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# Efficacy of needle-free administration of recombinant human growth hormone in adults with growth hormone deficiency

**Alberto M. Pereira, Agatha A. van der Klaauw, Hans P. F. Koppeschaar,[1] Jan W. A. Smit, Sjoerd W. van Thiel, Jaap van Doorn,[1] Nienke R. Biermasz, Ferdinand Roelfsema & Johannes A. Romijn**

*Department of Endocrinology and Metabolic Diseases, Leiden University Medical Centre, Leiden and [1]University Medical Centre Utrecht, Utrecht, the Netherlands*

**Correspondence**
**A. M. Pereira MD, PhD,** Department of Endocrinology and Metabolic Diseases C4-R, Leiden University Medical Centre, PO Box 9600, 2300 RC Leiden, the Netherlands.
**Tel:** + 31 7 1526 3082
**Fax:** + 31 7 2524 8136
**E-mail:** a.m.pereira@lumc.nl

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**Aim**
Needle-free administration of recombinant human growth hormone (rhGH) is effective in the treatment of growth hormone deficiency (GHD) in children, but has not been studied in adult patients. Therefore, we evaluated the efficacy of needle-free administration of rhGH in adults with GHD.

**Methods**
Insulin-like growth factor-I (IGF-I) concentrations were compared in newly diagnosed patients with GHD ($n = 21$) and in patients previously treated by subcutaneous injection of rhGH (switchers, $n = 34$), at baseline, 12 months and 24 months.

**Results**
In the new patients, IGF-I standard deviation scores (SDS) increased from $-1.82 \pm 0.46$ to $+0.75 \pm 0.33$ at 12 months and to $+0.65 \pm 0.41$ at 24 months ($P \leq 0.001$ *vs.* baseline). In switchers, IGF-I SDS remained unchanged with values of $+0.98 \pm 0.32$ at baseline, $+0.87 \pm 0.23$ at 12 months and $+0.73 \pm 0.29$ at 24 months ($P = 0.696$ *vs.* baseline). In new patients, the rhGH dose was $0.46 \pm 0.03$ mg day$^{-1}$ at 12 months and $0.47 \pm 0.03$ mg day$^{-1}$ at 24 months. In switchers, the rhGH dose was $0.53 \pm 0.04$ mg day$^{-1}$ at baseline (s.c. injection), $0.52 \pm 0.03$ mg day$^{-1}$ at 12 months and $0.48 \pm 0.03$ mg day$^{-1}$ at 24 months (NS between the different time points). There was no difference in the dose of rhGH at 12 and 24 months between the two groups. Side-effects were generally minor and consisted of local tissue reactions.

**Conclusion**
Administration of rhGH by needle-free, transdermal injection is effective in maintaining IGF-I concentrations in the normal range for age in adults with GHD, and is as effective as traditional subcutaneous injection of rhGH.

## Introduction

Recombinant human growth hormone (rhGH) is effective in the treatment of growth hormone deficiency (GHD) in children and adults. In the former patient group, administration of rhGH induces a marked acceleration in linear growth [1]. rhGH has beneficial effects on many of the changes observed in adult GHD, such as body composition, dyslipidaemia, bone mass and quality of life [2–4].

rhGH is usually injected subcutaneously by using a

pen device fitted with a needle. Although better injection devices with thinner needles have become available, some patients fear injections, which can result in non-compliance. In children administration of growth hormone by needle-free jet-injection devices has been approved for clinical use [5, 6]. These tend to lead to fewer adverse psychological reactions than injection by needle [7]. In adults, the pharmacokinetics and pharmacodynamics of rhGH administered by needle-free transdermal injection have been studied in a total of 36 healthy subjects, and this device was found to be a viable alternative to traditional injection techniques [8, 9]. However, the clinical efficacy of rhGH administered by needle-free jet-injection has not yet been documented in adult patients with GHD.

The specific objectives were to establish whether administration of rhGH by a needle-free, transdermal injection device can produce insulin-like growth factor-I (IGF-I) concentrations in the normal range for age in adults with GHD and whether transdermal needle-free jet-injection is equally effective as treatment with rhGH given by conventional subcutaneous injection.

## Patients and methods

### *Study design and definitions*

The study was designed as an open, two-centre, observational, prospective cohort study. We included all adult patients with GHD ($n = 55$) who received transdermal rhGH treatment for at least 24 months and from whom we had plasma samples stored before, at 12 and 24 months of treatment. The cohort included patients without previous rhGH treatment (new patients, $n = 21$) and patients who had received rhGH for at least 1 year by conventional subcutaneous administration (switchers, $n = 34$). Patients were diagnosed as being growth hormone deficient based on insufficient GH secretion after stimulation by insulin-induced hypoglycaemia (glucose nadir <2.2 mmol $l^{-1}$) reflected in a peak growth hormone concentration of <3 μg $l^{-1}$. When an insulin tolerance test was contraindicated, GH secretion was stimulated using the combined GHRH-arginine test (1 μg $kg^{-1}$ bodyweight GHRH i.v. bolus injection and 500 mg $kg^{-1}$ body weight arginine infusion with a maximum of 30 g for 30 min). The criterion for (severe) GHD using this test was a peak growth hormone concentration <3 μg $l^{-1}$ [10].

The study protocol was approved by the local Ethics Committees of both centres. All adult patients gave written informed consent to participation in the study.

Patients were reassessed after 12 and 24 months of treatment. Serum IGF-I concentration was the primary efficacy parameter, which was expressed as a standard deviation score (SDS) value of the normal concentration range for age and gender. The secondary efficacy parameter was the dose of rhGH used in the switchers.

### *Treatment protocol*

rhGH (Zomacton®; Ferring Pharmaceuticals, Hoofddorp, the Netherlands) was administered daily in the evening by a needle-free jet-injection system (MediJector; Antares Pharma Ltd, Minneapolis, MN, USA). This device consists of a coil spring and a steel chamber, and from 1997 onwards a disposable polycarbonate needle-free syringe. A trigger button is pressed to release the spring, pushing the GH solution out of the device, which under high pressure enters the skin into the subcutaneous space [11].

New patients were started at a dose of rhGH of 0.2 mg $day^{-1}$. Subsequently, the dose of rhGH was based on IGF-I concentrations, aiming to reach a value in the mid-normal reference range for age and gender. Switchers from a conventional pen system to needle-free injection were initially treated with the same dosage of rhGH that they used before. If necessary, the dose was also titrated in these switchers based on IGF-I concentration, aiming to reach a value in the mid-normal reference range for age and gender. Patients attended the outpatient clinic for dose titration and any other medication according to the discretion of the treating physician.

Local tissue reactions were scored by the physician at 12 and 24 months, at which times patients were asked to report any local adverse reactions by scoring the frequency of bruising in the last 4 weeks as 'Never/Rarely/Sometimes/Often'.

### *Hormone analysis*

Plasma IGF-I concentrations were measured using an immunometric technique on an Advantage Chemiluminescense System (Nichols Institute Diagnostics, San Juan Capistrano, CA, USA). The lower limit of detection was 6.0 ng $ml^{-1}$ and intra-assay variation ($n = 250$) was 8.0 and 6.0% at plasma concentrations of 30 and 450 ng $ml^{-1}$, repectively. Inter-assay variation was 8.7, 5.8 and 6.5% at IGF-I plasma concentrations of 33, 174 and 445 ng $l^{-1}$, respectively ($n = 115$). IGF-I concentrations were expressed as SDS, using lambda-mu-sigma (LMS) smoothed reference curves based on measurements in 906 healthy individuals [12, 13].

GH concentrations were measured by time resolved immunofluorometry (Wallac, Inc., Turku, Finland). Human biosynthetic GH (Pharmacia and Upjohn, Inc., Uppsala, Sweden) was used as standard, calibrated against WHO-IRP 80-505. The detection limit of the

assay was 0.01 μg $l^{-1}$ and the interassay coefficient of variation was 1.6–8.4% over the range 0.1 and 15 μg $l^{-1}$.

*Data analysis*

Statistical analysis was performed using SPSS for Windows, version 12.0 (SPSS Inc., Chicago, IL, USA). Results were expressed as mean ± standard error of the mean and as 95% confidence intervals (CI), unless specified otherwise. To assess possible differences in IGF-I SDS and dose with respect to time, ANOVA analysis with repeated measures were used to compare baseline, 12- and 24-month data. LSD (least significant differences)-adjusted pairwise comparisons for differences between IGF-I SDS and dose at the three time points were performed to provide 95% CI. *P*-value <0.05 was assumed to represent a significant difference.

## Results

The clinical characteristics of the 21 new patients and 34 switchers are summarized in Table 1. There were no significant differences in age, gender or onset (childhood onset or adult acquired) of GHD between these two groups.

Side-effects were generally minor and consisted of local tissue reactions. Bruising was reported as 'sometimes' in 31% and 33% of the patients at 12 months and at 24 months, respectively, and as 'often' in 8% and 9% of the patients at 12 months and 24 months, respectively. All patients completed the 24-month study.

At baseline, the mean IGF-I SDS for the new patients was −1.82 ± 0.46, which is below the reference value. After 12 months the IGF-I SDS significantly increased to +0.75 ± 0.33 [difference 2.57 ± 0.42 (95% CI 1.70, 3.44)] and to +0.65 ± 0.41 after 24 months [difference −0.10 ± 0.26 (95% CI −0.64, 0.45), $P \leq 0.001$ *vs.* baseline]. There was no difference between the values obtained at 12 and 24 months (Figure 1).

At baseline, the mean IGF-I SDS of the switchers was +0.98 ± 0.32. The IGF-I SDS did not change after 12 months [+ 0.87 ± 0.23, difference −0.12 ± 0.31 (95% CI −0.74, 0.51)] or after 24 months [+0.73 ± 0.29, difference −0.14 ± 0.26 (95% CI −0.67, 0.39), $P = 0.696$]. IGF-I SDS did not significantly differ at 12 and 24 months between new patients and switchers.

For the new patients, the starting dose of rhGH at baseline was 0.2 mg $day^{-1}$. These patients were receiving 0.46 ± 0.03 mg $day^{-1}$ at 12 months [difference 0.25 ± 0.03 (95% CI 0.19, 0.31)] and 0.47 ± 0.03 mg $day^{-1}$ at 24 months [difference 0.02 ± 0.02 (95% CI −0.02, 0.05)] (Figure 2).

For the switchers, the dose of rhGH was 0.53 ± 0.04 mg $day^{-1}$ (s.c. injection) at baseline, 0.52 ± 0.03 mg $day^{-1}$ at 12 months [difference −0.01 ± 0.02 (95% CI −0.06, 0.04)] and 0.48 ± 0.03 mg $day^{-1}$ at 24 months [difference −0.04 ± 0.03 (95% CI −0.09, 0.01); NS between the three time points]. At 12 and 24 months, the mean GH dose given to new patients and switchers was not significantly different.

## Discussion

The results of the present study indicate that long-term, needle-free transdermal administration of rhGH is an

**Table 1**
Clinical characteristics of the patients

| | | Switchers (*n* = 34) | New patients (*n* = 21) |
|---|---|---|---|
| Age | Mean (range) | 56 (25–80) | 50 (20–73) |
| Gender | Male (%) | 47 | 48 |
| | Female (%) | 53 | 52 |
| Onset | CO (%) | 20 | 24 |
| | AO (%) | 80 | 76 |
| Maximal GH increase | GH (μg $l^{-1}$) | 0.27 ± 0.07 | 0.68 ± 0.18 |
| Aetiology of GHD | Nonfunctional pituitary adenoma (*n*) | 10 | 9 |
| | Prolactin secreting pituitary adenoma (*n*) | 1 | 1 |
| | ACTH secreting pituitary adenoma (*n*) | 2 | 2 |
| | Craniopharyngeoma (*n*) | 6 | 2 |
| | Empty sella (*n*) | 1 | 2 |
| | Idiopathic (*n*) | 5 | 2 |
| | Sheehan's syndrome (*n*) | 1 | |
| | Other (*n*) | 8 | 3 |

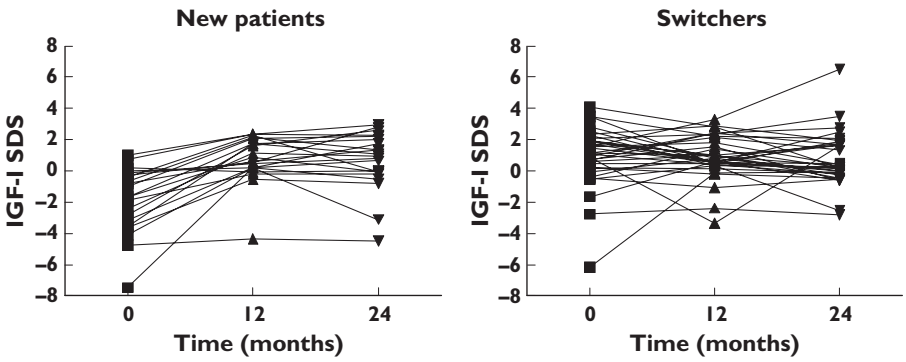


**Figure 1**
Individual insulin-like growth factor-I (IGF-I) SDS values in new patients with growth hormone deficiency ($n = 21$) and in switchers ($n = 34$), treated with a needle-free system at baseline, 12 and 24 months. There were no statistical differences at 12 and 24 months between the two groups

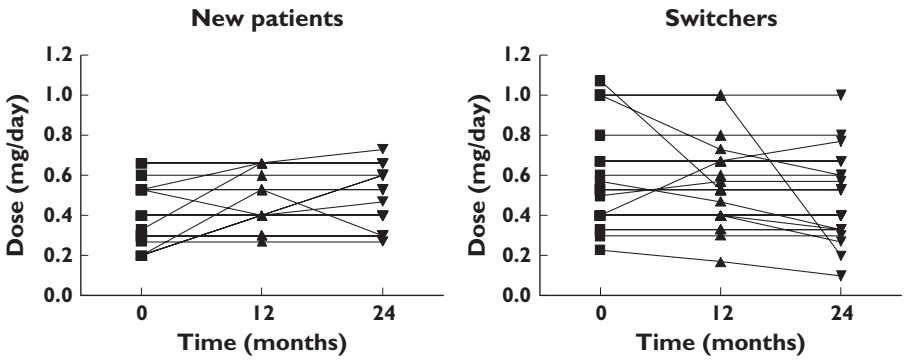


**Figure 2**
Individual doses of recombinant human growth hormone (rhGH) administered in new patients with growth hormone deficiency ($n = 21$) and in switchers ($n = 34$), treated with a needle-free system at baseline, 12 and 24 months. There were no statistical differences in rhGH dose at 12 and 24 months between the two groups

effective treatment for GH deficiency in adults. These observations are in line with previous data on needle-free systems obtained in children with GHD [5, 6]. In adult patients, administration of rhGH was effective in increasing IGF-I to concentrations within the normal range.

Target IGF-I concentrations during rhGH treatment are advised to be between 0 and +2 SDS above the mean for age [14]. In our study, GH therapy was initiated in the new patient group in full compliance with the GH Research Society guidelines, starting with a low dose [10] and resulting in mean IGF-I concentrations above the targeted mean being achieved.

Treatment with needle-free jet-injection proved to be equally effective as growth hormone given using a conventional needle pen, in increasing IGF-I concentrations without the need to change the dose of rhGH. Thus, the latter did not change significantly from baseline in patients who switched from a needle-based administration of rhGH. Moreover, the dose of rhGH was not significantly different between new patients and the switchers after using the needle-free system for 24 months. Side-effects were minimal and comparable to delivery of insulin by jet injection [11].

In conclusion, administration of rhGH by a needle-free injection device is effective in maintaining IGF-I concentrations in the normal range for age in adults with GHD. The needle-free system appears to be equally effective as a needle-based system. Therefore, needle-free administration of rhGH forms a viable alternative to the traditional subcutaneous injection technique in the treatment of GHD.

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