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Perspective

What is the Clue to Treat or Cure Achondroplasia in Childhood: A Future Perspective

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Abstract

Vosoritide, an CNP analogon, does not cure patients with achondroplasia. The drug helps to gain height and must be given life-long. Tyrosinkinase inhibitors like infigratinib, given orally, are not FGF3-receptor selective, the toxic side effects on other FGF receptor signaling pathways are not insignificant. Selective FGF3-receptor inhibitors are necessary to diminish toxic side effects in these children, but at all, help to gain height but do not cure them. New approaches were performed by Robert Hudkins, who developed a FGFR-3 selective inhibitor named TYRA-300. Further advances were published in initial results of FORAGER-1 study published in 2025. The focus to cure children with achondroplasia is a pre- or postnatal gene therapy to repair the point mutation of the fibroblast growth factor receptor gene FGFR3 on chromosome 4p16.3. The best treatment of curing the disease seems to be a one-time pre- or postnatal approach of a gene therapy intervention and for treating it specifically by the development of a selective FGFR3-tyrosinkinase inhibitor which high efficacy and low toxic side effects.

Perspective

In 1878, French physician Joseph Marie Jules Parrot coined the term achondrodysplasia, which is now considered a rare genetic disorder. It is caused by a gain-of-function point mutation in the FGFR-3 gene, leading to overexpression of the FGFR3 receptor pathway and inhibiting chondrocyte proliferation responsible for cartilage formation [1,2]. 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 leading to disproportionate short stature. Restricted growth, particularly in the arms and legs, leads to disproportionate short stature. It affects about one in every 26,000-28,000 live births. Current research is focused on developing therapies to reduce FGFR3 receptor overexpression and inhibit chondrocyte formation to treat achondroplasia. Achondroplasia 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 leads to complications like spinal stenosis and airway narrowing. Treatment recommendations aim to reduce morbidity and mortality, especially in infants and young children. It affects approximately 1 in 20,000 births worldwide. External symptoms include short upper arms and thighs, broad hands and feet, and a long trunk. 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 120-140cm. Early gene mutation suspicion led to the discovery of achondroplasia. Fibroblast growth factor receptor 3 is a receptor tyrosine kinase that binds fibroblast growth factors, regulating cell proliferation, differentiation, and migration. It plays a crucial role in bone ossification and cartilage remodeling. In achondroplasia, an overactive FGFR3 signaling pathway is present, affecting cell growth and differentiation. FGFR3 interacts with adapter proteins like GRB2 and Sos, forming complexes that link to the MAPK pathway. The activation of FGFR3 leads to phosphorylation of proteins like phospholipase C-γ, influencing cell signaling.

Vosoritide (BMN111) is a treatment for achondroplasia in patients over 2 years old with open epiphyses [3-5]. Marketed as Voxzogo, it comes in powder and solvent form for injection. Vosoritide acts as an agonist of NPR-B, promoting bone growth by inhibiting the MAPK pathway [4]. It is well-absorbed and metabolized via catabolic pathways. The recommended dosage is weight-based to ensure consistent exposure. Common side effects include injection site reactions, vomiting, hypotension, dizziness, and syncope. Vosoritide has minimal drug interactions due to its recombinant peptide nature. TransCon CNP is a modified form of CNP-38 attached to polyethylene glycol for sustained release in achondroplasia treatment. It offers continuous exposure to CNP, enhancing bone growth efficacy compared to intermittent exposure. Studies show it is well-tolerated with minimal cardiovascular effects. The prolonged exposure to CNP with TransCon CNP reduces the risk of hypotension. Recifercept targets FGFGR3 to treat achondroplasia by downregulating specific signaling pathways, improving bone growth, skeletal development, skull proportions, and reproductive capacity. It also shows promise in reducing atypical visceral obesity in achondroplasia. Further research is needed to understand its full efficacy and safety in humans. Vofatamab is a monoclonal antibody targeting FGFR3, studied for urothelial carcinoma treatment.

It blocks FGF ligand attachment to inhibit cancer cell growth. While considered for achondroplasia, its large size may limit its effectiveness in dense extracellular matrices. Clinical trials are ongoing for urothelial neoplasms and multiple myeloma. Erdafitinib, an FGFR inhibitor, is effective in treating certain cancers by inhibiting FGFR subtypes and other tyrosine kinases. Approved by the FDA in 2019, it is used for metastatic or locally advanced urothelial carcinoma with specific gene mutations. Common side effects include stomatitis, diarrhea, abdominal pain, nausea, constipation, and dysgeusia. Recent publications in the New England Journal of Medicine and the Lancet shed light on oral infigratinib as a valuable milestone in the treatment of achondroplasia [5-8]. Therapeutic strategies aim to reduce excessive signals from the FGFR3 gene, with potential treatments including C-Type Natriuretic Peptide (CNP), FGFR3-binding peptides, soluble FGFR3, meclizine, statin, and FGFR inhibitors. Vosoritide, a stable form of CNP, has shown positive effects on growth in clinical trials. Targeting FGFR3 with Tyrosine Kinase Inhibitors (TKIs) is another potential strategy, although current inhibitors are not specific to FGFR3. Research is ongoing to develop more specific inhibitors for FGFR3 [9,10]. Treatment in childhood is crucial, but current therapies do not cure all symptoms associated with achondroplasia. The current treatments are life-long treatments without curing the patients with this rare disease in childhood. Future research may focus on gene therapies like CRISPR-Cas9 therapy to correct the gene defect pre-or postnatally, a point mutation on chromosome 4 in a one-time approach.

Disclaimer (Artificial Intelligence)

Author hereby declares 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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