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LETTER TO THE EDITOR

Vosoritide: a drug providing a promising avenue for the treatment of short stature in children with achondroplasia

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Achondroplasia (OMIM 100800) is a prevalent skeletal dysplasia inherited as an autosomal dominant disease. It can arise from a sporadic fibroblast growth factor receptor 3 (FGFR3)gene gain-of-function mutation that results from a substitution of glycine to arginine at codon 380 on chromosome 4 (1,2). Achondroplasia is characterized by rhizomelic shortening of limbs, macrocephaly, midfacial retrusion, kyphoscoliosis, "trident" hands, hypermobile joints, and hypotonia, occurring at a frequency of 1 in 25-30,000 with 80% sporadic cases (3).

Recombinant growth hormone and surgical limb lengthening procedures are the currently available treatment options for increasing linear bone growth in affected children. However, the use of recombinant growth hormone is restricted to Japan only and has been associated with body disproportion, whereas surgery is an invasive option associated with risks such as fractures and nerve palsies (1).

On November 19, 2021, the Food and Drug Administration (FDA) approved a new drug called Vosoritide for the treatment of achondroplasia in children over 5 years of age. Vosoritide is an analog of C-Type Natriuretic peptide (CNP); it exerts its effects through precisely the same mechanism as CNP and regulates the homeostasis of cartilage and endochondral ossification. CNP, along with its receptor Natriuretic Peptide Receptor-B (NPR-B), has a stimulatory effect on ossification, while the FGFR3 gene mutation exerts an inhibitory effect on bone growth via activation of the mitogen-activated protein kinase (MAPK) inhibitory pathway in chondrocytes. This disturbs the normal antagonism between the two pathways that are required to ensure normal bone growth. Vosoritide, being an analogue of CNP, triggers the NRP-B, which upregulates intracellular cyclic guanosine monophosphate production, inhibiting the FGFR3-mediated MAPK pathway downstream. In turn, the effects of mutated FGFR3 are counteracted by Vosoritide, restoring the balance between the two pathways and resulting in endochondral bone growth (1).

A randomized, multi-centered, phase 3, double-blind, placebo-controlled trial was conducted that compared the once-daily administration of vosoritide subcutaneously with a placebo in children affected by achondroplasia. It was concluded that among these two groups, the corrected mean difference in annualized growth velocity (AGV) was 15.7 mm/year favoring vosoritide (95% confidence interval [1.22-1.93]; two-sided $p < 0.0001$). Afterward, these children participated in an open-label extension study, where the children randomized to vosoritide experienced an increase in AGV from a baseline value of 42.6 mm/year to 53.9 mm/year and 55.2 mm/year at weeks 52 and 104, respectively. In the extension study, children who were switched to vosoritide from a placebo showed an improvement in AGV from a value of 38.1 mm/year at 52 weeks to 54.3 mm/year at 104 weeks, thus establishing the efficacy of vosoritide (4).

In another phase II dose-finding study, the results approved daily subcutaneous dosing of 15 µg /kg vosoritide (1).

During the 2 years of daily subcutaneous dosing of vosoritide (15 µg /kg/day), its adverse effect profile was studied, and it was concluded that vosoritide causes mild, bearable reactions at the site of drug administration and low blood pressure. No life-threatening events such as cardiovascular accidents or anaphylaxis occurred, nor was any mortality recorded (1).

Patients being administered vosoritide should be appropriately cautioned about experiencing lightheadedness and fatigue after administration of

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the drug, with special consideration given to patients with significant cardiovascular disease or patients on medications that lower blood pressure (5).

In conclusion, given the incidence of achondroplasia and the lack of currently available medical treatments, Vosoritide seems like a promising option for increasing linear bone growth in the affected children. However, ongoing trials on vosoritide are further investigating its safety, efficacy, long-term effects, and side effects, and also its role in the mitigation of the serious complications of achondroplasia.

List of Abbreviations

AGV	Annualized growth velocity
CNP	C-Type Natriuretic peptide
FGFR3	Fibroblast Growth Factor Receptor 3
FDA	Food and Drug Administration
MAPK	Mitogen-activated protein kinase
NPR-B	Natriuretic Peptide Receptor-B

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