Bone mineral density in 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

ACH is characterized by defective endochondral ossification resulting from gain of function mutations in the fibroblast growth factor receptor 3 (FGFR3) gene, which is a negative regulator of chondrocyte bone formation.2,3

Characteristic clinical features of ACH are as follows: disproportionately short stature; smaller than average head size; macrocephaly with frontal bossing; midface hypoplasia; curved spine; hypermobile joints; leg bowing; and shortening of the fingers and toes.4,5

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 (NCT02005511) and PROPEL2 (NCT02465651) 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 for development in ACH. Infigratinib inhibits FGFR signaling downstream, offering a direct therapeutic strategy to counteract the hyperactivity of FGFRs in ACH.10

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

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 PROPEL 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 (44 males and 7 females; 11 children >8 years and 41 children <8 years) were included in this analysis (Table 1). BMD of the lumbar spine was measured using DXA (min –1.4; max –0.7; mean = –0.8).

No statistical difference was found between males and females.

86% of children (44/52) had a BMD Z-score of <2 SDS, from which 21 (44%) had a score between –2 and –1 SDS, 19 (37%) had 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 >2 SDS.

No correlations were observed between BMD Z-score and height Z-score or BMI (Figure 4).

Acknowledgements

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References


Table 1. Baseline characteristics

<table>
<thead>
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<th>Males (n=44)</th>
<th>Females (n=7)</th>
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<tbody>
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<td>Age (yrs)</td>
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<td>Sex</td>
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<tr>
<td>BMI (kg/m2)</td>
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<td>-2.0 ± 0.9</td>
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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 misleading.

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

Figure 3. BMD Z-score

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

Figure 5. Correlations between BMD Z-score and height Z-score or BMI

Figure 6. Correlations between BMD Z-score and height Z-score or BMI

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