it is known that in patients with JIA, a decrease in glucocorticoid dosage and the introduction of a biologic drug promote a slight increase in height velocity, which is not possible for clear catch-up growth (70, 71). In contrast, high doses of rhGH in a low-inflammatory state may trigger growth acceleration similar to that observed in GH-deficient individuals (4, 72). This is consistent with data suggesting that up to 18% of children with severe JIA may suffer from GH deficit, and with evidence showing that the time after a prolonged corticosteroid treatment is positive for height increase due to a relative glucocorticoid insufficiency (4, 60, 72). In recent years, the widespread use of new biological drugs has allowed the progressive withdrawal of systemic glucocorticoids and rhGH therapy in patients with JIA. Indeed, TNF-α and IL-6 inhibitors have been progressively more used in clinical practice, leading to a reduction of serious side effects, such as growth retardation and obesity, in children with JIA. However, contemporary literature on the biological era agrees that rhGH treatment provides good improvement in growth delay, with some variability (20).

Conclusions

High doses of rhGH administered to children with a long history of systemic glucocorticoid use in low inflammation settings may promote prepubescent growth and stature development. However, the effects of rhGH on JIA patients with short stature are not entirely understood and variable outcomes can occur, ranging from good growth reduction with growth delay to only small improvements. Patients receiving rhGH treatment have increased adult height, but are mostly insufficient to achieve their genetic potential in stature, and several studies have shown substantial heterogeneity. However, the increasing use of biological drugs has significantly decreased the use of systemic glucocorticoids, severely restricting adverse effects such as growth failure and subsequently reducing the need for rhGH in patients with JIA. Nonetheless, rhGH medication may be used to improve growth delay in patients with JIA and a long history of glucocorticoid use, although catch-up growth and target height remain challenging to achieve.

Conflict of interests: The authors have nothing to declare.

doi: 10.1297/cpe.33.2023-0036

Table 3. Positive and negative outcomes in juvenile idiopathic arthritis patients with growth delay treated with rhGH and effects on puberty and pubertal growth

Study	Interventions	Positive outcomes	Negative outcomes	Effects on puberty and pubertal growth
Butenandt *et al.*, 1979	20 children with growth failure and rheumatoid arthritis or Still's disease were treated with rhGH for up to 2 yr	Increased GV rate was observed in 12 patients	5 patients did not respond with better growth; GV decreased in 6 patients after rhGH was discontinued	During the second year of treatment the GV was slightly higher, possibly due to puberty. The increase in growth rate was generally much better during puberty
Svantesson *et al.*, 1991	6 children with juvenile chronic arthritis were treated with rhGH for up to 6 yr	The growth rate increased during the first year in 5 patients	1 patient showed no improvements	4 children entered puberty during the first year of treatment, and no adverse side effects were observed
Davies *et al.*, 1994	A group of children with persistently active juvenile chronic arthritis and growth delay, most of whom receiving steroid therapy, were treated with rhGH for 1 yr	There was a significant increase in height velocity in almost all children during the treatment period, especially those with mild to moderate disease activity, polyarticular disease, and those receiving high dose rhGH	Children with very active disease, systemic form, and those receiving low dose of rhGH had only a mild improvement	None
Davies *et al.*, 1997	18 prepubertal children with growth delay and juvenile rheumatoid arthritis were treated with rhGH for 1 yr	Height velocity and mean levels of insulin increased significantly	None	None
Touati *et al.*, 1998	14 sJIA children with growth delay were treated with rhGH for 1 yr	Mean GV in treated patients was higher than controls	Hyperinsulinemia and increased insulin resistance were observed; however, these results could be related also to glucocorticoid therapy. Furthermore, GV returned to pretreatment values 1 yr after the drug was discontinued, whereas after 2 yr HSDS was even lower than pre-treatment values	None
Simon *et al.*, 1999	14 children with growth delay, receiving steroid therapy for juvenile chronic arthritis were treated with rhGH for 1 yr	During the year of rhGH treatment, mean GV increased and mean fat mass decreased	Following the 1-yr rhGH treatment period, GV fell to pretreatment values, and the HSDS at the end of the second year was lower than before treatment. Weight and fat mass increased markedly after cessation of rhGH treatment.	None
Simon *et al.*, 2001	13 of the 14 patients of the previous study were treated again with rhGH for another 3-yr period	rhGH treatment strongly increased GV in such patients	rhGH treatment had a minor effect on HSDS, suggesting that these children could remain short when adults	None
Bechtold *et al.*, 2003	18 patients with sJIA and pJIA and growth delay were treated with rhGH for 4 yr	Mean improvement in height in the treated group was better than controls	None	None
Bechtold *et al.*, 2004	11 children with JIA were treated with rhGH for 4 yr	Volumetric bone mineral density increased significantly in treated patients as well as bone formation and resorption markers	None	None
Bechtold *et al.*, 2005	17 JIA children with growth delay were treated with rhGH for 4 yr	Treated JIA patients had significant higher bone mineral content	None	None
Simon *et al.*, 2007	30 sJIA and pJIA patients with growth delay on corticosteroid therapy were treated with rhGH for 3 yr	A larger mean increase in HSDS was observed in treated patients than controls. Treated patients reached their adjusted midparental height more than controls	Mean GV returned to normal within the first year of treatment and remained normal after the drug was discontinued. Significant changes in GV did not differ between groups at the end of the study	None
Bechtold *et al.*, 2007	13 pJIA and sJIA children with growth delay were treated with rhGH for a mean period of 6.7 yr	More rhGH-treated patients reached a final height within target height than untreated patients (11 of 13 vs 4 of 18)	2 treated patients did not reach a final height within target height	None
Bechtold *et al.*, 2012	34 JIA children were treated with rhGH to evaluate pubertal growth	Adult height with rhGH treatment was significantly higher compared to controls	None	Overall pubertal growth was higher in treated than untreated JIA patients, resulting in significantly increased final height. The mean total pubertal growth in rhGH-treated was lower than that of healthy children. The age at onset of puberty was the most influential factor for total pubertal growth, and rhGH therapy should be started early to minimize the height deficit at the outset of puberty
David *et al.*, 2017	Data from 58 JIA children (53 receiving rhGH for up to 7.9 yr) enrolled in three prospective clinical trials between 1997 and 2002 were analyzed	Significant independent determinants of growth outcome were age and height at rhGH initiation. In summary, long-term rhGH treatment significantly increased growth in JIA patients	rhGH did not often fully restore the genetic growth potential in JIA patients with growth delay	None

rhGH, recombinant human GH; JIA: juvenile idiopathic arthritis; pJIA, polyarticular JIA; sJIA, systemic JIA; GV, growth velocity; HSDS, height standard deviation.

doi: 10.1297/cpe.33.2023-0036

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doi: 10.1297/cpe.33.2023-0036