Improved adherence and growth outcomes with jet-delivered growth hormone

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Abstract

**Background:** We previously reported improved persistence and adherence to daily recombinant growth hormone (rGH) in children using jet transjection delivery compared to using needle-based devices. This study examines the relationship between improved adherence and medium-term growth outcomes in children receiving jet-delivered rGH (JrGH) at a single centre.

**Methods:** This was a retrospective longitudinal follow-up study of children (<16 years) treated with daily JrGH (somatropin; Ferring Pharmaceuticals) in the form of Zomacton® with the Zomajet® device. Delivery schedules of home distribution services were utilised to calculate adherence, quantified as the proportion of days covered (PDC) index (PDC > 0.8 adherent, PDC ≤ 0.8 less adherent).

**Results:** Of 75 patients eligible for JrGH, 52 had PDC treatment and height data for at least 1 year and 22 for 3 years. A greater proportion of patients were classified as adherent in both 1- and 3-year treated cohorts (adherent 30 [57.7%] and 14 [63.6%], less adherent 22 [42.3%] and 8 [36.4%]). After 1 year of JrGH treatment, HTSDS was not significantly different in either adherence group. After 3 years, only adherent patients demonstrated sustained year-on-year increments in HTSDS and significant improvement in target HTSDS positions (by 1.32 SDS) compared to baseline ($p=0.0008$). MPHSDS – HTSDS showed a similar significant improvement at 3 years in adherent patients only ($p=0.0043$).

**Conclusions:** Patients adherent to JrGH demonstrate significant growth improvement compared to baseline over 3 years.

**Keywords:** adherence; compliance; epidemiology; final height; growth hormone; jet-delivery.

Introduction

Short stature and growth failure in childhood can result from growth hormone (GH) deficiency, skeletal dysplasia as in Turner Syndrome or being born small for gestational age. Approximately one in 4000 children in the UK suffer GH deficiency due to either congenital pituitary maldevelopment or acquired brain injury (e.g. tumours, trauma) [1]. The treatment recommended by the National Institute for Health and Care Excellence (NICE) is subcutaneous recombinant growth hormone (rGH, somatropin) [2] in physiological replacement doses which with optimal use can lead to increments in adult height of up to 11 cm and a final height close to the genetic mid-parental target. However, adherence to rGH therapy is a major issue in this population [3] and although this is difficult to quantify, especially in the longer term [3], it may explain reduced efficacy outcomes including short stature, excess adiposity, abnormalities in skeletal maturation [4, 5] and arguably also increased cost through waste [6]. Alternative delivery options, likely to be better tolerated with improved adherence [3, 5], have been developed and include a range of devices. rGH is now administered via injection pens, autoinjector pens, single-use disposable syringe and needle, needle-free transjectors or electronic injectors. Individual studies of newer upgraded devices for both needle-based rGH, e.g. Norditropin® (somatropin; Novo Nordisk, Gatwick, UK) [7], and needle-free rGH, Zomajet® (somatropin; Ferring Pharmaceuticals, London, UK) [8], show increased patient satisfaction.

Commissioning pressures to improve cost benefit per incremental centimetre (cm) [2] mean the cheapest needle formulations are increasingly promoted. These are largely subcutaneous injections and may be associated with poor adherence and early termination due to needle phobia or injection pain [7, 9]. Jet-delivered rGH therapy in the form of Zomacton® with the Zomajet®
device (JrGH) transsects rGH through the skin without a needle [8] and is the only such delivery device available worldwide. A study has demonstrated bioequivalence between jet-delivered and needle administered rGH, with comparable absorption volumes and serum insulin-like growth factor 1 (IGF-1) levels [10]. In our previous national report of 4093 children aged ≤18 years, we reported improved persistence and adherence with daily JrGH therapy in 728 patients compared to 3365 patients using needle-based devices over a 3-year period [11]. This suggests that jet-delivery may improve long-term growth outcomes and cost-effectiveness in selected patients. The aim of this study was to investigate the impact of adherence on medium-term (3 years) growth outcomes, in the form of height standard deviation scores (HTSDS) and the difference from target mid-parental height in children treated with JrGH.

Materials and methods

Study design and patients

A retrospective, longitudinal follow-up study design was utilised to study a cohort of patients prescribed once-daily subcutaneous JrGH through the Healthcare at Home (HAH) service [12]. The study was approved by Great Ormond Street Hospital Research and Development Office as an evaluation/audit. They noted that ethical committee approval was not required. Patients were included as previously described [11] from the HAH database of delivery schedules and were under the management of Great Ormond Street and University College London Hospitals when JrGH treatment was initiated during the period 1st January 2010 and 31st December 2012 and followed up for up to 3 years (31st December 2015).

Hospital records and HAH database requests for home delivery of JrGH treatment were cross-referenced by hospital record number to identify a cohort of patients who met the inclusion criteria for analysis which included under 16 years of age at the start of treatment, confirmed delivery and use of JrGH and/or ancillaries and adequate records of disposable device-head counts year-on-year from which to assess adherence.

Study evaluations and analysis

Adherence was estimated using a validated measure known as proportion of days covered (PDC) [13], considered to provide a more conservative estimate of adherence compared to the medication possession ratio (MPR) [14] and more robust in this context as it captures patient access to both heads and the rGH medication [15] as opposed to just one parameter. PDC was calculated as the ratio of the number of days a patient had access to viable JrGH device-heads (quantity of device-heads delivered × length of time each head should last [1 week]) to the number of days they were prescribed GH treatment during the treatment period:

\[ PDC = \frac{\text{No. of device-heads} \times \text{Days each device-head should last}}{\text{No. of days prescribed treatment}} \]

Electronic hospital records and growth cards of those patients maintained on treatment for at least 1 year were reviewed. Baseline demographic parameters of mid-parental height standard deviation scores (MPHSDS) and HTSDS together with HTSDS and MPHSDS difference (MPHSDS – HTSDS) at 1, 2 and 3 years of treatment were assessed to within ±0.49 years at all time points.

Those patients with data points for HTSDS at baseline and a minimum 1-year treatment period were identified and sub-grouped into adherent (PDC > 0.8) and less adherent (PDC ≤ 0.8) groups. Demographic and treatment indication differences between adherent and less adherent groups at baseline were compared by unpaired t-test. HTSDS and MPHSDS – HTSDS outcomes were compared by analysis of variance (ANOVA) at yearly intervals compared to baseline data.

Results

A total of 75 patients were identified from the HAH records. Of these, 52 were under 16 years of age at the start of treatment, had 1-year data for HAH delivery information from which PDC could be determined and had height record data for at least 1 year of treatment (Figure 1). Of these, 22 had annual height records for at least two of the 3 years of treatment. A greater proportion of patients were classified as adherent in both the 1- and 3-year treated cohorts (adherent 30 [57.7%] and 14 [63.6%], less adherent 22 [42.3%] and 8 [36.4%]).

Demography and indications for rGH treatment within the 1-year patient cohort and 3-year sub-cohort are detailed in Table 1. Only three of these patients had previous rGH treatment prior to starting JrGH (two in the adherent cohort and one in the less adherent cohort).

Adherent patients within the 1-year treatment cohort were significantly younger than less adherent patients (median age [range] 7.15 [1.1–15.0] vs. 9.41 [2.7–14.4]); however, sex distribution, HTSDS and MPHSDS were not significantly different. Treatment indications (including post brain tumours and cancer) and the proportion of patients with potential confounder skeletal conditions that might adversely affect growth response were small and similarly distributed between the two groups. There was however a lower percentage of pubescent patients in the adherent group compared to the less adherent group at the end of the study, as expected by their ages at start of treatment. The same difference applied for the proportion of patients >13 years of age at the end of the study. The sub-cohort of patients who were treated for 3 years had similar age and puberty differences between the adherent and less adherent groups to the 1-year cohort.
After 1 year of JrGH treatment, HTSDS was not significantly different in either adherence group (Figure 2). JrGH significantly increased HTSDS year-on-year over a 3-year treatment period in the adherent group only (ANOVA $p=0.0029$), (Figure 3) and this difference was significantly different to baseline at 3 years of treatment ($p=0.0008$). The increment in HTSDS was greater in the adherent group at 3 years compared to the less adherent group (1.06 vs. 0.5 SDS) although this difference did not reach significance.

In those subjects with parental height records, and in whom MPHSDS − HTSDS could hence be determined, a similar significant ($p=0.0159$) height improvement was observed with JrGH therapy over 3 years in the
adherent group only (Figure 3). This difference was also significantly different to baseline at 3 years of treatment ($p=0.0043$) as supported by the observation that the adherent group was closer to their target height SDS at 3 years (by 1.32 SDS) compared to the less adherent group (0.00 SDS).

There were no significant differences between adherent and less adherent sub-groups at each year for both HTSDS and MPHSDS – HTSDS. This possibly reflects the wide variance of the data. However, combining the adherent and less adherent JrGH treated sub-groups resulted in HTSDS and MPHSDS – HTSDS outcomes which were significantly different across the 3 years (ANOVA $p=0.0015$ and $p=0.0473$) with significant improvement across the 3 years compared to baseline ($p=0.0004$ and $p=0.0149$).

Discussion

Studies with conventional rGH devices have suggested that long-term adherence is a major issue in this population [3]. Our previous study reported that children treated with JrGH in the short term (1 year) are predominantly adherent with this treatment device, especially at younger ages [11]. This may be clinically relevant as growth response, predominantly height velocity, during the first year of rGH treatment is a good predictor of overall growth response and final height outcomes [16]. One study has assessed adherence to rGH with a fully automated tracking injection device, but only reported 1-year height velocity data, and...
in just 57/97 of the original cohort [17]. There are no studies assessing growth outcomes in children treated with JrGH despite patient choice of delivery device and adherence being inextricably linked to growth outcomes [4]. This longitudinal study has addressed this issue by objectively examining adherence and growth outcomes expressed as height rather than height velocity and as difference from target height, in children treated with JrGH. Furthermore, it is the only study to examine short- and medium-term growth outcomes at time points up to 3 years.

The results suggest that improvement in height increment occurred in both JrGH treated adherence groups, but the less adherent group did not demonstrate any catch-up towards their target height SDS at 3 years whereas the adherent group had gained 1.32 SDS, a difference of at least 10 cm which is comparable to the best reported outcomes when using rGH treatment [2]. Given the similar height centile positions and mid-parental target heights at baseline, these group differences at 3 years re-enforce the importance of adherence in reaching predicted adult height in children with growth failure due to hormone deficiency. This medium-term relationship between adherence and growth outcomes was observed despite the less adherent group including a higher proportion of teenagers and pubescent children in whom an adolescent growth spurt might be expected at this early age. These demographic differences in adherence groups are likely to represent a self-fulfilling bias in our data where older patients are less incentivised to self-administer treatment; it is reported that 23% of teenagers miss at least two injections per week [18], a concordance measure which equates to 71% of days covered, comparable to our PDC adherence ratio of >0.8.

The assessment of adherence to GH is difficult to accurately determine in children. A study comparing two different adherence scales in the same cohort of GH treated patients yielded wide differences in adherence, with 56.7% of patients being classed as adherent using the Morisky Medication Adherence Scale and 95.3% of patients being classed as adherent using the self-declared auto-compliance scale [19]. Adherence assessment by PDC score does not involve self-declared patient reports of rGH use, which would likely introduce bias and inaccuracies in determining adherence; arguably the PDC score is a more sensitive tool than other adherence measures. PDC adherence >0.8 represents an arbitrary definition of adherence, but this index value has been used in our previous study [11] and in other studies across different therapeutic areas [15] and can thus form a basis for comparison. Some patients in the adherent group had PDC scores slightly higher than 1.0 defining them as over-adherent; this is most likely explained by patients using JrGH treatment heads more frequently than the required use of once a week, rather than over-use of GH treatment. Furthermore, heads were only available from a single source so only a limited excess supply could be despatched without this oversupply being highlighted.

A recent study in 42 rGH treated patients (with needle devices) suggested that those provided with a choice of different needle device at start of treatment had improved self-reported adherence together with improved height SDS and IGF-1 scores 3 years after start of treatment [18]. A study assessing treatment concordance by primary care prescriptions of rGH showed that lower concordance compromised height velocity over a 1–9-year treatment period [20] but a free choice of device counteracted this to a degree. In many previous studies [4, 16, 18, 20–22] (Supplementary Table), children were approximately 3 years older (median age 12.3 years) than even our less adherent group. Thus, we may expect to see in both our cohorts more dramatic changes over time with respect to target height given that children are further from skeletal fusion, though our older group may be nearer the pubertal growth spurt and hence expected to grow faster.

A large national cohort study in New Zealand of 150 children receiving rGH reported improved height velocity and adherence of >85% (≤1 missed injection per week calculated by the number of returned empty rGH vials over a 4-month period) [4]. In this study, children were again older, median age was 12.1 years, but the period of follow-up was only 8 months. An Italian case series described 106 treated patients of median age 10.5 years of whom 11 grew poorly, with non-adherence considered a factor in four cases who self-reported missing injections at medical interview [21]. By contrast, a prospective study [16] of height, IGF-1 levels and adherence in 53 patients using an automated injection device did not detect a correlation between adherence and height SDS in predominantly male patients aged 10 years; adherence cut-off was set high at two levels of 82% and 92% which might have affected results, whilst parents were also aware of monitoring. The retrospective nature of our study is more representative of patient behaviour and does not introduce such bias. Despite a limited sample size and a retrospective design, this study shows that baseline demographics, and indications/confounders, were distributed, in most cases, homogeneously between the two adherence groups which supports the statistical validity of our group comparisons. The greater proportion of patients with puberty onset during the study in the less adherent group may even have attenuated the observed differences, as more were likely to be approaching their puberal growth spurt. Other relative study strengths include
90–100% data ascertainment for all time points in patients attending a single centre with a single auxologist over many years. The PDC index we chose to determine adherence is widely recognised and validated [23–25]. We have examined two height outcome parameters and the effect of changes in adherence on these outcomes across time, in the few patients whose PDC scores changed minimally at cut-off borders; a similar number of patients changed adherence cohort group each way. Finally, there were few patients with skeletal conditions that might limit response to rGH and these were similarly distributed between adherent and less adherent groups. The medium-term data in the adherent cohort clearly demonstrate the height benefit which treatment adherence brings and which studies in older (and less adherent) children may not be sensitive enough to detect.

Overall, our analysis confirms that at 3 years of treatment, the growth of all children is improved by JrGH compared to pretreatment data; but those patients who are sub-optimally adherent achieve substandard growth outcomes which may not be cost-effective. Addressing factors that influence treatment adherence, especially more effective patient education, needle anxiety recognition and patient product choice may improve cost-effectiveness [26–29]. Further research in larger cohorts using national databases should now be undertaken to quantify the effect of good adherence on growth parameters with different rGH delivery devices.

Conclusions

This is the first study examining medium-term growth outcomes in young children using JrGH with adherence measures. Most patients were adherent, and this cohort demonstrated significant sustained improvements in 3-year catch-up towards target height positions compared to baseline, while less adherent patients did not demonstrate significant outcome benefits.

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