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Sermorelin

A Review of its Use in the Diagnosis and Treatment of Children with Idiopathic Growth Hormone Deficiency

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Data Selection

Sources: Medical literature published in any language since 1966 on sermorelin, identified using AdisBase (a proprietary database of Adis International, Auckland, New Zealand), Medline and EMBASE. Additional references were identified from the reference lists of published articles. Bibliographical information, including contributory unpublished data, was also requested from the company developing the drug.

Search strategy: AdisBase search terms were 'sermorelin', 'GHRH', 'GHRH-1-29-NH2', 'GHRF-1-29-NH2', 'HGRF-1-29-NH2', and 'GRF-1-29-NH2'. Medline and EMBASE search terms were 'sermorelin', 'GHRH', 'GHRH-1-29-NH2', 'GHRF-1-29-NH2', 'HGRF-1-29-NH2', and 'GRF-1-29-NH2'. Searches were last updated 11 June 1999.

Selection: Studies in patients with growth hormone deficiency who received intravenous or subcutaneous sermorelin. Inclusion of studies was based mainly on the methods section of the trials. When available, large, well controlled trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

Index terms: Sermorelin, growth hormone deficiency, pharmacokinetics, pharmacodynamics, tolerability, dosage and administration, therapeutic use.

Contents

Summary

Abstract

Sermorelin, a 29 amino acid analogue of human growth hormone-releasing hormone (GHRH), is the shortest synthetic peptide with full biological activity of GHRH. Intravenous and subcutaneous sermorelin specifically stimulate growth hormone secretion from the anterior pituitary.

Hormone responses to intravenous sermorelin 1 μg/kg bodyweight appear to be a rapid and relatively specific test for the diagnosis of growth hormone deficiency. False positive growth hormone responses are observed in fewer children without growth hormone deficiency after sermorelin than after other provocative tests. Adult data indicate that the combination of intravenous sermorelin and arginine is a more specific test and this merits evaluation in children with growth hormone deficiency. However, normal growth hormone responses to intravenous sermorelin cannot exclude growth hormone deficiency due to a hypothalamic deficit: subnormal growth hormone response to other provocative tests is needed to confirm the presence of disease in these patients.

Limited data indicate that once daily subcutaneous sermorelin 30 μg/kg bodyweight given at bedtime is effective in treating some prepubertal children with idiopathic growth hormone deficiency. Significant increases in height velocity were sustained during 12 months' treatment with sermorelin and data in a few children suggest the effect is maintained for 36 months of continued treatment. Sermorelin induced catch-up growth in the majority of growth hormone-deficient children. Slow growing, shorter children with delayed bone and height age appear to have a good response to treatment with sermorelin. The effect of long term treatment with once daily subcutaneous sermorelin 30 μg/kg bodyweight on final adult height is yet to be determined.

The effects of the recommended dosage of sermorelin have not been directly compared with those of somatropin. However, increases in height velocity from baseline values with subcutaneous sermorelin 30 μg/kg bodyweight per day, given as continuous infusion or as 3 divided doses, were less than those in children receiving once daily subcutaneous somatropin 30 μg/kg bodyweight.

Intravenous single dose and repeated once daily subcutaneous doses of

sermorelin are well tolerated. Transient facial flushing and pain at injection site were the most commonly reported adverse events.

Conclusions: Sermorelin is a well tolerated analogue of GHRH which is suitable for use as a provocative test of growth hormone deficiency when given as a single intravenous 1 μg/kg bodyweight dose in conjunction with conventional tests. Limited data suggest that once daily subcutaneous sermorelin 30 μg/kg bodyweight is effective in promoting growth in some prepubertal children with idiopathic growth hormone deficiency.

1. Introduction

Sermorelin is a synthetic analogue of growth hormone-releasing hormone (GHRH). Sermorelin contains the first 29 residues of the 44 amino acid native GHRH(1-44) which is reportedly the minimum required for complete biological activity.[1] This article reviews the pharmacology of sermorelin and examines its role in the diagnosis and treatment of children with idiopathic growth hormone deficiency. Since the majority (75 to 80%) of patients with idiopathic growth hormone deficiency have a deficit in hypothalamic GHRH synthesis or release rather than in growth hormone itself,[2] treatment with sermorelin appears to be a logical approach in the management of these patients.

2. Overview of Growth Hormone Deficiency in Children

2.1 Physiology of Growth Hormone

The physiological effects of growth hormone include positive influences on skeletal growth, such as stimulation of growth of bone, cartilage and connective tissue, and important effects on the metabolism of protein, fat, carbohydrates and minerals (table I).

The most abundant growth hormone isoform in the somatotroph cells of the anterior pituitary is the 191 amino acid peptide which has a molecular mass of 22 kDa (22K).[4] The 20 kDa (20K) isoform is reported to be the second most abundant isoform of pituitary growth hormone,[4] and mean basal serum concentrations of 22K and 20K were 2.4 and 0.15 μg/L, respectively, in 83 healthy boys and 2.5 and 0.13 μg/L, respectively, in 79 healthy girls.[5] Although the biological significance of other isoforms of growth hormone with molecular masses of 27, 17 and 5 kDa is unclear, increased proportion of circulating non-22K growth hormone isoforms may affect growth.[6]

Growth hormone secretion is regulated by 2 hypothalamic hormones: GHRH and somatostatin (fig. 1). GHRH stimulates the synthesis and release of all isoforms of growth hormone,[1] and the growth hormone secretory effects of GHRH are noncompetitively antagonised by somatostatin. In addition, a series of synthetic growth hormone secretagogues, derived from enkephalins and structurally unrelated to GHRH, with high potency in stimulating growth hormone release have also been characterised. The action of these growth hormone secretagogues on specific receptors located at the hypothalamus and the pituitary indicates that additional unelucidated mechanisms are involved in growth hormone secretion (for details see reviews[7-9]). Growth hormone secretion may also be induced by various physiological and pharmacological stimuli, by as yet uncharacterised mechanisms. While it has been reported that some stimuli

Table I. Physiological and metabolic effects of growth hormone[3]

↑ Skeletal growth (directly and indirectly via somatomedins)
Anabolic effects on skeletal and cardiac muscle
↓ Circulating levels of amino acids and urea (positive nitrogen balance)
↑ Amino acid transport and incorporation into proteins
↑ Mobilisation of fatty acids from adipose tissue
↑ Hepatic oxidation of fatty acids to ketones
↑ Blood glucose levels (↑ gluconeogenesis and ↓ glycolysis)
↑ Basal plasma insulin levels
↓ Insulin-stimulated lipogenesis
↑ Renal reabsorption of calcium, phosphate and sodium

↑ indicates increase; ↓ indicates decrease.

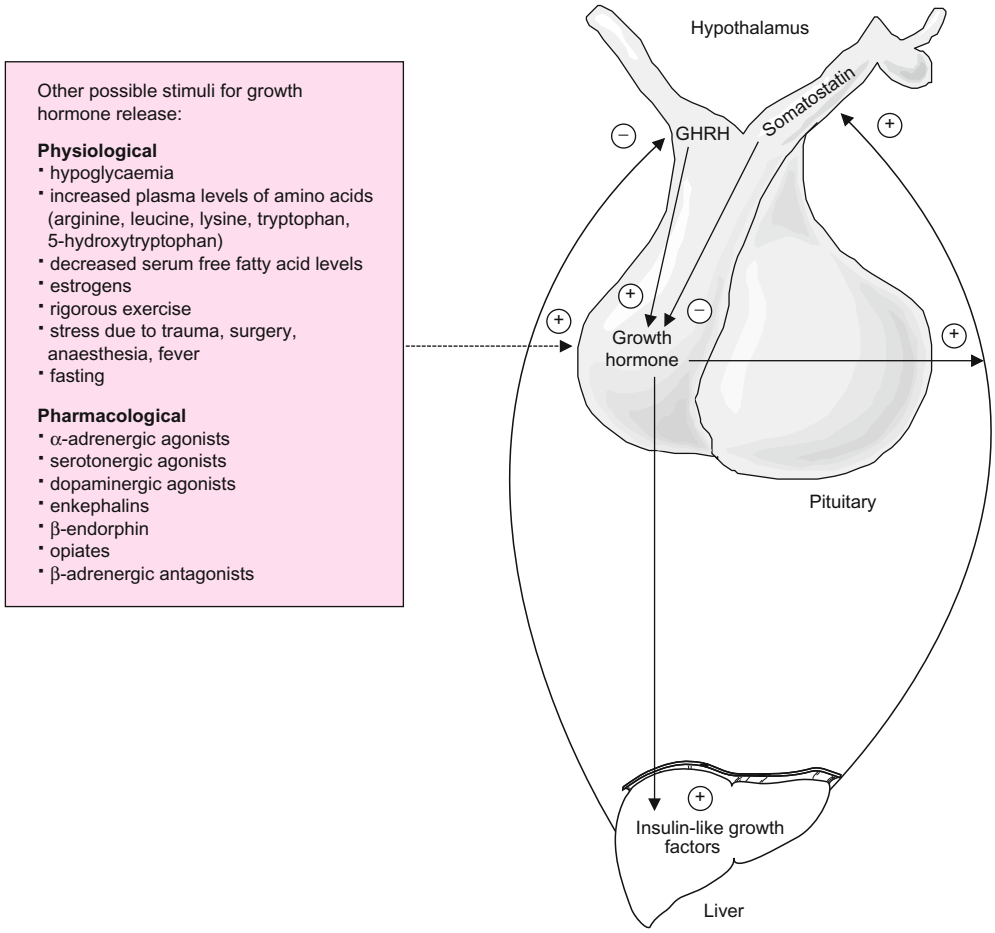

Fig. 1. Schematic representation of the regulation of growth hormone secretion. The synthesis and release of growth hormone from the somatotroph cells of the anterior pituitary are regulated by 2 hypothalamic hormones: growth hormone-releasing hormone (GHRH) and somatostatin. In addition, various physiological and pharmacological stimuli are capable of eliciting growth hormone release by uncharacterised mechanisms. The feedback mechanisms controlling growth hormone secretion are provided by growth hormone itself and insulin-like growth factors synthesised primarily in the liver.[3] + indicates stimulation; – indicates inhibition.

induce growth hormone secretion by inhibiting somatostatin release,[10-13] other data suggest endogenous GHRH-dependent mechanisms.[14]

Growth hormone itself and insulin-like growth factor (IGF)-I mediate the negative feedback regulation of pituitary growth hormone secretion by decreasing hypothalamic GHRH secretion, decreasing GHRH receptor density or increasing somatostatin release (for details see review by Chappel[15]).

2.2 Epidemiology, Aetiology and Presentation of Growth Hormone Deficiency

It has been estimated that severe growth hormone deficiency occurs in approximately 1 in 10 000 children worldwide, but growth failure due to partial growth hormone deficiency may be more common.[16] Indeed, a trial in 114 881 American children reported a growth hormone deficiency prevalence rate of at least 1 in 3480.[17]

Growth hormone deficiency may be congenital (with midline defects, with other pituitary hormone deficiencies, isolated growth hormone deficiency, pituitary agenesis) or acquired (associated with hypothalamic pituitary tumours, histiocytosis X, head injury, cranial irradiation, CNS vascular accidents, hydrocephalus, perinatal trauma and empty sella syndrome). Isolated idiopathic growth hormone deficiency is the most common type in childhood.[18] The focus of this review will be on the use of sermorelin in children with isolated idiopathic growth hormone deficiency.

Children with growth hormone deficiency have short stature and low growth velocity for age and pubertal stage. Specific signs in severe cases may include frontal bossing, depressed midfacial development, delayed dentition, central obesity and a high-pitched voice.[18,19] In combination with the above clinical features, children with growth hormone deficiency show delayed bone age on radiological examination and serum growth hormone levels <10 μg/L in response to provocative tests of growth hormone secretion, such as insulin, levodopa, arginine, glucagon, propranolol or clonidine challenge.[18] Peak growth hormone responses to conventional provocative tests between 5 to 10 μg/L and <5 μg/L indicate partial and complete growth hormone deficiency in children, respectively.[20]

3. Pharmacodynamic Properties

3.1 Effects on Growth Hormone

Intravenous or subcutaneous sermorelin specifically stimulates the release of growth hormone in animals and humans (table II). In the studies discussed in this section, growth hormone levels were measured in plasma or serum and reported in units of micrograms per litre (μg/L) or milliunits per litre (mU/L). For uniformity, results expressed as mU/L have been converted to μg/L using a conversion of 3 mU/L equal to 1 μg/L. Sermorelin binds

Table II. Overview of the effects of sermorelin on growth hormone (GH) secretion

Animal and *in vitro* studies
Sermorelin binds at growth hormone-releasing hormone (GHRH) binding sites in rat adenopituitary *in vitro*[21]
Single dose intravenous sermorelin 1 μg/100g bodyweight significantly increased serum GH levels within 5 minutes from pretreatment values in sham-operated rats (mean peak 560 *vs* 36.5 μg/L, $p < 0.001$)[22]
Serum GH levels remained below measurable levels before and after intravenous sermorelin 1 μg/100g bodyweight in hypophysectomised rats[22]
After 5 days, once daily sermorelin 0.22 to 6 μg/kg bodyweight was as effective as human GHRH(1-44) 0.34 to 9 μg/kg bodyweight in stimulating GH secretion in heifers (mean peak 73 *vs* 74 μg/L) and pigs (mean peak 40 *vs* 50 μg/L)[23]
12 days' administration of pulsed (1μg every 3 hours) intravenous sermorelin led to greater increases in plasma GH levels, total body weight and tibial growth in normal and GHRH-deficient rats versus saline-treated animals[24]
Continuous intravenous sermorelin 8 μg/day administration for 12 days did not stimulate GH levels or growth in normal and GHRH-deficient rats versus saline-treated animals[24]
Studies in healthy volunteers
Dose-dependent increase in peak and integrated GH levels[a] after intravenous sermorelin administered at a total dose of 10 to 100μg[25] or a dose of 0.25 to 4[26] or 0.015 to 0.5 μg/kg bodyweight[27]
Wide range of peak GH levels[a] after single doses of intravenous sermorelin 1 μg/kg bodyweight[26] and 100μg[28,29]
Subcutaneous sermorelin 3 μg/kg bodyweight increases mean peak serum GH levels versus pretreatment levels (3.83 *vs* ≤0.3 μg/L[b])[30]
Similar peak serum GH levels after an intravenous bolus dose (1 μg/kg bodyweight) of GHRH(1-40) or sermorelin (median values of 34.3 and 40.8 μg/L, respectively)[31]
Difference in peak serum GH levels after a 10μg intravenous dose of sermorelin or GHRH(1-40) was not significant (11.38 *vs* 5.56 μg/L[b])[25]
GH levels[a] peak 15 to 90 minutes after intravenous[25,27,29,32] or subcutaneous[30] sermorelin and return to near baseline values in 2[25,30,32] to 3 hours[27]

a In serum or plasma.

b Values estimated from graph.

to GHRH binding sites in rat adenopituitary *in vitro*.[21] Intravenous sermorelin 1μg per 100g of bodyweight significantly increased serum growth hormone levels from pretreatment values in sham-operated rats but not in hypophysectomised animals, indicating that the drug stimulates release of growth hormone from the anterior pituitary.[22]

3.1.1 Intravenous and Subcutaneous Administration

In groups of 5 to 12 healthy adult volunteers growth hormone levels increase dose-dependently after intravenous sermorelin[25-27] (table II). Dose-dependent increases were observed after intravenous sermorelin in doses ranging from 0.5 to 10μg in 1 trial (fig. 2), but the same investigators reported no significant difference in mean peak serum growth hormone levels after intravenous sermorelin 10 or 100μg in another trial (8 *vs* 8.7 μg/L), suggesting a plateau was reached with the 10μg dose.[28] However, a significant ($p < 0.01$) dose effect was reported in peak serum growth hormone responses (details not provided), and mean area under the serum growth hormone level-time curve (AUC) was 5.3-fold greater after a 100μg dose than after a 10μg dose (value estimated from graph), in a trial of intravenous sermorelin 10, 50 and 100μg.[25]

The dose-dependent increase in AUC tended to plateau at a dose of intravenous sermorelin 1 to 2 μg/kg bodyweight when doses of 0.25 to 4 μg/kg bodyweight were compared.[26]

As with intravenous administration, subcutaneously administered sermorelin 3 μg/kg bodyweight also increased serum growth hormone levels from pretreatment values in 6 healthy volunteers[30] (table II). Similarly, a single subcutaneous dose of sermorelin 30 μg/kg bodyweight led to a mean peak growth hormone level of 22.8 μg/L in 86 growth hormone-deficient children.[33]

3.1.2 Variations in Peak Growth Hormone Levels

Variations in peak plasma growth hormone levels after intravenous sermorelin may be related to spontaneous growth hormone secretion. Whereas mean peak plasma growth hormone levels of ≈26 μg/L (value estimated from graph) were reported in healthy volunteers after intravenous sermorelin 1 μg/kg bodyweight in one trial,[26] lower values were reported after intravenous sermorelin 100μg in other trials [8.7[28] and ≈7 μg/L (value estimated from graph)[29]]. A broad range of peak serum growth hormone levels (1.7 to 98.7 μg/L, mean 35.3 μg/L) has also been reported after intravenous sermorelin 1 μg/kg bodyweight in 36 short children.[34] Sermorelin-induced growth hormone release was correlated positively with spontaneous 24-hour growth hormone secretion, and was inversely correlated with spontaneous growth hormone secretion in the 3 hours preceding sermorelin administration.[34] The investigators suggest that variation in growth hormone response to sermorelin may be due to differences in the amount of releasable growth hormone present in the anterior pituitary at the time of sermorelin administration.

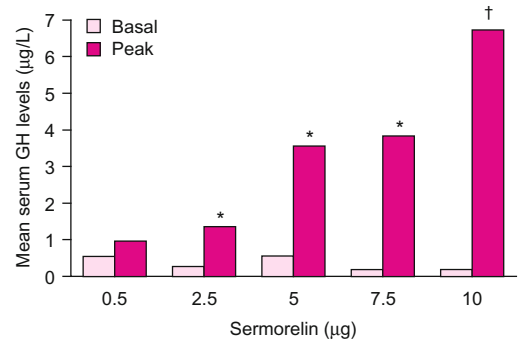

Fig. 2. Dose-dependent increase in serum growth hormone (GH) levels with sermorelin. Mean serum GH levels in 5 healthy adult male volunteers given increasing doses of intravenous sermorelin on 5 days at intervals of at least 1 week.[28] * indicates significant difference from the 0.5μg dose (p value not provided), † indicates significant difference from all other doses (p value not provided).

3.1.3 Effect of Repeated Subcutaneous Sermorelin on Growth Hormone Response

Administration of subcutaneous sermorelin 30 μg/kg bodyweight per day for 6 or 12 months may have a priming effect and may increase the responsiveness of pituitary somatotrophs to intravenous sermorelin in children with growth hormone defi-

ciency. Serum growth hormone levels in response to a single dose of intravenous sermorelin 1 μg/kg bodyweight were measured twice, once before and once after 6 months' treatment with subcutaneous sermorelin 30 (n = 15) or 60 μg/kg bodyweight per day (n = 12), in children with growth hormone deficiency.[35] Whereas serum growth hormone response to intravenous sermorelin remained unchanged from pretreatment values after subcutaneous sermorelin 60 μg/kg bodyweight per day, it significantly increased from pretreatment values in recipients of subcutaneous sermorelin 30 μg/kg bodyweight per day [≈14.9 *vs* ≈22.3 μg/L, p = 0.02 (values estimated from graph)].[35] Serum growth hormone responses to sermorelin were estimated before and after 12 months' treatment with once daily subcutaneous sermorelin 30 μg/kg bodyweight in another trial in 56 growth hormone-deficient children.[36] Peak growth hormone responses to a single dose of subcutaneous (30 μg/kg bodyweight) or intravenous (1 μg/kg bodyweight) sermorelin after the 12 months' treatment were significantly higher than pretreatment values: after subcutaneous sermorelin ≈23 *vs* ≈30 μg/L, $p \leq 0.02$ (values estimated from graph) and after intravenous sermorelin ≈23 *vs* ≈38 μg/L, $p \leq 0.01$ (values estimated from graph).[36]

It has been hypothesised that long term administration of GHRH may increase the number, duration and amplitude of growth hormone pulses from the pituitary somatotrophs. The postulated mechanisms for increased growth hormone release after long term treatment with sermorelin include one or more of the following: increased endogenous GHRH pulse amplitude, increased pituitary responsiveness to GHRH, increased releasable stores of growth hormone or decreased somatostatin tone (reviewed by Chappel[15]). At a molecular level, GHRH increases Ca^{2+} and Na^{+} conductance across somatotroph cell membranes, and it is proposed that this may increase electrical 'pacemaker' activity and also cause synchronisation of growth hormone-secreting cells (see review by Chappel[15] for details). However, currently there is no clinical evidence for these phenomena.

3.1.4 Effects of Repeated Subcutaneous Somatropin on Growth Hormone Response

In contrast with the effects of long term sermorelin, 6 months' treatment with somatropin appears to desensitise the somatotrophs to the action of GHRH. Serum growth hormone response to intravenous sermorelin 1 μg/kg bodyweight in 16 growth hormone-deficient children receiving 6 months' treatment with subcutaneous somatropin 30 μg/kg bodyweight per day was significantly lower than pretreatment values (≈16.5 *vs* ≈9 μg/L, p = 0.05, values estimated from graph), and also significantly ($p \leq 0.03$) lower than those in subcutaneous sermorelin recipients (30 or 60 μg/kg bodyweight per day for 6 months).[35]

3.1.5 Comparisons with Other Forms of GHRH

Sermorelin is as effective as the native forms of GHRH in stimulating growth hormone release. Similar peak serum growth hormone levels were reported after a single 1 μg/kg bodyweight intravenous dose of sermorelin or GHRH(1-40) in 11 healthy volunteers[31] (table II). Similarly in another trial in 5 healthy volunteers, the difference in mean peak serum growth hormone levels after a single 10μg intravenous dose of sermorelin or GHRH(1-40) was not statistically significant[25] (table II).

Furthermore, analysis of the peak and integrated growth hormone responses with sermorelin revealed half maximal growth hormone stimulation at a dose of 0.23 to 0.28 μg/kg bodyweight,[27] which is similar to that reported with GHRH(1-40) or GHRH(1-44) in other trials (0.33 to 0.4 μg/kg bodyweight),[37-39] and indicates similar molar potency of sermorelin, GHRH(1-40) and GHRH(1-44).[27]

The growth hormone-releasing activity of sermorelin has been compared with that of similar dosages by weight of other synthetic GHRH analogues in 4 small trials (n = 5 to 6 healthy volunteers per trial).[25,27,30,32] In general, the growth hormone-releasing activity of intravenous sermorelin was similar to[25] or less than[27] that of intravenous *D*-Ala^2-GHRH(1-29) and less than that of intravenous growth hormone-releasing pep-

tide-2.[32] Subcutaneous sermorelin was as effective as subcutaneous Ac-*D*-Tyr[1],*D*-Ala[2]-GHRH(1-29) in stimulating growth hormone secretion.[30]

3.2 Other Effects

Glucose-induced insulin release from cultured rat islets was unchanged by sermorelin *in vitro*, and a single dose of intravenous sermorelin 1 μg per 100g of bodyweight did not alter serum insulin or glucose levels in normal and hypophysectomised rats.[22]

Sermorelin administration does not influence other anterior pituitary hormone levels in healthy volunteers. Single intravenous doses of sermorelin 100μg[29] or 0.015 to 0.5 μg/kg bodyweight[27] did not affect plasma levels of luteinising hormone, thyrotropin, corticotropin, hydrocortisone or follicle stimulating hormone compared with levels in saline-treated controls in 2 trials in 9[29] and 5[27] healthy volunteers. Although plasma prolactin levels at 15 minutes were significantly ($p < 0.02$) higher in sermorelin recipients than in saline recipients in one trial, there was no difference in the integrated prolactin response in the 2 groups of volunteers[29] and plasma prolactin levels were unaltered from baseline values by sermorelin in the other trial.[27]

The effects of long term treatment with sermorelin on thyroid function are currently unclear. After 12 months' treatment with once daily subcutaneous sermorelin 30 μg/kg bodyweight in 101 prepubertal children with growth hormone deficiency and normal thyroid function tests at baseline,[33] there was a trend towards lower thyroxine, tri-iodothyronine and thyroid stimulating hormone levels but all mean levels remained within the normal range, and hypothyroidism was reported in 5 children. Overall, hypothyroidism has been reported in up to 6.5% of sermorelin recipients in clinical trials (section 6.1).

4. Pharmacokinetic Properties

There are no reliable data on the pharmacokinetic properties of sermorelin in children with idiopathic growth hormone deficiency. Although sermorelin levels, in serum[40] or in plasma,[35] were estimated in 2 trials in children with idiopathic growth hormone deficiency receiving subcutaneous sermorelin 30 μg/kg bodyweight per day, the results obtained were unreliable because immunoreactive fragments of the peptide and anti-GHRH antibodies may have contributed to the estimated sermorelin levels.

The pharmacokinetic properties of sermorelin, after subcutaneous and intravenous administration, have been studied in 2 small trials (n = 5[30] and 12,[26] respectively) in healthy adult male volunteers. Additional relevant data regarding the relative bioavailability of subcutaneously administered sermorelin and the tissue distribution of the drug have been cited from studies in rats.[41-43]

4.1 Absorption and Distribution

Data from healthy adult volunteers indicate that sermorelin is rapidly absorbed after subcutaneous administration and plasma drug concentrations decline quickly after subcutaneous or intravenous administration (section 4.2). Peak plasma immunoreactive sermorelin concentrations (0.22 μg/L) were reached within 10 minutes after subcutaneous sermorelin 3 μg/kg bodyweight in 5 healthy volunteers.[30] Mean peak serum sermorelin concentrations were ≈6 μg/L (value estimated from graph) after a single dose of intravenous sermorelin 1 μg/kg bodyweight in 12 healthy volunteers.[26]

Data from rats indicate that sermorelin has low bioavailability after subcutaneous administration: this has been estimated to be 4[41] and 5.1%[42] compared with intravenous administration.

There is specific uptake of sermorelin in the pituitary and some tissues of the gastrointestinal tract after intravenous, subcutaneous or intraperitoneal administration in rats. Radioactivity in the pituitary, gastric antrum, duodenum and ileum after intravenous, subcutaneous or intraperitoneal administration of a single dose of radiolabelled ^{125}I-sermorelin (8×10^6 cpm/kg bodyweight) in rats was significantly ($p < 0.05$) greater in the absence than in the presence of unlabelled sermorelin 5 μg/kg bodyweight. This indicates active uptake of

the drug in these tissues. In contrast, other tissues such as the thyroid, parathyroid and gastric fundus did not show any active uptake of sermorelin.[43] No comparable information is available for humans.

4.2 Metabolism and Excretion

The liver is traditionally the major of site of proteolytic peptide inactivation in the body, but sermorelin may also be rapidly degraded to inactive metabolites by cleavage at Ala^2-Asp^3 by dipeptidylpeptidase IV in plasma (94% of sermorelin was degraded after 60 minutes' incubation with human plasma *in vitro*).[44] In addition, sermorelin may also be degraded by as yet uncharacterised trypsin-like enzymes in plasma.[44]

Sermorelin had an elimination half-life of 6.1 minutes after intravenous administration in healthy volunteers.[26] No drug could be detected in serum 15 to 20 minutes after intravenous administration.[26] Plasma immunoreactivity fell below 50% of maximal values within 33 minutes after a subcutaneous dose of sermorelin in healthy volunteers.[30]

5. Therapeutic Uses

5.1 Diagnosis of Growth Hormone Deficiency

The accuracy of an intravenous bolus dose of sermorelin 1 μg/kg bodyweight in diagnosing growth hormone deficiency has been assessed in one trial in 131 children and adolescents, aged between 8.4 and 13.6 years, who were previously diagnosed as having (n = 45) or not having (n = 86) growth hormone deficiency.[31] In this trial, idiopathic growth hormone deficiency had been defined as total (n = 36) or partial (n = 9) on the basis of peak serum growth hormone levels <7 μg/L and between 7 and 10 μg/L, respectively, in response to previous tests with insulin or arginine or both. Based on clinical and auxological data, diagnoses in children without growth hormone deficiency included constitutional variable stature [constitutional short stature (n = 17), constitutional tall stature (n = 12), variable with normal stature (n = 9)], constitutional delay of growth and adolescence (n = 18), intrauterine growth retardation (n = 10), dysmorphic short stature (n = 8), Turner's syndrome (n = 8), simple obesity (n = 3) and primary hypothyroidism (n = 1).[31]

Intravenous sermorelin 1 μg/kg bodyweight appeared to be a rapid and relatively specific test for the diagnosis of idiopathic growth hormone deficiency in children in 2 trials,[31,45] and peak serum growth hormone levels after sermorelin were related to the underlying pathology. Median peak serum growth hormone levels after intravenous sermorelin 1 μg/kg bodyweight in children with and without growth hormone deficiency are illustrated in figure 3. The ± 2 standard deviations range of serum growth hormone response after sermorelin administration in healthy children (constitutional variable stature) was 11.8 to 172.4 μg/L (median 45.3 μg/L).[31] Therefore, serum growth hormone responses to sermorelin <10 μg/L were considered below normal by the investigators.[31]

The median peak serum growth hormone levels in response to sermorelin was below the normal limit of 10 μg/L in the group of children with idio-

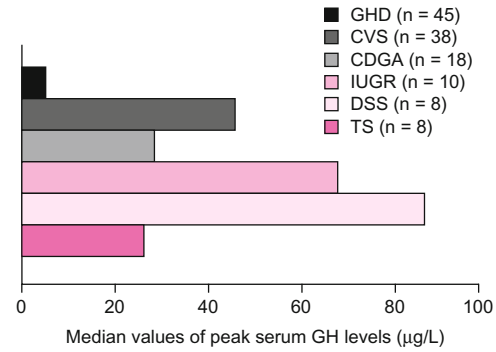

Fig. 3. Median growth hormone (GH) responses in children given intravenous sermorelin. Serum GH levels were estimated in children (mean ages between 8.4 and 13.6 years) with growth hormone deficiency (GHD), constitutional variable stature (CVS), constitutional delay of growth and adolescence (CDGA), intrauterine growth retardation (IUGR), dysmorphic short stature (DSS) or Turner's syndrome (TS) after an intravenous bolus dose of sermorelin 1 μg/kg bodyweight.[31]

pathic growth hormone deficiency (fig. 3). In the patient with hypothyroidism, serum growth hormone response to sermorelin before and after 6 weeks' treatment with thyroxine 100 μg/m^2 body surface area were 14.2 and 80.4 μg/L, respectively. Peak serum growth hormone levels were attained within 60 minutes after sermorelin administration in ≥92% of children with or without growth hormone deficiency, and showed a significant ($p < 0.05$) negative correlation with age in children with growth hormone deficiency.[31] The peak growth hormone response in 19 children with isolated growth hormone deficiency was greater than that in 26 children with multiple pituitary hormone deficiencies (median value ≈8 *vs* ≈5 μg/L, values estimated from graph).[31]

5.1.1 False Negative Results

Children with growth hormone deficiency due to hypothalamic deficits may have normal peak growth hormone levels in response to intravenous sermorelin. Peak serum growth hormone levels in response to sermorelin were <10 μg/L in 34 children, and between 10 and 40 μg/L in the remaining 11 growth hormone-deficient children (false negative result in 24.4% of children).[31] Similarly in children with growth hormone deficiency (diagnosed on the basis of clinical features and growth hormone responses <10 μg/L after insulin, levodopa, arginine or clonidine), growth hormone levels in response to intravenous sermorelin 1 μg/kg bodyweight were >10 μg/L in 3 trials[33,35,40] (section 5.2). Normal growth hormone responses to sermorelin in the presence of subnormal growth hormone responses to conventional provocative test in children with growth failure may indicate hypothalamic dysfunction as the cause of growth failure in these children. Therefore, serum growth hormone responses to sermorelin should be viewed together with the clinical features of growth failure and results of other provocative tests, such as basal serum IGF-I estimation, in the diagnosis of growth hormone deficiency.

Estimation of basal serum IGF-I levels may increase the sensitivity of the sermorelin test in diagnosing growth hormone deficiency. Basal serum IGF-I levels of 71.2 and 106.8 μg/L (converted from mU/L using a conversion of 178 μg/L equals 1 mU/L) were considered by the investigators to be the lowest normal limits in prepubertal and pubertal children, respectively.[31] In 11 children with idiopathic growth hormone deficiency who had false negative results in a sermorelin test, 8 had below normal basal serum IGF-I levels, and 3 had normal IGF-I levels.[31] The investigators suggest that either the initial diagnosis of growth hormone deficiency was inappropriate in these 3 children or the growth hormone deficiency was transient.

5.1.2 False Positive Results

Growth hormone levels <10 μg/L in response to intravenous sermorelin are observed in a few children without growth hormone deficiency, and the specificity of the sermorelin test may be further enhanced in combination with estimation of basal IGF-I levels. Below normal peak serum growth hormone levels in response to sermorelin were observed in 3 of 86 children without growth hormone deficiency (false positive in 3.5% of children). Of these 3 children, one had Turner's syndrome and the other 2 had simple obesity, and all 3 had normal basal serum IGF-I levels.[31]

Despite the occurrence of some false positive results intravenous sermorelin appears to be more specific than other provocative tests in the diagnosis of growth hormone deficiency. The incidence of false positive results in 472 normally growing children and adolescents was lower after intravenous sermorelin 1 μg/kg bodyweight than after other provocative tests[45] (table III). The addition of oral pyridostigmine 60mg or intravenous arginine 0.5 g/kg bodyweight to intravenous sermorelin 1 μg/kg bodyweight enhanced the serum growth hormone response and eliminated false positive results in normally growing children (table III).

The administration of an intravenous bolus dose of sermorelin 1 μg/kg bodyweight followed by a 30-minute infusion of arginine 0.5 g/kg bodyweight (up to maximum of 30g) has been reported to be a reliable, reproducible and age-independent provocative test of growth hormone secretion in adults,[46-48] and is reportedly at least as sensitive

as insulin-induced hypoglycaemia for the diagnosis of growth hormone deficiency in adults.[49] However, the efficacy of sermorelin and arginine remains to be assessed in the diagnosis of children with growth hormone deficiency.

5.2 Treatment of Children with Idiopathic Growth Hormone Deficiency

The efficacy of subcutaneous sermorelin (30 μg/kg bodyweight administered once daily) for 12 months in promoting growth in 80 prepubertal children with idiopathic growth hormone deficiency has been evaluated in one noncomparative, multicentre trial.[33] This trial design was selected because the investigators considered the child's pretreatment growth history to be an adequate control for assessing subsequent growth. Furthermore, a placebo arm requiring once daily injections without potential benefit was considered unethical, and a comparative trial with recombinant growth hormone would need a longer period of observation.[33] Children who remained prepubertal at the end of this trial continued to receive treatment with subcutaneous sermorelin for periods of 24 (n = 24)[50] and 36 months (n = 7),[51] and these results have been reported in separate abstracts.[50,51]

Table III. Serum growth hormone (GH) responses to various provocative tests of growth hormone secretion in normally growing children. 472 children and adolescents (aged between 3.8 and 17.4 years) of either sex with normal body mass index, height velocity, IGF-I levels and bone age similar to chronological age underwent at least one of the following provocative tests of growth hormone secretion[45]

Test	Number of recipents	Mean peak GH levels (μg/L)	Recipients with peak GH levels <10 μg/L (%)
Sermorelin 1 μg/kg BW IV	134	28.8	14.9
Physical exercise[a]	33	12.7	36.4
Insulin-induced hypoglycaemia[b]	59	13.2	49.1
Arginine 0.5 g/kg BW infused over 30 min	79	16.7	32.9
Clonidine 150mg PO	69	13.1	23.2
Levodopa[c] PO	55	13.0	36.4
Glucagon 1mg IM	40	16.9	35
Pyridostigmine 60mg PO	53	13.5	35.8
Sermorelin 1 μg/kg BW IV + pyridostigmine[d]	94	47.8	0
Sermorelin 1 μg/kg BW IV + arginine[e]	81	61.8	0

a Bicycle ergometer with progressive workload.

b Regular insulin 0.1 U/kg BW IV.

c Administered as 125, 250 and 500mg for BW <15, between 15 and 30 and >30kg, respectively.

d 60mg administered PO 60 minutes before sermorelin.

e Infused in a dose of 0.5 g/kg BW from 0 to 30 minutes.

BW = bodyweight; **IGF-I** = insulin-like growth factor-I; **IM** = intramuscular; **IV** = intravenous; **PO** = oral.

The efficacy of the recommended once daily dosage of sermorelin has not been compared with that of somatropin in the treatment of children with growth hormone deficiency. However, the effects of subcutaneous sermorelin 30 μg/kg bodyweight per day (either by continuous infusion or in 3 divided doses) were compared with those of once daily subcutaneous somatropin 0.1 IU/kg bodyweight (equals 30 μg/kg bodyweight) in 2 randomised nonblind trials of 6 months' duration in children with idiopathic growth hormone deficiency.[35,40]

5.2.1 Noncomparative Trial

Height velocity, height velocity standard deviation score and height standard deviation score all increased significantly from baseline values in prepubertal children with idiopathic growth hormone deficiency after up to 36 months of treatment with once daily subcutaneous sermorelin 30 μg/kg bodyweight (table IV). Treatment was started with once daily subcutaneous sermorelin 30 μg/kg bodyweight in 106 prepubertal children with idiopathic growth hormone deficiency.[33] Significant increases in mean height velocity from baseline values were reported in 80 evaluable children at 6 months and in 56 evaluable children at 12 months (table IV).

Short, slow growing children with delayed bone age and height age tended to have a good growth response (increase in height velocity ≥2 cm/year from baseline values) to 12 months' treatment with once daily subcutaneous sermorelin. Children re-

Table IV. Growth of prepubertal children with idiopathic growth hormone deficiency[a] treated with once daily subcutaneous sermorelin 30 μg/kg bodyweight in a noncomparative, multicentre trial

Reference	Trial duration (mo)	Number of evaluable patients	Mean HV (cm/year)		Mean HTSDS		Mean HVSDS	
			basal	end-point	basal	end-point	basal	end-point
Thorner et al.[33]	6	80	4.2	7.4**	–3.65	–3.37**	–2.11[b]	2.23[b]**
	12	56	4.1	7.2**	–3.71	–3.21**	–2.43[c]	1.87[c]**
Murray et al.[50][d]	24	24	4.4	5.94*	–3.59	–2.83*	–2.24	0.30*
Children's Mercy Hospital[51][d]	36	7	4.4	5.34[e]	–3.59	–2.49[e]	–2.24	–0.81[e]

a Defined as peak growth hormone levels <10 μg/L in response to 2 provocative tests (insulin-induced hypoglycaemia and arginine) in combination with 2 clinical features (height <2.5 or more standard deviations below standard and HV <10th percentile for chronological age in the preceding 6 months). Children who were not euthyroid (with or without thyroxine 5 μg/kg bodyweight or 100 μg/day) and those with other congenital anomalies, defined syndromes or underlying disorders, and those receiving drugs associated with growth failure (except glucocorticoids ≤20 mg/m^2 BSA per day) were excluded.[33]

b In 79 children.

c In 55 children.

d Abstract report of extension of 12-month trial.[33]

e Significantly greater than baseline value (p value not provided).

BSA = body surface area; **HTSDS** = height standard deviation score; **HV** = height velocity; **HVSDS** = height velocity standard deviation score; * $p < 0.001$, ** $p = 0.0001$ *vs* baseline values.

ceiving treatment with sermorelin were grouped by the investigators as either good or poor responders to treatment based on increases in height velocity of ≥2 or <2 cm/year from baseline values, respectively.[33] The majority of evaluable children were judged as good responders at 6 months and 12 months (74 and 84%, respectively). Analysis of the baseline characteristics of good and poor responders at 6 months revealed that good responders were initially slower growing (mean height velocity 4.1 *vs* 4.6 cm/year, $p = 0.0124$), had lower bone ages (mean 4.7 *vs* 5.9 years, $p = 0.0184$) and height ages (mean 4.3 *vs* 5.1 years, $p = 0.0489$), and tended to be shorter than poor responders (mean height 105.4 *vs* 110.7cm, $p = 0.0599$). However, peak growth hormone responses to a diagnostic dose of intravenous (1 μg/kg bodyweight) or subcutaneous (30 μg/kg bodyweight) sermorelin at baseline were not predictive of the response to prolonged treatment with sermorelin.[33]

Poor responders to sermorelin may respond to somatropin. Six children had an increase in height velocity of <2 cm/year from baseline values after 6 months' treatment with once daily subcutaneous sermorelin 30 μg/kg bodyweight and were switched to treatment with subcutaneous somatropin at a dosage of 200 μg/kg bodyweight per week administered daily for 6 months. Increases in height velocity from baseline values after 6 months with somatropin were greater than those after sermorelin for a similar duration, but the difference was not statistically significant ($p = 0.0669$).[33]

Mean height velocity standard deviation scores and mean height standard deviation scores were significantly increased from baseline values after 6, 12,[33] 24[50] and 36[51] months' treatment with sermorelin (table IV). Treatment with sermorelin induced catch-up growth in most children as indicated by a positive height velocity standard deviation score in 87% of children at 6 months and in 95% of children after 12 months.[33] Mean height velocity standard deviation score remained positive after 24 months[50] (table IV).

5.2.2 Sermorelin versus Somatropin

Increases in height velocity (from baseline values) were significantly greater after 6 months' treatment with once daily subcutaneous somatropin 30 μg/kg bodyweight than with subcutaneous sermorelin at a dosage of 30 μg/kg bodyweight per day, administered either by a constant infusion pump delivering a pulse every 24 minutes[40] or as 3 divided doses,[35] in prepubertal children with id-

iopathic growth hormone deficiency (table V). Children with growth failure who were included in these trials had a hypothalamic rather than a pituitary deficit in growth hormone secretion because pretreatment serum growth hormone responses were >10 μg/L after sermorelin and <10 μg/L after conventional provocative tests.[35,40]

The effects of a higher dosage of sermorelin (60 μg/kg bodyweight per day) delivered by a constant infusion pump or as 3 divided doses are less clear. Increases in height velocity from baseline values with the higher dosage were similar to those with the lower dosage given by a constant infusion pump,[40] but significantly ($p = 0.05$) greater when given as 3 divided doses.[35] While increases in height velocity from baseline values with somatropin were greater than those with the higher daily dosage of sermorelin in both trials,[35,40] the difference was statistically significant in only one trial.[40]

5.2.3 Long Term Effects on Height

The effect of long term treatment with subcutaneous sermorelin on final adult height has not yet been determined.[52] After 12 months, bone age increased by 1.05 years in 56 children receiving once daily subcutaneous sermorelin 30 μg/kg bodyweight.[33] Similarly, 12 months' treatment with subcutaneous sermorelin 30 μg/kg bodyweight per day in 2 divided doses led to an increase in bone age of 1.1 years in 9 children with radiation-induced growth hormone deficiency.[53] In a trial of shorter duration, bone age increased by 0.7 years after 6 months' treatment with subcutaneous sermorelin 30 or 60 μg/kg bodyweight per day in 27 prepubertal children with growth hormone deficiency.[35]

6. Tolerability

6.1 General Profile

Transient facial flushing was the only adverse event reported after a single intravenous dose of sermorelin 1 μg/kg bodyweight in 2 trials in healthy adult volunteers[31] and in healthy children.[45] In a crossover trial in 11 adult volunteers, transient facial flushing developed in 10 individuals after intravenous sermorelin and 2 given intravenous GHRH(1-40) 1 μg/kg bodyweight.[31] Facial flushing was reported in 30% of 134 normally growing children after intravenous sermorelin 1 μg/kg bodyweight in another trial.[45] Flushing was reported in 20% of children with ($n = 45$) or without ($n = 86$) growth hormone deficiency after intravenous sermorelin 1 μg/kg bodyweight, and the incidence of flushing increased with age ($p <$

Table V. Comparative effects of subcutaneous sermorelin (SER) and somatropin (SOM) in prepubertal children with growth hormone deficiency[a] treated for 6 months in randomised trials

Reference	Treatment and daily dosage (μg/kg bodyweight)	Frequency of administration	Number of evaluable patients	CA	Mean HV (cm/year)		Mean HTSDS	
					basal	end-point	basal	end-point
Chen et al.[40]	SER 30	Continuous infusion[b]	20	9.7	<4	9.2	NR	NR
	SER 60	Continuous infusion[b]	20	10.4	<4	9.3	NR	NR
	SOM 30[c]	once daily	20	10.6	<4	14.6‡	NR	NR
Neyzi et al.[35]	SER 30	3 times daily	15	10.3	3.1	7.9*	–4.1	–3.9*
	SER 60	3 times daily	12	11.3	2.5	10.3*†	–4.3	–3.9*
	SOM 30[c]	once daily	16	9.7	2.7	12.4*††	–3.9	–3.1*

a Peak plasma growth hormone levels <10 μg/L after 2 provocative tests (levodopa and clonidine or insulin) and >10 μg/L after sermorelin,[35,40] and with height <2 standard deviations for age and bone age ≥2 years behind chronological age.[35]

b With a portable syringe pump set to deliver a pulse every 24 minutes.

c Equals 0.1 IU/kg bodyweight.

CA = chronological age; **HTSDS** = height standard deviation score; **HV** = height velocity; **NR** = not reported; **‡** $p < 0.01$ *vs* SER 30 or 60 μg/kg bodyweight; * $p < 0.05$ *vs* baseline; **†** $p = 0.05$, **††** $p = 0.0008$ *vs* SER 30 μg/kg bodyweight.

0.01).[31] Transient pain at the injection site is also associated with the use of a single intravenous dose of sermorelin 1 μg/kg bodyweight.[54]

Once daily subcutaneous sermorelin 30 μg/kg bodyweight was well tolerated over a period of 12 months by 110 children with growth hormone deficiency. Local reactions at the injection site, such as pain, swelling or redness,[33] were the most common adverse events and occurred in 16 children. Only 2 patients withdrew from the trial because of adverse events (1 with urticaria and 1 with generalised malaise).[33] Less common adverse events with subcutaneous sermorelin include headache, flushing, dizziness and hyperactivity.[55]

Hypothyroidism has been reported in up to 6.5% of sermorelin recipients in clinical trials[56] (section 3.2), which is similar to the incidence of clinical or biochemical hypothyroidism (approximately <10%) observed in children receiving recombinant growth hormone preparations.[16] However, the mechanism by which hypothyroidism develops is unknown.[16]

Some adverse events which are reported to occur significantly more frequently in recombinant growth hormone recipients than in placebo recipients, such as benign intracranial hypertension, oedema, arthralgia and myalgia, and paraesthesia and anaesthesia,[57,58] have not been reported in sermorelin recipients. However, the results of long term trials in sufficient numbers of patients are required to assess the relative incidence of these adverse events in sermorelin recipients.

6.2 Development of Antibodies

Serum antibodies to GHRH develop in most children receiving treatment with subcutaneous sermorelin. Antibodies to GHRH were not detected in serum before treatment with subcutaneous sermorelin 30 μg/kg bodyweight per day, but were found in 20, 54[35] and 62%[33] of recipients after 3, 6 and 12 months, respectively. Administration of subcutaneous sermorelin 30 and 60 μg/kg bodyweight per day by a constant infusion pump for 6 months led to the development of anti-GHRH antibodies in the plasma of 95 and 100% of recipients, respectively, in another trial.[40] Antibody titres declined sharply 3 months after cessation of therapy and were almost undetectable after 9 months.[40]

The clinical relevance of anti-GHRH antibodies is uncertain, as there was no correlation between their presence and the effects of sermorelin on growth or on the incidence of adverse events in recipients.[33,35,40] Similarly, anti-growth hormone antibodies have been reported in <20% of children after treatment with recombinant growth hormone preparations, but their clinical relevance is unclear.[16]

7. Dosage and Administration

7.1 For Diagnosis

A single dose of intravenous sermorelin 1 μg/kg bodyweight administered in the morning after an overnight fast is recommended for the assessment of growth hormone secretion from the anterior pituitary.[59] Patients being treated with growth hormone preparations should discontinue therapy 1 to 2 weeks before undergoing the test with sermorelin. In addition, the sermorelin test should be carried out in the absence of drugs which can affect growth hormone release such as insulin, clonidine, levodopa, atropine, glucocorticoids, aspirin, indomethacin and β-adrenoceptor agonists and antagonists.[59]

Untreated hypothyroidism, obesity, hyperglycaemia and elevated plasma fatty acid levels are associated with subnormal growth hormone responses in the sermorelin test.[59] The use of sermorelin is contraindicated in patients with known hypersensitivity to the drug or any of its excipients.[59] Sermorelin should be used with caution in patients with epilepsy or diabetes mellitus.[54]

7.2 As Treatment

Once daily subcutaneous sermorelin 30 μg/kg bodyweight at bedtime is recommended by the manufacturer for the treatment of prepubertal children with idiopathic growth hormone deficiency and growth failure.[52] Treatment with subcutane-

ous sermorelin should be initiated at a bone age of <7.5 years for females and <8 years for males. Before commencing treatment with subcutaneous sermorelin, the manufacturer recommends a provocative test with intravenous sermorelin in all children.[52] The relative growth hormone response to the diagnostic dose of sermorelin is not predictive of the growth response to subcutaneous sermorelin,[33,52] and repeated administration of subcutaneous sermorelin appears to have a priming effect on the pituitary somatotrophs of children with growth hormone deficiency[35,36] (section 3.1.3). However, the manufacturer does not recommend treatment with subcutaneous sermorelin in children with serum growth hormone responses ≤2 μg/L in the sermorelin test.[52] Periodic assessment of growth response should be conducted at least every 6 months in children receiving sermorelin, and treatment should be continued until the fusion of the epiphysis.[52]

Those with a poor or waning response to subcutaneous sermorelin should be considered for treatment with somatropin.[52] In addition, thyroid hormone determinations are recommended before and during treatment with sermorelin, as untreated hypothyroidism can decrease growth response to sermorelin. Although no drug interaction studies are currently available, concomitant administration of glucocorticoids may inhibit growth response to sermorelin.[52]

8. Place of Sermorelin in the Diagnosis and Treatment of Children with Idiopathic Growth Hormone Deficiency

Sermorelin, a 29 amino acid synthetic analogue of GHRH, is the shortest peptide with complete biological activity of the native GHRH. A single dose of intravenous sermorelin 1 μg/kg bodyweight is used for the diagnosis of growth hormone deficiency, and once daily subcutaneous sermorelin 30 μg/kg bodyweight at bedtime is approved in the US for the treatment of children with idiopathic growth hormone deficiency.[2]

Provocative tests of growth hormone secretion with pharmacological stimuli, such as insulin, glucagon, levodopa, clonidine, arginine or propranolol, are widely used to confirm growth hormone deficiency. The minimum normal peak serum growth hormone response to provocative tests has been arbitrarily set at 10 μg/L,[16,18,60] and values between 5 to 10 μg/L and <5 μg/L indicate partial and complete growth hormone deficiency, respectively.[20]

The limitations of these provocative tests include sparse normative data, unclear mechanism of action, and highly variable growth hormone responses. Because of the pulsatile nature of growth hormone secretion, single estimations of serum growth hormone levels are unlikely to be helpful, and serial blood sampling, every 15 to 30 minutes, for 12 to 24 hours is expensive and time consuming.[16] It has been reported that growth hormone responses in provocative tests depend on the nature of the agent used, puberty, height standard deviation score, bodyweight standard deviation score, genetic target height standard deviation score and severity of disease.[20] Because of this variability, it is recommended that at least 2 provocative tests should be performed to confirm the diagnosis of growth hormone deficiency.[16,18,60]

Available data suggest that intravenous sermorelin 1 μg/kg bodyweight is a rapid and relatively specific test for the diagnosis of growth hormone deficiency in children. Peak serum growth hormone levels after intravenous sermorelin were attained within 60 minutes after administration in the majority of prepubertal children with or without growth hormone deficiency. In normally growing children, false positive results (peak growth hormone levels <10 μg/L) were reported in up to 14.9% of children after intravenous sermorelin 1 μg/kg bodyweight, and in 23.2 to 49.1% of children after other provocative stimuli. No false positive responses were observed in children without growth hormone deficiency when the results of the sermorelin test were combined with the basal serum IGF-I levels, or after intravenous sermorelin and oral pyridostigmine 60mg or intravenous arginine 0.5 g/kg bodyweight. Intravenous sermorelin and arginine is reported to be a reliable, reproduc-

ible and age-independent test of growth hormone deficiency in adults, and merits evaluation in children with growth hormone deficiency.

A drawback of the sermorelin test is that normal growth hormone responses to sermorelin in children with growth failure cannot exclude growth hormone deficiency due to hypothalamic deficits.[18] False negative results (peak growth hormone levels >10 μg/L) after intravenous sermorelin were reported in 24.4% children previously diagnosed with growth hormone deficiency using conventional provocative tests. The results of the sermorelin test alone are inconclusive in these patients and additional data from other provocative tests are required to reach an accurate diagnosis. Normal growth hormone responses to sermorelin in children with subnormal serum growth hormone responses to other provocative tests and growth failure indicates that the growth hormone deficiency in these children is due to a hypothalamic deficit. Estimation of basal serum IGF-I levels may increase the sensitivity of the sermorelin test in the diagnosis of growth hormone deficiency in children with growth failure but this approach requires further study.

The goal of treatment in children with growth hormone deficiency is to increase growth so that a normal or normally expected adult height is attained.[60] Traditionally, recombinant human growth hormone has been used to treat children with growth hormone deficiency, and treatment with subcutaneous or intramuscular recombinant human growth hormone increases the final adult height of children with growth hormone deficiency.[60] However, recombinant human growth hormone is expensive and its use has been associated with adverse events such as benign intracranial hypertension, oedema, arthralgia and myalgia, and paraesthesia and anaesthesia.[57,58]

Limited data from one noncomparative trial indicate that treatment with once daily subcutaneous sermorelin 30 μg/kg bodyweight is effective in children with growth hormone deficiency. Sermorelin administration significantly increased height velocity, height velocity standard scores and height standard deviation scores in children with growth hormone deficiency for periods of up to 12 months, and data in a few patients indicate that efficacy is maintained for up to 36 months. Catch-up growth induced by sermorelin in the majority of children with growth hormone deficiency was sustained for up to 24 months. However, the effect of treatment with sermorelin on final adult height is yet to be determined.

Identifying patients likely to respond to sermorelin would maximise successful outcome. Predictors of a good growth response to subcutaneous sermorelin in children with growth hormone deficiency include a slow growth rate, short stature, and delayed bone age and height age at baseline, but not peak growth hormone responses to intravenous sermorelin 1 μg/kg bodyweight. Finally, children with growth hormone deficiency who do not respond to sermorelin may respond to somatropin.

Short term and long term (12 months) administration of sermorelin is well tolerated. Minor adverse events such as facial flushing and pain, swelling or redness at injection site have been reported after single dose intravenous sermorelin 1 μg/kg bodyweight or once daily subcutaneous sermorelin 30 μg/kg bodyweight for 12 months. The clinical relevance of anti-GHRH antibodies, reported in most recipients after long term administration of once daily subcutaneous sermorelin 30 μg/kg bodyweight, is uncertain.

The recommended once daily dosage of sermorelin 30 μg/kg bodyweight has not been directly compared with once daily somatropin in the management of children with growth hormone deficiency. However, available short term (6 months) data indicate that increases in height velocity from pretreatment values in children receiving subcutaneous sermorelin 30 or 60 μg/kg bodyweight per day in other regimens were less than in children receiving once daily subcutaneous somatropin 30 μg/kg bodyweight. Although no formal pharmacoeconomic studies comparing the cost of treatment with sermorelin versus that with somatropin in children with growth hormone deficiency are currently available, the treatment of an average 6-

year-old child with growth hormone deficiency with sermorelin reportedly costs $US7000 versus $US10 000 for recombinant human growth hormone preparations.[55] In the absence of direct comparative data, is not possible to accurately position sermorelin and somatropin in the treatment of children with idiopathic growth hormone deficiency.

In conclusion, sermorelin is a well tolerated analogue of GHRH which is suitable as a provocative test of growth hormone deficiency when given as a single intravenous 1 μg/kg bodyweight dose in conjunction with conventional tests. Limited data suggest that once daily subcutaneous sermorelin 30 μg/kg bodyweight is effective in promoting growth in some prepubertal children with idiopathic growth hormone deficiency.

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