Indian Academy of Pediatrics (IAP)

nRICH

Newer **R**esearch and recommendations **I**n **C**hild **H**ealth

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UNDER THE AUSPICES OF THE IAP ACTION PLAN 2023

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Dear fellow IAPans,

nRICH

Newer **R**esearch and recommendations **I**n **C**hild **H**ealth-aims to bring you the abstracts of some of the breakthrough developments in pediatrics, carefully selected from reputed journals published worldwide.

Expert commentaries will evaluate the importance and relevance of the article and discuss its application in Indian settings. nRICH will cover all the different subspecialities of pediatrics from neonatology, gastroenterology, hematology, adolescent medicine, allergy and immunology, to urology, neurology,vaccinology etc. Each issue will begin with a concise abstract and will represent the main points and ideas found in the originals. It will then be followed by the thoughtful and erudite commentary of Indian experts from various subspecialties who will give an insight on way to read and analyze these articles.

I'm sure students, practitioners and all those interested in knowing about the latest research and recommendations in child health will be immensely benefitted by this endeavor which will be published online on every Monday.

Happy reading!

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Safe and persistent growth-promoting effects of vosoritide in children with achondroplasia: 2-year results from an open-label, phase 3 extension study

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BASED ON ARTICLE

Savarirayan R, et al. Safe and persistent growth-promoting effects of vosoritide in children with achondroplasia: 2-year results from an open-label, phase 3 extension study. Genet Med. 2021 Dec;23(12):2443-2447.
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ABSTRACT

Title: Safe and persistent growth-promoting effects of vosoritide in children with achondroplasia: 2-year results from an open-label, phase 3 extension study

Background: Achondroplasia results from impaired endochondral ossification due to fibroblast growth factor receptor 3 (FGFR3) gene mutation. Vosoritide, an analog of C-type natriuretic peptide that stimulates endochondral bone growth, was developed for the treatment of achondroplasia. The authors aimed to document the efficacy and safety of continuous, daily vosoritide in children with achondroplasia in this phase 3 extension study.

Methods: Children with achondroplasia aged 5 to <18 years completed at least six months in a baseline observational growth study, and 52 weeks in a double-blind, placebo-controlled study following which they were eligible to continue treatment in an open-label extension study, where all of them received vosoritide at a dose of 15.0 µg/kg/day for another 52 weeks.

Results: In children randomised to vosoritide, annualised growth velocity increased from 4.26 cm/year at baseline to 5.39 cm/year at 52 weeks and 5.52 cm/year at week 104. In children who crossed over from placebo to vosoritide in the extension study, annualised growth velocity increased from 3.81 cm/year at week 52 to 5.43 cm/year at week 104. No new adverse effects of vosoritide were detected.

Conclusion: Vosoritide treatment has safe and persistent growth-promoting effects in children with achondroplasia treated daily for two years.

COMMENTARY

Achondroplasia is the most common skeletal dysplasia causing rhizomelic limb shortening. It is caused by a gain-of-function mutation in the FGFR3 gene that results in inhibition of chondrocyte proliferation and differentiation leading to impaired matrix synthesis and bone growth (1).

So far, Recombinant human Growth hormone(rhGH) in combination with surgical tibial and/or femoral elongation were the principal symptomatic treatment options in practice for this condition. In Japan rhGH has been used for 20 years to treat Achondroplasia at a dose of 0.05 mg/kg/day. Although the available data are still limited, compared to untreated controls, total gain in adult height has been greater in males than in females, reported at 3.5-8.0 cm and 2.8-4.2 cm, respectively(2). There is a theoretical risk of increase in foramen magnum narrowing with growth hormone (3).

Vosoritide, an analog of C-type natriuretic peptide, inhibits the intracellular signalling pathway of the FGFR3 receptor and thus serves as precision therapy in achondroplasia(3). Promising results from a dose-establishing phase 2 trial led to the commencement of a phase 3 double-blind randomised controlled trial that further confirmed the findings of significant increase in the annualised growth velocity with once daily administration of Vosoritide(4). Also, there was no evidence of tachyphylaxis in the extension study.

Vosoritide was approved by the US FDA in November 2021 for use in children with achondroplasia aged 5 years and above with open growth plates(5).

Currently, two other phase 2 clinical trials of vosoritide are underway, to assess it's safety and efficacy in children under 5 years of age and in those at risk of cervicomedullary compression(6).

In March 2023, the US FDA accepted BioMarin Pharmaceutical's supplemental new drug application to expand the use of Vosoritide in children under 5 years of age(7). Other drugs in the pipeline include TransCon CNP (another C-type natriuretic peptide with a longer half-life, enabling once weekly administration), Recifercept (a soluble FGFR3 ligand of FGF) and Infigratinib (a tyrosine kinase inhibitor of FGFR3)(3). The synergistic effect of these drugs have a great potential in the management of this condition in the years to come.

In the current study, the authors also recorded an improvement in body proportions with Vosoritide treatment.

In conclusion, this short term data showed that vosoritide at a dose of 15 µg/kg/day has good safety and efficacy in the treatment of achondroplasia in the short term but long-term effects and the final adult height achieved remain to be seen. However discovery of these new molecules have certainly raised the hopes for children with Achondroplasia.

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