当かなど，治験の骨格の一つひとつをとっても，通常の臨床試験より細かい検討が必要である．筆者の経験でもたった1つの安全性評価項目のグレーディングを決定するためだけに2時間近い議論をしたこともある．とくにこれまでほとんど治験が実施されてこなかったような希少疾病などの領域では，評価方法の決定にはかなりの時間を費やす必要があろう．国内外での過去の類似医薬品の治験や臨床試験のプロトコルが入手可能であればそれを参考にするとよいが，その際には海外での評価方法が国内でも利用可能であるか，バリデートされているかなどにも配慮が必要である．

医師主導の臨床試験と異なり，プロトコルは「作成した医師が理解できる（理解したつもりになっている？）」だけではだめで，他施設の医師やCRCなどの支援スタッフにも内容が十分に理解でき，流れが明確になっていなければ，いざ実施しても逸脱が多かったり，十分な評価ができなかったりと，問題が起きることが多い．医師主導臨床試験ではあまり気にとめないことが多いであろう，プロトコルと症例報告書（Case Report Form；CRF）の整合性のチェックも必ずやっておかなければならないし，モニタリングを実施するモニターの視点からのチェックも必要である．CRFの記載方法などが曖昧であると，あとでモニタリングの際にチェックが困難であったり，データマネジャーによるデータの処理が困難であったりする．

医師主導の臨床試験では，医師の医学的興味から仮説が立てられることも多いかもしれない．しかし，医師主導治験は「製薬企業による将来的な承認申請」を念頭において，既存の非臨床試験のデータや臨床試験・治験のデータを踏まえたうえで，どのような位置づけで医師主導治験を実施するかを十分に考えておかなければならない．医薬品の治験では，薬物動態（吸収，分布，代謝，排泄）の情報とそれに基づく至適用量の判断も重要となる．用量設定が十分に行われていないと，十分な有効性が得られなかったり，副作用が頻発して評価を中止せざるをえなくなる可能性もでてくる．

医師主導治験を考える際には，省令GCPなど治験の前提となる法令はもちろん知っておかなければならないし，必要な支援体制も十分に考えておかなければならない．われわれの経験からすると，データマネジメント，モニタリング，統計の委託先は極力同一にしておいたほうが作業の連携が楽である．治験薬概要書などの情報提供，治験薬の提供，将来的な承認申請のことを考えると，製薬企業の開発・申請担当者とも密な連携をとるべきであることは，火を見るより明らかである．

医師主導治験で試してみたいこと

製薬企業主導の治験はある意味とても保守的である．かつてどこかの企業が申請の際に規制当局にこのような指摘をされたらしい，という過去の経験の積み重ねで，細かいところのチェックが厳しくなり，一方で新しい試みをすることはなかなか難しい．外資であれば，海外で実施されたのと同じ方法を国内にもちこむこともあるが，時に国内の臨床実態にそぐわないで，実施の際に現場が苦労することもある．

われわれ小児科の領域では希少疾病などほとんどこれまで日本で治験が実施されていない領域で，製薬企業が着手に尻込みするような治験に医師主導で取り組んでいることも多い．平成18（2006）年度には世界初のL-アルギニンのミトコンドリア脳筋症（Mitochondrial myopathy, Encephalopathy, Lactic Acidosis and Stroke-like episode；MELAS）の脳卒中様発作に対する適応について，その効果

と安全性の評価を行う予定である．これまで治験を実施したことのない領域では，その有効性評価方法などもかなり試験的にならざるをえない．製薬企業の治験では，なかなかこのようなリスクをおかすことはできないが，医師主導治験であるからこそ試験的評価方法を試し，その方法論を将来的に製薬企業主導治験にも応用していくことができるのではないかと考えている．

医師主導治験プロトコル概要
―クエン酸フェンタニルを例として―

筆者が治験調整医師をしているクエン酸フェンタニルの治験について，その概要を例として以下に示す．併用麻酔薬の投与量を細かく規定しすぎたなどの理由でかなり逸脱も多いが，大枠での有効性評価と安全性評価には大きな問題はないのではないかと考えている．平成17(2005)年12月に，症例登録は終了し，平成18(2006)年4月に症例検討会も終了，平成18(2006)年内の製薬企業による承認申請を目指している．

対象疾患：挿管，呼吸管理，全身麻酔のもとに，手術もしくは処置を受ける症例で，麻薬系鎮痛・鎮静薬の補助的投与が必要となる患者．硬膜外麻酔を行う患者は除く．

目的：新生児(低出生体重児を含む)から6歳以下の小児患者を対象として，クエン酸フェンタニルを全身麻酔時の鎮痛薬として使用した際の，至適投与量・有効性・作用時間の確認と，安全性の評価，また可能な限り薬物動態を検討する．さらに安全性については，年齢によって，とくに2歳以下(3歳未満)の児で3歳以上の小児に比べて大きな問題がないかの検討を行う．

治験デザイン：非対照，非盲検，多施設共同臨床試験

投与期間：術中の麻酔期間

術直後観察期間：抜管までの評価および抜管後15時間までの評価(ただし低出生体重児などで術後すぐの抜管が困難だった場合，手術室出室後15時間までの評価)

最終観察日：退院時もしくは退院後(術後3日から14日後)の調査(ただし低出生体重児などで術後すぐの抜管が困難だった場合，抜管後安定した状態での調査)

治験期間：手術前調査期：1日

治療期：手術期間のみ，原則として24時間以内

術後フォローアップ期：術後3～14日(ただし低出生体重児などで術後すぐの抜管が困難だった場合，抜管後安定した時点)

実施医療機関：多施設共同治験(大阪府立母子保健総合医療センター，北里大学病院，神戸大学医学部附属病院，国立成育医療センター，東京大学医学部附属病院，独立行政法人国立病院機構岡山医療センター)

被験者数：目標症例数：全体で120症例

1)受胎後週数45週未満：全体で24症例

2)受胎後週数45週以上，2歳以下(3歳未満)：全体で48症例

3)3歳以上6歳以下(7歳未満)：全体で48症例

血中濃度測定症例数：

全体で1)群5症例以上，2)群10症例以上，3)群10症例以上を目標とし，可能な限り収集する．原則として投与後1時間～1時間30分の1点採血とする．検体量は全血で0.5mL程度(一回測定に血漿0.1mL必要)である．

主な組み入れ基準：

1)入院患者で，挿管，呼吸管理，全身麻酔のもとに手術もしくは処置を受ける症例のうち，麻薬系鎮痛・鎮静薬の補助的投与が必要となる患者

2)6歳以下(7歳未満)の症例

3)同意：代諾者(保護者)から文書による承

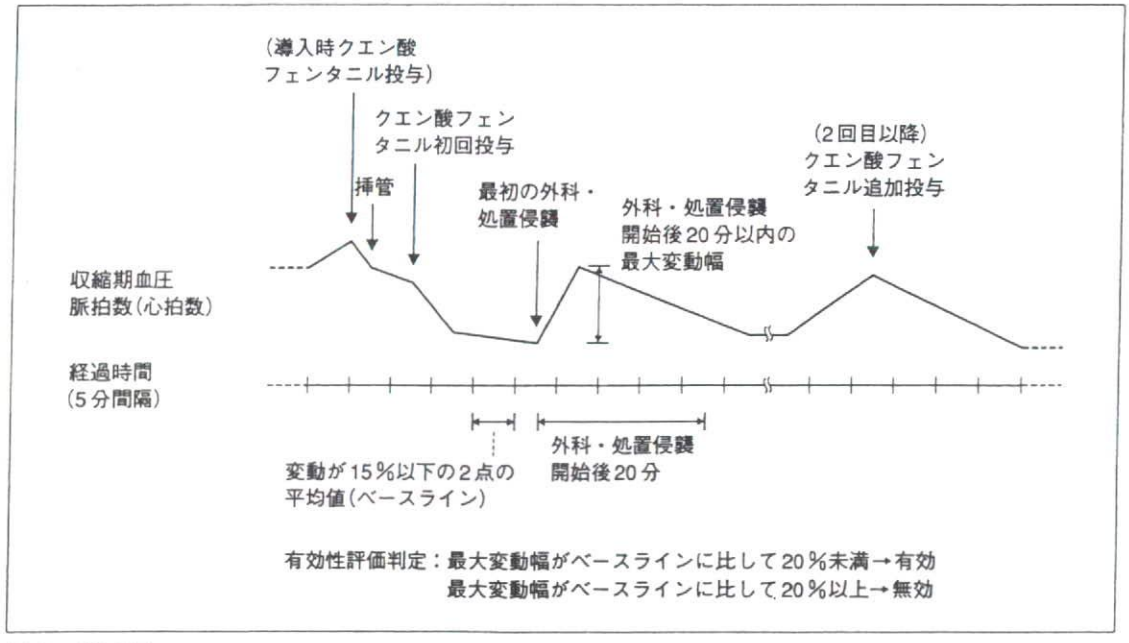

図1　模式図

諾(インフォームド・コンセント)が得られた児

治験薬の投与方法：

初回投与：本治験における初回投与は，気管内挿管後の最初のクエン酸フェンタニル投与と規定し，導入時の気管内挿管前のクエン酸フェンタニル投与は初回投与とはしない．クエン酸フェンタニルは，場合により導入時の気管内挿管の前にクエン酸フェンタニルとして0.02～0.1mL/kg(フェンタニルとして1～5μg/kg)を，また麻酔導入後，手術開始約10分前に導入時の投与量と合わせてクエン酸フェンタニルとして0.04～0.3mL/kg(フェンタニルとして2～15μg/kg)を投与する．クエン酸フェンタニルは原液をそのまま，あるいは1アンプル(2mL)をブドウ糖液などで5～20mLに希釈し，側管からゆっくり投与後，輸液を数mL流す(時間としてトータル30秒から1分かける)ことにより確実に血管内に全薬液が入るようにする．

追加投与：投与については，医師の裁量により行い，その根拠を記載する．一度の投与量はクエン酸フェンタニルとして0.02～0.2mL/kg(フェンタニルとして1～10μg/kg)とする．希釈および投与方法は初回投与時と同様とする．

有効性の評価項目：

主要評価項目：挿管後のクエン酸フェンタニル初回投与後の最初の外科・処置侵襲開始後20分以内の最大変動を示す収縮期血圧，脈拍数(心拍数)を指標とした医師の総合判定(有効または無効)

副次評価項目：挿管後のクエン酸フェンタニル初回投与後の最初の外科・処置侵襲開始後20分以内の最大収縮期血圧，脈拍数(心拍数)の変動率からの判定(**図1**)

収縮期血圧による有効率(%)

＝(クエン酸フェンタニル初回投与後の収縮期血圧平均値からの最大変動率が切り捨て＋20%未満の症例数)/(クエン酸フェンタニル初回投与後に5±2分間隔で隣接する時

表1　治験スケジュール(観察・検査スケジュール)

	術前	術中	術後	
			抜管後次の日の診察まで/手術室出室後次の日の診察まで	最終観察日(フォローアップ)
診察	●	○	●	●
同意取得	●	—	—	—
選択・除外基準確認	●	—	—	—
被験者背景の確認	●	—	—	—
登録	●	—	—	—
治験薬投与	—	●	—	—
併用薬・併用療法の確認	●	●	●	●
収縮期血圧	●	●	●	●
脈拍数・心拍数	●	●	●	●
心電図	—	●	—	—
SpO₂	—	●	—/●	—
$ETco_2$	—	●	—	—
体温	●	●	—	●
呼吸数	●	—	●/—	●
自覚症状・他覚所見	●	●	●	●
臨床検査 血液学的検査	○	—	—	○
臨床検査 血液生化学検査	○	—	—	○
臨床検査 尿検査	○	—	—	○
血中薬物濃度測定用採血(クエン酸フェンタニル初回投与後1～1.5hr)	—	◇	—	—

「術前」は手術室に入る前まで，「術中」は手術室に滞在している期間，「術後」は手術室を退出した時点以降とする．
●：必須実施事項，○：必要に応じて実施，◇：代諾者(保護者)の同意のもと，可能な限り実施

点の収縮期血圧の変動率が切り捨て±15%以内となった症例数)×100

クエン酸フェンタニル初回投与後の収縮期血圧平均値：挿管後，クエン酸フェンタニル初回投与後に5±2分間隔で隣接する2時点の収縮期血圧の切り捨て算術平均値

安全性の評価項目：

治験薬投与開始後から術後15時間まで：因果関係を否定できない有害事象(自覚症状・他覚所見などの発現または悪化，臨床検査値異常変動)の発現頻度

治験薬投与開始後からフォローアップまで：亜急性の有害事象(肝機能障害，腎機能障害を明らかに疑わせる所見など)

観察・検査スケジュール：**表1**を参照

医師主導治験の審査の際の留意点

製薬企業の治験では，その道のプロが半年近くをかけて入念にプロトコルを練り，社内でのIRBで承認され，さらに治験届を提出し，大きな問題点については規制当局のチェック

を受けたものが施設に提出される．その意味では，すでにかなり完成度が高いプロトコルが治験実施医師の元に届けられ，IRBの審査にかけられることになる．一方，医師主導治験では，省令GCPに準拠した治験というものに慣れていない医師が中心となってプロトコルを作成しており，しかも各参加施設のIRBで承認された後に治験届が提出されることになる．したがって，治験審査の際には，「すでに完成しているはずのもの」と安心して審査資料に目を通すのではなく，資料の隅々まで漏れがないか，またとくに治験の科学性・倫理性について問題がないか，適切に評価が可能であるかなどを検討する必要がある．

医師主導治験では，プロトコルやCRFなどの版管理なども各施設で適切に行わなければならない．版管理を厳重に行っておかないと「最新版」ではない古い版で審査が行われてしまうことなども起こりうる．さらに治験薬概要書などについても十分に目を通しておく必要がある．われわれが実際に経験した事例としては，製剤の安定性試験の結果が掲載されていないまま審査にかけられたことがあり，IRBからの指示で，安定性試験の結果を盛り込んだうえで再度諮られたことなどもある．

われわれが関与している医師主導治験は，すべて日本医師会治験促進センターからの研究費によって実施されている．しかし，それ以外の財源による医師主導治験もありうるわけであり，医師主導治験の審査においては，その財源がどうなっているか，実施者との関係はどうなっているか(実施者が利益をこうむることがありうるかなど)についても慎重に審議されるべきであろう．

また，製薬企業の治験では当たり前のように整備されているデータマネジメント，モニタリング，統計，メディカルライティング，監査，プロジェクトマネジメントなどについても，体制が整備され確実に実施されなければ，治験を円滑にすすめることは難しい．自ら治験を実施する者である治験責任医師が十分に治験の内容や実施体制を理解しており，またCRCなどによる支援体制が十分であるかを入念に検討する必要がある．

医師主導治験について，そのプロトコルの臨床試験や製薬企業主導治験との違い，作成上の留意点，審査の際の留意点などについて概説した．現状では，まだ手探り状態で，その実施にかなりの困難を伴う医師主導治験であるが，医薬品開発の新しい道筋として，一刻も早く体制整備がすすむことを祈っている．

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Original Article

No Improvement of Adult Height in Non-growth Hormone (GH) Deficient Short Children with GH Treatment

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Abstract. It is still in doubt whether the standard-dose growth hormone (GH) used in Japan (0.5 IU/kg/week, 0.167 mg/kg/week) for growth hormone deficiency is effective for achieving significant adult height improvement in non-growth hormone deficient (non-GHD) short children. We compared the growth of GH-treated non-GHD short children with that of untreated short children to examine the effect of standard-dose GH treatment on non-GHD short children. GH treatment with recombinant human growth hormone (rhGH) was started before the age of 11 yr in 64 boys and 76 girls with non-GHD short stature registered at the Foundation for Growth Science who have now reached their adult height. In 119 untreated boys and 127 untreated girls whose height standard deviation score (SDS) was below –2 SD at the age of 6 yr, height growth was followed until 17 yr. Height SDS was significantly lower before GH treatment in the GH-treated group than at the age of 6 yr in the untreated group, in both sexes. Adult height and adult height SDS were significantly greater in the untreated group than in the GH-treated group, in both sexes, although the change in height SDS did not differ significantly. Height SDS was significantly lower before GH treatment in the GH-treated group than at the age of 6 yr in the untreated group, so 57 boys and 57 girls whose height SDS at the age of 6 yr in the untreated group closely matched the height SDS before GH treatment in the GH-treated group were chosen for comparison. Height SDS did not differ significantly between the GH-treated group before GH treatment and the untreated group at the age of 6 yr, nor were there differences between these subgroups in adult height, adult height SDS, or height SDS change, in either sex. The effect of GH treatment is reported to be dose-dependent and doses over 0.23 mg/kg/week are reported to be necessary to improve adult height in non-GHD short children. Currently, the GH dose is fixed at 0.175 mg/kg/week in Japan, and we expected to find, and indeed concluded, that ordinary GH treatment in Japanese, non-GHD short children does not improve adult height.

Key words: non-GHD short children, GH treatment, GH dosage

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Introduction

The effectiveness of growth hormone (GH) treatment on adult height in non-growth hormone deficient (non-GHD) children is controversial. A recent double-blind, placebo-controlled study clearly demonstrated that children with idiopathic short stature treated with high-dose GH are significantly taller than placebo-treated short children when they reach adult height (1). It is still unclear whether the standard dose used in Japan has any significant efficacy on increasing the adult height of non-GHD short children.

It is known that approximately 60% of non-GHD short children show a tendency toward delayed puberty and reach an adult height within the normal range (> –2 SD) without any treatment (2). Therefore, the normalization of adult height following GH treatment does not prove the efficacy of GH treatment in these patients, unless we establish this through comparison of the resulting adult heights with the adult heights of untreated non-GHD short children. In Japan, since it is now practically impossible to study the efficacy of GH treatment on adult height in non-GHD short children in a controlled study, we compared data on file at the Foundation for Growth Science and epidemiological data in Akita Prefecture (2).

The Foundation for Growth Science was founded in 1977 and has been monitoring the use of GH by its registration system, which includes judgment of eligibility to start and to continue GH treatment, and a system for reporting adverse events. The data on the application sheets were utilized as they are the largest database of GH treatment in Japan. The epidemiological data in Akita Prefecture was collected through the collaborative activity of pediatric endocrinologists and the local committee of education.

Subjects and Methods

The following two groups were compared:

1) GH-treated group: 64 boys and 76 girls for whom data were on file at the Foundation for Growth Science and had started growth hormone (GH) treatment with recombinant growth hormone (rhGH) at a dose of 0.5 IU (0.167 mg)/kg/week before the age of 11 yr and thereafter reached their adult height (as defined below). They were diagnosed as having non-GHD short stature because their peak GH values were below 10 ng/ml in two GH provocation tests but over 10 ng/ml in at least one test. Their tallest height after their height velocity became less than 2 cm/yr was defined as their adult height. The age at adult height estimation was 16.89 ± 1.01 yr and 15.34 ± 0.93 yr in boys and girls, respectively.

2) Untreated group: 119 boys and 127 girls whose height SDS was below –2 SD at 6 years of age were followed until 17 yr old. Height at the age of 17 yr was defined as adult height in these patients.

In the second comparison, height SDS at start of GH treatment in the GH-treated group and at the age of 6 yr in the untreated group were matched and 57 boys and 57 girls were selected from the both groups.

The height standard of the national survey of 1990 was used for the calculation of height SDS. Student's t-test was used for comparisons of the two groups. The significance level was set at 0.05.

Results

In the GH treated group, the age at the start of GH was 10.7 ± 0.9 yr and 9.6 ± 0.9 yr, and the duration of GH treatment was 6.2 ± 1.0 yr and 5.7 ± 1.0 yr for boys and girls, respectively. Table 1 shows the height SDS before GH treatment in the GH-treated group and the height SDS at the age of 6 yr in the untreated group, and adult height and adult height SDS in both sexes, as

Table 1 Comparison of clinical characteristics between GH-treated and untreated groups of non-GHD short children

	boys		girls	
	GH-treated	untreated	GH-treated	untreated
n	64	119	76	127
height SDS at start of GH or at 6 yr	−2.68 ± 0.36*	−2.36 ± 0.36	−2.87 ± 0.63*	−2.39 ± 0.43
adult height	159.2 ± 4.8*	161.1 ± 4.3	146.0 ± 6.0*	148.8 ± 4.4
adult height SDS	−2.01 ± 0.86*	−1.66 ± 0.76	−2.38 ± 1.20*	−1.83 ± 0.88
change in height SDS	0.67 ± 0.77	0.71 ± 0.80	0.49 ± 0.85	0.56 ± 0.68

*$p<0.05$ vs untreated.

Table 2 Comparison of clinical characteristics between the GH-treated and untreated groups of non-GHD short children, when GH-treated short children were matched with untreated short children whose height SDS at 6 yr of age was similar to the height SDS of GH-treated short children before treatment

	boys		girls	
	GH-treated	untreated	GH-treated	untreated
n	57	57	57	57
height SDS at start of GH or at 6 yr	−2.61 ± 0.39	−2.60 ± 0.39	−2.68 ± 0.47	−2.68 ± 0.49
adult height	159.8 ± 4.8	161.1 ± 5.1	147.4 ± 5.1	146.8 ± 4.4
adult height SDS	−1.90 ± 0.81	−1.66 ± 0.91	−2.11 ± 1.02	−2.21 ± 0.95
change in height SDS	0.71 ± 0.77	0.94 ± 0.93	0.57 ± 0.85	0.47 ± 0.68

well as the change in height SDS in the GH-treated group between before GH treatment and after attaining adult height and in the untreated group between the ages of 6 yr and 17 yr. In both sexes, the height SDS was significantly smaller in the GH-treated group before GH treatment than in the untreated group at the age of 6 yr, and adult height and adult height SDS were significantly smaller in the GH-treated group than in the untreated group. Change in height SDS, however, did not differ significantly: gains in height SDS were observed not only in the GH-treated group but also in the untreated group.

Because there was a significant difference between height SDS in the GH-treated group before GH treatment and height SDS in the untreated group at the age of 6 yr, 57 boys and 57 girls whose height SDS at the age of 6 yr in the untreated group closely matched the height SDS of patients in the GH-treated group before GH treatment were chosen and compared with the GH-treated group. Table 2 shows height SDS in the GH-treated group before GH treatment and in the untreated group at the age of 6 yr, adult height, and adult height SDS in both sexes. The changes in height SDS in the GH-treated group between before GH treatment and adult height and in the untreated group between the ages of 6 yr and 17 yr are also shown. No significant differences were found in height SDS between the GH-treated group before GH treatment and the untreated group at the age of 6 yr, or in adult height or adult height SDS, nor did the change in height SDS differ significantly between the GH-treated group and the untreated group.

Table 3 Adult height after GH treatement in non-GHD short children in Europe and the United States

	dose (mg/kg/week)	n	Height SDS			AH-PAH		AH-start (ΔSDS)
			At start	PAH	AH	Δcm	ΔSDS	
Wit[3]	0.19	53 (FSS)	−2.6		−1.9			0.8
	0.2	36 (NFSS)	−2.8		−1.3			1.4
Bernascovi[4]	0.21	71	−2.8	−1.7	−1.7	0	0	1.1
Leschek[1]	0.23	22	−2.7	−2.1	−1.77		0.32	0.93
	placebo	11	−2.8	−2.3	−2.34		−0.14	0.42
Hintz[6]	0.3	57 (m)	−2.9	−2.5	−1.7	5	0.8	1.2
		23 (f)	−2.7	−2.6	−1.6	5.9	1	1.1
MaCaughey[5]	0.33	8 (f)	−2.5	−1.8	−1.1	3.5	0.7	1.3
Wit[7]	0.24	17	−3.26	−2.5	−1.69	5.4		1.55
	0.24→0.37	16	−3.08	−2.6	−1.48			1.52
	0.37	17	−2.88	−2.3	−1.12	7.2		1.85

( ): Reference No. PAH: Predicted adult height, AH: Adult height, FSS: Familial short stature, NFSS: Non-familial short stature. m: male, f: female.

Discussion

Table 3 shows data on GH treatment outcomes in non-GHD short children from six important studies conducted in Europe and the United States (1, 3–7), which have used recombinant hGH. Evaluation reveals some problems with these reports: 1) ages at the start of treatment and durations of therapy differ; 2) therapeutic doses differ; and 3) therapeutic effects cannot be evaluated, since most reports did not include untreated controls. Many reports, like the studies cited in Table 3, evaluate the effect of GH treatment by comparing the measured outcome with predicted adult height (PAH) instead of by comparison with controls. Despite these problems, it is clear that in all the studies higher doses than the Japanese standard dose were used and the change in height SDS from the start of GH treatment to adult height was greater in these studies than that of this study. The change in height SDS reported by the studies varied from 0.8 to 1.85 SD (Table 3). The studies employing higher doses (5–7) of GH achieved more improvement.

Leschek *et al.* (1) conducted a randomized, double-blind, placebo-controlled trial. Sixty-eight non-GHD short children received either GH (0.23 mg/kg/week) or placebo. Adult height was finally evaluated in 22 GH-treated children and 11 placebo-treated children and was significantly greater in the GH-treated group than in the placebo-treated group by 0.51 SDS. However the injection frequency was three times per week in both groups. When these resuits are compared with those of Wit *et al.* (7) who used daily injections of a similar dose of GH, the effect on adult height was greater in daily injection.

McCaughey (5) compared GH effects with untreated controls, though few in number. At a dose of 30 IU/m^2/week (about 0.33 mg/kg/week), adult height was 7.5 cm taller on average in GH-treated children after a mean treatment period of 6.2 yr than in the untreated control group. Hintz *et al.* (6) estimated the effect of GH treatment on the adult height of non-GHD short children at a dose of 0.3 mg/kg/week for 5.5–6.0 yr, the difference between predicted adult height before treatment and achieved adult height was 9.2 cm greater in boys and 5.7 cm in girls than the corresponding difference in the untreated historical controls.

Wit *et al.* (7) compared the adult height of 50 GH-treated patients with idiopathic short stature. Patients were treated with GH at 0.24 mg/kg/week, 0.24 mg/kg/week for the first year and at 0.37 mg/kg/week thereafter, or 0.37 mg/kg/week, and their mean height SDS increased by 1.55, 1.52, and 1.85 SD, respectively. They concluded that the effect of GH treatment on adult height was dose-dependent and that regimens increasing dosage from the second year were less efficacious.

One study in Japan found that after 4.2 yr of GH treatment at a dose of 0.5 IU/kg/week (0.167 mg/kg/week), the average adult height of 9 GH-treated non-GHD short boys, 154.2 cm, was significantly shorter than the adult height of 18 untreated short boys, 162.0 cm (8). Bone age at the onset of puberty did not differ significantly between the groups, but pubertal height gain was significantly greater in the untreated boys. Yet the approximately 1-yr bone age difference at the start of treatment, though it was not statistically significant, might cause to early epiphyseal closure and hence lower the adult height in the GH-treated group rather than GH treatment itself. Another study by the same group (Kawai *et al.* (9)) compared adult height in 11 GH-treated non-GHD short girls treated at the same dose, 0.5 IU/kg/week for 4.2 yr on average, with 11 untreated short girls, and found no significant difference.

The long-term effect of GH treatment is usually evaluated in terms of adult height. Since adult height, however, depends heavily on height SDS at the start of GH treatment (10), change in height SDS from the start of GH treatment to adult height is a more precise evaluation. In our study, the tallest height after the timing of less than 2 cm/yr of height velocity was defined as adult height, and adult height was taller in untreated short children than in GH-treated non-GHD short children. But this is because the pre-treatment height SDS of the GH-treated non-GHD short children was significantly lower than the baseline height SDS of the untreated short children. Adjusted for pre-treatment height SDS, adult height SDS was not significantly different between the GH-treated patients and the untreated controls. In no situation did the change in height SDS in the two groups differ significantly. It can only be concluded that, in this study, GH treatment in non-GHD short children was ineffective in improving adult height.

In GHD, there is a significant positive correlation between age at onset of puberty and age at the start of GH treatment (11–13). Increasing evidence points to an important role for GH in gonadal function through induction of local production of IGF-I in the ovary or in the testis and by increase of gonadotropin-dependent gonadal functions such as sex steroid production and ovulation (13–16). These facts demonstrate that GH accelerates pubertal onset and that the resulting relatively early pubertal development adversely effects decompensates the catch-up growth observed for the first few years following initiation of GH treatment. The lack of improvement in adult height in GH-treated non-GHD short children is attributable mainly to the early induction of puberty by GH treatment and the relatively poor response to GH in non-GHD short children, even though GH treatment improves growth velocity during the first two or three years (10). It is well known that adult height shows a strong positive correlation with height at the onset of puberty in GH-treated short children (11). Therefore, to achieve normal adult height in GH-treated short children, height must be normalized at onset of puberty.

In this study, puberty was not analyzed since the onset of the puberty is often not correctly evaluated and in our experience tends to be judged later than its actual occurrence. Therefore, the prepubertal height SDS and adult height SDS were analyzed. The GH dosage used in Japan now (0.175 mg/kg/week) induces catch-up growth for only a few years, but in non-GHD short children it seems insufficient to normalize

height by the onset of puberty and to increase height SDS to an extent exceeding natural improvement in untreated short children.

Natural improvement of height SDS in short children has been reported to range between 0.4 and 0.7 SD (1, 2, 17), as it did in our study. To prove that GH treatment is effective in non-GHD short children, it is necessary to achieve a gain in height SDS greater than 1 SD through GH treatment. Leschek *et al.* (1) report 0.93 SD improvement on average by GH at a dose of 0.23 mg/kg/week injected thrice a week, significantly greater than the natural improvement in placebo-treated short children (0.42 SD on average). Other studies employing higher doses reported greater than 1 SD improvement (5–7).

There may be a small possibility that the real adult height is different from the adult height defined in this study. It is possible that both GH treated and untreated groups will grow after the adult height of this definition. GH-treated non-GHD short children will grow after the growth velocity drops below 2 cm/yr, but such growth is around 5 mm in our experience. Untreated non-GHD short children have a tendency of delayed puberty. Boys with delayed puberty will grow after 17 yr, but the growth is less than 1 cm with a few exceptions (18). Therefore, these minimal differences in adult height do not essentially change our conclusion.

The above findings and considerations demonstrate that the effect of GH treatment is dose-dependent and suggest that doses over 0.23 mg/kg/week are necessary to achieve meaningful improvements in adult height in non-GHD short children. We conclude that GH treatment in non-GHD short children in Japan does not improve the adult height of treated children because the GH dose currently being administered, 0.175 mg/kg/week, is insufficient.

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ORIGINAL ARTICLE

Effect of growth hormone treatment on trunk fat accumulation in adult GH-deficient Japanese patients: a randomised, placebo-controlled trial

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Key words: Abdominal obesity – GH deficiency – GH treatment – Trunk fat

ABSTRACT

Objective: Patients with growth hormone deficiency (GHD), both Japanese and Caucasian, have an abnormal body composition with pronounced abdominal obesity. This study aimed to evaluate changes in trunk fat with GH treatment.

Design: Double-blind, placebo-controlled study.

Patients and measurements: Sixty-one Japanese adult GH deficient patients (mean age 37 years) were randomised to either GH, titrated to 0.012 mg/kg/day, (n = 30) or placebo (n = 31) for 24 weeks. Body composition, by dual-energy X-ray absorptiometry (DXA), was evaluated at a central laboratory for trunk fat, total body fat and lean body mass. Serum lipid levels were also determined centrally.

Results: At baseline, 26 (42.6%) patients had a body mass index (BMI) ≥ 25 kg/m^2, the threshold for obesity-related complications for Japanese subjects. Median trunk fat mass (FM) was ≥ 9.0 kg for each treatment and gender group, higher than the cut-off for increased age-adjusted risk for cardiovascular complications reported in the

normal Japanese population. After 24 weeks of GH treatment, the change in percentage trunk FM was −3.4 ± 0.6%, versus 0.4 ± 0.6% with placebo ($p < 0.001$). Change in total body FM was −2.8 ± 0.5% with GH and 0.0 ± 0.5% with placebo, indicating that the decrease in trunk fat was more pronounced than for total body fat. Total and low density lipoprotein (LDL)-cholesterol were both significantly ($p < 0.001$) decreased compared with placebo. One patient discontinued due to a subdural haematoma and one had GH dose reduced due to hyperglycaemia.

Conclusions: Japanese patients with GHD have abnormal central fat accumulation, which is reduced by GH treatment over 24 weeks. This may reduce cardiovascular risk but the GH dose should be individualised to maintain IGF-I in the normal range.

Introduction

One of the most prominent features of the adult growth hormone deficiency (GHD) syndrome is the abnormal body composition with increased body fast mass (FM) and decreased lean body mass (LBM)[1,2]. Specifically, the increase in FM in these subjects is characterised by pronounced abdominal obesity[3], a well known risk factor for the development of metabolic abnormalities leading to cardiovascular complications[4,5]. In fact, epidemiological studies in Caucasian subjects have shown that the risk of cardio- and cerebrovascular morbidity and mortality in adult hypopituitary patients with GHD is increased compared to the normal population[6–8]. The increased vascular risk, with high prevalence of angina pectoris, myocardial infarction, hypertension and hyperlipidaemia, has been confirmed in adult Japanese GH deficient subjects by epidemiological surveys and cohort studies[9–11].

There is, therefore, evidence demonstrating that, in spite of differences in racial intrinsic factors and in nutritional habits, Japanese adult GH deficient subjects carry the same causes and risks for cardiovascular complications as Caucasian patients. GH replacement in adult patients with GHD decreases overall fat mass and improves lipid status, and in Caucasian patients, studies suggested that the FM reduction involves predominantly abdominal fat, thus acting on one of the primary causes of increased risk[3]. Studies in the normal Japanese population have examined the relationship of direct measurements of body fat distribution to cardiovascular complications and provided age-adjusted cut-off values for dual-energy X-ray absorptiometry (DXA) trunk FM for increased cardiovascular risk[12]. Based on this background, we designed a study to assess upper body obesity by DXA measurement of truncal fat in adult GH deficient patients and to examine the hypothesis that GH replacement has a significant effect on this measure.

Patients and methods

This was a 24-week, randomised, placebo-controlled, double-blind study performed in 20 Japanese study centres. All patients gave informed consent and the study was performed with appropriate ethical approval and according to the Declaration of Helsinki. Japanese patients aged 20–64 years, with organic or idiopathic, isolated or multiple, childhood onset (CO) as well as adult onset (AO) GHD were recruited. AO patients were defined as having onset of GHD at 18 years or above and CO patients as having had onset before 18 years of age. For diagnosis of GHD, the criteria set in the GRS guidelines were used[13]; patients had to have a serum GH peak < 3.0 µg/L in the insulin tolerance test (ITT) or, in the presence of a contraindication to the ITT, in an arginine or glucagon test. For patients with isolated GHD confirmation was required by a peak GH value < 3.0 µg/L in an additional test to the ITT, either arginine or glucagon test. Replacement therapy for other missing hormones had to be stable and adequate during the 3 months prior to entering the study and throughout the study. Malignancy, diabetes, severe organ dysfunction, severe hypertension and pharmacologic treatment with glucocorticoids were major exclusion criteria.

A total of 61 patients, 32 with CO and 29 with AO GHD were enrolled and randomly assigned to treatment with either recombinant human GH (Nutropin AQ, Genentech Inc., San Francisco, USA) or placebo, with stratification by gender and onset. GH was started at a dose of 0.003 mg/kg/day for the first 4 weeks, then increased to 0.006 mg/kg/day until Week 12 and thereafter given at the final dose of 0.012 mg/kg/day until the end of the study at 24 weeks; maximum total daily dose had to not exceed 1.0 mg/day. In the event of side effects that were thought to be GH-related at the final dose of 0.012 mg/kg/day, a 50% dose reduction was permitted at the physician's discretion.

At the baseline, 12- and 24-week visits, LBM, total FM and trunk FM were measured by DXA. All DXA measurements performed in each investigative centre were evaluated centrally; a hard copy of the DXA scan data was sent to the DXA Central Evaluation Committee which was responsible for the analysis of the individual patient scans in a blinded manner. Serum IGF-I concentrations, as well as triglycerides and total, high density lipoprotein (HDL-) and

LDL-cholesterol levels, were measured centrally (Hachioji Laboratories, SRL Inc., Japan). Standard deviation (SD) scores were calculated from serum IGF-I concentrations by comparison to age- and gender-matched subjects[14].

Safety was assessed by the recording of treatment-emergent adverse events, laboratory test values and blood pressure. Laboratory determinations were performed centrally and included measurements of liver and kidney function, thyroid hormones and glycosylated haemoglobin (HbA_{1c})concentrations.

All results were analysed on the full dataset in an intent-to-treat basis. Change in the percentage trunk fat for GH-treatment versus placebo was the primary efficacy measure of the study. The baseline to 12-week and baseline to 24-week differences in actual and percentage changes in body composition between GH- and placebo-treated patients were compared by analysis of variance (ANOVA) after adjustment for gender and onset. Group comparisons were made using Fisher's exact test, chi-square test and Mann–Whitney test as appropriate. Significance levels were set at a two-sided level of 5%.

Results

The baseline demographic, anthropometric and diagnostic criteria of the patients by assigned treatment group are presented in Table 1. The patients were well randomised and no significant differences were seen in baseline presentation between GH and placebo-treated patients. Mean age of GH-treated and placebo-treated patients were 40 ± 14 years and 35 ± 11 years ($p = 0.155$), respectively. More than two thirds of the patients had an organic cause of hypopituitarism and GHD, and all except one placebo-treated patient had multiple pituitary deficiencies. Peak GH values in the stimulation tests, as well as baseline IGF-I status demonstrated severe GHD for all patients. In total for the two treatment groups, 42.6% of the patients had a BMI ≥ 25.0 kg/m^2.

Baseline DXA body composition values are presented in Table 2 for male and female subjects by treatment group. The median trunk fat mass values in males were 9.4 kg in the GH-treated and 9.0 kg in the placebo group and in females were 9.1 kg in the GH-treated group and 11.6 kg in the placebo group.

Table 1. *Baseline characteristics of Japanese GH deficient patients, by assigned treatment group*

	GH ($n = 30$)	Placebo ($n = 31$)	p-value
Age (years), mean ± SD	40 ± 14	35 ± 11	0.155
Onset, *n* (%)			1.000
childhood, *n* (%)	16 (53.3%)	16 (51.6%)	
adult, *n* (%)	14 (46.7%)	15 (48.4%)	
Male/female, *n/n*	15/15	17/14	0.800
Aetiology of GH deficiency			0.749
idiopathic, *n* (%)	5 (16.7%)	7 (22.6%)	
organic, *n* (%)	25 (83.3%)	24 (77.4%)	
Duration of GHD (years), mean ± SD	15.8 ± 9.1	13.5 ± 8.2	0.413
Height (cm), mean ± SD	159.7 ± 8.3	159.2 ± 7.4	0.634
BMI (kg/m^2), mean ± SD	24.8 ± 3.2	24.2 ± 4.2	0.609
≥ 25.0 kg/m^2, *n* (%)	14 (46.7)	12 (38.7)	0.445
< 25.0 kg/m^2, *n* (%)	16 (53.3)	19 (61.3)	0.585
Peak GH (μg/L), mean ± SD	0.25 ± 0.56	0.17 ± 0.27	0.171

Table 2. *Body composition measurements, from dual-energy X-ray absorptiometry, at baseline, by gender and assigned treatment (mean ± SD [median])*

	Males		Females	
	GH	Placebo	GH	Placebo
Fat mass (kg)	17.6 ± 5.1 (19.4)	17.8 ± 5.8 (18.9)	20.4 ± 5.4 (18.6)	22.1 ± 8.0 (20.7)
Fat mass (%)	27.1 ± 5.6 (27.1)	32.0 ± 8.8 (30.4)	39.5 ± 6.3 (38.8)	38.6 ± 7.3 (41.2)
Trunk fat mass (kg)	9.6 ± 3.1 (9.4)	8.8 ± 3.3 (9.0)	10.0 ± 2.8 (9.1)	11.3 ± 3.9 (11.6)
Trunk fat mass (%)	27.7 ± 5.9 (28.0)	30.3 ± 9.4 (27.8)	37.5 ± 7.5 (37.8)	37.9 ± 7.8 (40.6)
Lean body mass (kg)	44.9 ± 7.4 (4.2)	36.6± 10.1 (3.3)	29.7 ± 5.8 (3.1)	32.0 ± 5.1 (3.0)
Lean body mass (%)	70.0 ± 5.6 (70.3)	65.2 ± 8.7 (67.1)	57.8 ± 6.1 (58.1)	58.7 ± 6.9 (56.4)

There were three GH-treated and four placebo-treated patients who did not complete the 24-week study; the reason for discontinuation was an adverse event for one placebo patient and withdrawal of patient consent for the remainder. With GH treatment, serum IGF-I levels increased significantly in the GH-treated group (Table 3) overall, as well as for both CO and AO patients. Values at Week 12 were not as high as at Week 24, reflecting the stepwise increase in dosage. Overall, AO patients had higher mean IGF-I concentrations and SD scores than CO patients at baseline as well as under GH replacement. At the 24-week endpoint, AO patients had a mean SD score of 2.74 ± 1.84 and CO a mean SD score of –0.07 ± 1.60.

The primary efficacy measure was the change in percentage of fat mass in the trunk with GH treatment versus placebo. Mean changes from baseline to Week 12 and to the endpoint at Week 24 are presented in Table 4, together with the changes from baseline for total body FM and LBM. At Week 24, GH-treated patients had lost 3.4 ± 0.6% of trunk fat and the placebo-treated group had gained 0.4 ± 0.6%; the difference, 3.8 ± 0.8%, was statistically significant ($p < 0.001$). Over the same time period, GH-treated patients lost 2.8 ± 0.5% of total FM compared with no change (0.0 ± 0.5%) in the placebo group ($p < 0.001$), which indicated that the trunk fat reduction was more pronounced that the overall body fat reduction. The ratio of % trunk FM/% total FM decreased from baseline to Week 24 by –1.2 ± 0.5 ($p = 0.023$ for within-group change) in the GH-treated patients.

In parallel with the changes in the DXA FM measures, a significant increase in DXA LBM for GH versus placebo was observed. The net increase in LBM after 24 weeks of GH treatment was 1.17 ± 0.28 kg (Table 4).

Table 3. *IGF-I concentrations and SD scores after 12 and 24 weeks of GH or placebo treatment in Japanese CO and AO GHD patients (mean ± SD [median])*

	Childhood onset		Adult onset	
	GH ($n = 16$)	Placebo ($n = 15$)	GH ($n = 13$)	Placebo ($n = 15$)
IGF-I, µg/L				
baseline	58 ± 41 (43)	63 ± 27 (59)	82 ± 42 (77)	71 ± 36 (71)
Week 12	156 ± 86 (140)	69 ± 32 (65)	255 ± 137 (250)	71 ± 35 (71)
Week 24	194 ± 101 (205)	63 ± 29 (57)	337 ± 152 (320)	74 ± 38 (82)
IGF-I SD score				
baseline	–2.71 ± 1.19 (–2.83)	–2.75 ± 0.85 (–2.68)	–1.18 ± 1.05 (–1.32)	–1.62 ± 0.83 (–1.40)
Week 12	–0.70 ± 1.64 (–0.74)	–2.63 ± 0.96 (–2.56)	1.67 ± 1.89 (1.96)	–1.62 ± 0.87 (–1.33)
Week 24	–0.07 ± 1.60 (0.00)	–2.76 ± 0.92 (–2.64)	2.74 ± 1.84 (2.47)	–1.52 ± 0.90 (–1.50)

Table 4. *Change from baseline in body composition measured by DXA after 12 and 24 weeks of GH or placebo treatment of adult Japanese GHD patients*

	GH	Placebo	*p*-value*
Total fat mass (kg)			
Week 12	–0.72 ± 0.19	–0.21 ± 0.19	0.069
Week 24	–1.64 ± 3.20	0.18 ± 0.31	< 0.001
Total fat mass (%)			
Week 12	–1.3 ± 0.3	–0.4 ± 0.3	0.032
Week 24	–2.8 ± 0.5	0.0 ± 0.5	< 0.001
Trunk fat mass (kg)			
Week 12	–0.46 ± 0.13	–0.16 ± 0.12	0.112
Week 24	–1.05 ± 0.19	0.12 ± 0.19	< 0.001
Trunk fat mass (%)			
Week 12	–1.6 ± 0.4	–0.3 ± 0.4	0.009
Week 24	–3.4 ± 0.6	0.4 ± 0.6	< 0.001
Lean body mass (kg)			
Week 12	0.78 ± 0.21	0.36 ± 0.20	0.155
Week 24	1.17 ± 0.28	0.37 ± 0.27	0.046
Lean body mass (%)			
Week 12	1.3 ± 0.3	0.4 ± 0.3	0.033
Week 24	2.8 ± 0.5	–0.0 ± 0.5	< 0.001

*p-value for between group difference in change from baseline, by ANOVA adjusted for gender and GHD onset

Baseline values for serum total cholesterol and LDL-cholesterol concentrations were comparable in GH and placebo patients (Table 5). Serum total cholesterol was significantly ($p < 0.001$) decreased, from 217 ± 36 mg/dL to 192 ± 35 mg/dL, in the GH-treated patients and remained virtually unchanged in the placebo group. The between-group difference for the change from baseline to Week 24 was highly significant ($p < 0.001$). The same pattern of change was also seen for LDL-cholesterol values. There were no significant within-group changes or between-group differences for HDL-cholesterol (data not shown).

Treatment emergent adverse events were reported by 28 of 30 patients (93.3%) in the GH group and 27 of 31 subjects (87.1%) in the placebo group. There were no significant differences between the two groups in the incidence of adverse events or the incidence of events considered to have a possible causal relationship to the investigational product. In the GH group all adverse events were mild or moderate, and none was severe. Discontinuation due to adverse events was necessary in only one patient who developed a subdural haematoma during placebo treatment. One patient had increased HbA_{1C} level with hyperglycaemia that required a GH dose decrease, and one patient experienced a decrease in the T_4 level requiring an increase in the dose of thyroid hormone.

Discussion

The main purpose of the present study was to assess the short term effect of GH replacement on obesity status in a cohort of adult GHD Japanese patients using a double-blind, placebo-controlled design. In the Japanese population, obesity-associated risk increases at lower levels of BMI, waist or waist/hip ratio than in Caucasians. Obesity-related complications, such as hyperglycaemia, hyperlipidaemia and hypertension, significantly increase in the Japanese population at values higher than 25 kg/m^2 for BMI[15,16]. Using this threshold, it has recently been reported that up to 30% of adult GHD patients were obese[17]. In the present study, an even higher proportion of patients (46.7% males and 38.7% females) had a BMI higher than 25 kg/m^2. Thus, overall obesity is, as in Caucasians, a presenting symptom of adult GHD in Japanese subjects.

In population studies, variables indicating fat distribution, such as waist or waist/hip ratio, are used as predictive factors for cardiovascular risk[18]. These measures, however, are less suitable when precise measurement is required to quantify treatment effects in smaller cohorts and, for this reason, direct quantification of regional fat mass is preferable. Bengtsson *et al.*[3] used CT scanning and showed decreases in abdominal fat accumulation with GH treatment in Caucasian adult GHD patients. We have used DXA trunk fat mass to assess upper body obesity, because this measure has been validated as a good surrogate of abdominal fat mass in healthy Japanese subjects[19]. In addition, cut-off points for trunk fat have been developed for cardiovascular risk in the Japanese population; a cut-off of 7.8 kg trunk fat for males and 8.9 kg for females was reported to increase the age-adjusted risk for cardiovascular complications in Japanese subjects[12]. Median values for trunk fat in the present study indicated that more than 50% of the patients had abnormal upper body fat accumulation and resulting increased cardiovascular risk. Therefore, our data confirm and extend previous descriptions of body composition abnormalities in Japanese patients with the adult GHD syndrome.

Significant changes in body composition occurred with GH replacement, versus placebo, and these changes were in line with other published studies in both Caucasians and Japanese[1,3,17,20–22]. Specifically, the magnitude of the changes at 6 months for LBM and total FM were comparable with those seen in recent studies in Japanese patients, which also used DXA and a similar GH dose regimen but with different GH preparations[17,21]. On average in the present study, total

Table 5. *Serum total and LDL-cholesterol concentrations at baseline and after 24 weeks of GH or placebo treatment in Japanese GHD patients*

	GH	Placebo	*p*-value
Total cholesterol (mg/dL)			
baseline (mean ± SD)	217 ± 36	222 ± 47	
24-weeks (mean ± SD)	192 ± 35 (196)	224 ± 47	
change (mean ± SE)	−26 ± 5	1 ± 5	< 0.001
LDL-cholesterol (mg/dL)			
baseline (mean ± SD)	126 ± 31	134 ± 42	
24-weeks (mean ± SD)	108 ± 31	139 ± 42	
change (mean ± SE)	−18 ± 4	5 ± 4	< 0.001

Normal ranges: total cholesterol 150–219 mg/dL; LDL-cholesterol 70–139 mg/dL

FM at Week 24 had decreased by 1.64 kg, and trunk fat by 1.05 kg. Since the total FM change included the trunk fat change, it follows that almost 65% of total fat loss took place in the truncal region and, in fact, the change in the ratio of % fat in the trunk/% fat in the body was statistically significant. Thus, a 6 month GH treatment had a statistically and clinically significant effect on body fat distribution in Japanese adult GHD subjects. Baseline total cholesterol and LDL cholesterol concentrations, as well as the magnitude of their change under GH, were comparable with other results and confirm the short-term lipid-lowering effect of GH in Japanese adult GHD patients[17,21].

With the fixed dosage regimen used in the study, mean IGF-I levels were normalised for most patients. Baseline as well as GH-stimulated levels were higher in AO compared with CO patients, consistent with results in Caucasians but also in Japanese[16,19,20–23]. In addition, the median IGF-I SD score at 24 weeks in GH-treated AO patients indicated that a proportion of these patients had an IGF-I level exceeding the upper normal range. However, higher than normal IGF-I levels have previously been reported in studies with fixed dose regimens and, while this cannot be avoided in the context of a double-blind, placebo-controlled trial, an individualised dose regimen as recommended by the GRS guidelines[13] would avoid excessive IGF-I stimulation.

At the time of study, GH replacement in adult GH deficient patients was not an approved indication in Japan. There were 20 study centres involved in recruiting the 61 patients enrolled in the study, which may be a limitation; however, all of the investigators involved in this careful study were highly experienced in the treatment of hypopituitarism. The investigators provided replacement therapies for other missing pituitary hormones, which had to be stable and adequate for at least 3 months before enrolment. While GH is believed to affect the risk of cardiovascular disease directly, it is recognised that this will also be affected by the other elements of the hypopituitarism. GH replacement for adult GH deficient patients has been an approved indication in other countries for some years and the GH doses in the present study were based on previously published results in Caucasian patients. These doses may be higher than optimal but in order to maintain the blind they could not be individualised according to IGF-I and had to be fixed doses.

The safety profile in the present 6-month study does not differ from that reported in other studies with similar design, GH dosage and duration, either in Caucasians or in Japanese. In spite of the chosen dosing algorithm, by which GH dose was progressively increased, reporting rate of adverse events was high (93.3% in the GH-treated and 87.1% in the placebo-treated patients). However, reported adverse events did not disclose any uncommon pattern and the safety profile did not differ from that reported in other similar studies, either in Caucasians or in Japanese. Thus, we assume that the high reporting rate primarily reflected the careful attitude of investigators previously inexperienced with adult GH replacement because this was not an approved indication in Japan at the time of the study.

Conclusion

This study confirms and extends previous studies on the short-term effects of GH replacement in adult Japanese GHD patients. Although overall less obese than Caucasians, Japanese patients with the adult GHD syndrome have abnormal central fat accumulation, which is highly responsive to GH replacement. Follow-up studies will be required to confirm this beneficial effect over the longer term and to show if, as postulated, it will translate into a clinically measurable reduction in cardiovascular risk.

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Growth Hormone (GH) Effects on Central Fat Accumulation in Adult Japanese GH Deficient Patients: 6-month Fixed-dose Effects Persist during Second 6-month Individualized-dose Phase

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Abstract. Both Japanese and Caucasian adults with GH deficiency (GHD) have pronounced abdominal obesity, which is associated with increased risk of cardiovascular complications. We investigated the effects of GH treatment in 27 adult Japanese GHD patients, 15 with adult onset (AO) and 12 with childhood onset (CO) GHD. Patients initially received GH titrated to 0.012 mg/kg/day for 24 weeks in a double-blind design and the dose was then individualized for each patient according to IGF-I for a further 24 weeks. Dual-energy x-ray absorptiometry (DXA) data were evaluated for percentages of trunk fat, total body fat and lean body mass. Serum IGF-I and lipid concentrations were determined at a central laboratory. There were 25 patients who completed 48 weeks of treatment, with 7, 6 and 12 patients then receiving GH at 0.003, 0.006 and 0.012 mg/kg/day, respectively. With the reductions in dose when individualized between weeks 24 and 48, mean serum IGF-I level was reduced and excessively high values, observed in AO patients on the fixed GH dose, were no longer seen. The decrease from baseline in trunk fat was similar at week 24 (–3.8 ± 3.3%, $p<0.001$) and week 48 (–3.1 ± 3.7%, $p<0.001$), and the difference between changes was not significant. Total cholesterol was decreased from baseline by –24 ± 28 mg/dl ($p<0.001$) at week 24 and –17 ± 28 mg/dl ($p = 0.007$) at week 48. Two patients had elevated HbA1c levels: one continued GH treatment after a dose reduction and the other discontinued due to persistent impaired glucose tolerance. Therefore, excessively high IGF-I levels can be avoided by individualized dosing during long-term GH treatment. Individualized dosing maintains the decrease in abdominal fat in adult Japanese GHD patients and should reduce the cardiovascular risk.

Key words: Adult GH deficiency, Trunk fat, GH treatment, Abdominal obesity, Japan

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ABNORMAL body composition with increased body fat mass (FM) and decreased lean body mass (LBM) is one of the characteristic features of the adult GH deficiency (GHD) syndrome [1, 2]. The increase in fat mass in these patients is particularly in the abdominal area [3]. Epidemiological studies have shown that this abdominal obesity is a risk factor for development of metabolic abnormalities leading to cardiovascular complications [4, 5]. In studies in Japanese adult patients with GHD it has been shown that there is an increased risk of cardio- and cerebro-vascular morbidity and

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