Bone mineral density in a cohort of children with ACH participating in the PROPEL studies

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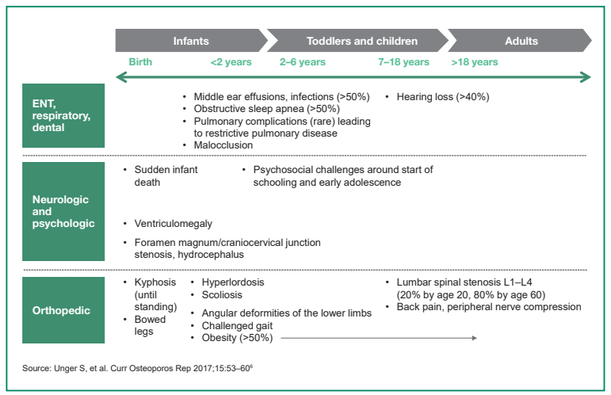
Background

- **Achondroplasia (ACH)** is the most common short-limbed skeletal dysplasia, affecting between 1 in 15,000 to 1 in 30,000 live births in the US, with an estimated global prevalence of 250,000.[1,2]
- ACH is characterized by defective endochondral ossification resulting from gain of function pathogenic variants in the fibroblast growth factor receptor 3 (*FGFR3*) gene,[3,4] which is a negative regulator of endochondral bone formation.
- Characteristic clinical features of ACH are as follows: disproportionately short stature; smaller than average chest; macrocephaly with frontal bossing; midface hypoplasia; curvature of the spine; hypermobile joints; leg bowing; and shortening of the fingers and toes.[5]
- Individuals with ACH experience a variety of physical, functional, and psychosocial complications and challenges throughout their lifetime (Figure 1).[6]
- Decreased bone mass has been reported in gain-of-function mutations in *Fgfr3* mice, and a decrease in **bone mineral density (BMD)** has been observed in children and adults with ACH.[7,8]
- The **PROPEL** (NCT04035811) and **PROPEL2** (NCT04265651) studies (Figure 2) were designed to provide preliminary evidence of the safety and efficacy of infigratinib as a potential precision treatment option for children with ACH.[9]
- Infigratinib is an orally bioavailable and selective FGFR1–3 tyrosine kinase inhibitor in development for ACH. Infigratinib inhibits FGFR downstream signaling, offering a direct therapeutic strategy to counteract the hyperactivity of FGFR3 in ACH.[5]
- The long-term efficacy and safety of daily use of oral infigratinib is being assessed in the **PROPEL OLE** study.

Figure 1. Medical complications associated with ACH[6]

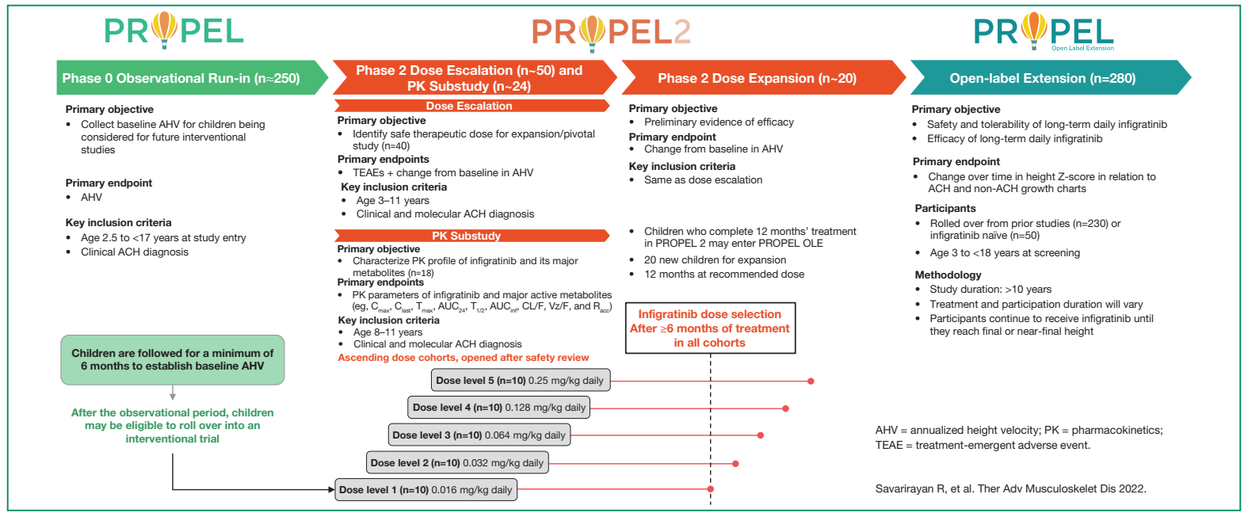


Source: Unger S, et al. Curr Osteoporos Rep 2017;15:53–60[6]

Objective

- Here we describe BMD in a cohort of children participating in PROPEL2, a phase 2 study evaluating preliminary efficacy and safety of infigratinib, an oral FGFR-1–3 tyrosine kinase inhibitor in development for ACH.

Figure 2. PROPEL, PROPEL2, and PROPEL open-label extension study designs



AHV = annualized height velocity; PK = pharmacokinetics; TEAE = treatment-emergent adverse event.

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Methods

Study design

- PROPEL2 is a prospective, phase 2, open-label study designed to provide preliminary evidence of the safety and efficacy of oral infigratinib in children with ACH, and to identify the dose of infigratinib to be explored in future studies.
- Children 3–11 years of age with ACH who completed ≥6 months of observation in the non-interventional PROPEL study are eligible to participate in PROPEL2.

Assessments

- Dual energy X-ray absorptiometry (DXA) scans of the spine (L1–4) were collected at baseline in children participating in PROPEL2 using a Hologic or GE Lunar scanner following a pre-specified image acquisition procedure.
- Images were evaluated by a single reviewer. Results are expressed as Z-score for age and sex based on average-height children.

Results

- In total, 52 children (mean ± SD age: 7.97 ± 1.9 years; 29 female; mean ± SD height z-score: –5.4 ± 1) were included in this analysis (Table 1). BMD of the lumbar spine was –1.0 ± 0.9 SDS (min –4.1; max 0.7 SDS).
- No statistical difference was found between males and females.
- 85% of children (n=44) had a BMD Z-score of <0 SDS, from which 21 (40%) had a score between –2 and < –1 SDS, 18 (35%) has a score between –1 and 0, and 5 (10%) had a score of < –2 SDS (Figure 3). Eight children (15%) had a BMD Z-score of >0 SDS.
- No correlations were observed between BMD Z-score and height Z-score or BMI (Figure 4).

Figure 3. BMD Z-score

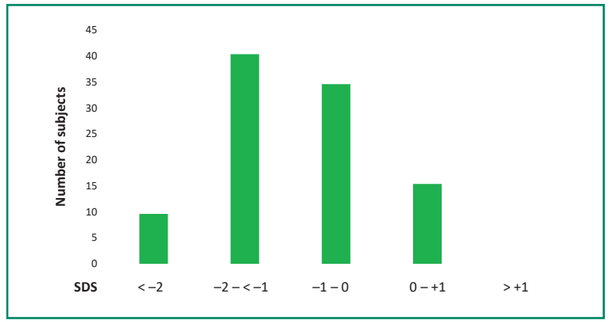

Figure 4. Correlations between BMD Z-score and height Z-score or BMI

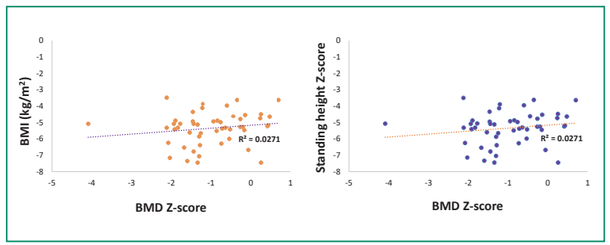

Table 1. Baseline characteristics

Characteristic	Total (n=52)
Sex, n (%)	
Female	29 (55.8)
Male	23 (44.2)
Age, years[a]	
Median	8.1
Mean ± SD	8.0 ± 1.9
Height Z-score	
Mean ± SD	–5.4 ± 1.0
BMD Z-score of lumbar spine	
Value ± SD	–1.0 ± 0.9
Range (min–max)	–4.1 – 0.7

Conclusions

- Our findings show lumbar spine BMD to be lower in children with ACH compared with normative data from children of average height.
- Low BMD in the context of short stature is difficult to interpret, raising the question of the degree to which low bone status can be attributed to smaller bone size relative to age.
- Even though our findings do not take into account children's height, no correlation between BMD and baseline height Z-score was identified in this cohort, suggesting that the findings may not be solely attributable to overall height.
- These findings reinforce the need to better understand how to circumvent this limitation in children with skeletal dysplasias in order to improve DXA interpretation and avoid misdiagnoses.

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