Editorial

Feyza Darendeliler

Growth and growth hormone: recent papers on efficacy and adverse effects of growth hormone and World Health Organisation growth standards

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Response to growth hormone (GH) therapy depends on several factors including the age at onset of therapy, the height at onset of therapy, midparental height, dose of GH, frequency of injections and, last but not the least, adherence to GH therapy [1]. It has been shown in several studies that adherence may be impaired in up to 82% of children and noncompliance is inversely correlated with insulin-like growth factor 1 (IGF-1) levels and height velocity during therapy [2].

In a study from Iran by Mohseni et al. [3], the authors have evaluated adherence to GH therapy in 169 children between the ages of 2 and 19 years based on a questionnaire, the quality of which was tested before the study. The 8-item Morisky Medication Adherence Scale (MMAS) was used for the assessment of patients' adherence and auto-compliance method as described in the paper.

The results show that, in general, 16.6% of patients had high adherence, while 40.8% and 42.6% had intermediate and low adherence to GH therapy, respectively. There were no differences with respect to adherence between children and adolescents, level of education of the parents and duration of therapy. Several factors were noted for poor compliance such as being away from home, painful injection and exhaustion. Self-reported methods yielded a higher percentage of compliance showing that this method may be poor in evaluating adherence.

The authors conclude that overall adherence of the patients was low as has been shown in other studies. Every center should check the adherence of their patients to GH therapy and, taking into account the barriers, should implement strategies to overcome these barriers and increase adherence to GH therapy accordingly.

It is well known that testosterone therapy given in high doses causes side effects [4]. It has also been shown in case reports that when given in low doses, for example, to patients with constitutional delay of growth and puberty, it may cause adverse effects [5].

In their study, Albrecht et al. [6] analyze the short-term side effects of testosterone used for priming in prepubertal boys prior to GH stimulation tests.

One hundred and eighty-eight short prepubertal boys were primed with testosterone enanthate (50 mg in 136 and 125 mg in 51, 250 mg in 1) 7 days prior to the GH test. In general, five boys developed adverse side effects, two boys developed severe low-flow priapism and required intervention, one boy had self-limiting priapism and testicular pain and two boys had testicular pain. The overall side effect rate was 2.7%. There was no difference in serum testosterone levels between boys who had adverse side effects and those who did not.

This study shows that parents have to be informed about rare but potential side effects of testosterone injection given with the aim of priming.

Short stature homeobox-containing gene (*SHOX*) deficiency is a licensed indication for GH therapy and it has been shown that GH therapy increases short- and long-term height prognosis in these patients [7].

Growth response varies greatly among patients on GH therapy and prediction of the growth response remains a challenge [8]. As it has been shown in several studies that first year height velocity is an important predictor of adult height, it would be good to predict the growth response during the first year and tailor the treatment accordingly. Among several prediction models developed to predict growth response, the Cologne prediction model is a model developed to predict growth response in children with GH deficiency. The Cologne prediction model measures the relative bone age retardation, serum IGF-1 at onset of therapy, deoxypyridinoline after 1 month of treatment and annualized height velocity after the first 3 months [9]. It predicts the first year height velocity after 3 months of treatment.

The study by Hoyer-Kuhn et al. [10] investigates whether the Cologne prediction model can be applied to patients with *SHOX* deficiency on GH treatment with a dose of 0.05 mg/kg/day. This multinational, multicenter, open-label randomized study included 27 treated and

25 untreated patients. The control group was offered GH treatment in the extension period. Thus, this study included 48 prepubertal patients with *SHOX* deficiency on GH treatment for at least 1 year. All patients were genetically tested and confirmed for *SHOX* deficiency.

Height velocity and height standard deviation score (SDS) increased significantly during the first year of therapy, and predicted and observed height velocity (cm/year) showed a correlation coefficient of 0.5 ($p < 0.001$, root mean square error = 1.63) and the first year change of height SDS showed a correlation coefficient of 0.751 ($p < 0.001$, root mean square error = 0.32). These results show that growth response to GH treatment could be predicted to a certain extent by the Cologne prediction model in the first year of therapy. The study concludes that prediction of poor response may be useful for patients with *SHOX* deficiency as an individual decision-making aid.

The World Health Organization (WHO) 2006 [11] Child Growth Standards have been proposed for international use. Several countries have compared their national data with those of WHO standards to test whether these curves can be used in their countries.

In their study published in this issue, Inokuchi et al. [12] compare the WHO standards with their own national data from Tokyo, Japan, in a cohort of 0–5-year-old children (3430 boys, 3025 girls). Compared with the WHO standards, Japanese children were shorter at birth, 1, 3 and 5 years of age (height SDS difference ranging between −0.15 and −0.84 in girls and boys at different ages) and lighter (weight SDS ranging between −0.17 and −0.62 in girls and boys at different ages).

Thus, the authors conclude that the WHO 2006 standards overestimate short stature and underestimate overweight in Japanese children. For example, the percentage of short stature varied between 0.0% and 6.1% in males by Japanese standards, whereas by WHO standards the percentage ranged between 4.3% and 10.3 % at different ages. The overweight percentage ranged between 1.1% and 3.0% by Japanese standards and by WHO standards between 0.0% and 0.8%. Similar figures were noted in females. The national data of some other populations, such as Danish, Dutch, Polish, German, Belgian, UK and Norwegian, also show some differences when compared to WHO standards as reviewed in this paper. The study highlights that the WHO growth standards should be compared with national data from countries where national data are available to examine the applicability of these standards.

Allergic and non-allergic skin reactions to recombinant human growth hormone (rhGH) are very uncommon. The study by Mehta et al. [13] describes a 12-year-old boy with idiopathic short stature who developed an itchy skin rash 15 min after the administration of a first dose of GH. The rash was later found to be the exacerbation of the underlying atopic dermatitis in this patient.

Although rare, allergic reactions to GH include immediate type 1 immunoglobulin E (IgE)-mediated hypersensitivity (HS) or type III immune complex-mediated HS due to GH molecules [14]. Preservatives used in rhGH formulation can also cause allergic reactions. Alternatively, non-allergic reactions can occur in the case of an underlying skin disorder, as it has been described in this boy. The paper reviews the possible mechanisms of allergic/non-allergic reactions to GH based on the experience the authors had with their patient. The paper also summarizes the commonly used preservatives and buffers in different rhGH formulations.

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References

1. Richmond E, Rogol AD. Treatment of growth hormone deficiency in children, adolescents and at the transitional age. Best Pract Res Clin Endocrinol Metab 2016;30:749–55.
2. Fisher BG, Acerini CL. Understanding the growth hormone therapy adherence paradigm: a systematic review. Horm Res Pediatr 2013;79:189–96.
3. Mohseni S, Heydari Z, Qorbani M, Radfar M. Adherence to growth hormone therapy in children and its potential barriers. J Pediatr Endocrinol Metab 2018;31:13–20.
4. de Waal WJ, Torn M, de Muinck Keizer-Schrama SM, Aarsen RS, Drop SL. Long term sequelae of sex steroid treatment in the management of constitutionally tall stature. Arch Dis Child 1995;73:311–5.
5. Donaldson JF, Davis N, Davies JH, Rees RW, Steinbrecher HA. Priapism in teenage boys following depot testosterone. J Pediatr Endocrinol Metab 2012;25:1173–6.
6. Albrecht A, Penger T, Marx M, Hirsch K, Dörr HG. Short-term adverse effects of testosterone used for priming in prepubertal boys before growth hormone stimulation test. J Pediatr Endocrinol Metab 2018;31:21–4.
7. Blum WF, Ross JL, Zimmermann AG, Quigley CA, Child CJ, et al. GH treatment at final height produces similar height gains in patients with SHOX deficiency and Turner syndrome: results of a multicenter trial. J Clin Endocrinol Metab 2013;98:E1383–92.

8. Wit JM, Ranke MB, Albertsson-Wikland K, Carrascosa A, Rosenfeld RG, et al. Personalized approach to growth hormone treatment: clinical use of growth prediction models. Horm Res Paediatr 2013;79:257–70.
9. Schonau E, Westermann F, Rauch F, Stabrey A, Wassmer G, et al. A new and accurate prediction model for growth response to growth hormone treatment in children with growth hormone deficiency. Eur J Endocrinol 2001;144:13–20.
10. Hoyer-Kuhn H, Franklin J, Jones C, Blum WF, Schoenau E. Growth response to growth hormone treatment in patients with SHOX deficiency can be predicted by the cologne prediction model. J Pediatr Endocrinol Metab 2018;31:25–31.
11. WHO Multicenter Growth Reference Study Group. WHO Child Growth Standards based on length/height, weight and age. Acta Pediatrica 2006;(Suppl 450);76–85.
12. Inokuchi M, Matsuo N, Takayama JI, Hasegawa T. WHO 2006 Child Growth Standards overestimate short stature and underestimate overweight in Japanese children. J Pediatr Endocrinol Metab 2018;31:33–8.
13. Mehta S, Oza V, Potashner R, Zamora P, Raisingani M, et al. Allergic and non-allergic skin reactions associated with growth hormone therapy: elucidation of causative agents. J Pediatr Endocrinol Metab 2018;31:5–11.
14. Junprasert J, Javier FC 3rd, Rodriguez JA, Moore C, Sorensen RU. Successful intravenous desensitization of growth hormone hypersensitivity. J Pediatr Endocrinol Metab 1997;10:223–6.

Feyza Darendeliler, Istanbul University, Istanbul Faculty of Medicine, Department of Pediatric Endocrinology, Istanbul, Turkey,
E-mail: feyzadarendeliler@gmail.com, feyzad@istanbul.edu.tr