Growth and Chronic Disease

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Key Words

Acquired growth hormone resistance · Catch-up growth · Cystic fibrosis · Crohn's disease · Juvenile idiopathic arthritis · Delayed puberty · Growth failure/impairment · Skeletal growth · Somatic growth

Abstract

Growth impairment occurs with many chronic conditions. Cystic fibrosis, Crohn's disease and juvenile idiopathic arthritis are relatively common chronic diseases in childhood associated with substantial growth impairment. While growth failure may be the initial presenting feature of pathology, the pattern of growth is also a useful measure of disease severity and response to treatment. In addition to its diagnostic value, the resulting short stature cannot only be unacceptable to patients but can also have detrimental effects on the physical health of patients with conditions such as cystic fibrosis. Growth impairment in children with chronic disease is associated with disruption of the growth hormone (GH)–insulin-like growth factor (IGF) axis, and predominantly results from undernutrition, chronic inflammation and prolonged corticosteroid treatment. Undernutrition leads to major adaptations in the endocrine system geared towards conserving energy, diverting substrates away from growth and reproduction, and providing alternative sources of energy for critical body homeostasis. Although chronic inflammatory processes exacerbate undernutrition, proinflammatory cytokines such as interleukin-6, tumor necrosis factor- α and interleukin-1 β also adversely affect growth, independent of nutrition, by disrupting the integrity of the GH–IGF

axis and by direct local effects on growth plate chondrogenesis. These growth-regulating mechanisms are disturbed further by corticosteroids used in some chronic conditions for their anti-inflammatory and immunosuppressive properties. It is likely that the growth-suppressing processes slow growth plate senescence, and this in turn enables catch-up growth on recovery from chronic disease and withdrawal of corticosteroid treatment. Trials of recombinant human GH (rhGH) in patients with growth failure suggest improvement in linear growth as well as beneficial effects on body composition and clinical course. These have been of relatively short duration, and long-term benefits as well as the safety of rhGH need to be evaluated particularly when given concomitantly with corticosteroids.

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Introduction

Chronic disease adversely affects growth, and the resulting impairment in height may be transient or sustained depending on the nature and course of the illness (table 1). The impairment in linear growth can be further exaggerated by delayed puberty which is commonly associated with chronic disease. Deviations from the normal pattern of growth may be the first clues to pathology as in celiac disease, Crohn's disease [1, 2] or renal tubular acidosis. In children known to have a chronic illness, serial records of height/length and weight plotted on standard distance charts are vital for monitoring wellbeing, disease activity, adverse clinical events and response to

Table 1. Chronic conditions associated with growth impairment

Cystic fibrosis
Celiac disease
Crohn's disease
Chronic liver disease
Juvenile idiopathic arthritis
Chronic renal failure
Renal tubular acidosis
Congestive heart disease (large ventral septal defect)
Cyanotic heart disease (tetralogy of Fallot)
Human immunodeficiency virus infection
Asthma
Atopic dermatitis
Chronic hemolytic anemia (thalassemia major)
Long-term treatment with methylphenidate

treatment. Advances in management have altered the natural history of many conditions, reduced morbidity and improved survival. Where long-term remission of the primary disorder can be achieved, the outcome for growth and attainment of normal adult height are good. For children with refractory disease, impaired growth, short stature, delayed puberty and reduced adult height are increasingly highlighted as being problematic both physically and psychologically. This article presents an update on the general pathophysiology of impaired linear growth in chronic diseases and some key conditions in which substantial growth impairment occurs.

Pathophysiology of Growth Impairment in Chronic Disease

Acquired Growth Hormone Resistance

Growth in childhood is principally regulated by growth hormone (GH) and insulin-like growth factors (IGFs). Impaired growth in children with chronic disease is associated with a state of relative GH resistance, reflected by normal or high spontaneous and stimulated serum GH, low IGF-1 and low IGF-binding protein-3 (IGFBP-3) levels [3, 4]. GH resistance is further illustrated by the relatively small increase in IGF-1 and IGFBP-3 levels (31 and 14%, respectively) compared to age-matched controls (85 and 73%) with the IGF-1 generation test in children with systemic juvenile idiopathic arthritis (JIA) [4]. The major factors disrupting the integrity of the GH–IGF-1 axis in children with chronic disease are undernutrition, chronic inflammation and corticosteroid treatment.

Undernutrition

Undernutrition is common in chronic diseases and results from multiple interrelated factors, such as anorexia, limited nutrient intake, malabsorption and unmet increased energy requirements. Prolonged lack of macronutrients leads to adaptive mechanisms geared towards conserving energy, diverting substrates away from growth and reproduction, and providing alternative sources of energy for critical body homeostasis. One consequence is relative GH resistance, and both IGF-1 and IGFBP-3 levels correlate with measures of nutrition in chronic illness [3]. Energy deficiency also has an inhibitory effect on the hypothalamic–pituitary–reproductive axis so that there is decreased pulsatile secretion of gonadotropins, possibly from reduced activity of the hypothalamic gonadotropin-releasing hormone pulse generator, and this accounts for the delay in pubertal development [5].

The key regulator of body weight and signal of energy stores is leptin and it is thought to be the modulator that links the nutritional state with neuroendocrine function at the level of the hypothalamus and pituitary [6]. In malnourished children, circulating leptin levels are low and correlate with low insulin as well as low IGF-1 concentrations [7]. In addition to an influence on the GH–IGF-1 axis and gonadotropin secretion, low circulating leptin may be the trigger that activates the hypothalamic–pituitary–adrenal axis and increases cortisol levels [8]. Along with low insulin and high GH levels, elevated levels of cortisol facilitate the switch from carbohydrate to fat-based metabolism by augmenting fatty acid mobilization, proteolysis and gluconeogenesis. Hypercortisolemia may also contribute to the growth impairment associated with nutritional deprivation by inhibiting IGF-1-dependent actions of GH [7]. These adaptive endocrine effects from chronic undernutrition are partly reversed by nutritional recovery but sustained weight gain is required for linear growth to improve.

Chronic Inflammation

Chronic inflammation underlies the pathophysiology of a number of chronic diseases. The tissue damage that ensues triggers a host of events including increased energy expenditure, fat mobilization, proteolysis, negative nitrogen balance, gluconeogenesis, anorexia and weight loss. Growth impairment occurs even when nutrition is adequately supplemented and highlights a direct modulatory effect of the inflammatory process on the integrity of the GH–IGF-1 axis and the growth plate [9, 10]. Studies in animal models have unraveled some of the mechanisms which underlie this [11–14].

Interleukin-6 (IL-6), tumor necrosis factor- α (TNF- α) and interleukin-1 β (IL-1 β) play a key role in modifying the immune response to tissue injury and maintaining the chronic inflammatory response. In addition to high concentrations of these proinflammatory cytokines which correlate with disease activity [15, 16], levels of IGF-1 and IGFBP-3 are low in children with JIA [11], inflammatory bowel disease [16, 17], cystic fibrosis (CF) [3, 18].

Rats with experimental colitis demonstrate reduced linear growth in conjunction with increased concentrations of IL-6 [12] and significant improvements in growth when circulating IL-6 is blocked by antibody [14]. Transgenic mice chronically overexpressing IL-6 from birth also have markedly reduced growth and delayed puberty despite normal food intake [11]. Like children with chronic inflammation, these animals exhibit a state of GH resistance with normal or high GH levels and low levels of IGF-1 and IGFBP-3, and circulating IGF-1 and IGFBP-3 correlate inversely with IL-6 levels. These disease models suggest that low circulating IGFBP-3 results from IL-6-induced proteases and increased proteolysis. While the corollary to this is shortened half-life and accelerated clearance of IGF-1, decreased levels of IGF-1 may also be due to reduced hepatic synthesis through downregulation of the GH receptor [11, 13]. As GH-binding protein is generated from proteolytic cleavage of the GH receptor, low levels of GHBP in GH-resistant states consequent to chronic inflammation provide surrogate evidence for a GH receptor defect in children [19]. By downregulating GH-induced expression of the GH receptor gene in hepatocytes in vitro, IL-1 and TNF- α are also implicated in the dysregulation of the GH-IGF-1 system [20]. In addition, there is experimental evidence to suggest that these cytokines have local effects on the epiphyseal growth plate. IL-1 β and TNF- α act in synergy to disrupt longitudinal bone growth in fetal rat metatarsals by inhibiting chondrocyte proliferation and inducing apoptosis, and these effects are partially reversed by IGF-1, anti IL-1 β or anti-TNF- α [21].

Corticosteroid Treatment

The beneficial effects of corticosteroids as immunosuppressive and anti-inflammatory agents in the treatment of chronic diseases are accompanied by adverse effects on growth particularly when supra-physiological doses are administered long-term [22]. The mechanisms which lead to growth impairment are complex and include disruption of the GH-IGF axis at various levels, direct effects on the epiphyseal growth plate, and inhibi-

tory effects on gonadotropin secretion and adrenal steroid production [23].

Treatment with recombinant human GH (rhGH; 43 μ g/kg/day) has the potential to partly reverse the growth retardation from corticosteroids [24]. Retrospective analysis of 83 patients enrolled in the National Cooperative Growth Study who had received corticosteroid treatment for at least 12 months (mean prednisone equivalent dose 0.5 mg/kg/day) revealed short stature (mean height standard deviation score, SDS, -3.7) and growth failure (mean height velocity 3 cm/year) at baseline [24]. rhGH treatment resulted in an increase in levels of IGF-1 and IGFBP-3, and height velocity in the first 2 years (mean 6.3 cm/year) [24]. Although only one patient in this cohort had transient hyperglycemia, rhGH in children on long-term corticosteroid treatment warrants careful evaluation owing to potential adverse effects on carbohydrate metabolism, immunostimulatory effects and oncogenic potential [24].

Catch-Up Growth

There is potential for catch-up growth if the underlying growth-inhibiting condition can be suppressed or modified. Catch-up is seen as accelerated linear growth and normalization of height towards parental target. It is described to be complete or incomplete depending on whether the final height attained is within or below the genetic potential, the latter defined by mid-parental target height range [25]. The extent to which growth is impaired and consequently the degree and duration of catch-up are determined by the nature of the chronic disease, age at onset, age at diagnosis, severity of disease activity and duration, nature and success of interventions, skeletal maturation and pubertal stage. In turn, adult height attained depends on the severity of growth retardation during the active phase of the disease, the extent of catch-up growth after remission, and the timing and progression of puberty.

Catch-up growth is thought to be due to changes in the epiphyseal growth plate [26]. Linear growth is the result of endochondral ossification of long bones and vertebrae when cartilage is formed and remodeled into bone at the growth plate. Chondrogenesis comprises proliferation and hypertrophy of the growth plate chondrocytes and synthesis of cartilaginous matrix. It is regulated by systemic endocrine as well as local paracrine growth factors and IGF-1 acts as both [27]. With age, growth rate slows in conjunction with functional and structural changes in the growth plate. There is a steady decrease in the rate of chondrocyte proliferation, number of chondrocytes and

height of the growth plate, and linear growth finally stops with ossification of the growth plate [28]. This decline in growth rate is likely to be due to programmed mechanisms intrinsic to the growth plate and has been referred to as 'growth plate senescence' [29]. Recent work in rabbits suggests that chondrocytes in the resting zone of the growth plate serve as a pool of stem-like cells, and over time the number of cells as well as their proliferative capacity gradually decline [30]. Chronic disease, inflammation and corticosteroid treatment suppress the depletion and proliferation of cells, and thereby conserve the population and proliferative capacity of resting zone chondrocytes. Thus growth plate senescence is slowed and this allows for catch-up growth when the growth-inhibiting conditions are removed [26]. As bone age represents skeletal maturation, is considered a surrogate marker for growth plate senescence and is inversely related to linear growth potential, delayed bone age is a good predictor of catch-up growth [26].

Specific Chronic Diseases Associated with Substantial Growth Impairment

Cystic Fibrosis

CF is the commonest autosomal recessive condition in the Western world. It is a chronic progressive multisystem disease affecting exocrine glands, primarily the respiratory tract, pancreas and sweat glands. Patients have chronic respiratory infections and inflammation, pancreatic insufficiency, restricted quality of life and reduced life expectancy. Undernutrition results from malabsorption, anorexia, inadequate intake and increased requirements. Poor weight gain and linear growth occur from birth until the time of diagnosis, and failure to thrive is one of the classical presenting features of CF after the neonatal period [31]. The National Cystic Fibrosis Patient registry data revealed that approximately 40% of infants were below the 5th percentile for weight and length at diagnosis [31]. Owing to some catch-up growth associated with treatment interventions following diagnosis, a smaller proportion (20–25%) had weight and length below the 5th percentile at 2 years of age. However, despite aggressive management, patients with CF continue to have deficits in growth throughout childhood [31, 32]. In addition the growth impairment is more severe during adolescence owing to the progressive nature of the disease and increased morbidity with age. This is associated with a delay in skeletal maturation of up to 24 months and in onset of puberty in some patients [32]. Delayed

timing of the pubertal growth spurt is illustrated by a delay in age at peak height velocity by 9–10 months in male and 10–14 months in female patients [33, 34]. The greater the delay, the lower the peak height velocity, and patients with an extreme delay in puberty fail to demonstrate a significant growth spurt [33]. Thus adult height is significantly compromised and a cross-sectional survey of male and female patients in the UK found it was –1 and –0.5 SDS, respectively, below the reference population [32].

Aggressive nutritional intervention with a high fat, high calorie diet and a higher dose of pancreatic enzyme treatment has positive effects on growth and survival but is not sufficient to completely normalize weight and height [35]. In addition, despite failing to reach the critical body fat of 17% and weight of 47.8 kg, 20% of girls with CF achieve menarche [33, 34, 36]. These observations highlight that undernutrition is not the sole factor which contributes to impaired growth and delayed puberty in patients with CF. The impact of undernutrition and chronic inflammation on growth is further determined by age and mode of diagnosis, presentation with meconium ileus and need for surgery, nature of the therapeutic interventions (e.g. oral/inhaled corticosteroid treatment and nutritional management), and additional morbidity such as insulin deficiency and liver dysfunction. Children diagnosed early from neonatal screening have better growth than those diagnosed by a positive family history or clinical features of CF (mean age at diagnosis 13 vs. 100 weeks) [37]. In comparison to children diagnosed through neonatal screening before 12 weeks age and prior to the development of symptoms, those with meconium ileus necessitating surgery have significant growth impairment from birth with mean weight and height across all ages around the 30th percentiles [38].

Serial measurements in individual children with CF illustrate the longitudinal variations in growth and that periods of weight loss and growth failure are closely associated with adverse clinical events (mainly respiratory exacerbations and gastrointestinal complications) [39]. As might be expected, the severity of lung disease and airway colonization with *Pseudomonas aeruginosa* have a negative influence on growth and onset of puberty [33]. The observations of a relationship between plasma insulin area under curve (intravenous glucose tolerance test) and height velocity as well as serum IGFBP-3 suggests that declining insulin secretion is another factor which adversely affects growth by disturbing the GH-IGF-1 axis [40].

In patients with CF, weight gain and stature are closely related to lung function [41], and inadequate weight gain and poor linear growth have major repercussions on physical health, survival and effectiveness of treatment. In the context of GH resistance in these patients, the anabolic and growth-promoting effects of recombinant human IGF-1 (rhIGF-1) and rhGH treatment have been explored. One placebo-controlled trial of rhIGF-1 treatment for 6 months in 7 CF patients found an increase in IGF-1 levels but no effects on linear growth and weight gain with treatment [42]. Its tendency to induce hypoglycemia might be beneficial in patients with impaired glucose tolerance but detrimental when glucose homeostasis is normal.

rhGH treatment in children with CF has the potential to enhance linear growth and weight gain, and thereby improve lung function and slow disease progression. Indeed improvements in weight and height in prepubertal children with CF have been reported from randomized trials of rhGH treatment for up to 2 years [43–45]. The first randomized controlled trial over 12 months in 19 prepubertal patients, whose initial height and weight were ≤ 10 th percentile despite adequate calorie intake, documented greater height velocity (8.1 vs. 3.8 cm/year), weight velocity (4.5 vs. 2.1 kg/year) and an increase in lean mass (4.7 vs. 2.1 kg) in those who received rhGH 0.43 $\mu\text{g/kg/day}$ [43]. Comparable results were reported from randomized cross-over trials with rhGH for 6 months in 10 children [45] and for 12 months in 61 patients [44]. Pubertal adolescents studied retrospectively (25 patients, of whom 13 were given rhGH 0.43–0.5 $\mu\text{g/kg/day}$ for 12 months) also had better growth in height and weight with treatment [46]. The improvements in growth and lean mass with rhGH may be due to improved whole body protein catabolism and improved efficiency of whole body protein kinetics [43]. Although there was improved exercise tolerance [45], fewer hospitalizations [44, 46] and reduced outpatient intravenous antibiotic courses [43] with rhGH, the effects on lung function and clinical state in these studies are not consistent and may be explained by the relatively short duration of rhGH treatment as well as differences in management of patients at the various centers. None of the patients in these trials developed diabetes mellitus during treatment with rhGH [43, 45]. Long-term studies should provide evidence for the potential benefits of rhGH treatment on lung disease, body composition, bone density, adult height, quality of life and survival, as well as cost and safety, particularly for glucose tolerance.

Crohn's Disease

Crohn's disease and ulcerative colitis are the two most common forms of chronic inflammatory bowel disease in children. Inflammation commonly affects the small and/or large intestine, but can affect the entire gastrointestinal tract in Crohn's disease and is restricted to the large intestine in ulcerative colitis. Classical symptoms are chronic diarrhea, abdominal pain and weight loss, but the diarrhea is classically bloody in ulcerative colitis. Reduced height and weight velocities are common features of both conditions in the year preceding diagnosis. After diagnosis and initiation of treatment, growth impairment is common in children with Crohn's disease but unusual in ulcerative colitis [2, 47]. A large population-based series of children with Crohn's disease and ulcerative colitis found height SDSs of -0.5 and -0.1 , respectively, and height was less than the 3rd percentile for 13 and 3%, respectively, at diagnosis [46]. In Crohn's disease, growth failure may precede intestinal symptoms as well as weight loss and its pathological significance as the sole initial feature in children should not be undermined [1]. Delay in onset and progression of puberty are frequently seen particularly in prepubertal patients with active disease or frequent relapses.

The deficits in growth and delay in puberty are not fully reversed by adequate calorie intake. In addition to undernutrition, uncontrolled intestinal inflammation is important in the etiology of growth impairment and other contributing factors are duration of symptoms before diagnosis and thus delay in diagnosis, disease severity and location particularly in the jejunum [2, 47]. Deficits in attained adult height are seen in up to a third of the patients [48] and have been found to be related to height at diagnosis as well as the presence of jejunal disease [48]. Although polymorphisms in the *NOD2* gene are independent risk factors for susceptibility to Crohn's disease and are associated with disease severity, ileal involvement and the need for surgery, they do not appear to have a direct link with growth impairment [49].

Treatment strategies aimed to suppress inflammation and improve nutritional status include enteral nutrition with polymeric diet for widespread disease, intestinal resection for localized disease and monoclonal anti-TNF- α antibody infliximab. They result in increased circulating levels of IGF-1 and IGFBP-3 [17, 50, 51] and an acceleration in linear growth [17, 52]. Catch-up growth and improvement in final height are likely if the interventions are prior to or in early puberty [52].

There has been some attempt to investigate the potential benefits of rhGH treatment to reverse the catabolic

state of active Crohn's disease, enhance mucosal healing and improve linear growth [53]. While rhGH treatment (50 µg/kg/day) was associated with an increase in IGF-1 and IGFBP-3 levels over a brief duration of up to 2 years, no firm conclusions can be drawn from the small number of children studied.

Juvenile Idiopathic Arthritis

JIA replaces the previously used terms juvenile chronic arthritis and juvenile rheumatoid arthritis, and includes heterogeneous forms of chronic arthritis of unknown cause that begin before the age of 16 years and persist for more than 6 weeks [54]. The subtypes classified under JIA (systemic, oligo-, rheumatoid factor-positive poly-, rheumatoid factor-negative poly-, enthesitis-related, psoriatic and undifferentiated arthritis) have distinct features and varying spectrums of disease severity. Although uncommon at presentation, growth impairment is evident within a few years in patients with unremitting disease and is influenced by the duration of disease [55]. Deficits in height are greater in patients with systemic and rheumatoid factor-positive polyarticular arthritis than oligo- and rheumatoid factor-negative arthritis [55, 56]. Delayed puberty further compromises linear growth in these patients and greater growth impairment is observed during the pubertal years compared to before puberty (mean height SDS -0.71 vs. -0.1) [56].

In addition to disease subtype, course and duration, corticosteroid treatment further impairs growth and the onset of puberty in JIA. A mean loss of height of -2.7 SDS has been observed in the first year of the disease in patients receiving prednisone [57]. The adverse effect on height is influenced by the treatment duration especially if it is longer than 12 months. On discontinuing treatment, 70% showed some catch-up growth and although the mean adult height in this subgroup was better than in those without catch-up (-1.5 SDS compared to -3.6 SDS), a significant impairment persisted [57]. Overall, final height was less than -2 SDS in 40% of patients and below the target height in over 80% [57].

Trials of rhGH in selected children with persistently active JIA and severe growth failure have reported improvements in linear growth after 6 months of treatment [58] as well as a sustained effect for up to 4 years [59, 60]. Intervening with rhGH earlier on in the course of the disease is speculated to minimize the significant loss in height, especially in patients treated with corticosteroids [59]. A significant increase in height velocity compared to baseline but no change in height SDS were observed in the first 2 years in an open uncontrolled study in 13 ex-

ceptionally short corticosteroid-treated patients (mean height -4.6 SDS) [59]. Additional benefits of rhGH proposed from this study were an increase in lean mass and lumbar bone mineral density. In a recent study of 38 prepubertal children with severe systemic or polyarticular disease and treated with corticosteroids, 6 were identified to have GHD [60]. The 12 non-GHD patients treated with rhGH (47 µg/kg/day) were observed to have increase in IGF-1 and IGFBP-3 levels, height velocity and height SDS during 4 years of treatment (mean height SDS increased from -2.8 to -1.9 compared to decline from -2.3 to -3.0 SDS in the untreated patients) [60]. Whereas disease activity and the dose of prednisolone have a negative effect, the dose of rhGH has a positive effect on the growth response [60]. Although no adverse effects were observed in these patients, transient glucose intolerance with rhGH reported in a previous study highlights the need to evaluate safety long-term [59].

Effects on Growth of Anti-TNF-α Treatment

For Crohn's disease and JIA refractory to conventional treatment, anti-TNF-α agents can induce and maintain remission and reduce the need for corticosteroids. In addition to dampening the inflammatory process, these agents are also postulated to counteract the modulatory effect of proinflammatory cytokines on the GH-IGH-1 axis and to thereby enhance linear growth. Changes in linear growth have been described in an observational study of 32 children (age 4.7–17.3 years and mean height -0.4 SDS at diagnosis) with refractory Crohn's disease given infliximab. The mean height SDS prior to this treatment was -1.1 SDS. After a median of 26 months of infliximab treatment, prepubertal and early pubertal patients had a greater increase in mean height SDS compared to those in advanced stages of puberty (+0.5 vs. +0.2 SDS) [52]. Increased height velocity in the 1st year (mean 7.6 vs. 3.7 cm before treatment), catch-up growth after 2 years (mean height SDS -1.1 vs. -2.4 before treatment) and a significant increase in serum IGF-1 and IGFBP-3 levels have been reported from a study of 18 patients with refractory JIA given etanercept [61]. A further study in 71 patients (mean age 9.6 years, mean duration of JIA 5.7 years) suggested growth failure before the intervention was the strongest predictor of catch-up growth during 2 years of treatment with etanercept or infliximab [62]. While such anti-inflammatory treatments hold great promise for patients in the future in concurrently modifying the disease process, reducing associated morbidity and improving growth outcome, their long-term benefits and risks need to be explored.

Conclusion

Studies over the last decade have provided greater understanding of the etiology of growth impairment in chronic disease, in particular the molecular mechanisms which disrupt the integrity of the GH-IGF axis and cellular changes in the epiphyseal growth plate. Although advances in management have altered the natural history of many conditions, reduced morbidity and improved survival, significant growth impairment is still seen in patients with conditions such as CF, Crohn's disease and JIA. This can have detrimental effects on physical health, especially for patients with CF. Along with delayed puberty and the potential for short stature in adulthood,

growth impairment is also a psychological burden for patients with chronic disease. A treatment which has the potential to optimize growth in this context is rhGH. Trials of rhGH in selected patients with growth failure are thus far limited by the relatively short duration of treatment but suggest improvements in linear growth as well as beneficial effects on body composition and clinical course. The long-term safety of rhGH needs to be evaluated particularly when given concomitantly with corticosteroids. Although not yet extensively studied, new anti-TNF agents hold great promise in concurrently modifying the inflammatory process, reducing associated morbidity and improving growth outcome for patients with refractory Crohn's disease and JIA.

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