REVIEW
THERAPY OF ENDOCRINE DISEASE

GH therapy in adult GH deficiency: A review of treatment schedules and the evidence for low starting doses

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Abstract

Recombinant human GH has been licensed for use in adult patients with GH deficiency (GHD) for over 15 years. Early weight- and surface area-based dosing regimens were effective but resulted in supraphysiological levels of IGF1 and increased incidence of side effects. Current practice has moved towards individualised regimens, starting with low GH doses and gradually titrating the dose according to the level of serum IGF1 to achieve an optimal dose. Here we present the evidence supporting the dosing recommendations of current guidelines and consider factors affecting dose responsiveness and parameters of treatment response. The published data discussed here lend support for the use of low GH dosing regimens in adult GHD. The range of doses defined as 'low dose' in the studies discussed here ($\sim$1–4 mg/week) is in accordance with those recommended in current guidelines and encompasses the dose range recommended by product labels.

European Journal of Endocrinology **168** R55–R66

Introduction

The goal of GH replacement therapy for children with GH deficiency (GHD) is normalisation of height during childhood and attainment of normal adult height. However, even after final height is achieved, there is evidence that GH is still required, and it is generally accepted that it may be beneficial to continue GH therapy beyond final height in order to achieve peak bone mass, muscle mass, and strength (1). Negative consequences associated with cessation of therapy, such as reduced psychological well-being, adverse changes in lipid profile and changes in body composition, suggest that for some patients there may be ongoing GHD. After retesting to confirm a diagnosis of GHD, continuation of therapy is necessary for maintenance of normal body composition, metabolic processes, and psychological functioning.

In adults, GH is important for supporting various physiological and metabolic processes, and those who develop GHD in adulthood (e.g. acquired from damage to the pituitary gland or hypothalamus) can have a wide variety of morphological, metabolic, physical, and psychological problems (2, 3, 4). These include increased fat mass and visceral adiposity, abnormally low lean body mass, higher-than-normal blood total cholesterol (TC) and LDL-C and triglycerides, and lower than normal HDL-C, reduced muscle strength and exercise performance, low bone mineral content leading to osteoporosis and increased fracture risk, increased cardiovascular morbidity and mortality, an impaired sense of well-being, decreased energy levels and a general reduction in quality of life (QoL).

Treatment goals for adults with GHD are to correct the clinical alterations described above, using insulin-like growth factor 1 (IGF1) levels as a marker of treatment, in order to achieve or maintain IGF1 levels in the middle of the normal range appropriate for age and sex, with an optimal level of physical and psychosocial function (5, 6, 7). GH dosing in adult GHD (AGHD) was initially adopted from paediatric practice and was subsequently found to cause supraphysiological levels of IGF1 and to cause increased levels of common side effects such as arthralgia and peripheral oedema (8).

Following these early attempts to correct AGHD, dosing plans have evolved, and a number of guidelines relating to treatment initiation, titration, and monitoring have been published (Table 1) (4, 5, 7). Rather than the weight- and surface area-based dosing strategies used initially with important side effects related to arthralgia and peripheral oedema (7), treatment regimens now use tailored dose-titration strategies to account for inter-individual differences in GH sensitivity (which are dependent on age, gender and various baseline characteristics), with lower doses than

Table 1 Current guidelines on the use of GH in adult patients with GHD.

Endocrine Society (4)	Recommend that GH-dosing regimens be individualised, rather than weight-based
	Recommend start with low doses and titrate according to clinical response, side effects and IGF1 levels
	Recommend that dosing take gender, oestrogen status, and age into consideration
	Suggest that during treatment, patients be monitored at 1–2-month intervals during dose titration and semi-annually thereafter with a clinical assessment and an evaluation for adverse events, IGF1 levels and other parameters of GH response
American Association of Clinical Endocrinologists (AACE) (5)	Starting dose
	Age <30 years, 0.4–0.5 mg/day (may be higher for patients transitioning from paediatric treatment)
	Age 30–60 years, 0.2–0.3 mg/day
	Age >60 years, 0.1–0.2 mg/day
	Use lower GH doses (0.1–0.2 mg/day) in all patients with diabetes or who are susceptible to glucose intolerance
	At 1–2-month intervals, increase dose in increments of 0.1–0.2 mg/day based on clinical response, serum IGF1 levels, side effects and individual considerations such as glucose intolerance. Longer time intervals and smaller dose increments may be necessary in older patients
	Aim for serum IGF1 levels in the middle of the normal range appropriate for age and sex, unless side effects are significant. Consider a trial of higher GH doses to determine whether this provides further benefit as long as the serum IGF1 levels remain within the normal range and the patient does not experience side effects
	Monitor at 6-month intervals once maintenance doses are achieved. Monitoring should include clinical evaluation and assessment of side effects, serum IGF1 and fasting glucose levels. The lipid profile should be assessed annually, and QoL measurements may be done every 6 or 12 months. If the initial bone DXA scan is abnormal, repeat evaluations at 2–3-year intervals are recommended. If pituitary microadenomas or post-surgery residual pituitary tumour is still present, periodic MRIs should be undertaken. Patients on concurrent thyroid, glucocorticoid and gonadal hormone replacement may need dose adjustments after starting GH replacement therapy
	It is important to retest patients transitioning from paediatric to adult care, especially those who had isolated GHD, and consideration should be given to minimising lengthy interruptions in their GH therapy
	The appropriate length of GH therapy is unclear. If benefits are achieved, treatment should continue, but if no apparent or objective benefits of treatment are achieved after at least 2 years, discontinuing GH therapy may be considered. If patients decide to discontinue GH replacement therapy, a 6-month follow-up appointment should be offered, because a substantial number of patients may wish to resume therapy, noting in retrospect that they did feel better on treatment
Growth Hormone Research Society (GRS) (6)	Recommended that the starting dose in young men and women be 0.2 and 0.3 mg/day respectively, and in older individuals, 0.1 mg/day. Dose determination based on body weight is not recommended due to large inter-individual variation in absorption and in sensitivity to GH, and the lack of evidence that a larger replacement dose is required for heavier individuals in adults
	Dose escalation should be gradual, individualised, and guided by clinical and biochemical response
	In elderly patients with GHD, treatment can be achieved with lower doses, concordant with the observed physiological decrease in GH secretion. Elderly patients are known to be more sensitive to GH and prone to side effects; therefore, the dose should be adjusted carefully
	A careful clinical exam should be undertaken with weight, height, and BMI recorded before commencing therapy. Objective parameters such as body composition should be used to monitor the response
	IGF1 should be measured at least yearly and should be maintained below the age- and gender-related upper limit of normal. In the event of dose adjustment, assessment should be performed no sooner than 6 weeks after a dose change
	Cardiovascular risk markers and fasting glucose levels should be measured yearly
	A careful history of QoL with attention to energy level, partner satisfaction, sick days and vitality is of value in monitoring treatment response

DXA, dual-energy X-ray absorptiometry; GHD, GH deficiency; IGF, insulin-like growth factor; MRI, magnetic resonance imaging; QoL, quality of life.

in paediatric GHD being successful. Current guidelines recommend that, during initial therapy, patients are monitored monthly and the GH dose is titrated to reach target IGF1 levels (5). Once maintenance doses are reached, patients should be monitored every 6–12 months, with a clinical assessment and an evaluation for adverse effects, level of serum IGF1 and other parameters of GH response, such as body composition, cardiovascular risk factors and QoL.

Clinical studies drive published guidelines, which, in turn, inform product labelling. In European countries, current label information for the major brands of recombinant human GH on the market recommends starting doses of about 0.15–0.30 mg/day in adult patients (0.20–0.50 mg/day for those with childhood-onset (CO) GHD) and seldom exceed 1 mg/day (9, 10, 11, 12, 13). In the USA, non-weight-based (generally,

0.15–0.30 mg/day) and weight-based (generally, ≤0.006 mg/kg per day) dosing recommendations are provided in product labels (14, 15, 16, 17, 18).

Here we undertook a systematic approach to gather evidence in support of current recommendations on GH therapy for adult patients with GHD (4, 5, 7). We reviewed the studies that explore GH dosing schedules, titration strategies and factors affecting responsiveness to GH, and discuss different approaches to treatment monitoring.

Literature selection methodology

Searches for relevant publications were carried out in PubMed using the search terms growth hormone deficiency AND growth hormone plus one of the following terms: ('start* dose' OR 'start* dosage') and

'schedule', 'titrat*', 'regimen', and 'algorithm'. Results were limited to human studies published in English between January 1990 and March 2011. Following the removal of duplicates, abstracts were assessed for suitability for inclusion in the review. Abstracts that were judged relevant for the main scope of the work were selected; the studies selected were those judged to represent the 'best evidence' (i.e. were of a given level of scientific substantiation or proof) such as large, prospective, randomised, controlled trials; observational studies and experimental studies (5): additional papers that provided useful background information and/or insightful comment were also included. Full-text articles of suitable abstracts were then screened to select articles of relevance. Search results were supplemented with additional references of interest as identified by the authors (Fig. 1). References that explore GH starting dose and lower-dose regimens are listed in Table 2.

GH dosing schedules and titration strategies

The response to GH therapy in adults is variable. A dosing schedule that is suboptimal in one patient may lead to overdose in another, and normalisation of serum IGF1 can induce side effects in some. Therefore, it is recommended that each patient's GH dosing regimen should be titrated to balance clinical efficacy against overtreatment, as determined by serum IGF1 measurements and the occurrence of side effects (19).

Practical guidance for GH dosing was developed over 10 years ago. Starting doses of > 300 µg/day were not recommended. Dosing was guided by serum IGF1 concentrations (monitored every 6–8 weeks until levels of IGF1 were in the mid-to-high normal range for age

and sex) and tolerability. If musculoskeletal pain, carpal tunnel symptoms, or aggravation of hypertension appeared within the first 10 days of initiation of therapy or a dose increment, which then resolved within 2 weeks, it was recommended that patients remain on that dose; dose reductions were recommended for symptoms that persisted beyond 2 weeks. Two or three dose changes may be required before a satisfactory dose is defined. Additionally, patients should be advised that complete resolution of the side effects may require 1–2 months (2, 3, 4, 20, 21).

Although IGF1 is recognised as the most useful serum marker for GH dose titration in adults, the American Association of Clinical Endocrinologists (AACE) guidelines (5) acknowledge that no data are available regarding titrating the dose to the ideal target serum IGF1 level (i.e. whether to target the middle or the upper half (> 50th percentile or > 0 SDS of the reference range for maximum benefit). The AACE therefore recommend targeting IGF1 to the middle of the age- and sex-appropriate reference range quoted by the laboratory used (50th percentile or 0 SDS), unless side effects are significant; a trial of a higher dose may be considered to determine whether this provides further benefit, provided that the levels of IGF1 remain within the normal range and that the patient does not experience side effects.

Clinical studies use slightly different IGF1 targets within the reference range, although all have demonstrated the clinical efficacy of their particular GH replacement therapy regimen in adult patients. Ahmad *et al.* (22) maintained IGF1 concentrations between the median and upper end of the age-related reference range, while Pincelli *et al.* (23) aimed to restore IGF1 concentrations to the low-normal sex- and age-related reference range. The regimen used in the
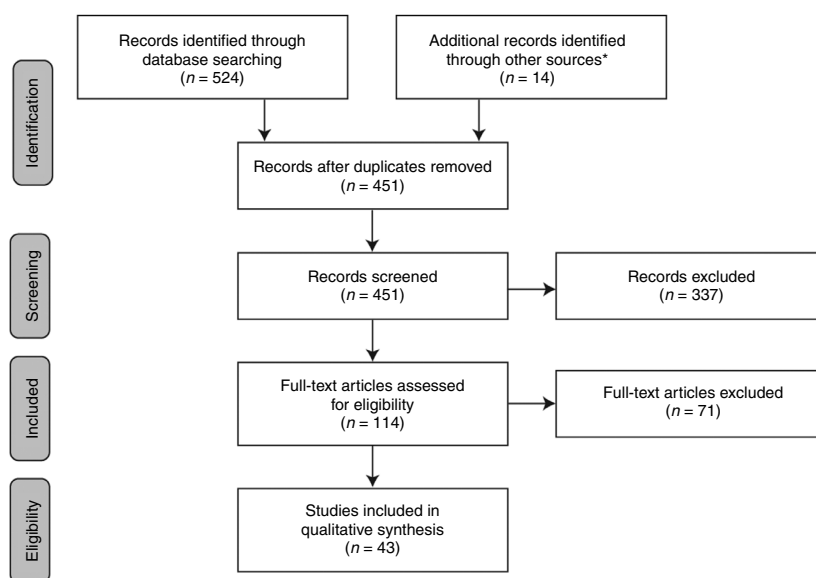

Figure 1 Literature identification. *Based on the expertise of the authors or suggestions during the peer review process.

studies of Murray *et al.* (24) normalised the IGF1 SDS between −2 and +2 s.d. of the age-related normal range. A review article by Alexopolou *et al.* (25) concluded that the objective of AGHD therapy is to obtain an IGF1 level in the upper half of the normal range for age and gender, ideally between the median and +1 s.d., although some advocate values between +1 and +2 ss.d. Johansson *et al.* (19), as part of the

Table 2 Studies included in the review. Studies listed here are original studies identified in the literature selection that specifically explore GH starting dose and lower-dose regimens.

Authors	Year of publication	Case load (*n*)	Age	Duration of study	Dose/regimen used
Ahmad *et al.* (22)	2001	46	Mean, 50.4 years; range, 26–72 years	3 Months	Initiated at 0.4–0.5 IU/day and titrated to achieve IGF1 SDS between median and upper end of age-related reference range
Amato *et al.* (34)	1996	9	Range, 25–34 years	24 Months	70 µg/kg per week for 12 months
Hoffman *et al.* (29)	2004	387	Mean, 48.1 ± 13.3; 45.1 ± 14.1	32 Weeks	Fixed-dose group: subjects received sequentially 4 (4 months), 8 (2 months), and 12 (2 months) µg/kg per day GH. Individualised-dose group: started at 0.2 mg/day (2 months) and increased by 0.2 mg/day increments at 2-month intervals, based on clinical and serum IGF1 responses, to a maximum of 0.8 mg/day
Johannsson *et al.* (28)	1997	60	Mean, 48 years; range, 18–67 years	12 Months	High-dose group: daily dose of 4.8 µg/kg (0.1 IU/kg per week) during first 4 weeks, with a target dose thereafter of 12 µg/kg per day (0.25 IU/kg per week). Individualised-dose group: initial daily dose 0.17 mg (0.5 IU) or 0.33 mg (1.0 IU)/day, independent of body weight, with dose adjustments thereafter
Møller *et al.* (30)	1993	10	Range, 21–43 years	12 Weeks	1, 2, and 4 IU/m^2 per day (three consecutive 4-week study periods)
Mukherjee *et al.* (45)	2005	30	Range, 17–65 years	6 Months	Patients started on 0.3 mg/day and dose adjusted as necessary
Murray *et al.* (24)	1999	65	Mean, 38.7 years; range, 17–72 years	∼9.5 Months at maintenance dose	Treatment initiated at 0.8 U/day and subsequently adjusted by increments of 0.4 U/day to normalise the IGF1 SDS between −2.0 and +2.0 s.d. of the age-related normal range
Murray *et al.* (35)	2002	67	Mean, 37.5 ± 14.7 years	24 Months	GH was commenced at a dose of 0.27 mg/day and was subsequently adjusted at intervals of 4–6 weeks to normalise the serum IGF1 within the range of +2 to −2 s.d. of the age-adjusted mean in the absence of GH-related side effects
Orme *et al.* (33)	1992	8	Mean, 50 years; range, 22–75 years	8 Weeks	4 U three times per week, for 8 weeks
Porretti *et al.* (54)	2002	66	Mean, 39 ± 16 years, range, 18–71 years	6 Months	Low-dose regimen, 3 µg/kg per day for 3 months followed by 6 µg/kg per day for another 3 months. Higher dose regimen, 6 µg/kg per day for 3 months followed by 12 µg/kg per day for another 3 months
Verhelst *et al.* (27)	1997	148	Mean, 43.8 years	2 Years	During month 1, 0.125 IU/kg per week, followed by 0.25 IU/kg per week for next 5 months (maximum dose 4 IU/day). The open period (additional 18 months) commenced with a dose of 0.125 IU/kg per week for 1 month and then 0.25 IU/kg per week (∼1.5 IU/m^2 per day). Dose adjustments were made in case of adverse effects or when deemed appropriate by the investigators
Yuen *et al.* (31)	2002	13	Range, 23–63 years	Four 7-day treatment phases, with a 10-day to 2-week washout in between each phase	7-Day treatment course of two 'physiological' ('lowest' dose, 0.0017 mg/kg per day; 'low' dose, 0.0033 g/kg per day) vs two 'supraphysiological' ('high' dose, 0.010 mg/kg per day; 'highest' dose, 0.025 mg/kg per day) GH doses
Yuen *et al.* (51)	2006	26	Range, 20–63 years	8 Weeks	Fixed regimen of non-weight-based low-dose GH replacement (0.2 mg/day) for 8 weeks

IGF1, insulin-like growth factor 1.

Growth Hormone Research Society (GRS) Consensus Workshop held in 2007, reported that it was agreed that most published trials showing beneficial effects of GH have achieved a mean serum IGF1 level of $+1$ SDS, but for the individual patient, determination of the level of IGF1 SDS to be obtained should be guided by other biochemical response markers and the clinical response.

Adult patients with GHD but normal IGF1 levels remain a therapeutic challenge, as there are few data to help understand whether they benefit from GH therapy and how to monitor therapy in the clinical setting.

Weight-based vs individualised regimens

Current guidelines acknowledge that high inter-individual variability in both GH absorption and sensitivity makes the individualised, stepwise, upward titration method preferable to standard weight-based dosing strategies (5, 7, 26). The finding of suboptimal high or low levels of serum IGF1 in $>60\%$ of patients in a 2-year study of GH replacement therapy in adults with GHD given a weight-dependent dose reinforces the guidelines and emphasises that the dose should be titrated individually for each patient by monitoring levels of IGF1 (27).

Head-to-head comparisons of individualised and weight-based dosing strategies provide evidence that individualised-dose (ID) titration leads to similar beneficial effects and fewer side effects than weight-based regimens. In the study of Johannsson *et al.* (28), two groups of patients were treated for 12 months using one of two schedules. The high-dose (HD) group ($n=30$) received a conventional weight-based regimen of 4.8 µg/kg per day (0.1 IU/kg per week) during the first 4 weeks, with a target dose of 12 µg/kg per day (0.25 IU/kg per week) thereafter; the ID group ($n=30$) received initial doses of either 0.17 or 0.33 mg/day (0.5 and 1 IU/day respectively), independent of body weight, with ID adjustments made thereafter to match a combination of clinical response, normalisation of serum IGF1 concentration and body composition. After 12 months, the daily GH dose was 0.55 ± 0.03 and 0.45 ± 0.03 mg in the HD and ID groups respectively ($P<0.05$). In the HD group, mean IGF1 level increased to well above the predicted level, while in the ID group, the mean IGF1 normalised. Side effects were experienced by 70% of the HD group and 30% of the ID group ($P<0.001$). A similar response was observed in both groups in terms of changes in body composition, glucose homoeostasis, lipoprotein levels and blood pressure, although dose dependency was observed for the response in markers reflecting calcium and bone metabolism. Overall, the study concluded that similar efficacy, with lower dose and fewer side effects, was obtained by considering individual responsiveness to GH compared with higher doses adjusted to match body weight. This conclusion was supported by a large,

multicentre, randomised controlled study (29) in which 387 adults with GHD were randomised to receive either a fixed dose (FD; $n=200$) or an ID ($n=187$) of GH for 32 weeks. Subjects in the FD arm began therapy at a dose of 4.0 µg/kg per day for 4 months, increasing to 8.0 µg/kg per day for 2 months, followed by 12.0 µg/kg per day for the final 2 months of the study. Patients in the ID arm received an initial dose of 200 µg/day, which was increased by 200 µg/day at 2-month intervals, according to an algorithm based on the clinical response and serum IGF1 concentrations, to a maximum dose of 800 µg/day. Data indicated that individualised dosing had similar clinical efficacy but improved tolerability, compared with the fixed, weight-based regimen, with lower occurrence of peripheral oedema (9.1 vs 16.5%, $P=0.03$) and rash (1.1 vs 5.5%, $P=0.02$) in the ID vs the FD arm.

Studies directly comparing different doses of GH support the use of lower starting doses. Møller *et al.* (30) examined the effects of different doses of GH on IGF1, IGF-binding protein 3 (IGFBP3), body composition, energy expenditure and various metabolites in ten adult patients (20–45 years of age) with GHD, who were studied after 4 weeks without GH followed by three consecutive 4-week periods during which they received 1, 2, and 4 IU/m^2 per day (0.33, 0.67, and 1.33 mg/m^2 per day respectively) GH. The use of 1 and 2 IU/m^2 per day GH was associated with normalisation of IGF1 levels, whereas the higher dose of 4 IU/m^2 per day caused distinct side effects in four of the ten patients and yielded supranormal levels of IGF1 compared with a matched control group. The authors concluded that a replacement dose of 1–2 IU/m^2 per day was relevant and expedient in adults with GHD between 20 and 45 years of age. Yuen *et al.* (31) compared the metabolic effects of short-term administration of two doses representing a close approximation to daily physiological GH production rates in adults ('lowest' dose, 0.0017 mg/kg per day; 'low' dose, 0.0033 mg/kg per day) with two 'supraphysiological' ('high' dose, 0.010 mg/kg per day; 'highest' dose, 0.025 mg/kg per day) GH doses. Results suggested that short-term administration of the highest GH dose induced insulin resistance, whereas the low and lowest GH doses did not compromise insulin sensitivity. Interestingly, an increase in β-cell function was observed with the lowest dose, suggesting that this dose had direct insulinotrophic effects on β-cells. The authors concluded that their findings were in agreement with the recommendations of the GRS (32) to commence treatment with low GH doses, and that their lowest dose could be the optimal starting dose, as it seemed to provide the additional benefit of enhancing β-cell function, at least initially, without compromising insulin sensitivity.

A number of studies using low-dose regimens to treat adults with GHD (most of which were individualised by upward titration against serum IGF1 levels) have achieved good efficacy and safety outcomes, providing

support for such dosing strategies. Orme et al. (33) assessed the effects of low-dose GH in eight adults with GHD on body composition and physical performance. Patients received 4 IU (1.33 mg) GH, three times per week (tiw) for an 8-week period. Although a lower than previously used mean dose of GH (0.025 IU/kg per day) was given, and the frequency of administration was also less than generally used, biological effects were seen in this patient group. This finding showed that a low dose of GH could increase IGF1 levels and have a pronounced physical effect in the GH-deficient adult (an increase in exercise capacity and in fat-free mass, and a decline in fat mass), without the side effects observed at higher dosage schedules. In the study by Amato et al. (34), the lowest dose so far used in trials focusing on bone metabolism and structure in AGHD was used in a dosing regimen of 70 µg/kg per week divided into three injections. Results suggested that 12 months of low-dose GH therapy normalised bone metabolism and cortical bone density, and improved trabecular bone density without causing adverse events. The effects of low-dose GH replacement on body composition and QoL were studied by Ahmad et al. (22). A starting daily dose of 0.4–0.5 IU (0.13–0.17 mg) that was titrated to achieve and maintain IGF1 SDS between the median and upper end of the age-related reference range (mean GH dose of 0.77 ± 0.08 IU at 1 month and 0.80 ± 0.12 IU at 3 months) was associated with an improvement in body composition and QoL. These changes were apparent as early as 1 month after initiation of treatment, with beneficial effects continuing at 3 months, an earlier effect than reported previously on such outcomes with either high- or low-dose therapy. Importantly, these changes occurred in the absence of side effects.

Murray et al. (35) explored whether the beneficial effects on serum lipids found when using weight-based GH replacement regimens were retained with low-dose, individually optimised regimens, and which patient characteristics best predicted outcome. GH was commenced at 0.27 mg/day, and the dose was subsequently adjusted, with the objective of normalising levels of serum IGF1. This dosing regimen was associated with significant improvements in TC, LDL-C, triglycerides, and the TC/HDL-C ratio. The effects on cardiovascular and heart parameters of a 1-year low-dose titrated, tiw GH-replacement regimen, aimed at achieving and maintaining IGF1 levels within the low-normal limits for age and sex, were studied by Pincelli et al. (23) in a small group of patients with adult-onset (AO) GHD ($n=8$). The starting dose used was 5 µg/kg per day, and the mean final GH dose was 6.7 ± 0.8 µg/kg per day. This regimen was effective in improving and/or normalising heart structure and performance, together with lipid profile, body composition and bone density in AO patients. Chihara et al. (36) studied the effects of long-term GH replacement therapy in Japanese adults with GHD in a multicentre, uncontrolled, open-label

study, which followed on from a previous randomised, double-blind, placebo-controlled trial, in which patients received either GH replacement therapy (GH–GH group, $n=35$) or placebo (placebo–GH group, $n=36$). In the open-label study, patients received GH for 48 weeks. Treatment was started at a dose of 0.003 mg/kg per day for the first 8 weeks, after which the dose was adjusted to maintain patients' serum IGF1 levels within the reference range adjusted for age and gender. Overall, long-term, individualised GH administration based on IGF1 levels was well tolerated and effective. Treatment with GH maintained the improvements in body composition and lipid profiles in the patients previously treated in the double-blind study (GH–GH group) and improved these parameters in previously untreated patients (placebo–GH group). Compared with the FD titration regimen of the preceding double-blind comparative phase, the dosing methodology used in the extended study allowed lower GH dose increases, and the incidences of oedema and cases of high levels of IGF1 were lower.

Timing and frequency of GH administration

Some studies have explored the frequency and timing of GH injections for the optimal AGHD treatment schedule. Regimens employing three injections per week have been shown to improve and/or normalise heart structure and performance, together with lipid profile, body composition, and bone metabolism and structure (23, 34). In a randomised, prospective, controlled study comparing daily vs tiw injections (37), the tiw injection regimen was effective in normalising IGF1 levels and improving lipid profile, body composition, bone metabolism and bone density; this effect was comparable with that observed in patients treated with daily injections, with few side effects and good compliance. Given that the benefits of GH therapy have been observed to reverse after 12 months off treatment (34), and that lifelong therapy might be necessary, compliance is an important issue in the treatment of AGHD. Indeed, current guidelines (5) suggest that, for patients with compliance issues, clinicians may consider administering injections on alternate days or tiw using the same total weekly dosage.

Jørgensen et al. (38) investigated whether the timing of GH administration in patients with GHD had any impact on its action. It was concluded that the modulatory effects of GH replacement therapy were substantially influenced by the time of its administration; evening injections were more successful than morning injections in normalising the circadian patterns of hormones and metabolites crucial for intermediary metabolism.

Evidence suggests that there is no clinically relevant difference between continuous vs intermittent

delivery of GH (39, 40, 41); therefore, patient preference may play more of a role in the selected regimen in this context.

In the last few years, new sustained-release GH preparations have been developed (both for paediatric and adult populations) in order to increase patients' adherence to treatment (injections administered once per week) while avoiding overtreatment (42). Long-term treatment with a weekly sustained-release GH preparation over both 26 and 52 weeks in adults with GHD demonstrated a reduction in fat mass with a favourable side-effect profile, confirming the potential value and safety of such agents for long-term GH replacement.

Factors affecting dose responsiveness

Treatment guidelines recognise the need to adjust the GH dose for certain categories of patients to reflect variations in physiological GH secretion. GH secretion is greater in younger individuals than older ones, and in women than men, and secretion is reduced in obesity (7, 20). Therefore, there are differences in the recommended starting doses for different patients in the GRS guidelines (7): 0.2 and 0.3 mg/day in young men and women respectively, and 0.1 mg/day in older individuals.

AACE guidelines (5) also take into account factors that may affect dosing and recommend dose changes in the following circumstances: increase the dose for young patients, regardless of onset type, with the addition of oral oestrogen or change from transdermal to oral oestrogen and decrease the dose for elderly patients, with discontinuation of oral oestrogen, change from oral to transdermal oestrogen or the addition of testosterone.

Gender

During childhood, there are no differences between boys and girls with respect to GH production. However, at pubertal and adult ages, differences can be found. GH production in healthy women of reproductive age is about twofold higher than in men, but IGF1 levels are similar, suggesting a lower responsiveness to GH in women (43, 44). This gender difference is closely related to oestrogen secretion and is possibly influenced by serum testosterone as well. In contrast to healthy men and women, IGF1 levels in adults with GHD are lower in women than in men, and there is a gender difference in GH requirement, with women needing higher doses and a longer duration to achieve the same clinical effects and IGF1 levels. The AACE guidelines state that women require higher initiation and maintenance doses than their male counterparts to achieve an equivalent clinical and biochemical response (5).

In clinical studies, gender differences in the doses required to normalise IGF1 levels have indeed been noted in subgroup analyses, with females receiving a higher GH replacement dose than males in some studies (28, 35), although some have found no significant differences in GH dose needed between men and women (22, 45) when dose adjustments are made for baseline factors such as age, BMI, and dose of GH itself (46).

Differences in the response to GH, as reflected by changes in body composition, have been observed, with several studies demonstrating greater effects in males than in females. In the 6-month, low-dose GH replacement study of Mukherjee *et al.* (45), the percentage changes in lean body mass and fat mass were significantly greater in males. Likewise, Bell *et al.* (47) reported that males responded significantly to treatment with GH in terms of changes in waist circumference, trunk fat, conicity index and somatotype, whereas in females, the only significant change was in trunk fat, and Chihara *et al.* (36) reported changes in mean lean body mass and mean body fat mass at week 48 of $+4.1\pm4.5$ and $-2.4\pm10.5\%$, respectively, in females compared with $+5.0\pm6.7$ and $-8.9\pm11.8\%$, respectively, in males. Mixed results were found by Hoffman *et al.* (29), who compared outcomes for FD and ID regimens and found that the decrease in fat mass was greater with the FD than the ID regimen for men but not for women, and the change in waist circumference was greater with the FD than the ID regimen for women but not for men.

Age

Current age and age of GHD onset are also factors that may influence dose responsiveness. The doses used during adolescence have typically been intermediate doses between the paediatric doses required during the growth years and the adult dose (7).

As the sensitivity to side effects of exogenous GH is greater in elderly patients with GHD, AACE guidelines advise that the starting dose, size of dose adjustments and target serum IGF1 levels should be reduced when GH replacement is considered in elderly patients (5, 7). GRS guidelines state that in elderly patients with GHD, treatment can be achieved with lower doses, concordant with the observed physiological decrease in GH secretion (7).

Differences in dose requirements and responses have been observed in patients with AO GHD and CO GHD. In the study by Chihara *et al.* (48), individualised GH dosing resulted in a lower mean dose for patients with AO compared with CO GHD (0.032 ± 0.019 vs 0.061 ± 0.023 mg/kg per week). Dosing patterns in the two groups were paralleled by the changes in IGF1 and IGFBP3. Similarly, Murray *et al.* (35) noted that low-dose individualised GH replacement, aimed at normalisation of serum IGF1 levels, was associated with a significantly greater mean dose for CO than AO patients at 12 months (0.45 ± 0.18 vs 0.32 ± 0.16 mg/day respectively; $P=0.004$) and at 24 months (0.53 ± 0.24 vs 0.33 ± 0.20 mg/day; $P=0.024$). Differences

in the baseline characteristics between the two patient subgroups (AO patients had a more adverse lipid profile at baseline) and also in the response of serum lipids to GH replacement (changes in TC, LDL-C, and the TC/HDL-C ratio were greater in AO patients) were noted. A difference in the response to GH therapy in patients with AO and CO GHD was also observed in a later study by the same group (36), in which mean lean body mass was increased by $6.2 \pm 6.8\%$ in CO patients and by $3.0 \pm 4.4\%$ in AO patients after 48 weeks of replacement. The authors suggested that this difference probably reflected the fact that CO patients had lower mean IGF1 levels at baseline and received higher average doses of GH.

Current guidelines recommend that patients with CO GHD should be retested after final height is achieved and therapy discontinued for at least 1 month to ascertain their GH status before considering restarting therapy (4, 5). However, guidelines for downward dose titration from a childhood to an adult dose are still lacking. Based on the age-related reduction in the spontaneous rate of GH production from puberty to young adulthood (49), one could hypothesise that progressive titration of GH dose during the transition phase to mimic physiological changes would lead to a dose reduction of $\sim 50\%$ in 2–4 years. This progressive reduction could lead to attainment of the appropriate dose for replacement in a young adult in another 4 years (the time at approximately which peak bone mass is physiologically obtained (50)). In the transition phase, it is important to identify safe regimens that can maximise linear growth potential and final adult height; it is also important to investigate the impact of age-adjusted regimens on carbohydrate and lipid metabolism, bone accretion, attainment of peak bone mass, body composition, behaviour, psychosexual function, and QoL. Once again, it has to be recommended that side effects are carefully monitored, although they are unlikely to occur if the replacement GH dose is appropriate.

Obesity

Decreased basal and stimulated GH and basal IGF1 levels and increased responsiveness to GH treatment are frequently reported in obesity. The role of obesity in affecting hepatic IGF1 generation in response to GH was explored by Yuen *et al.* (51) in a cohort of severely GH-deficient non-obese and obese adults treated with a fixed low GH dose (0.2 mg/day). Results demonstrated a larger increment and decreased individual variability of IGF1 to the low GH replacement dose in obese compared with non-obese adults with severe GHD. A positive association of IGF1 increment with baseline BMI suggested that the increased hepatic responsiveness to GH stimulation was more dependent on the degree of obesity rather than the GHD itself. The authors cautioned that the increased variability of IGF1 in non-obese adults with severe GHD questions the reliability

of interpreting an isolated single measurement of serum IGF1 in guiding dose adjustments.

Current guidelines give special consideration to patients who are obese, in stating that initiating and maintaining GH therapy using low doses (0.1–0.2 mg/day) may be more appropriate in GH-deficient patients with concurrent diabetes or obesity, and in those with previous gestational and family history of diabetes so as not to increase blood glucose levels. Mild and often transient changes in glucose metabolism have been demonstrated to be associated with GH replacement therapy in adults with GHD when compared with untreated adults with GHD (52).

Adult patients with Prader–Willi syndrome should be considered on an individual basis, due to the coexistence of obesity with a variable degree of GHD severity in a large majority of cases (53).

Interactions with other therapies

Given the interaction of GH with other pituitary hormone axes, it is advised that dose adjustments may be needed for those on more than one type of replacement therapy (5, 7, 44).

Studies on the interactions between sex steroid replacement and GH action have shown that oestrogen, administered orally, impairs GH action, leading to higher GH dose requirements (7, 44). In addition, the suppression of hepatic IGF1 generation by oral oestrogen (20) means that it is preferable for oestrogen to be replaced by a non-oral route, as the GH requirements will be reduced (7).

In patients with central adrenal failure, initiation of GH treatment may require an increase in hydrocortisone dose (7). Furthermore, by accelerating the peripheral metabolism of cortisol, GH therapy may precipitate adrenal insufficiency in susceptible hypopituitary patients (44).

Porretti *et al.* (54) reported that low doses of GH may unmask the presence of a mild central hypothyroid state or might even worsen a pre-existing central hypothyroidism, making it necessary to adjust replacement thyroid hormone doses in patients receiving thyroxine replacement.

Baseline disease characteristics

The degree of severity at the start of therapy has also been found to affect responsiveness to GH therapy in adults, with greater responses being observed in those with a more severe disease profile. Murray *et al.* (35) demonstrated that the greatest improvements in the serum lipid values after 2 years of GH therapy occurred in those patients with the highest levels at baseline. Female patients, AO patients and patients with multiple pituitary hormone deficits had a significantly more adverse lipid profile at baseline than male patients, CO patients and patients with isolated GHD, respectively,

and beneficial changes were confined to the former subgroups. In addition, a study that selected severely GH-deficient adult patients with poor QoL and replaced GH using a low-dose titration regimen aimed at normalising the IGF1 level found that the observed improvement in QoL was proportional to the degree of impairment (QoL score) before commencing therapy (24).

The influence of age, sex, and obesity on GH requirements has been attributed to differences in baseline serum IGF1 levels. From a multiple linear regression analysis, age, gender, weight, and age at onset of GHD had no independent effect on GH requirement, and the observed effect of these variables on the final GH dose was accounted for by the lower pre-treatment IGF1 s.d. in young, female and CO patients compared with older, male and AO patients respectively (55).

Treatment monitoring: assessments before and/or during treatment

Treatment guidelines recommend regular assessment of a number of efficacy measurements and safety variables known to be modulated by GH to monitor the effects of treatment. Unlike in paediatric GHD, where the outcome of treatment is clearly visible (i.e. growth), there is no one single optimal marker used to monitor efficacy in AGHD. As each efficacy measurement is only a crude marker of GH status, the use of several markers is thought to extend the dimension of normalisation in the individual and therefore improve safety during long-term replacement (28). In addition, there is no fixed treatment target to attain; studies often assess efficacy by comparing parameters with pre-treatment values and look for a shift in the right direction, or by comparing values against those for a control group (usually healthy subjects matched for sex, age, and BMI), with pre-treatment values being significantly lower than in controls and normalising following GH therapy.

As discussed above, serum IGF1 is the best available marker to guide therapy, and most endocrinologists recommend slowly increasing GH until a target in the normal range is reached with reduction instigated if overdosage is apparent. In the event of dose adjustment, it is advised that assessment should be performed no sooner than 6 weeks after the dose change. After these initial adjustments, the frequency of IGF1 measurements can usually be decreased to once or twice per year (56). The use of other biochemical parameters as treatment targets, such as free IGF1, IGFBP3, or acid labile subunit, is not perceived to be of value, as the general consensus is that these will not add to the monitoring power of IGF1 analysis alone (56).

Current guidelines recommend that, once maintenance doses are achieved, objective parameters such as body composition should be used to monitor the response. Body composition can be assessed by anthropometric measurements and also dual-energy

X-ray absorptiometry (DXA), which provides a measure of lean mass and fat mass (and is also a tool for assessing bone density).

In recognition of the increased risk of cardiovascular morbidity and mortality in hypopituitary patients, a number of cardiovascular risk markers may be considered for yearly monitoring, including fasting lipid profile, diastolic blood pressure, and electrocardiogram results. Echo-Doppler assessment of arterial intima media thickness and heart morphology and function may shed further light. Fasting glucose levels should also be monitored yearly because of increased prevalence of obesity and the potential for GH replacement to affect insulin sensitivity in these patients (7).

Measurement of bone mineral content and density before starting therapy is also recommended due to the increased risk of patients with AGHD developing osteopaenia and osteoporosis. If the initial bone DXA scan is abnormal, repeated scans are recommended at 2–3-yearly intervals to assess the need for additional bone-treatment modalities (5).

Adults with GHD have diminished QoL, and therefore, it is recommended that a specific questionnaire is administered before the start of treatment and evaluated annually thereafter to ascertain whether there is a change or sustained effect of therapy on QoL (5). Attention to parameters, such as energy level, partner satisfaction, sick days, and vitality, is thought to be of value in monitoring treatment response. Unlike other outcome measures discussed above, QoL is a subjective measure of treatment response. Whether alterations in lean body mass and/or total body water homoeostasis contribute to the perceived QoL deficit in GHD and whether favourable changes in these parameters translate into clinically meaningful improvements in QoL was explored by Mukherjee *et al.* (45). It was concluded that improved QoL was not explained by favourable changes in body composition.

The responses to GH therapy described above may only be observed after long-term therapy. As 6–8 months may be required to define a satisfactory dose of GH, with body changes following, it has been recommended that parameters such as body composition and lipid profile may be best assessed semi-annually/annually (20).

The limitations of short-term placebo-controlled trials in a condition in which treatment responses may occur gradually were recognised by Widdowson & Gibney (57). In a meta-analysis to determine whether evidence exists to support a beneficial effect of GH replacement on strength, it was found that, although long-term open-label studies provide compelling evidence that GH replacement in GHD improves muscle strength over a period of 1–10 years, the meta-analysis of placebo-controlled trials failed to confirm this. The authors concluded that this was almost certainly due to the short-term nature of such studies; unless carried out for a duration exceeding 12 months (which is an unlikely

situation given the ethical implications involved), the 'gold standard' randomised controlled trial was unlikely to provide appropriate answers to the question of whether, in GHD, there is an improvement in muscle strength with GH replacement.

Closing remarks

The aim of this review was to assess and present the evidence supporting the current guidelines on starting doses of GH for use in adult patients. This review also summarises the benefits, adverse events, and factors affecting dose responsiveness as derived from the scientific literature. Although the guidelines published most recently also discuss the evidence supporting treatment regimen recommendations to some extent (1, 3, 4, 5, 7), the current review expands on the information presented in the guidelines and includes a fuller discussion of the findings. Guidelines published by the Endocrine Society consider the strength of each recommendation and the quality of the supporting evidence (4). The recommendation that 'GH-dosing regimens be individualised rather than weight-based and start with low doses and be titrated according to clinical response, side effects and IGF1 levels' is considered a 'strong' recommendation, was developed using high-quality evidence.

The published data discussed here also support the use of low GH dosing regimens in AGHD. The range of doses defined as 'low dose' in the studies discussed here (∼1–4 mg/week, based on studies in which dose was expressed in mg/IU per day per week) is in accordance with those recommended in current guidelines (0.7–3.5 mg/week) (4, 5, 7) and encompasses the dose range recommended by product labels (∼1.1–2.1 mg/week) (9, 10, 11, 12, 13, 14, 15, 16, 17, 18). Low GH doses here are associated with few adverse effects, while the first proposed doses to treat AGHD were associated with a greater occurrence of adverse events.

The literature included here was selected using a systematic approach but was not a fully systematic review, and we acknowledge that the literature search and selection process may have limited the scope of the review. However, the data from the literature reported here are the most frequently cited on the subject and provided conclusions similar to the recent consensus guidelines.

Aside from being associated with good efficacy and safety outcomes, there are other potential benefits of such regimens. Long-term adherence to treatment is a potential issue associated with GH therapy, especially if the patient does not feel any obvious beneficial effect. It is estimated that 20–30% of patients will discontinue treatment, permanently or for extended periods, making objective evaluation of the long-term therapeutic effects difficult (25). Indeed, it has been demonstrated that the beneficial effects of GH, particularly on body composition, disappear quite rapidly after stopping treatment (58, 59). Alternate day or tiw dosing in adults has been shown to be as effective as daily dosing (37). As the frequency of injections is thought to be one of the factors contributing to non-adherence to GH therapy (60), a lower frequency dosing schedule is likely to be less burdensome to patients and may have the potential to improve adherence to treatment. New sustained-release weekly GH preparations could improve therapeutic adherence if their safety and efficacy were similar to that of daily dosing (42).

Chronic, lifelong GH therapy may be associated with considerable costs for both patients and society. Low-dose schedules may potentially have pharmaco-economic benefits, as lower doses could lead to reductions in healthcare costs. However, there are few data on pharmacoeconomic evaluations in GHD, and more studies are needed in this area (61). Moreover, low doses show similar, or even long-term greater, clinical effect than higher doses, with reduced likelihood of adverse effects. Given that the occurrence of adverse effects may require out-patient visits or hospital admission, or other treatments, and result in diminished productivity, the cost implications of inappropriate dosing are also an important consideration (4, 5, 7, 56).

Author contribution statement

V Gasco and G Aimaretti designed the purpose of the review, did the literature search and selection, and wrote the manuscript. F Prodam, P Marzullo, S Grottoli, S Longobardi, and E Ghigo collaborated equally in the literature search and selection, and in the paper revision.

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