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Preferences for Injection Device Settings and the Association with Adherence to Growth Hormone Treatment in Patient with Growth Disorders

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Abstract. Adherence to recombinant human growth hormone (r-hGH; somatropin, [Saizen®], Merck Healthcare KGaA, Darmstadt, Germany) treatment is important to achieve positive growth and other outcomes in children with growth disorders. Automated injection devices can facilitate the delivery of r-hGH, injections of which are required daily for a number of years. The ability to adjust injection device settings may improve patient comfort and needle anxiety, influencing adoption and acceptance of such devices, thereby improving treatment adherence. Here, we present the results of a retrospective observational study which investigated the association between injection device settings and adherence in the first 3 months of treatment in patients with growth disorders. Patients aged ≥2 and <18.75 years of age at treatment start, with ≥3 months of adherence data from start of treatment with the third generation of the easypod® device (EP3; Merck Healthcare KGaA, Darmstadt, Germany) were selected (N=832). The two most chosen combinations of device settings at treatment start were the default settings for injection speed, depth and time, or a slow injection speed and default depth and time. These combinations also demonstrated the highest adherence rates (94% and 95%, respectively) compared to other device settings (89%). A higher proportion of patients with intermediate/low adherence in the first month of treatment (31%, n=18/59) changed the device settings during treatment compared with those with high adherence (16%, n=128/803) (p=0.005). The ability to adjust injection device settings offers a valuable opportunity for personalizing treatment, improving patient comfort and treatment adherence.

Keywords. Adherence, device settings, growth disorders, injection device, recombinant human growth hormone

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1. Introduction

Recombinant human growth hormone (r-hGH; somatropin [Saizen®], Merck Healthcare KgaA, Darmstadt, Germany) therapy is an effective treatment for children with some growth disorders [1]. However, poor adherence to treatment may lead to suboptimal growth and other outcomes [2]. The treatment of growth disorders involves the administration of daily injections of r-hGH and automated devices may help in this regard [3]. The ability to adjust injection device settings, which are pre-set to a default value unless changed by healthcare professionals (HCPs), may improve patient comfort and needle anxiety and thereby improve adherence [4]. In a previous study, we investigated the association between injection settings of the second generation of the easypod® device (EP2) and adherence [5]. Recently, the third generation of the easypod® device (EP3; Merck Healthcare KGaA, Darmstadt, Germany), as part of the growzen™ digital health ecosystem, was launched. EP3 is the only connected digital health device that delivers r-hGH and monitors real-time adherence to therapy, and is perceived by HCPs as more intuitive, comfortable, user-friendly, simpler, and easier to use than the previous generation EP2 device [6]. Therefore, we aimed to examine the preferences for injection device settings of the new generation EP3 and explore the association between these settings and adherence in patients with growth disorders.

2. Methods

Adherence data and information on device settings collected between March 2023–February 2024 were extracted from EP3 and the growzen™ digital health ecosystem. Patients aged ≥2 and <18.75 years of age at treatment start, with ≥3 months of adherence data from treatment start with EP3 were selected. Mean adherence was stratified as high (≥85%) versus intermediate/low (<85%). Injection device (comfort) settings and the default settings of EP3 are shown in Table 1. Injection depth is how far the needle goes into the skin when injecting r-hGH. Injection speed is the rate at which r-hGH is delivered during the injection. Injection time is the duration for which the needle remains in the skin after r-hGH has been delivered. Needle speed controls how fast the needle is inserted into the skin, but this is not programmable for EP3 (set to Fast: 20 mm/s as per patients' preference). There are two needle types: 29G and 31G (31G is the thinnest). There is no default setting for needle type.

Table 1. Injection device comfort settings of the third generation of easypod® device (EP3)

Device settings					
Injection depth	4 mm	6 mm [default]	8 mm	10 mm[a]	12 mm[a]
Injection speed	Slow[b]	Medium[c] [default]	Fast[d]		
Injection time	3 sec	6 sec [default]	9 sec	12 sec	15 sec
Needle type	29G	31G			

[a]Only available with 29G needle; [b]Slow: 0.8 mm/s; [c]Medium: 1.2 mm/s with 29G needle and 1.0 mm/s with 31G needle); [d]Fast: 1.8 mm/s with 29G needle and 1.2 mm/s with 31G needle.

3. Results

Adherence data for the first three months of treatment were available for 862 patients (Spain, n=486; Germany, n=152; France, n=135; UK, n=89) with a mean (standard deviation) age at treatment start of 9.8 (3.3) years. In total, 731 patients had growth hormone deficiency, 81 were born small for gestational age, 27 had Turner Syndrome, and 24 were categorized as 'other' or 'unknown'. The proportion of patients with high adherence was 92% (n=792/862) in the first three months of treatment. In total, 716 patients (83%) retained the same settings during treatment that were chosen by their HCPs at treatment start. Out of 333 patients with default settings at start, 42 patients (13%) changed their settings, while this proportion was higher (20%, n=104/529) in patients with no default settings at start (p=0.008). More patients with intermediate/low adherence in the first month of treatment (31%, n=18/59) changed their device settings during treatment compared with patients with high adherence in the first month of treatment (16%, n=128/803) (p=0.005). The proportion of patients with high adherence in the second or third month of treatment was slightly higher in patients who had low/intermediate adherence in the first month and changed device settings during treatment compared to those who retained device settings (50% vs 44%); however, this did not reach statistical significance (p=0.67). Table 2 shows the three most chosen combinations of injection device settings at treatment start, which were similar in younger (<9 years) compared with older (≥9 years) patients. The proportion of patients with high adherence was slightly lower in patients with a 4 mm injection depth, default injection speed and injection time at treatment start compared with patients with all default settings or with a slow injection speed and default injection depth and injection time (88% vs 94%) (p=0.02), and more often had a change in settings during treatment (24% vs 12%, p=0.002). In patients with other (besides the top three combinations) settings at treatment start (n=285), the proportion of patients with high adherence was 89%, and 23% changed device settings during treatment.

Table 2. The three most chosen combinations of injection device comfort settings at treatment start with the third generation of easypod® device (EP3)

Injection depth at treatment start	Injection speed at treatment start	Injection time at treatment start	n (%)	Change in settings during treatment, n (%)	% high adherence first 3 months
6 mm [default]	Medium [default]	6 sec [default]	333 (39%)	42 (13%)	94%
6 mm [default]	Slow	6 sec [default]	148 (17%)	15 (10%)	95%
4 mm	Medium [default]	6 sec [default]	96 (11%)	23 (24%)	88%

Almost all patients in France (96%, n=130/135) and Germany (88%, n=134/152) used the 31G needle during treatment; the 29G needle was most popular in the UK (99%, n=88/89). In Spain, both needle types were used, with a significantly lower mean age at treatment start for the 31G needle (8.9 vs 11.0 years, n=280 vs n=206, p<0.001). There was also a significantly lower mean age at treatment start with the 4 mm injection depth compared with 6 and ≥8 mm (8.5 vs 10.3 and 12.3 years, p<0.001), with a fast injection speed compared with a slow or medium injection speed (8.1 vs 9.9 years, p<0.01), and with a shorter injection time compared with a longer injection time (6.9 years at 3 sec vs

11.7 years at 15 sec, p<0.001). After adjustment for age, the proportion of Spanish patients with high adherence was comparable between the 31G and 29G needle types (p=0.74, with default other settings and no changes during treatment; both 96%).

4. Discussion

In total, 39% of patients (333/862) had the default settings at treatment start, and 34% (291/862) of patients retained the same default settings during treatment. As one out of three patients made no adjustments to the device settings, it is important that default settings are programmed to ensure optimal adherence. Our study provides indications that the default settings on EP3 at treatment start can ensure optimal adherence, as the proportion of patients with high adherence was high among these patients who retained the default settings at the start of treatment (94%); however, a slow injection speed with other default settings also gave a similarly high adherence rate (95%). A higher proportion of patients with intermediate/low adherence in the first month of treatment changed the device settings during treatment compared with those with high adherence in the first month of treatment (31% vs 16%). The ability to adjust injection device settings offers a valuable opportunity for personalizing treatment. Allowing patients to customize their injection experience to suit their individual preferences and needs may improve adherence. This empowerment fosters a sense of control and ownership over their therapy, ultimately promoting greater engagement with the treatment process. Furthermore, the ability to personalize device settings enables patients to improve their comfort and needle anxiety. As a result, the overall treatment experience becomes more tolerable and manageable, which may contribute to enhanced treatment adherence and, consequently, improved clinical outcomes. Further quantitative research involving larger sample sizes and longer treatment periods, and observational studies assessing user experience are needed to gain a better understanding of optimal age-specific injection device settings during treatment with EP3. Studies defining the acceptability of device settings and the impact of personalized device settings on adherence, with a focus on patients with low/intermediate adherence, may be helpful to develop a best practice flow chart for device settings that can be used by patients, patient support programs or HCPs. This may improve patient comfort and, consequently, achieve high adherence and optimal growth. Selecting an optimal combination of default settings is paramount. Additionally, it is important that patients, patient support programs, or HCPs proactively verify default settings of EP3 or personalize the settings for patients with low/intermediate adherence to improve adherence. Previous real-world studies have demonstrated the positive effect the EP2 device and easypod™ connect ecosystem had on adherence to r-hGH treatment [7]. This study demonstrates that the EP3 device, which was designed to improve on the previous version of easypod™ and enables adjustment of device settings and real-time monitoring of adherence, can help optimize treatment and ensure optimal adherence.

5. Conclusions

In this observational study, we found that the two most chosen combinations of settings at treatment start were the default settings for injection speed, depth and time, or a slow injection speed and default depth and time. These combinations of settings also

demonstrated the highest adherence rates. More patients with intermediate/low adherence appeared to modify the device settings during treatment in comparison with highly adherent patients, highlighting the importance of personalized treatment approaches to improve treatment adherence.

Acknowledgments and Conflicts of Interest

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References

[1] Richmond E, Rogol AD. Current indications for growth hormone therapy for children and adolescents. Endocr Dev. 2010;18:92-108. doi: 10.1159/000316130.

[2] Cutfield WS, Derraik JG, Gunn AJ, Reid K, Delany T, Robinson E, et al. Non-compliance with growth hormone treatment in children is common and impairs linear growth. PLoS One. 2011 Jan 31;6(1):e16223. doi: 10.1371/journal.pone.0016223.

[3] Assefi A, van Dommelen P, Arnaud L, Otero C, Fernandez-Luque L, Koledova E, et al. Adherence to Growth Hormone Treatment Using a Connected Device in Latin America: Real-World Exploratory Descriptive Analysis Study. JMIR Mhealth Uhealth. 2022 Jan 20;10(1):e32626. doi: 10.2196/32626.

[4] Spataru A, van Dommelen P, Arnaud L, Le Masne Q, Quarteroni S, Koledova E. Use of machine learning to identify patients at risk of sub-optimal adherence: study based on real-world data from 10,929 children using a connected auto-injector device. BMC Med Inform Decis Mak. 2022 Jul 6;22(1):179. doi: 10.1186/s12911-022-01918-2.

[5] van Dommelen P, Arnaud L, Zucchiatti C, Koledova E. Optimal injection device settings to achieve high adherence to growth hormone treatment in patients with growth disorders. Horm Res Paediatr. 2023;96:1-643. doi: 10.1159/000533803.

[6] Rivera-Romero R, Perge K, Cochet S, Trouvin MA, E. K. Healthcare professionals' perceptions on the quality and evolution of digital health devices to support paediatric growth hormone therapy: Results of a French participatory study. Horm Res Paediatr. 2023;96(1-643). doi: 10.1159/000533803.

[7] Koledova E, Stoyanov G, Ovbude L, Davies PSW. Adherence and long-term growth outcomes: results from the easypod(™) connect observational study (ECOS) in paediatric patients with growth disorders. Endocrine connections. 2018 Aug;7(8):914-23. doi: 10.1530/ec-18-0172.