

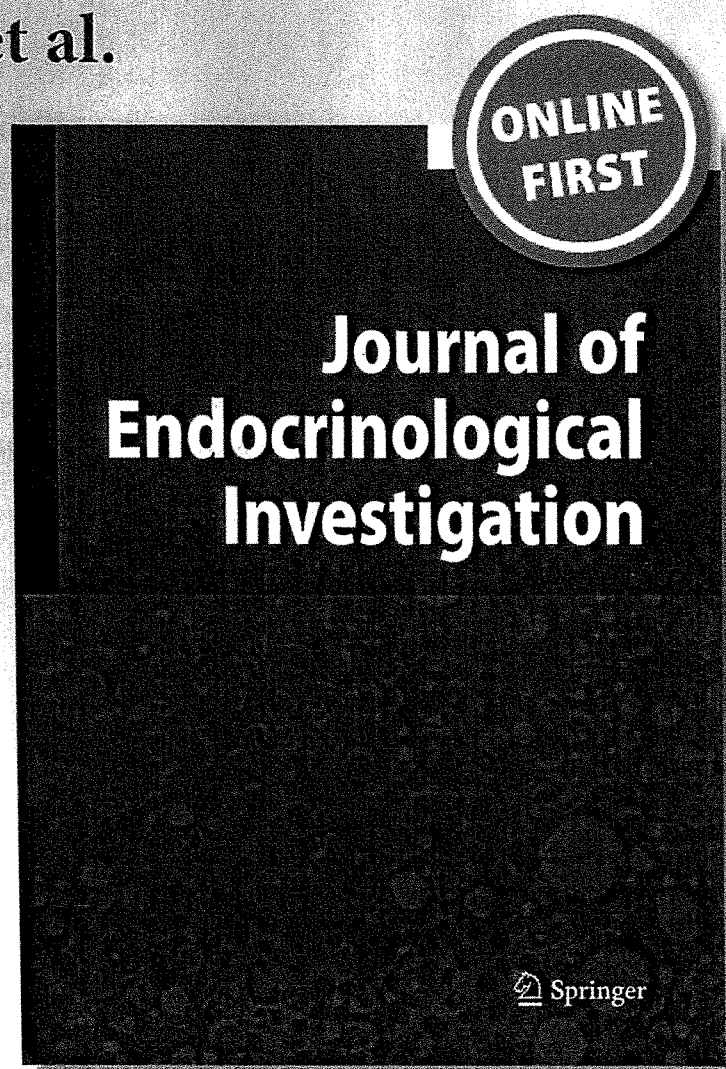
*Adherence in children with growth hormone deficiency treated with r-hGH and the easypod™ device*

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## Adherence in children with growth hormone deficiency treated with r-hGH and the easypod™ device

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### Abstract

**Purpose** Poor adherence to recombinant human growth hormone (r-hGH) therapy is associated with reduced growth velocity in children with growth hormone deficiency (GHD). This twelve-month observational study was to assess adherence in r-hGH patients treated with the easypod™, an electronic, fully automated injection device designed to track the time, date and dose administered.

**Methods** Ninety-seven prepubertal patients receiving r-hGH therapy were included in the study from ten Italian clinical sites and 88 completed the study. To avoid possible

confounding effects, only GHD patients (79/88; 89.7 % of the overall study population) were considered in the final analysis. The primary endpoint—adherence to treatment—was calculated as the proportion of injections correctly administered during the observational period out of the expected total number of injections. The relevant information, tracked by the easypod™, was collected at months 6 (V1) and 12 (V2) after baseline (V0). At study termination, adherence data were partially available from 16 patients and fully available from 53 patients. As secondary endpoints, serum IGF-1 levels, fasting serum glucose and insulin levels and key anthropometric characteristics (height, waist circumference and BMI) were also determined.

**Results** The easypod™ data showed that 56.7 % of the patients were considered to be fully ( $\geq 92$  %) adherent to their treatment throughout the period V0–V2. Treatment improved stature, significantly increased IGF-1 and produced a non-significant increase in blood glucose and insulin levels.

**Conclusions** The injection-recording system and other characteristics of easypod™ could enhance the ability of physicians to monitor adherence to r-hGH treatment.

**Keywords** Growth disorders (GD) · IGF-1 · Easypod™ · Adherence

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### Introduction

Growth hormone (GH) has been used as an elective treatment for severely GH-deficient children and adolescents since the 1960s [1]. Due to the limited availability of human pituitary-derived hormone, GH use for other conditions related to short stature could not be seriously considered until the mid-1980s, when recombinant human

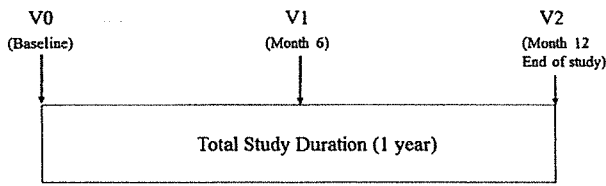


Fig. 1 Study design and plan

Pursuant to the observational nature of the study, the r-hGH treatment was administered according to routine clinical practice, independent of the patient’s participation in the study. The outcome measurements for both the primary and the secondary endpoints were assessed at visits V0, V1 and V2, respectively. The adherence to the treatment for each patient was estimated as the proportion of injections correctly administered during the observational period out of the expected total number of injections. The target rate for full adherence was defined as  $\geq 92\%$  at the start of the study.

Adherence was calculated only for patients reporting at least 150 injections every 6 months (at least 300 injections throughout the overall 12-month observational period). The adherence rate was calculated as follows:

Treatment adherence rate (%)

$$= \frac{\text{Number of days injections received during period}}{\text{Number of days injections planned during period}} \times 100$$

The statistical analysis was performed with SAS® software, version 9.2 (SAS Institute, Cary, NC, USA). As this was an observational study, no distinction between intention to treat and per protocol data sets was made, no subsets were identified and only descriptive statistical analysis was performed. IGF-1 concentrations were measured by local laboratories using standard assays. IGF-1 SDS was calculated using the normative data for the method [11].

**Results**

Within an overall study population composed of 88 enrolled subjects, 79 patients, all with GHD, were included in the final analysis. Of these, 52 (66 %) were male and 27

(34 %) were female. Median age at enrolment was 10 years (interquartile range 9–12).

**Adherence to treatment**

Adherence data were available from 53/79 (67.09 %) participants for the whole 12-month study period and from 16/79 (20.25 %) patients for a 6-month follow-up (either from V0–V1 or from V1–V2). Only 16 patients reported  $\geq 150$  injections over 6 months between V0–V1 and V1–V2. Overall, 30/53 patients reported a total number of injections  $\geq 300$  across the whole observation period. Easy-pod™ data showed that 17/30 (56.67 %) patients administering at least 300 injections across the 1-year follow-up period completed the study with the preset target adherence rate 92 %. With respect to the length of the follow-up period, administration data collected through the easypod™ were available from 28/53 (52.83 %) adherent patients. Relevant results are summarised in Tables 2 and 3.

Changes from baseline of height SDS were evaluated, showing a significant increase in height across the 12 months of follow-up (Table 4).

No correlation was found, using a linear regression model, between the change in height SDS among fully adherent patients (300 injections in the whole period) and the adherence rate (coefficient  $\beta = 0.01241$ ,  $p = 0.123$ ).

Serum glucose and insulin concentrations increased slightly, but not significantly, from baseline to V1 and V2, while IGF-1 significantly increased, as expected (Table 5).

Assessment of anthropometric characteristics revealed a statistically significant increase in height both at visit V1 and V2 (Table 6).

A linear regression model showed no relationship between the changes observed in IGF-1 standard deviation score (IGF-1 SDS) and the adherence rate of patients with at least 300 injections in the whole period (coefficient  $\beta = 0.01122$ ,  $p = 0.8517$ ). Detailed results are summarised in Fig. 2.

**Discussion**

In this study, we report the adherence rate measured by easypod in the 53 of 79 prepubertal patients with GHD (52

Table 2 Adherence by number of injections

	Adherence by number of injections (V0–V2)			
	Adherence rate	Number of injections		Total
		<300	$\geq 300$	
Frequency (%)	<92 %	12 (22.64 %)	13 (24.53 %)	25 (47.17 %)
Frequency (%)	$\geq 92\%$	11 (20.7 %)	17 (32.1 %)	28 (52.8 %)
Total (%)		23 (43.4 %)	30 (56.6 %)	53 (100 %)

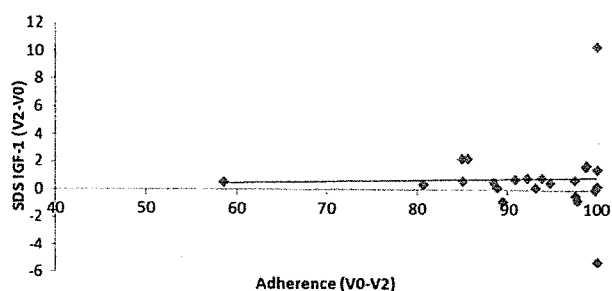


Fig. 2 Linear regression IGF-1 SDS/adherence

has no clinical significance [14, 15]. IGF-1 significantly increased but always remained within the normal range of concentrations.

The data collected by easypod™ Clinical Kit showed that 56.67 % of patients were fully adherent (adherence 92 %) to treatment for the whole period of observation (V0–V2). Our results did not show a relationship between the changes observed in IGF-1 SDS and the adherence rate of patients with at least 300 injections in the whole period. Notably, IGF-1 concentrations significantly increased in the whole studied population both at V1 and at V2. Consequently, IGF-1 concentrations were increased to therapeutic levels in the overall population. Further studies are needed, either to specifically assess the minimum number of injections necessary to achieve a therapeutic effect or to compare IGF-1 SDS levels between adherent and non-adherent patients.

Adherence to treatment has been demonstrated to be critical for the achievement of both medical and economic expected outcomes of GH therapy [16–18]. However, Fisher et al. [18] have shown that non-adherence to GH therapy in paediatric patients is affected by several factors, among which the adoption of a needle-free injection device in place of a multi-dose injection pen may not play a crucial role, according to Verrips et al. [19]. Nevertheless, Cutfield et al. [20] have pointed out how subjective (parent-reported) and objective (empty vial count) adherence rates may differ from one another, thus demonstrating unequivocally the usefulness of a device, like the easypod™, that is able to collect objective data.

## Conclusions

The results of the present study suggest that easypod™ may represent a helpful option that could assist physicians in effective monitoring of adherence to r-hGH treatment. The treatment resulted in significant changes in height SDS and IGF-1 concentrations. Further studies are needed to compare growth and IGF-1 levels between adherent vs non-adherent patients. Nevertheless, our study demonstrates

that, even when therapeutic adherence is not strictly observed, but IGF-1 levels are maintained at therapeutic levels, with modern, easy to use, recombinant hormone formulations, r-hGH supplementation is safe and efficacious.

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## Compliance with ethical standards

**Conflict of interest** The authors take full responsibility for the content of the paper. All authors have read and approved the final version of the manuscript. Raffaella Perrone is an employee of Merck Serono SpA, Italy, and Salvatore Longobardi is an employee of Merck KGaA, Darmstadt, Germany. Mariacarina Salerno, Piernicola Garofalo, Giuliana Cardinale, Maria Rosaria Licenziata, Guiseppa Citro, Manuella Caruso Nicoletti, Marco Cappa and Mohamad Maghnie declare no conflicts of interest. Sandro Loche has received fees as a consultant to Merck Serono.

**Ethical approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

**Informed consent** Informed consent was obtained from all individual participants included in the study.

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