VOSORITIDE TREATMENT IMPROVES LINEAR GROWTH AND ABSOLUTE BONE CONTENT AND DENSITY IN CHILDREN WITH HYPOCHONDROPLASIA: A 12-MONTH PROSPECTIVE STUDY

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INTRODUCTION

Hypochondroplasia (HCH) is a fibroblast growth factor receptor 3 (FGFR3)-related skeletal dysplasia characterized by disproportionate short stature and altered body proportions. Vosoritide, a C-type natriuretic peptide (CNP) analog that promotes endochondral bone growth by antagonizing FGFR3 signaling, is approved by FDA for achondroplasia. It has recently shown efficacy in improving growth velocity in children with HCH. However, there is limited data on bone mineral density in hypochondroplasia and specifically effects of vosoritide on bone mineral density remain largely unexplored.

OBJECTIVE

To evaluate the impact of vosoritide therapy on height and bone mineral density on dual-energy X-ray absorptiometry (DXA) in children with hypochondroplasia (HCH) over 12 months.

METHODS

This is a prospective, single-arm phase 2 study (NCT04219007) conducted at Children's National Hospital. Twenty-four children ages 2–10 years with genetically confirmed HCH received daily subcutaneous vosoritide (15 µg/kg/day) for 12 months. Height was measured using calibrated Harpenden stadiometer. Bone mineral content (BMC) and bone mineral density (BMD) were assessed by DXA at baseline and month 12, at subtotal and lumbar spine sites. Z-scores were calculated using sex-, age-, and height-adjusted pediatric reference data (Kalkwarf et al., JCEM 2022).

RESULTS

At 12 months, standing height SDS improved significantly (−3.28 ± 0.69 to −2.91 ± 0.68; Δ +0.37 SDS; $p < 0.0001$). TBLH BMC and BMD increased significantly, while age- and sex-adjusted Z-scores remained unchanged; height-adjusted subtotal BMD Z-score showed a small but significant decrease. Lumbar spine BMC and BMD increased significantly, with corresponding BMD z-scores (age/sex and age/sex/height-adjusted) also significantly improved (Table 1).

Table 1. Bone health parameters in children with hypochondroplasia before and after 12 months of vosoritide treatment.

	Day 1 Mean (SD)	Month 12 Mean (SD)	Change during treatment period (95% CI)*	Two-sided p value
Total body less head BMD				
BMD (g/cm²)	0.46 (0.06)	0.48 (0.07)	0.03 (0.02, 0.04)	**<0.0001**
Sex/age adjusted Z-score	-2.65 (0.81)	-2.69 (0.99)	-0.04 (-0.24, 0.16)	0.67
Height/sex/age adjusted Z-score	-0.12 (0.73)	-0.55 (0.91)	-0.40 (-0.50, -0.10)	**0.001**
Total body less head BMC				
BMC (g)	371.02 (109.54)	410.18 (119.76)	54.84 (23.09)	**<0.0001**
Sex/age adjusted Z-score	-3.03 (0.67)	-2.79 (1.44)	0.20 (-0.30, 0.50)	0.20
Height adjusted Z-score	-0.01 (0.72)	-0.53 (1.11)	-0.20 (-0.50, 0.10)	**0.03**
Lumbar BMD				
BMD (g/cm2)	0.46 (0.07)	0.48 (0.07)	0.03 (0.03)	**<0.0001**
Sex/age adjusted Z-score	-1.30 (1.18)	-1.07 (1.05)	0.25 (0.53)	**0.04**
Height/sex/age adjusted Z-score	0.29 (1.20)	0.44 (1.02)	0.20 (-0.03, 044)	0.08
Lumbar BMC				
BMC (g)	14.07 (4.25)	16.02 (4.51)	2.19 (2.04, 2.40)	**<0.0001**
Sex/age adjusted Z-score	-1.05 (1.20)	-1.20 (0.97)	0.34 (0.09, 0.59)	**0.01**
Height/sex/age adjusted Z-score	1.00 (1.17)	1.13 (1.05)	0.16 (-0.01, 0.34)	0.07

BMD – bone mineral density; BMC – bone mineral content; BMD and BMC was adjusted using https://www.cincinnatichildrens.org/special-forms/dxa-scan-calculator

**Changes are presented as mean differences with 95% CIs for normally distributed variables and median differences with 95% CIs for non-normally distributed variables.*

CONCLUSION

Vosoritide treatment over 12 months showed a statistically significant increase in the absolute parameters of BMC and BMD at both subtotal and lumbar-spine sites, but this change was less significant when adjusted BMC and BMD z-score for sex, age and height. These findings support continued longitudinal monitoring to determine whether bone accrual is achieved after height gain. It is also important to follow long-term skeletal outcomes as interpretation of DXA results in patients with skeletal dysplasia is complex due to short stature, different bone shape, and disproportionate limb-to-torso ratios. Our single-arm design and relatively short 12-month follow-up limits the ability to infer fracture risk or peak bone mass outcomes. Longer controlled trials across ACH and HCH populations are needed to determine the long terms effects on bone mineral accrual relative to growth, and whether composition improvements translate into durable functional and cardiometabolic benefits.

DISCLOSURES

AD has served as a consultant for BioMarin, BridgeBio, Novo Nordisk, Pfizer, Ascendis, and Eton Pharmaceuticals. He has grant funding from Pfizer and BioMarin. RKS had a grant from BioMarin. NM served as a consultant for BioMarin, BridgeBio, Pfizer, Ascendis, KyowaKirin, Alexion and Catalyst.

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