Prediction of poor growth response to growth hormone treatment in prepubertal short children with growth hormone deficiency and born small for gestational age

Chapter 10

Impactparagraaf

It is common practice to evaluate the growth response to growth hormone (GH) treatment in children after the first year to detect poor responders in order to reassess the diagnosis, adapt the GH dose or stop the treatment to avoid unnecessary daily injections and expenses. While for the physician the purpose of assessing the growth response is multifold, for the patient/caregivers the most important question is whether the patient has grown "well". However, there is no agreement as to which criterion is most appropriate for this purpose. Consequently, different physicians use different criteria, or sometimes none at all. In this thesis we compared the different criteria for growth response after the first year of GH treatment and concluded that these criteria gave high and comparable percentages poor responders but may identify different patients. This study does not provide evidence that one criterion is better than another. Thus, a patient may be labeled a poor responder by a physician using criterion A, while not being considered a poor responder by a physician using criterion B. In addition, a good response for one patient may be different from a good response for another patient. This depends on the responsiveness (= the ability of a person to respond to GH) and is determined by, among other things, the age and the indication for GH treatment. We developed age-specific growth response curves for prepubertal idiopathic GH deficient (GHD) children which correspond to the published growth targets derived from the KIGS database. These curves can be used by physicians to rapidly identify patients with poor response to first-year GH treatment. However, until now these curves have not been used frequently because they are not integrated into existing growth curve software programs. Implementing this would increase ease of use and consequently its use.

In order to identify poor growth responders much earlier than after the first treatment year, we tried to find GH induced metabolic changes which predict the first-year growth response. We showed that GH treatment had a positive effect on basal metabolic rate and total energy expenditure (TEE) in prepubertal children after 6 weeks. The increase in TEE appeared to be valuable for the prediction of good first-year growth responders but not for poor responders to GH treatment. Therefore, these metabolic criteria cannot be used as predictors for poor response.

Another question that patients and/or their care givers often ask is whether the patient will have a normal final height and preferably also what the final height will be. We validated Ranke's prediction models predicting the near adult height (nAH). Ranke's models accurately predicted nAH in females and overpredicted nAH in males by about 1.5 cm. In most individuals, predicted nAH was within 6.8 cm (= 1 SDS) of observed nAH. These models can be of help in giving realistic expectations of adult height.

The diagnosis "poor responder" may result in discontinuation of GH treatment after the first year. However, current criteria do not take into account the ultimate growth response after years of GH treatment. We were the first to investigate the value of the different first-year growth response (FYGR) criteria as predictors of a poor final height outcome after long-term GH treatment in GHD patients. We showed that the amount of correctly diagnosed poor final responders (=poor responder after first year AND poor final responder) equals the amount of falsely diagnosed poor final responders (=poor responder after first year BUT good final responder). Therefore, FYGR criteria perform poorly as predictors of poor final height outcome after long-term GH treatment in prepubertal GHD children and alone should not be used to decide to discontinue treatment. We hypothesized that a lower waning effect in the second year might compensate for a lower first year response, translating in a better predictability of a poor total height gain after two years of GH treatment. However, we found that the growth response after 2 prepubertal years of GH treatment did not meaningfully improve the prediction of poor adult height outcome after GH treatment compared to first-year growth response parameters. We concluded that the evaluation of the growth response should not be postponed for another year, as the prediction after 2 years has no added value in GHD children.

With the insights obtained from the results of these studies, we have drawn up an advice for an optimized strategy for an individualized approach for identification and management of poor first-year response in GHD children. Responsiveness (using prediction models or our developed expected height velocity curves) should play a prominent role in the assessment of first-year growth response, which has rarely been the case in clinical practice until now. This way, the first-year growth response will be interpreted more correctly, resulting in more

adequate management as suggested in our advice. After the second treatment year, reevaluation of the growth of poor responders who had a treatment adjustment after the first year should take place and action taken upon findings. This could lead to a better cost effectiveness of this yet expensive GH treatment and less burden for the patient and his family.

These new insights were shared with other healthcare professionals through the published articles, several presentations at (inter)national conferences and this thesis. However, an update of the (inter)national guidelines regarding the interpretation of the first-year growth response would only really lead to a change in mindset and treatment behavior of health care professionals.

Furthermore, it would be worth re-evaluating the indications for GH treatment. Since response and responsiveness are highly variable, even within diagnostic groups, decisions about GH treatment could also be made on the likelihood of benefit, depending not only on diagnosis and sufficiency of GH secretion, but also on the responsiveness to GH. This way children with idiopathic short stature with a good predicted first-year height velocity could benefit from GH treatment. In our new proposal for management of poor responders we suggest that discontinuation of GH treatment in children with poor growth response ánd poor responsiveness should be considered. This way an expensive treatment with marginal or no benefit will be avoided in poor responders while short children with expected good response, who currently have no access to GH treatment, could benefit from it.