Does Vosoritide Treatment Affect Bone Strength in Children with Achondroplasia?

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Introduction

- Achondroplasia is an autosomal dominant disorder affecting endochondral bone formation, commonly characterized by disproportionate short stature[1,2].
- The primary objective of this study was to determine whether vosoritide, an FDA-approved drug meant to increase endochondral bone linear growth, affects both length and development of bone strength in children with achondroplasia using measurements of the second metacarpal.

Methods

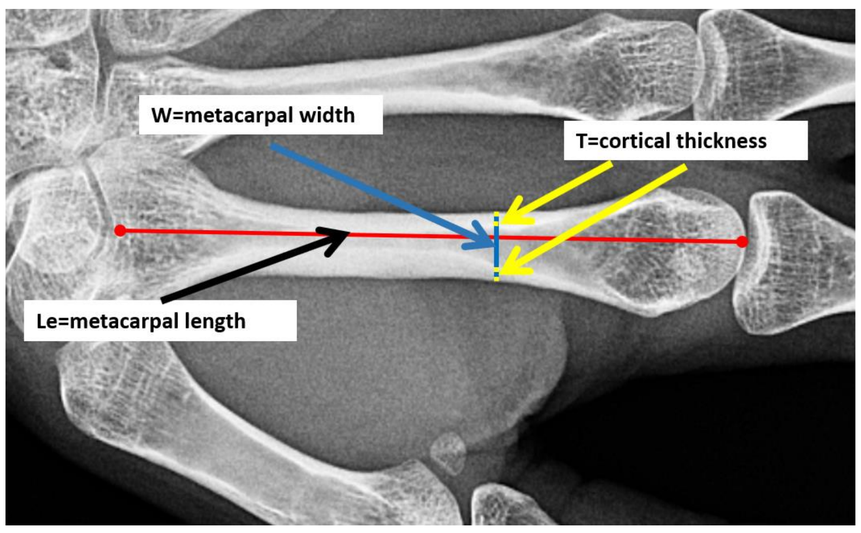
- This study included 103 deidentified AP hand/wrist radiographs from 30 children with achondroplasia (13M, 17F; ages 7.8-16 years).
- Proprietary data included hand films available from the 111-205 clinical trial sponsored by BioMarin, collected at four time points: 2 years (at rollover into the phase II extension study), 3 years, 4 years, and 5 years on treatment.
- Second metacarpal length and midshaft width, cortical thickness, robustness (total area/length), cortical area (correlated with strength), and relative cortical area (RCA, cortical area/total area) were measured[3].
- Achondroplasia measurements were compared to 378 radiographs from 114 average-stature controls (61M, 53F; ages 6-16 years).
- Non-parametric Kruskal-Wallis tests were conducted to determine differences between groups ($p<0.05$).

Table 1. Measurements of the second metacarpal (mean±SD) at each time point in treatment.

	Baseline (n=27)	2 Years (n=29)	3 Years (n=29)	4 Years (n=28)	5 Years (n=17)	Controls (n=378)
Le (mm)	35.71±4.51°^▪	39.75±4.49°	42.13 ± 4.36°	44.12±4.56°*	45.00±4.98°*	56.83±9.40*#‡^▪
T.Ar (mm^2)	39.30±12.04‡#	42.84±11.82▪	45.79±12.49°*	49.80±14.63°*	54.29±17.64°*#	39.01±11.79‡^▪
Ct.Ar (mm^2)	21.80±6.29‡#^▪	25.60±6.59°^▪	28.12±6.72*▪	32.06±7.93*#	35.60±9.59°*#‡	29.64±9.57*#▪
M.Ar. (mm^2)	17.50±7.84°	17.24±9.38°	17.67±10.54°	17.73±12.15°	18.68±12.06°	9.37±4.81*#‡^▪
Ct. Th. (mm)	1.20±0.27°▪	1.39±0.35°	1.49±0.37°	1.67±0.43°	1.77±0.41*°	1.10±0.35*#‡^▪
RCA	0.57±0.10°^▪	0.61±0.12°	0.63±0.12°	0.66±0.12*°	0.67±0.12*°	0.76±0.10*#‡^▪
T.Ar/Le (mm)	1.10±0.30°	1.08±0.30°	1.09±0.29°	1.13±0.32°	1.20±0.37°	0.68±0.13*#‡^▪

*significantly different ($p<0.05$) than baseline, #significantly different ($p<0.05$) than 2 years, ‡significantly different ($p<0.05$) than 3 years, ^significantly different ($p<0.05$) than 4 years, ▪significantly different ($p<0.05$) than 5 years, °significantly different ($p<0.05$) than controls

Fig. 1. Method of Measuring Metacarpal Parameters.



$$\text{Robustness} = (\text{Total Area})/\text{Le} = \frac{\pi(\frac{W}{2})^2}{L}$$

Fig. 2. Representative Hand Radiograph of a 10-year-old Male with Achondroplasia.

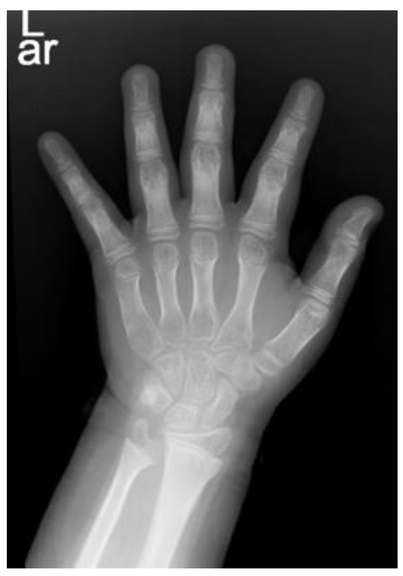
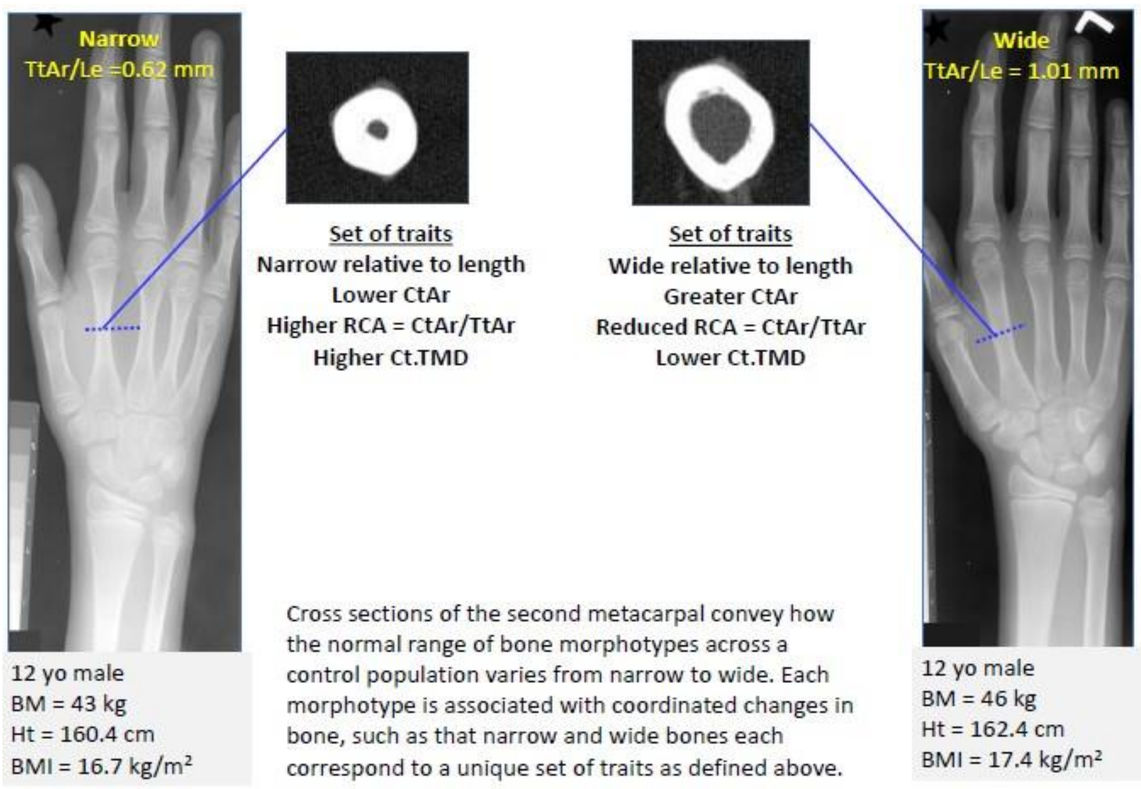


Fig. 3. Hand Radiographs Comparing Narrow vs. Wide Bone in a Control Population.



Results

- Children with achondroplasia on 4 and 5 years of treatment demonstrated longer metacarpals with increased cortical area compared to baseline; those at year 5 also displayed increased cortical thickness (all $p<0.05$) (Table 1, Fig. 4).
- There was no significant difference in metacarpal robustness compared to screening across the treatment timepoints (Fig. 5).
- No differences were seen between males and females with achondroplasia at any time point.

Fig. 4. Metacarpal cortical area (mm^2) at each time point in treatment.

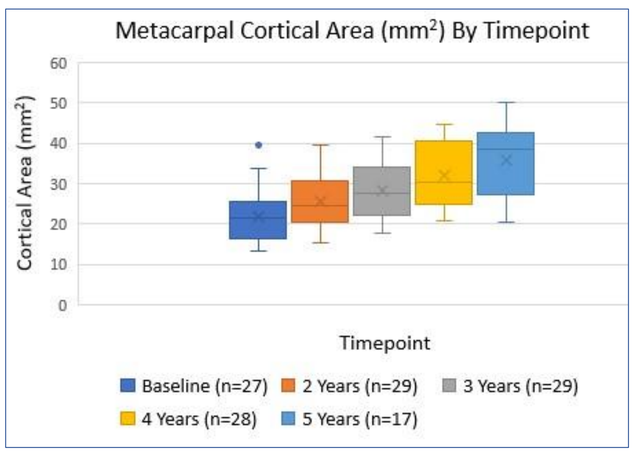
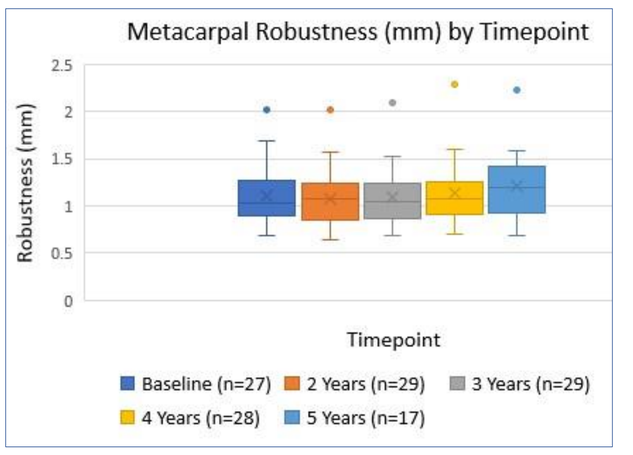


Fig. 5. Metacarpal robustness (mm) at each time point in treatment.



Box and horizontal line indicate the median with quartile 1 and quartile 3; cross indicates mean, whiskers indicate the minimum and maximum values, and dots indicate outliers.

Conclusions

- We observed that 4-5 years of vosoritide treatment was associated with significant increases in bone length compared to baseline, as well as increases in metacarpal cortical area, which is correlated with strength.
- This preliminary clinical trial suggests this bone lengthening treatment did not adversely affect bone strength in children with achondroplasia.
- The lack of a significant difference in robustness after treatment indicated that periosteal expansion continued outward at a pace which maintains robustness, allowing the bone to remain strong as it lengthened.
- Future work comparing treated and untreated children with achondroplasia at each timepoint is necessary to understand the long-term impact treatment has on the development of bone strength.
- Overall, this work may have important clinical implications in terms of treatment choices for children with achondroplasia.

References

1. Bellus GA, Hefferon TW, Ortiz de Luna RI, et al. (1995). Achondroplasia is defined by recurrent G380R mutations in FGFR3. Am J Hum Genet 56:368–373.11.
2. Shiang R, Thompson LM, Zhu YZ, et al. (1994). Mutations in the transmembrane domain of FGFR3 cause the most common genetic form of dwarfism, achondroplasia. Cell 78:335–342.
3. Citron, K., Veneziale, C., Marino, J., Carter, E. M., Jepsen, K. J., & Raggio, C. (2017). Bone robusticity in two distinct skeletal dysplasias diverges from established patterns. Journal of Orthopaedic Research, 35(11), 2392–2396.

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