Taiwan Pediatric and Endocrinology Expert Meeting: GH Treatment Optimization with Patient Journey

Background

- **Taiwan**

At present, children who suffer from GHD (Growth Hormone Deficiency) follow NHIA reimbursement criteria. In most short children no diagnosis can be made, and these are labeled as having idiopathic short stature (ISS). However, there is still no clear consensus on ISS in Taiwan. In 2020, Taiwan Precision Child Health Association (TPCHA) conducted preliminary interviews across Taiwan. The interviewees included 14 key opinion leaders. In order to understand physician views on the treatment methods, dosage adjustments, and response to GH treatment under ISS treatment. In September 2021, TPCHA held a meeting of experts in the field of growth disorder in Taichung to share the interview results and international guidelines* with the participating physicians, focusing on the following topics: the time and conditions, initial treatment dose, treatment complete time, treatment response definition, and dose adjustment. The consensus is quantified using a score of 1 to 10 points (1 being the lowest, and 10 being the highest). The expert opinions were collected as followed.

- **International Status**

The diagnosis of ISS must exclude recognizable conditions that may lead to short stature. Scientific researches indicate that nearly 60 to 80% of short stature are classified as ISS. At present, only a few countries such as the United States and South Korea have ISS indication for GH treatment. ISS treatment can start from the age of five. The initial treatment is mainly based on the following conditions:

(1) Bone age within 2 SD (Standard Deviation) of chronological age
(2) Height less than 2.25 SDS (Standard Deviation Score) of growth chart
(3) Epiphyseal plate not close yet

*Drug and Therapeutics Committee of the Pediatric Endocrine Society, US & Canada, 2017
*Growth Hormone Research Society consensus guideline, Australia, 2019
*Korean Endocrine Society and Korean Society of Pediatric Endocrinology, Korea, 2020

Diet and Lifestyle

Most physicians said that tracking the patient‘s diet, lifestyle, and sleep habit for half a year is a necessary step before starting the treatment. The experts at the meeting mentioned that the growth status is caused by various factors. The purpose of treatment is for the health of the child, not only for height growth. Therefore, collecting clinical data as much as possible is extremely useful for clinical judgment. For example, physicians can take digital medical equipment (inBody) to analyze body composition to understand some children’s problems with nutritional imbalance. The current treatment guidelines use a growth velocity less than 4 cm/year as the start to treatment criteria. Doctors believe that the growth rate of each child is unique. This criteria is quite narrow. It should be compared with patients’ recored height, which is more appropriate. During the follow-up period, physicians will consider further treatment if the height development is not as expected.

Early treatment-optimize treatment benefits

Early treatment is the key that all experts agree on. Most school-age children in Taiwan have been screened by schools to find the problems associated with insufficient growth. Children with height less than 3rd percentile or a growth velocity less than 4 cm/year would receive a notice reminding parents to take their children to the doctor. There were some children from 2 to 3 years old who were brought to the hospital by their parents for examination proactively.

International studies indicate that the treatment time delay may not result in the expected efficacy. At the beginning of treatment, the body height and mid parental height (MPH) are both important. Especially in the first year of treatment, which is a critical factor for future height improvement. It is also important to start treatment before puberty.

Discussion of timing and condition for early treatment

Under which circumstances parents are advised to take their children to seek treatment proactively, the participating experts discussed the following four points:
(1) The relationship between bone age and chronological age
(2) Current height
(3) Growth velocity (cm/year)
(4) Predicted adult height

Most experts mentioned that for ISS patients, genetic height, predicted adult height, expectations of parents and children for growth, and communication of lifestyle modification would be referenced. Based upon the target bone age and current height, physicians might discuss with parents the cost of treatment and the potential side effects, thus making the appropriate assessments. Physicians will track patients' growth for at least half a year to decide whether to start treatment. During the follow-up period, if there is a gap between the predicted height and the genetic height, physicians will start a treatment based on the patient's condition. It should be noted that different physicians have different interpretations of bone age. In addition, follow-up is crucial for the patient.

CONSENSUS

Patients should adjust their lifestyle first before starting a treatment course. During the follow-up period, patients can consider receiving treatment if they meet any of the following conditions:
(1) Bone age within 2 SD (Standard Deviation) of chronological age
(2) Height < the percentile of the genetic height
(3) Growth velocity < 4 cm/year
(4) Predicted height of adult female < 153 cm,
and adult male < 165 cm

AVERAGE SCORE OF CONSENSUS 9.33/10

EXPERT OPINION

- Balancing nutrition and lifestyle must be considered before treatment. Potential height may be affected by a deficiency of vitamins and minerals, or over intake of fats.
- For self-payers, the attitude of parents and patients towards treatment is important, which may affect the adherence and the persistence to the treatment.

Initial dosage

- **GHD**

In Taiwan, there is NHIA reimbursement criteria for the initial treatment dose of GHD. Most physicians start treatment from the lowest initial dose of 0.18 mg/kg/week, and increase the dose gradually according to the treatment outcome. The United States and Canada's International Treatment Guidelines (PES) suggest that the starting dose can be 0.16 to 0.24 mg/kg/week depending on the severity of the patient's condition.

- **Self-payer**

The dose of GH used for ISS patients is generally higher than that for GHD patients. Mostly, the treatment for self-payers in Taiwan starts at 0.25 mg/kg/week, and the maximum does not exceed 0.35 mg/kg/week, which is mainly determined by physicians' experience. According to PES, the average initial dose is from 0.24 to 0.47 mg/kg/week. The general recommended starting dose is from 0.18 to 0.35 mg/kg/week.

Some physicians believe that if the value of IGF-1 is low at the beginning, a higher dose of GH will be used for treatment; if IGF-1 is at an intermediate value, a lower dose of GH will be selected. The follow-up observation will help physicians decide whether to increase the dose. In addition, some doctors mentioned that during the high-dose treatment, the patient's growth and various biochemical data should be continuously monitored to avoid side effects, such as headaches.

CONSENSUS

For ISS patients, the starting dose of GH is generally recommended from 0.18 to 0.35 mg/kg/week. The dosage should be adjusted by the value of IGF-1.

AVERAGE SCORE OF CONSENSUS 9.63/10

EXPERT OPINION

- The initial dose can be determined based upon GH stimulation test values. Those patients with GH <7 ng/ml will be reimbursed by NHIA with a GH dose of 0.18 mg/kg/week. It is recommended to treat with GH 0.18 mg/kg/week. If GH > 10 ng/ml, physicians should prescribe a dose of 0.25 mg/kg/week; the highest dosage is from 0.3 to 0.35 mg/kg/week.
- Follow-up actions should be taken during treatment and various biochemical values should be monitored to avoid possible side effects due to excessive IGF-1.

Discussion of treatment complete time

Continuous tracking of the patient's height and various biomedical values is a key reference point for clinicians to adjust treatment. Many physicians said that the most important thing is to see whether the child has room for growth and whether the child has reached the predicted height based on the bone age and growth rate. Moreover, doctors will respect parents' own wishes and financial status.

CONSENSUS

Patients with ISS can consider completing treatment under any of the following conditions:
(1) Growth velocity < 2 cm/year.
(2) The bone age of boys is close to 16 years old, and that of girls is close to 14 years old.
(3) Close to the predicted height (the genetic height of boys is ± 7.5 cm, and the predicted height of girls is ± 6 cm).

AVERAGE SCORE OF CONSENSUS 9.6/10

Definition of treatment response

International review studies indicate that ISS leads to an increase in height growth of 3.5 to 7.5 cm during 4 to 7 years of GH treatment. The efficacy of initiating GH treatment after adolescence is worse than that of prepuberty. The treatment response is worsened if patients delay receiving treatment. The definition of poor response is that the growth rate is less than 2 cm/year. In general, physicians will increase the dose if the response is not ideal.

CONSENSUS

Definition of poor treatment response:
For prepubertal children, the increased growth velocity is less than 2 cm/year after treatment.

AVERAGE SCORE OF CONSENSUS 9.6/10

EXPERT OPINION

- In Taiwanese physicians' experience, the annual growth velocity can be 8 to 10 cm in the first year, 6 to 8 cm in the second year, and 6 cm in the third year.

Dose adjustment discussion

Physicians will determine how to adjust the dosage by understanding the patient's lifestyle, regularly tracking body weight and bone age, and observing the value of IGF-1. The dosage will be adjusted according to the patient's body weight at each visit.

Some doctors will check the IGF-1 value every 3 to 6 months to ensure that IGF-1 has a normal range for that age. Physician may consider to increase the dosage if treatment outcome is not as expected. A good treatment response is often related to adherence.

EXPERT OPINION

- If the efficacy is lower than expected, physicians can monitor the IGF-1 value and body weight every 3 to 6 months to adjust the GH dosage in between the interval of 0.18 to 0.35 mg/kg/week. International treatment guidelines state that monitoring adherence is crucial for maintaining efficacy.

CONSENSUS

If the treatment response is not ideal, physicians suggested to adjust the dose according to body weight and IGF-1 level.

AVERAGE SCORE OF CONSENSUS 9.7/10

The importance of adherence

The overall adherence rate of GH treatment needs to reach 85%. The treatment should be maintained for at least 2 to 3 years in order to achieve a good response. There is digital medical device that can help monitor patients' adherence. Physicians must explain expected heights and costs as early as possible to help parents and children build confidence in treatment.

Future plan

Both "bone age> actual age (BA > CA)" and "bone age = actual age (BA = CA)" are critical for the timing of epiphyseal plate close. A treatment course may consider puberty, and the combination of GH and gonadal hormone-releasing hormone promoter (GnRHa). At the coming expert meeting, the issues related to adolescent treatment will be further discussed, such as the timing of treating boys and girls before epiphyseal plate close.

MODERATOR

Dr. Der-Ming Chu (TSGH) Dr. Pen-Hua Su (CSMU)

EXPERT (list in alphabetical order)

Dr. Chia Chi Hsu (VGHTC)
Dr. Chen Yang (IHMED / TMUH)
Dr. Chung-Hsing Wang (CMUH)
Dr. Dau-Ming Niu (VGHTPE)
Dr. Ja Wei Hou (CGH)
Dr. Mei-Hong Wen (BOAIHS)
Dr. Mei-Chyn Chao (CCH)
Dr. Yi-Shou Lin (TNHOSP)