Editorial: Achondroplasia in Childhood: Treat or Cure?

In 1878, French physician Joseph Marie Jules Parrot first used the term achondrodysplasia to describe a rare genetic disorder caused by a gain-of-function point mutation in the

FGFR-3 gene [1]. This mutation leads to an overexpression of the FGFR3 receptor pathway, inhibiting chondrocyte proliferation responsible for cartilage formation [2-12]. The specific mutation in the FGFR3 gene that causes achondroplasia is a substitution of glycine with arginine at codon 380, disrupting normal bone formation and resulting in disproportionate short stature, particularly in the arms and legs [2-12]. Achondroplasia affects about one in every 26,000-28,000 live births [3].

Current research is focused on developing therapies to reduce FGFR3 receptor overexpression and inhibit chondrocyte formation to treat achondroplasia [10-12]. It is the most common form of short stature, caused by a dominant FGFR3 gain-of-function mutation that activates the FGFR3 and MAPK signaling cascade, inhibiting chondrocyte differentiation and growth plate activity. This can lead to complications such as spinal stenosis and airway narrowing. Treatment recommendations aim to reduce morbidity and mortality, especially in infants and young children. External symptoms of achondroplasia include short upper arms and thighs, broad hands and feet, and a long trunk [3]. Breathing and hearing issues are common due to chest size and narrow nasopharynx. Physical development may be delayed, but intelligence is not affected. Leg axis changes and spinal curvature may occur, with growth typically ending around 120-140 cm [3].

Therapeutic strategies aim to reduce excessive signals from the FGFR3 gene, with potential treatments including CNP, FGFR3-binding peptides, soluble FGFR3, meclizine, statin, and FGFR inhibitors.

Vosoritide (BMN111), marketed as Voxzogo, is a treatment for achondroplasia in patients over 2 years old with open epiphyses [4-6]. It acts as an agonist of NPR-B, promoting bone growth by inhibiting the MAPK pathway [4-6]. Common side effects include injection site reactions, vomiting, hypotension, dizziness, and syncope. TransCon CNP, a modified form of CNP-38, offers sustained release in achondroplasia treatment, enhancing bone growth efficacy compared to intermittent exposure [4]. Recifercept targets FGFR3 to improve bone growth and skeletal development in achondroplasia. Vofatamab, a monoclonal antibody targeting FGFR3, is studied for urothelial carcinoma treatment. Oral Infigratinib has shown promise in the treatment of achondroplasia [7-9].

Treatment in childhood is crucial, but current therapies do not cure all symptoms associated with achondroplasia. Research is ongoing to develop more specific inhibitors for FGFR3. First attempts were done by Robert Hudkins et al., who developed a specific FGFR3 inhibitor named TYRA-300 [10-12]. Another selective FGFR3-specific target under development, LY3866288 (Loxo-435), was described by early results from the FORAGER-1 trial [13]. Future research may focus on gene therapies like CRISPR-Cas9 therapy to correct the gene defect pre- or postnatally as a curing one time-approach.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

CONSENT

As per international standards, parental written consent has been collected and preserved by the author.

ETHICAL APPROVAL

As per international standards or university standards written ethical approval has been collected and preserved by the author.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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