

# Managing idiopathic short stature: role of somatotropin (rDNA origin) for injection

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**Abstract:** Idiopathic short stature (ISS) is a term that describes short stature in children who do not have growth hormone (GH) deficiency and in whom the etiology of the short stature is not identified. Between 1985 and 2000, more than 40 studies were published regarding GH therapy for ISS. Only 12 of these had data to adult height, of which only 4 were controlled studies. A subsequent placebo-controlled study that followed subjects to adult height indicated that there was a gain of 3.7–7.5 cm in height with GH treatment. In 2003, the US Federal Drug Administration (FDA) approved GH for treatment of short stature. Even before FDA approval, patients with ISS made up about 20% of patients in GH databases, which is largely unchanged since FDA approval. There remains some controversy as to whether GH should be used to treat ISS. This controversy centers on the fact that there has been no definitive demonstration that short stature results in a disadvantage or problems with psychological adjustment, and thus, no demonstration that GH therapy results in improvement in quality of life.

**Keywords:** idiopathic short stature, ISS, growth hormone therapy, somatotropin, somatotropin, insulin-like growth factor I, IGF-1

## Introduction

Idiopathic short stature (ISS) is one of several terms that have been used to describe short stature in children who do not have growth hormone (GH) deficiency and in whom the etiology of their condition is not understood. Other terms that have been used in the past to describe these children, some overlapping those that describe ISS, include familial short stature, normal variant short stature, idiopathic growth failure, non-GH-deficient short stature, and nonendocrine short stature. Some patients with ISS have been diagnosed with GH neurosecretory dysfunction (ie, low spontaneous GH secretion) as a means of justifying GH therapy. All recognizable causes of short stature (ie, intrauterine growth retardation, genetic or syndromic causes of short stature, and psychosocial deprivation) should be ruled out before a diagnosis of ISS is made.<sup>1</sup> As a group, children with ISS do not achieve their adult height predictions, and many have adult heights that are quite short.<sup>2,3</sup> As more is understood about the causes of short stature, it is hoped that many of these children may eventually have a more definitive diagnosis. An example of this situation is a recent report of a child with ISS who was ultimately diagnosed with a deletion in exon 5 of the Short Homeobox X (SHOX) gene.<sup>4</sup>

## A short history of GH therapy

The first report on GH therapy for growth hormone deficiency (GHD) was produced in 1958.<sup>5</sup> The first GH preparations (somatotropin) used therapeutically were derived

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from human cadaver pituitaries. In the United States, human-derived growth hormone was produced and distributed by the National Institute of Health's (NIH) National Pituitary Agency. The preparation was in short supply, resulting in lower than ideal dosing and frequent drug holidays. Potential recipients were required to participate in a research protocol and, in order to ration the cadaveric GH, the diagnosis of GH-deficiency required that the patient have a peak GH level in response to provocative stimuli below a certain level. This requirement gradually increased in response to a better supply of cadaveric GH, starting at 5 ng/mL, then 7 ng/mL, and finally 10 ng/mL in the early 1980s. In 1985, this preparation was linked to a risk for Creutzfeldt-Jacob disease,<sup>6,7</sup> and its use was discontinued. In 1979, GH was produced in large quantities by expressing the human GH gene in *Escherichia coli*.<sup>8</sup> In 1985, Genentech Inc. (San Francisco, CA, USA) was approved by the Food and Drug Administration (FDA) to market recombinant human growth hormone (rhGH),<sup>9</sup> which was identical to human growth hormone, with the addition of a methionine as a necessary start signal for the bacteria to initiate protein synthesis. Use of methionyl GH did result in antibody production, but this was rarely associated with growth attenuation.<sup>10</sup> Present-day commercial preparations (somatropin) all have the identical 191-amino acid sequence of native human pituitary hormone.<sup>11</sup>

Initially, GH was injected intramuscularly. But, in the mid-1980s (about the time of introduction of rhGH), it was shown to be as effective if given as a subcutaneous injection,<sup>12</sup> which is the practice today. Early in its use, GH was given twice weekly, but this was increased to three times weekly when the higher frequency was shown to result in an increased growth response.<sup>13</sup> At about the time of the transition from cadaveric GH to rhGH, it was demonstrated that daily injections (6 or 7 per week) yielded an even better growth response than the three times per week schedule,<sup>14-17</sup> and daily administration is commonly used today.

## GH treatment of ISS

During the time of cadaveric growth hormone, usage was limited to GHD because of the scarcity of supply. However, even before the advent of rhGH, there was interest in investigating whether treatment of other conditions associated with short stature would increase adult stature. Between 1964 and 1971, there were a number of small studies that examined the treatment of non-GH-deficient short stature with GH.<sup>18</sup> In 1964, the National Institute of Child Health and Human Development (NICHD), a branch of the NIH, sponsored an international conference that recommended analysis of

GH treatment in non-GH-deficient conditions. In 1983, a conference sponsored by the NICHD, entitled International Conference on Uses and Abuses of Growth Hormone, brought up this topic, resulting in the following statement: "... there is an urgent need for therapeutic trials to determine the effect of growth hormone in short children who do not have a growth hormone deficiency". In 1987, a FDA committee recommended a placebo-controlled study of GH treatment for ISS that would follow subjects to adult height.

A placebo-controlled trial of treatment of children with ISS in collaboration with Eli Lilly (Indianapolis, IN, USA) and the NIH was carried out between 1988 and 2001. Data from this trial were presented to the NIH. In July 2003, the FDA approved the use of GH in children with ISS. They defined children with ISS as those having a height that was greater than 2.25 standard deviations (SD) below the mean (one of the inclusion criteria of the Eli Lilly/NIH collaborative trial), open epiphyses, a growth velocity that makes it unlikely that the child's adult height will be in the normal range (ie, within 2 SD of the mean), and a diagnostic evaluation that has excluded other causes associated with short stature, which would better be managed by observation or treatment by other means. One of the concerns has been the possibility of misdiagnosing and treating children for ISS who actually have constitutional delay in growth and maturation (CD), particularly if the child's bone age is delayed. Certainly, there are such patients. However, if the FDA guidelines are adhered to, a child who is more than 2.25 SD below the mean, and has a predicted adult height that is more than 2 SD below the mean, is probably more appropriately considered to have ISS than to be classified as having CD. There is evidence that adult height tends to be overpredicted, particularly in boys.<sup>19</sup>

According to a recent survey of pediatric endocrinologists, there is still not agreement as to whether or when children with ISS should be treated.<sup>20</sup> Most of the respondents to the survey agreed that there was a need for indication. Respondents were asked about the cut-off height of  $-2.25$  SD. 71% responded that it was appropriate, 21% thought it should be set higher, and 8% thought it should be set lower. When asked about factors contributing to willingness to prescribe (78% selected more than one response), 53% selected "patient expression of understanding potential risk and benefits", 32% selected "family insistence", 14% selected "family's desire to pay", and 7% selected "male gender". The case against treatment is that there is not a convincing body of evidence to indicate that short stature is actually a real problem, or that treatment (or taller stature) leads to any psychological benefit.<sup>21</sup> Treatment of

GHD is justified because it represents replacement of a missing hormone. On the side of treating ISS patients, Saenger<sup>22</sup> argues that the diagnosis of GHD is very difficult to make with certainty, and in the absence of meaning psychological outcome data, we should follow the recommendation of the American Academy of Pediatrics,<sup>23</sup> which recommends treatment of very short children whose ability to participate in basic activities of daily living is limited because of their short stature. One of the fears after ISS became an FDA-approved indication was that there would be a change in the paradigm determining which short children are treated (resulting in the treatment of many more children who were not as short). We compared demographic data in the National Cooperative Growth Study (NCGS) of children who were treated for ISS before 2003 and from 2003–2006 (ie, after FDA approval).<sup>24</sup> Although no major changes were seen, there was a very small decrease in the severity of the growth retardation at entry, and a slight increase in the treatment doses. Mean height velocities during treatment were the same before and after FDA approval.

## Efficacy of GH treatment in ISS

Children with ISS who are treated with GH are as short at the beginning of GH therapy as children with chronic renal insufficiency, Turner syndrome, or those who are born small for gestational age: that is, their heights before treatment average from  $-2.6$  SD to  $-2.9$  SD.<sup>25–29</sup> In this group of children, insulin-like growth factor-1 (IGF-1) levels are often normal. However, approximately 25% of them are low, suggesting that some children in this group may have GH-insensitivity. Many of the published studies of GH therapy in children with ISS have involved small sample sizes and did not have control groups (28 uncontrolled vs 10 with a control group).<sup>18</sup> Even with these limitations, a meta-analysis of these studies suggested that the overall height gain may have been from  $-3.0$  to  $-1.5$  SD with GH therapy,<sup>18</sup> which represents a height increase of 4–6 cm. In studies with a control group, it appeared that the control group also had an increase in height (consistent with a previous report of spontaneous growth in children with ISS),<sup>30</sup> but the treated group exceeded the control group by approximately 0.78 SD. Subsequent to this meta-analysis, results of a placebo-controlled study on the effect of GH therapy on adult height in peripubertal children with ISS demonstrated a height increase of 3.7–5.0 cm with GH therapy, despite a low dose of GH (0.22 mg/kg/week) and an injection schedule of three times per week.<sup>31</sup> A second study evaluating two treatment protocols demonstrated a dose effect with a dosage of 0.37 mg/kg/week resulting in

an increase in adult height of 7.2 cm compared with 5.4 cm in the group receiving only 0.24 mg/kg/week.<sup>32</sup> A recent report of comparison of two doses (0.23 and 0.47 mg/kg/week) of GH and an untreated population in a group of 177 children, most of whom had ISS, showed that there was a dose-dependent increase in adult height,<sup>33</sup> with a gain of about 1.5 SD in the group treated with the higher dose. An evaluation of data from children with ISS treated with GH, taken from a large GH database, showed that GH treatment resulted in an increase in height from  $-3.0$  to  $-1.2$  SD over the course of 7 years.<sup>26</sup> Factors that tend to predict a positive response to GH treatment include GH dose, degree of height deficit compared to parents' heights, young age, and first year height velocity.<sup>1,34</sup>

## Safety of GH treatment in ISS

An evaluation by Quigley et al<sup>35</sup> of safety data from the controlled trial of GH therapy of children with ISS<sup>31</sup> and the subsequent dose-response study,<sup>32</sup> as well as an evaluation of more than 8,000 ISS patients followed in a large post-marketing database for children treated with GH,<sup>26</sup> have shown that there are no safety issues in GH therapy different from those seen with treatment of GH deficiency.

## Psychosocial effect of treating ISS

It is assumed that short stature is associated with disadvantages and problems of psychological adjustment. Anecdotal reports include teasing, treating children in relation to their height rather than their age (juvenilization), and academic underachievement.<sup>36</sup> Some studies seem to confirm these notions,<sup>37–40</sup> while others have failed to demonstrate any disadvantage to short stature, including any problem with psychological adjustment.<sup>41–44</sup> In fact, Kranzler et al<sup>45</sup> evaluated 90 children who were sent to a stature clinic, and determined that they had normal psychological function without externalizing behavior problems, attention problems, or poor social skills, as had been previously reported.<sup>39,46,47</sup> Sandberg<sup>48</sup> reported that juvenilization does occur, but short stature is not associated with any social advantage. Balen et al<sup>49</sup> have suggested that patients referred for ISS seem to be more at risk for psychological problems than those who are not referred. Further, they indicate that, in addition to stature, there are other risk factors for psychological difficulty, including being juvenilized, being a boy, having low intelligence, having a younger but taller sibling, and being part of a family with low socioeconomic status. In light of this controversy, it is not surprising that it has been difficult to demonstrate that treatment of ISS (and short stature

in general) improves the quality of life of the individual. Many who treat children with ISS believe that by increasing adult height they are improving quality of life.<sup>50</sup> However, there is little objective data to support this notion.<sup>51</sup> In fact, the idea that short stature is a problem that can be addressed by GH treatment has been recently challenged in the popular press.<sup>52</sup> Recent reviews of available instruments for evaluating quality of life in children with GHD or ISS suggest that it should be possible to do the studies that could help answer whether treatment with GH has a positive or negative effect on quality of life.<sup>53,54</sup> The question of efficacy of GH treatment is particularly relevant because of the expense of GH therapy: perhaps as much as US\$52,634 per inch.<sup>55</sup> In spite of the difficulty of demonstrating that an increase in height also results in increased quality of life, children with ISS have been treated with GH since at least the inception of the NCGS in 1985, accounting for approximately 20% of those patients treated with GH.<sup>56</sup> Savage<sup>57</sup> has suggested that 1) if growth hormone therapy is restricted to a height threshold of  $-2.5$  or  $-3.0$  SD, and 2) if treatment would be limited to those children with slow height velocity, there might be fewer children who would experience a benefit in terms of taller stature than would have been attained without treatment. Further, Savage indicates that continued treatment should depend upon an increase in height velocity of at least 2 cm/year; if such an increase in height velocity does not occur, GH therapy should be discontinued.

## Evidence that some ISS cases may be caused by genetic mutations in GH-IGF-I axis

The GH receptor gene is the first gene that was associated with growth failure, possibly including ISS. It is well recognized that mutations in the GH receptor are responsible for complete GH-resistance (also known as GH-insensitivity syndrome), in which it has been possible to identify about 70%–80% of patients with low levels of GH binding protein (GHBP), which is the extracellular portion of the GH receptor. About 30 distinct mutations have been described.<sup>58</sup> Point mutations of the intracellular domain have also been described. However, most of these have also been found in subjects with normal height, and have been considered to be polymorphisms.<sup>59–61</sup> In order to determine whether partial GH-insensitivity was responsible for growth failure in children with ISS, data were analyzed from 773 children who were being treated with GH and were enrolled in a post-marketing surveillance project, the NCGS.<sup>62</sup> Patients enrolled

in this study had their levels of insuline-like growth factor 1 (IGF-1) and GHBP determined. In addition, these patients had been evaluated for GH-deficiency by their response to provocative stimuli. Patients with a GH response of more than 10 ng/mL were classified as having ISS. Children with ISS had GHBP levels more than 2 SD below the normal control patients, IGF-1 levels lower than controls (108–120  $\mu\text{g/L}$  vs 217–308  $\mu\text{g/L}$ ), but higher than in patients with GH-deficiency (84–99  $\mu\text{g/L}$ ), and mean 12 hour GH concentrations similar to controls (2.2  $\mu\text{g/L}$  vs 2.1–2.7  $\mu\text{g/L}$ ), but higher than in patients with GH-deficiency (1.2–1.4  $\mu\text{g/L}$ ). A subset of 14 of these patients (height more than 2.5 SD below mean, normal GH secretion, IGF-1 levels more than 2 SD below the mean, and serum concentrations of GHBP more than 2 SD below the mean) were further studied.<sup>63</sup> Of the 14 patients, four had mutations in the GH receptor (none of the 24 control subjects had mutations). One of these patients was a compound heterozygote with respect to the GH receptor. Due to these findings, it has been suggested that partial GH-insensitivity may be a cause of growth failure in some children with ISS. It may be possible that they would respond to GH at higher doses, or it may be that these children should be treated with IGF-1 instead of GH. Certainly, the case can be made that mutations in the GH receptor could explain ISS in some of the patients. In a recent study, a pool of 188 patients with ISS were analyzed for mutations in the GH receptor in order to determine if finding these mutations would predict response to therapy. Mutations were present in fewer than 5% of the patients, and discovery of single-gene defects did not predict treatment response.<sup>64</sup>

A second area of inquiry has been the SHOX gene. This gene resides on the distal ends of the short arms of chromosomes X and Y (in the pseudoautosomal region).<sup>65</sup> It appears that two functional copies of this gene are required for attainment of normal stature. Thus, absence of this gene from the loss of one or part of one X chromosome is associated with the short stature of Turner syndrome. Likewise, a mutation in one of the SHOX genes has been shown to be the cause of Leri-Weill syndrome, also known as dyschondrosteosis.<sup>66,67</sup> Screening of ISS patients for abnormalities in the SHOX gene has been a logical step. Rao<sup>65</sup> reported one patient with a functionally significant mutation in the SHOX gene out of 91 patients with ISS screened. Ogata<sup>68</sup> expanded the screen to include 400 patients with ISS, and found the aforementioned patient, along with 3 others with SHOX gene mutations. In an analysis of 68 patients with ISS, one female patient was identified who had a normal karyotype but a deletion of one SHOX allele.<sup>69</sup>

Other gene defects that have recently been discovered to result in growth failure include defects in the growth hormone receptor's intracellular signaling, in particular, signal transducer and activator of transcription 5b (STAT5b),<sup>70</sup> and a defect in the acid-labile subunit (ALS) of the circulating IGF-1 complex.<sup>71</sup> STAT5b-deficiency results in a phenotype of GH-insensitivity and immunodeficiency, while ALS-deficient patients have rather subtle growth failure, with height tracking at about or just below the 3rd centile. Neither of these defects has been identified in patients diagnosed as having ISS,<sup>64,72</sup> perhaps in part because they represent very rare disorders. Also, it has been pointed out that the phenotype of STAT5b-deficiency is that of severe GH-resistance, and it is not likely to be mistaken for ISS.<sup>64</sup> Perhaps the reason that ALS-deficiency has not been identified in a population of ISS patients is because the growth failure associated with it is too subtle for the affected child to be labeled as having ISS.

It appears that mutations in the GH receptor and the SHOX gene account for between 1% and 5% of the cases of growth failure that are designated ISS. As more patients with ISS are investigated, it is likely that additional genes responsible for growth failure will be discovered. As we recognize various causes for ISS, the pool of children with this designation should continue to decrease.

## IGF-1 treatment of ISS

In August and December of 2005, mecasermin IGF-1 (Increlex<sup>®</sup>, Tercica Inc, Brisbane, CA, USA) and mecasermin rinfabate IGF-1 (Insulin-like growth factor binding protein 3) (Iplex<sup>®</sup>, Inmed, Glen Allen, VA, USA) received approval from the FDA for the treatment of children with severe primary IGF-deficiency or children with a GH gene deletion who have developed neutralizing antibodies to GH. Mecasermin rinfabate is no longer available for treating conditions with short stature because of a legal agreement. These compounds have been shown to be effective in treating cases of GH-insensitivity<sup>73,74</sup> and IGF gene deletion.<sup>75</sup> In spite of ISS being an off-label use, there was a poster presentation of data from the Increlex Growth Forum Database Registry at the 2007 meeting of the Endocrine Society,<sup>76</sup> which showed that 17% of enrolled patients were identified as having ISS. Rosenbloom<sup>77</sup> has assented that "partial GH-insensitivity" is not evidence-based, but represents an attempt by the manufacturer to promote use of their product by a wider market than the rather small number of patients with true GH-insensitivity.<sup>77</sup> Because of the paucity of published data regarding the treatment of ISS (or partial GH-insensitivity), the role of treatment of ISS with IGF-1 remains to be determined.<sup>78,79</sup>

Treatment of GH receptor-deficiency with IGF-1 has resulted in a number of mild to moderate adverse events. Most commonly reported adverse events have included pain at the injection site and headaches. Data from a European study indicate that these events occur during the first month of treatment and then improve.<sup>80</sup> Other adverse events that have been reported following IGF-1 therapy have included lipohypertrophy at the injection site, papilloedema related to increased intracranial hypertension, and facial nerve paralysis.<sup>81,82</sup> With these events, symptoms resolved after interrupting treatment and re-starting with a lower dose.<sup>80,83</sup>

A second concern has been hypoglycemia, which occurred in some of the patients receiving IGF-1, but only rarely resulted in seizures.<sup>73,84</sup> This problem was lessened by administering the IGF-1 dose with meals, and hypoglycemia was usually a problem when there was an intercurrent illness resulting in loss of appetite.

Another effect of IGF-1 therapy has been the growth of lymphoid tissue, in particular, splenic enlargement and tonsillar hypertrophy. Renal size also increased, but renal function remained normal.<sup>73</sup> There were changes in facial appearance, with coarsening of features and an increase in hair growth, which were most noticeable during puberty. A complex of IGF-1 and IGFBP-3 appears to prolong the half-life and might counteract acute adverse events, particularly hypoglycemia associated with administration of IGF-1.

A recent report of treatment of 136 short children (presumable ISS) with IGF-1<sup>85</sup> showed that there was a statistically significantly increased growth velocity in the groups receiving 80 or 120 µg/kg twice daily vs a non-treated control group. However, there were significant reports of adverse events in the group: headaches 38%, vomiting 25%, and hypoglycemia 14%; in fact, six subjects withdrew because of adverse events. In an accompanying editorial, Rosenbloom and Rivkees<sup>86</sup> question whether there is adequate growth promotion to justify the apparent risks of treating with IGF-1 in this population.

## Other approaches to treatment of ISS

### LHRH agonists

It is well-recognized that treatment of early-onset precocious puberty with luteinizing hormone-releasing hormone (LHRH) agonists such as gonadotropin-releasing hormone agonist (GnRHa) allows adult height to approach target height.<sup>87</sup> It has been postulated that GH may hasten the

progression of puberty, and that the addition of GnRHa treatment may permit further growth in children with ISS. Kamp et al demonstrated that the addition of GnRHa to GH therapy in children with ISS or intrauterine growth restriction resulted in an increase in predicted adult height of 8.0 cm in girls and 10.4 cm in boys.<sup>88</sup> A prospective study comparing treatment of normal short girls with GH alone or with GH plus GnRHa suggested that while GH alone resulted in an increase in predicted adult height, the addition of GnRHa combined with GH resulted in an even greater increase in predicted adult height.<sup>89</sup> The evaluation of two large GH registry databases,<sup>90</sup> GH prediction models,<sup>90</sup> and a recent report of lack of efficacy in increasing adult height when treatment is initiated after the age of 7–8 years<sup>91</sup> do not support the success of this treatment. At present, there are no universally agreed upon guidelines for the use of GnRHa with (or without) GH in children with ISS. Thus, this therapy is still considered experimental.

## Aromatase inhibitors

A recent study has demonstrated a 5.9 cm increase in predicted adult height in boys with ISS using an inhibitor of aromatase (letrozole) without GH treatment for 24 months.<sup>92</sup> The same group has reported a similar finding in boys with constitutional delay treated to near adult height with letrozole.<sup>93</sup> The group receiving letrozole reached a near adult height which was 6.7 cm taller than those who did not. Although these reports appear quite promising, further studies carried out to adult height, with a careful evaluation of safety, are needed before this therapy can be adopted in a clinical setting.<sup>87</sup>

## Conclusion

ISS describes a group of children who are very short (more than 2 SD below the mean) and who are not GH-deficient. As early as 1983, there was interest in determining whether treating these children increased their adult height. Between 1985 and 2000, there were more than 40 studies published on the treatment of ISS. Most involved small patient populations, only 12 had adult height data, and only four were controlled. A controlled study was undertaken between the NHI and Eli Lilly. Subsequently, that study demonstrated an increase in adult height from 3.7–7.5 cm (1.5–3 inches) with GH treatment.<sup>31,32</sup> The FDA approved the ISS indication in July 2003. An analysis of the data from a large registry of patients receiving GH demonstrated a similar response to therapy and no differences in safety than for the treatment of GH-deficiency. Genetic explanations for ISS have occurred

in approximately 5% of the patients evaluated, including genetic mutations of the GH-IGF-1 axis, including STAT5b mutations, SHOX gene mutations, and ALS mutations. With time, there will likely be a larger group of patients in which the etiology of their short stature is elucidated. There are few data regarding whether a psychological advantage is gained by patients with ISS treated with GH. Other approaches to treating ISS include treating with IGF-1 (alone or in combination with GH), which has the added risk of adverse events, or delaying puberty with LHRH agonists or aromatase inhibitor. Both of the latter approaches are still in experimental stages.

## Disclosures

The authors reports no conflicts of interest in this work.

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