New treatment for severe short stature shows promise

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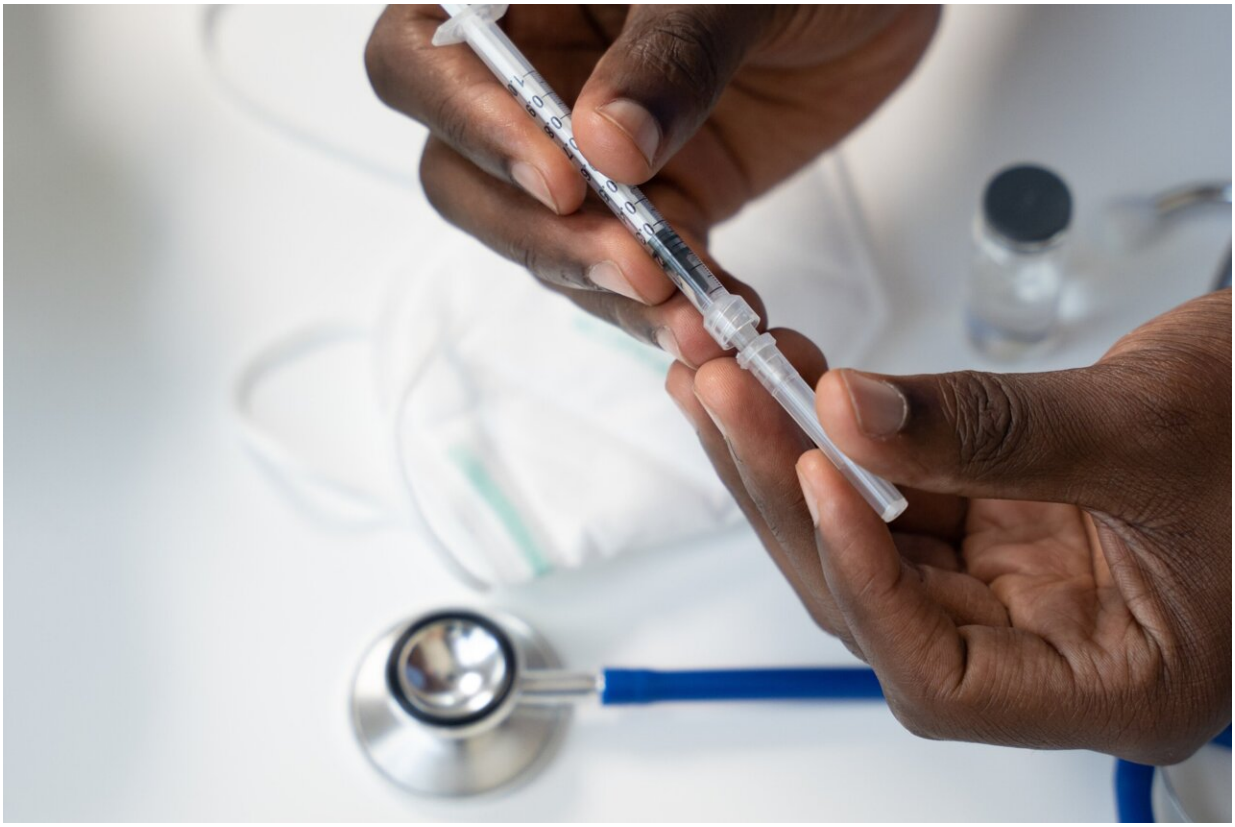

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Teresa Quattrin, MD, University at Buffalo Distinguished Professor of pediatrics, is a co-author on a new global study that suggests a novel treatment option for children with achondroplasia—a form of severe

short stature.

Achondroplasia is one of the most frequent bone disorders that prevents bone growth, especially in the arms and legs, resulting in very severe short stature, with average height for males and females being only 52 and 49 inches, respectively.

Additionally, affected individuals are likely to experience other problems that include, but are not limited to, an unusually large head that can be due to hydrocephalus (water in the brain), limited mobility of the elbows, spine curvature, sleep apnea, frequent ear infections, and back and leg pain.

Achondroplasia is due to a genetic mutation in about 80% of affected individuals, while about 20% can inherit it from their mother or father if they are affected.

It affects 250,000 people worldwide, with a prevalence of 4.6 cases in every 100,000 births, or 1 in every 22,000 births.

"The issue is the lack of conversion of cartilage into bone," says Quattrin, senior associate dean for research integration in the Jacobs School of Medicine and Biomedical Sciences at UB and a physician with UBMD Pediatrics. "This is due to a genetic mutation in the fibroblast growth factor receptor 3 (FGFR3)."

Improved annualized growth velocity

The study was published Oct 2. in *eClinical Medicine*.

Fifty-seven study participants (prepubertal, aged 2–10 years, with genetically confirmed achondroplasia) were randomized 3:1 to once-weekly subcutaneous injections of TransCon C-type natriurtic peptide

(CNP); 6, 20, 50, or 100 μg CNP/kg/week or placebo for 52 weeks.

At the 100 μg CNP/kg/week dose, TransCon CNP demonstrated significantly improved annualized growth velocity compared to the placebo, the study found, providing the first evidence that TransCon CNP significantly increased annualized growth velocity in children with achondroplasia with a favorable safety profile.

Reducing the number of injections

The first drug that showed height improvement in achondroplasia patients was the FDA-approved Voxogo by BioMarin Pharmaceutical, but its dosing regimen is burdensome, requiring daily subcutaneous injections in pediatric patients.

Quattrin says one of the breakthrough successes of the ACcomplisH trial is the use of weekly injections instead of daily.

TransCon CNP is an investigational prodrug of C-type natriuretic peptide (CNP). The TransCon technology allows for continuous CNP exposure with once-weekly dosing.

"The problem with the FGFR3 is that the receptor is overactive. The medicine used in this trial, CNP, is to counteract the over activation," she says. "CNP half-life is very short, but the medicine used in this trial took advantage of a new technology called TransCon that prolongs the half-life, allowing for weekly injections."

"Using a technique that improves life in circulation is a great stride forward," Quattrin adds.

This is similar to what Ascendis has accomplished with growth hormone therapy, Quattrin says, noting Ascendis has received FDA approval for

weekly growth hormone injections that were traditionally administered daily.

ACcomplisH is the first randomized, double-blind, placebo-controlled, dose-escalation of TransCon CNP in children with achondroplasia ages 2–10 years.

TransCon CNP was well tolerated and resulted in a low frequency of injection site reactions with no incidence of symptomatic hypotension, which has been a potential concern with the development of CNP therapeutics based on the role of CNP in regulating vascular homeostasis, including systemic blood pressure.

Investigations are ongoing in an open-label extension period in which participants will be followed for two years, as well as in a pivotal trial, to further evaluate the balance of harms and benefits of the 100 μg CNP/kg/week dose of TransCon CNP.

More information: Ravi Savarirayan et al, Once-weekly TransCon CNP (navepegritide) in children with achondroplasia (ACcomplisH): a phase 2, multicentre, randomised, double-blind, placebo-controlled, dose-escalation trial, *eClinicalMedicine* (2023). DOI: 10.1016/j.eclinm.2023.102258

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