Long-Acting Growth Hormone in Idiopathic Short Stature

Paul Saenger Luis Zamora-Siliezar

Division of Pediatric Endocrinology, Department of Pediatrics, NYU Winthrop Hospital, Mineola, NY, USA

The report by Hwang et al. [1] from Seoul, South Korea, is the first report to describe the safety and efficacy of long-acting growth hormone (LAGH) in the treatment of idiopathic short stature (ISS). To date, a number of LAGH formulations have been studied [2], and their efficacy in phase 2 studies is quite good [3]. The only successful phase 3 study that led to the approval of LAGH for pediatric and adult growth hormone deficiency (GHD) in Europe was done with the same formulation used by Hwang and coworkers [4].

The use of LAGH raises the question of how physiologic the regimen is, but none of the currently used or previously recommended growth hormone (GH) regimens to treat GHD or ISS are physiologic. Once-daily injections do not mimic even remotely the 6–8 bursts of pituitary GH that growing children secrete per day. Yet, since the introduction of daily GH in the clinic in 1958 [5], that is exactly what has been universally accepted and highly successful.

Many different approaches have been taken for the development of LAGH [2]. These formulations to prolong the action of GH have included the following: forming emulsions (using gelatin and triglycerides), GH encapsulation (using biodegradable microspheres), adding poly-

mers to GH (PEGylation), GH conjugation to endogenous proteins (albumin) or exogenous polypeptides (which have increased the size of the molecule almost 5 times, reaching as much as 120 kDa), and GH fusion proteins (by means of linking an inert peptide to a region of the GH molecule that would not interact with the GH receptor). Increased molecular size may lower efficacy of a long-acting GH [6].

However, as we have learned from the successful and the many failed trials, pharmacokinetic (GH levels on treatment) and pharmacodynamic changes (especially insulin-like growth factor-1 [IGF-1] levels) can influence the safety and efficacy of LAGH.

Recently, the Growth Hormone Research Society published a position paper on LAGH concluding that it may offer patients and families an advantage over daily GH because of the potential for improved adherence and outcomes [7]. Better methods to assess adherence need to be developed and validated, but to our knowledge, this has not happened. Long-term surveillance registries in phase 4 studies will include assessment of long-term efficacy, cost-effectiveness, and disease burden; also, quality of life evaluations and safety measures are needed to understand the impact of chronic exposure to preparations of

LAGH. It remains to be proven whether LAGH formulations will provide a true benefit and will have the same safety profile as current formulations of daily GH in use since 1985 [6, 8].

Hwang et al. [1] used 2 doses of GH, 0.5 mg/kg/week (the recommended and approved dose for GHD in a phase 3 trial [4]) which was inferior to daily GH, and 0.7 mg/kg/week that proved to be noninferior to daily GH. These results are congruent with several reports in which the GH dose for ISS is usually higher than the dose required for GHD, accounting for the well-recognized mild GH resistance postulated in ISS [7, 8].

One should keep in mind that this was a small-scale ($n = 16$), brief (26 weeks) phase 2 study that barely met noninferiority criteria. We can only hope that in a larger 1-year phase 3 study these criteria are met as well. However, past experience tells us that this is not always the case, as illustrated by the recent failure of the phase 3 Versartis trial with VRS 317 (Somavaratan). The Versartis phase 2 trial had promising data, yet the phase 3 study did not meet noninferiority criteria based on height velocity compared to daily GH [9].

The safety profile seen in this 26-week study was comparable for both doses of LB03002 to daily recombinant human GH, and no neutralizing antibodies were reported. Anti-GH antibodies are also often seen with daily GH and generally do not affect efficacy. While standard laboratory tests do not raise red flags, more detailed analysis of lipid profiles, visceral fat, and weight gain will hopefully be addressed in a phase 3 study.

In the pharmacodynamic evaluation of the drug, the IGF-1 levels were above 2 SD in 11 subjects at 36 h after the last injection, which is of concern as the authors concede, yet IGF-1 levels returned to baseline in all subjects before the next LAGH injection.

We are therefore eagerly awaiting the outcome of a phase 3 clinical trial of LB03002 to confirm that LAGH is as efficacious in ISS as daily GH is [7, 8].

Disclosure Statement

Paul Saenger, MD, is a clinical investigator for Ascendis, OPKO, and Novo Nordisk. Luis Siliezar, MD, has no conflicts of interest to declare.

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