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Original Article

Self–reported vs Electronically Recorded Adherence to GH Therapy

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Abstract

Introduction: adherence to the prescribed injection schedule is critical for the success of treatment of growth disorders with recombinant human growth hormone (r–hGH), so monitoring adherence is an important component of effective management.

Methods: we directly compared self–reported injection adherence data with data recorded from a digitally enhanced electromechanical injection device and software – the easypod™ connect system. Patients with an active easypod™ connect account were identified in seven Latin American countries. Participants completed a survey requesting data including recollection of the number of doses missed in the previous month. These data were compared with the electronically captured date, time, and dose administered by easypod™.

Results: of 402 patients receiving r–hGH treatment, 337 (84%) had an active easypod™ connect account and 301 completed the survey. The self–reported adherence data showed that overall, patients or their parents/caregivers believed that their average rate of adherence was 90.5%, equivalent to missing approximately 33 doses a year, or one month of treatment. The easypod™ data showed that the average adherence rate was 80.9%, equivalent to missing 67 injections, or approximately 2 months of treatment, per year.

Conclusions: our results show that patients over–estimate their own adherence by ~10%. This disparity between perceived and actual adherence represents approximately one month of missed injections a year, which is likely to lead to sub–optimal growth and clinical outcomes. Electronic monitoring with the easypod™ connect system appears to be an effective technique for identifying low adherence, providing healthcare professionals with the opportunity of intervening to help patients improve their adherence.

Keywords: adherence; easypod™; growth disorders; growth hormone; injection device; somatropin

Highlights

- Monitoring patient adherence is critical to the success of recombinant human growth hormone (r–hGH) therapy to treat growth disorders.

- Patient self–reported adherence to r–hGH was directly compared with electronically monitored adherence recorded by a digitally enhanced electromechanical injection device (easypod™) as part of a digital health ecosystem (easypod™ connect) in patients from seven Latin American countries.

- Patients over–estimated their own adherence by ~10%. This disparity between self–reported and actual adherence represents approximately one month of missed injections a year and may lead to sub–optimal growth and clinical outcomes.

- Electronic monitoring with easypod™ connect appears to be effective in identifying low adherence in patients receiving r–hGH for growth disorders, providing clinicians with an opportunity to intervene to improve patient adherence and optimize treatment outcomes.

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Adherencia reportada vs electrónica de terapia con hormona de crecimiento

Resumen

Introducción: la adherencia al esquema de inyecciones prescrito es crítica para el éxito del tratamiento de los trastornos del crecimiento con la hormona del crecimiento humana recombinante (r–hGH), por lo que monitorear la adherencia es un componente importante de un tratamiento eficaz.

Métodos: comparamos directamente los datos auto informados sobre la adherencia a la inyección con los datos registrados por un software y un dispositivo de inyección electromecánico mejorado digitalmente: el sistema easypod™ connect. Se identificó a los pacientes con una cuenta easypod™ connect activa en siete países de América Latina. Los participantes completaron una encuesta que recolectaba el número de dosis omitidas en el mes anterior a la encuesta. Estos datos se compararon con la fecha, hora y dosis registradas electrónicamente por easypod™.

Resultados: de 402 pacientes que recibieron tratamiento con r–hGH, 337 (84 %) tenían una cuenta de easypod™ connect activa y 301 completaron la encuesta. Los datos de adherencia auto informados mostraron que, en general, los pacientes o sus padres/cuidadores creían que su tasa media de adherencia era del 90,5 %, equivalente a omitir aproximadamente 33 dosis al año o un mes de tratamiento. Los datos de easypod™ mostraron que la tasa de cumplimiento promedio fue del 80,9 %, equivalente a faltar 67 inyecciones, o aproximadamente 2 meses de tratamiento, por año.

Conclusiones: nuestros resultados muestran que los pacientes sobrestiman su propia adherencia en ˜10 %. Esta disparidad entre la adherencia percibida y real representa aproximadamente un mes de inyecciones omitidas al año, lo que probablemente conducirá a un crecimiento y resultados clínicos subóptimos. La monitorización electrónica con el sistema easypod™ connect parece ser una técnica eficaz para identificar una baja adherencia, proporcionando a los profesionales sanitarios la oportunidad de intervenir para ayudar a los pacientes a mejorar su adherencia.

Palabras clave: Adherencia; easypod™; desórdenes del crecimiento; hormona del crecimiento; dispositivo de inyección; somatropina

Destacados

- Monitorear la adherencia del paciente es fundamental para el éxito de la terapia con la Hormona del Crecimiento humana recombinante (r–hGH) para tratar los trastornos del crecimiento.

- La adherencia a la r–hGH autoinformada por los pacientes, se comparó directamente con la adherencia monitoreada electrónicamente registrada por un dispositivo de inyección electromecánico mejorado (easypod™), como parte de un ecosistema de salud digital (easypod™ connect), en pacientes de siete países de Latinoamérica.

- Los pacientes sobreestimaron su propia adherencia en ˜10%. Esta disparidad entre la adherencia autoinformada y la adherencia real representa aproximadamente un mes de inyecciones perdidas al año y puede desencadenar en crecimiento y resultados clínicos subóptimos.

- Monitorización electrónica con easypod™ parece ser eficaz para identificar la baja adherencia en pacientes que reciben r–hGH para trastornos del crecimiento, lo que brinda a los médicos la oportunidad de intervenir para mejorar la adherencia del paciente y optimizar los resultados del tratamiento.

Introduction

Adherence to the treatment regimen is critically important for children being treated with recombinant human growth hormone (r–hGH) for growth disorders, in order for them to achieve optimal growth and clinical outcomes (1, 2). Growth rates are significantly lower in patients with low adherence; height velocity has been reported as being 6.3 cm/year for those missing >3–4 injections per week versus 9.4 cm/year in patients missing fewer injections (3). In another study, patients with good adherence (≥85%) had significantly greater linear growth over the study period than those with suboptimal adherence (p<0.05) (4). Treatment with r–hGH involves daily subcutaneous injections over periods of several years and, as many children and parents find this unpleasant and/or painful, adherence is very often suboptimal, which has negative effects on the potential increase in growth that treatment offers these children with growth disorders (1–7). Even patients who start with good adherence can show signs of treatment fatigue over the long duration for which GH treatment is required, especially younger children (8). Other reasons for suboptimal adherence include lack of awareness, understanding, and knowledge of their condition and their treatment, as well as forgetfulness, failure to renew prescriptions, poor injection technique, perceived lack of treatment effect, disrupted lifestyle, other illnesses and poor HCP/patient communication (9).

Therefore, monitoring adherence is an important part of the management of growth disorders, so that, where necessary, healthcare providers (HCPs) can intervene with strategies aimed at improving the adherence of the children, with support from their parents or caregivers. Until recently, however, monitoring adherence has been problematic, given that the only methods available have been potentially unreliable proxy measures, such as self–reporting by the children or their parents/caregivers, prescription fulfillment records, or counting returned vials of r–hGH (5, 8).

The development of an electromechanical auto–injection device called easypod™, linked to the easypod™ connect platform, has made it possible to record and transmit the date, time, and dose of r–hGH (somatropin; Saizen®, Merck KGaA, Darmstadt, Germany) delivered with every injection administered (10, 11). This information enables HCPs to review the injection history and settings used and to evaluate the adherence of the individual patient using the easypod™ device. Use of the easypod™ device is now considered to be a more robust and accurate way or method of monitoring adherence than the more widely used, yet less reliable proxy methods (8, 12).

The key objective of this study was to compare self–reported adherence to r–hGH with the electronically monitored adherence data recorded by easypod™ connect in a cohort of patients receiving r–hGH via the easypod™ device.

Methods

The number of patients with an active easypod™ connect account in the CENTRO region was determined as a first step. All seven countries of the region were involved: Honduras, Costa Rica, El Salvador, Dominican Republic, Nicaragua, Panama, and Guatemala in ascending order of number of patients. The easypod™ connect ecosystem includes the easypod™ device, its base transmitter, and the 'connect' web–based software used by the patient to send their data to the relevant HCP. Also, it anonymizes data and adds it to a secure database.

The only inclusion criteria for this study were treatment with r–hGH via the easypod™ device and active use of their easypod™ connect account. Patients without an active easypod™ connect account were excluded from the study. Participation in the study was entirely voluntary. All data were anonymized and could not lead to identification or tracking of individual patients by the prescribing HCPs or the sponsor and no commercial use could be made of the data. For this reason, the age and indication for r–hGH treatment for individual patients were not recorded. The study was conducted during March and April 2019 and involved the Saizen® patient support program (PSP) call center staff and nurses. Specifically, the nursing team scheduled visits to patients to collect data during the visit; patients who did not have a scheduled visit were contacted via the call center staff to collect their data. The data collected were delivered to the PSP coordinator.

The adherence rate of the patients with active easypod™ connect accounts was calculated from data recorded by easypod™ connect to compare with the same patients' self–reported adherence rates for the month of April 2019. These data were collected either by the nursing team during routine patient visits or by PSP call center staff contacting the patient or caregiver when a visit could not be scheduled during the study period. A single–question survey was sent to all the patients to obtain their perceived adherence rate to provide the data for the comparison and for other analyses of interest, such as adherence rates by country. The survey was validated before use by the Compliance, Pharmacovigilance, Medical, and Patient Support Program departments of the study sponsor.

The data requested in the survey questionnaire were the patient's country of residence, origin of their data (state–provided or private healthcare), gender and date of birth of the patient, duration of treatment, and what they believed their treatment adherence to have been over the previous month (Supplementary Table 1). To enable the comparison between self–reported and easypod™–recorded adherence rates, only data recorded by easypod™ during the same one–month period were used. All data collected were collated and tabulated by the PSP coordinator.

Results

A total of 402 patients in the CENTRO region were receiving treatment with r−hGH and 337 of these (84%) had an active easypod™ connect account. The survey was completed by 301 patients (89%) of the 337. By breaking the results down by country, we can see a wide range of average numbers of days with missed injections for the previous month (Table 1, Figure 1), although, in some countries, the number of patients eligible for the survey was low. In fact, there were no patients in Honduras who had an active easypod™ connect account and who completed the survey during the study period. Therefore, data from patients in the other 6 countries are reported representing a total of 299 patients (Table 1). The self−reported adherence data showed that participating patients or their parents/caregivers believed that their average rate of adherence across all countries/centers was 90.5% (Figure 2).

Table 1. Countries in ascending order of the number of participating patients

Country	Number of patients	Percentage of total patient population	Average number of missed injections in study month
Honduras	2	0.67	n/a*
Costa Rica	6	1.99	1.2
El Salvador	17	5.64	4.2
Dominican Republic	41	13.62	2.7
Nicaragua	47	15.61	7.7
Panama	84	29.90	2.3
Guatemala	104	34.55	1.1
TOTAL	301		

*n/a, not available. No data are shown for Honduras as there were no patients with active easypod™ connect accounts in this country who completed the survey during the study period.
Source: The authors.

Assuming these data are accurate, this would mean that, on average, each patient would be missing approximately 33 doses a year or the equivalent of one month of treatment. However, the data provided by the easypod™ connect system showed that the actual rate of adherence across all countries/centers was 80.9%, equivalent to missing injections on 67.28 days, representing approximately 2 months of treatment per year. This ˜10% disparity between perceived and actual adherence represents approximately one month of missed injections a year averaged across countries, with variations between the different countries in the degree of the disparity (Figure 2).
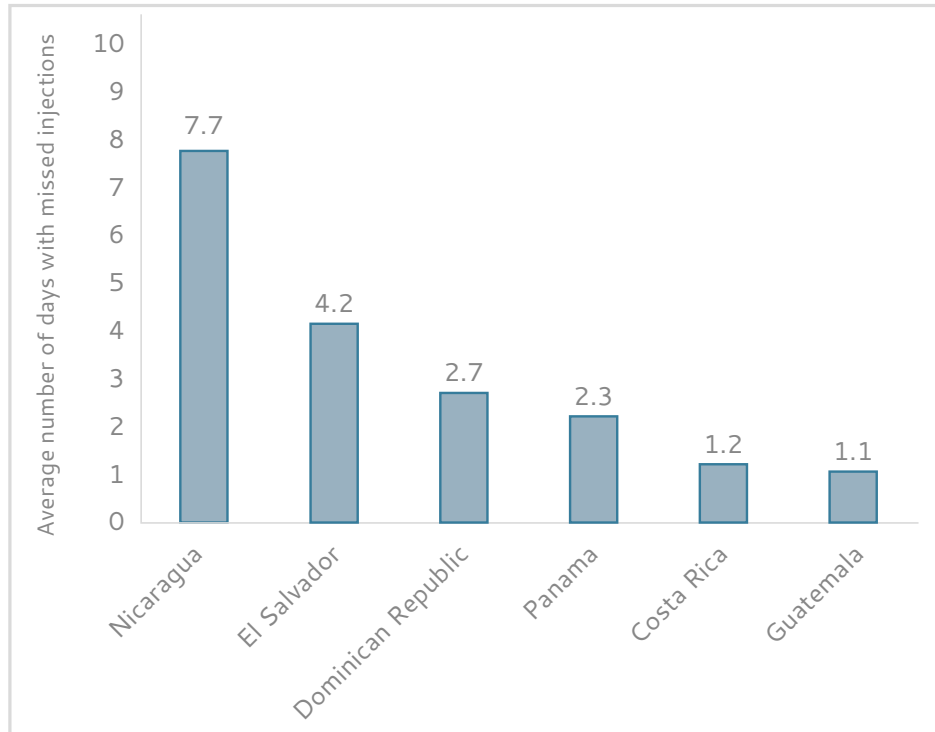
Figure 1. Average number of days with missing injections by country

Note: No data are shown for Honduras as there were no patients with active easypod™ connect accounts in this country during the study period.
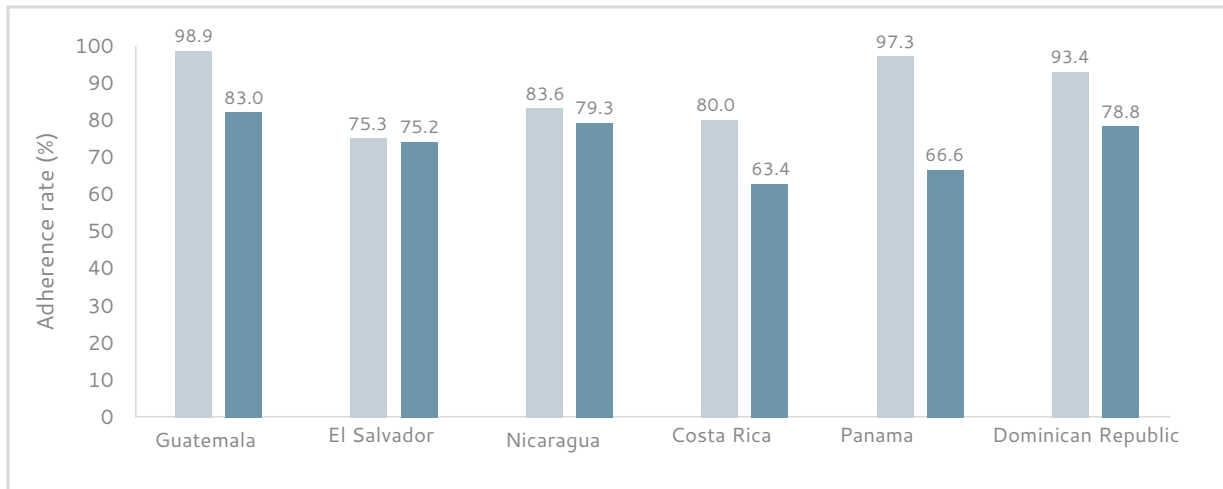
Source: The authors.

Figure 2. Comparison of adherence rates (%) by country: self–reported adherence rate versus easypod™ connect–reported adherence rate

Note: No data are shown for Honduras as there were no patients with active easypod™ connect accounts in this country during the study period.

Light blue = Self–reported adherence rate; Dark blue = easypod™ connect–reported adherence rate

Source: The authors.

Discussion

To our knowledge, our study is the first to directly compare self-reported adherence against objective, electronically monitored adherence behavior in the CENTRO region. We found that the self-reported adherence rate was ~10% higher than the actual rate recorded by easypod™ connect, which indicates that the equivalent of one month's treatment per year is being missed and not reported by the patients. These results highlight the need for accurate, objective recording of adherence data in young patients receiving r-hGH for growth disorders, such as those with GH deficiency, Turner syndrome, and children born small for gestational age, to enable HCPs to intervene where needed to try to improve adherence and clinical outcomes. Use of easypod™ in this way has been shown in several studies to improve adherence and growth and other clinical outcomes [11, 13–16].

Previous studies using different methodologies have reported a wide range of adherence rates for children receiving r-hGH therapy [1, 3, 5, 6]. This may be due to differences in the study population or to the methodology used in the various studies. A study in the UK, which estimated adherence based on prescription data over a 12-month period, reported that 29 of 75 patients (39%) missed more than one injection a week, while 17 of 75 (23%) missed more than two a week, indicating the scale of the problem (5). Physician-reported adherence from a US registry study over 2 years found that 76–85% of patients missed 0–3 doses per month (3). Furthermore, a systematic review of the literature found rates of non-adherence ranging from 5 to 82% among children receiving r-hGH therapy and noted that most patients are non-adherent to some degree occasionally [17], as our survey results clearly confirm.

Because of the ≥85% adherence, missing no more than one injection a week is generally considered to be optimal [8, 16, 18]. The perceived level of adherence of 90.5% reported by the patients and caregivers in our study appears to be promising, but the objective data provided by the easypod™ device show clearly that this is an over-estimate. The reasons why patients tend to over-report the number of injections they take

or underestimate the number they have missed can vary [5, 8, 9, 11]. Forgetting to take a dose is common and the number of doses missed may also be forgotten when the patient is asked about this at clinic visits [4, 7, 19].

Another possible explanation is deliberate under-reporting of missed doses, given that even when the patient or parent/caregiver does remember missing doses, they may not want to disappoint their HCP by reporting this or they may feel too embarrassed to report it [4, 20]. The reasons behind the non-adherence behavior can also vary, but, in addition to treatment fatigue over the long course of treatment, the discomfort or perceived unpleasantness of injections is an important factor for many young patients [21]. The easypod™ device was also designed to address this factor and to help to improve adherence and reduce fear of injections [8, 10, 21]. The GH dose to be administered is set by the HCP but the patient or parent can adjust four different comfort settings for the speed, depth, and duration of the injection process, and the needle is hidden to help patients with a fear or dislike of needles [8]. In one study, 61% of 780 patients reported that they felt no pain when using the easypod™ to inject their r-hGH [8]. The device is also designed to be easy to use and, in contrast to other injection devices, it minimizes wastage by recording when only a partial dose has been administered from an emptied cartridge and calculating how much needs to be delivered to complete the dose when a fresh, full r-hGH cartridge is inserted [10]. The automatic recording of adherence data (date, time, and administered dose) enables HCPs to reliably assess the true level of adherence of their patients, rather than relying on patients' self-reported adherence. Thus, the ease of use and overall 'patient-friendliness' of the easypod™ connect ecosystem could help HCPs to ensure that their patients gain the optimal benefits from their r-hGH treatment [10, 16, 21].

The strengths of our study are the use of the same individuals in both comparator groups, so that we could ensure an exact comparison over the same period, as well as the use of electronic monitoring to provide accurate, reliable real-world data on adherence to compare with the self-reported data. Study feasibility, the relatively

low cost and the availability of a dedicated work force are other strengths of this study. Possible weaknesses are the retrospective nature of the study design, absence of a head-to-head comparison, detailed knowledge of factors that affect over-reporting, and assessment of socioeconomic background which might be different in each country, the relatively small number of patients involved, the cross-sectional design of the study, and the short study period of one month. Larger, longer studies with additional assessments applied to understand the factors behind over-reporting of adherence data by caregivers and children could be conducted to address these factors.

Conclusions

In conclusion, our study shows that patients in this region tend to over-estimate their adherence by around 10%, and the true, lower level of adherence is likely to lead to sub-optimal growth and clinical outcomes. Use of electronic monitoring with the easypod™ connect system appears to be an effective and potentially valuable technique for identifying suboptimal adherence, providing HCPs with the opportunity of intervening with patients and parents/caregivers to try to improve their level of adherence to long-term treatment with r-hGH.

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Conflicts of Interest

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