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REVIEW ON VOSORITIDE: ACHLONDROPLASIA

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ABSTRACT: BioMarin Pharmaceutical is developing Vosoritide, a modified recombinant human C-type natriuretic peptide (CNP) analogue for the treatment of achondroplasia. A gain-of-function mutation in the fibroblast growth factor receptor 3 gene (FGFR3), a negative regulator of bone growth, causes achondroplasia. Vosoritide works to restore chondrogenesis by attaching to the natriuretic peptide receptor B (NPR-B), which inhibits the hyperactive FGFR3 gene's downstream signalling pathways. In August 2021, the European Union approved Vosoritide for the treatment of achondroplasia in children under the age of two whose epiphyses are not closed; the diagnosis of achondroplasia should be validated by genetic testing. In the United States, the medication is also undergoing regulatory assessment for the treatment of achondroplasia and clinical trials. Several countries are in the process of developing. The milestones in the development of vosoritide that led to this first approval for achondroplasia in children under the age of two whose epiphyses are not closed are summarized in this article. Vosoritide is a medication that was designed to treat achondroplasia and has shown to improve the growth rate of children with the condition. Achondroplasia, often known as dwarfism, is a skeletal dysplasia (a disorder affecting children's bones and joints that causes them to grow abnormally). Achondroplasia currently has no approved treatments, with the exception of growth hormone in Japan. Clinical studies are required after many other processes in the development of a new treatment to determine how effectively the drug works and whether it is safe.

INTRODUCTION: With a prevalence of 1 in 25,000 live births, achondroplasia is the most frequent form of disproportionate low height [1-5]. The disease is caused by an autosomal dominant mutation in the fibroblast growth factor receptor 3 gene (FGFR3), which affects endochondral ossification by constitutively activating the mitogen-activated protein kinase (MAPK)–extracellular signal-regulated kinase pathway in chondrocytes [6].

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Short stature with rhizomelic limb shortening and macrocephaly are the most common clinical characteristics. Hydrocephalus, hypotonia, back and leg pain, conductive hearing loss and speech delay are all medical consequences. Obstructive sleep apnea and respiratory insufficiency can be caused by relative tonsillar hypertrophy. Central apnea can be caused by foramen magnum stenosis and cervicomedullary compression, increasing the risk of sudden death in children [7-9].

Achondroplasia is linked to a unique set of developmental milestones, functional limits that impact quality of life, and chronic pain, all of which contribute to psychosocial difficulties [8, 10-13]. From birth to four years of age, as well as in the fourth and fifth decades of life, mortality rates rise [14].

Except for growth hormone, which is available for this indication in Japan, no pharmacologic therapy for achondroplasia have been licenced [15]. Children with achondroplasia who are treated with growth hormone gain height primarily during the first two years of treatment [16]. Growth hormone therapy in patients with achondroplasia increased final height by a standard deviation of 0.60 in male patients and by a standard deviation of 0.60 in female patients in a long-term trial with a mean follow-up of ten years [17] Growth hormone's effects on disproportionality remain unknown, as are the long-term consequences of such treatment [16-18]. Limb-lengthening surgery improves height but does not avoid medical issues; also, the procedure is controversial due to its invasiveness and high complication rate. NPPC encodes [19] C-type natriuretic peptide, which stimulates endochondral ossification, and its receptor, natriuretic peptide receptor 2 (NPR2) [20]. In mice, reduced or absent Nppc or Npr2 expression results in severe dwarfism due to defective endochondral ossification [21, 22]. Overexpression of Nppc in mice [23] and NPPC in human illness models [24-26,] on the other hand, causes an increase in endogenous C-type natriuretic peptide [27], resulting in skeletal overgrowth. Exogenous C-type natriuretic peptide is continuously infused intravenously [28]. By blocking the FGFR3-mediated MAPK signalling pathway, it rescues the decreased bone growth seen in mice with achondroplasia and increases long-bone growth in wild-type monkeys [29].

Diagnosis: There are no diagnostic criteria for Achondroplasia and recognition is based on clinical and radiological symptoms and genetics.

Diagnosis during Pregnancy: Non-invasive procedures such as ultrasound, CT (computed tomography), MRI (magnetic resonance imaging), and cell-free foetal DNA (deoxyribonucleic acid) testing, as well as invasive amniotic fluid examination are used to diagnose achondroplasia during pregnancy. If the femur length is below the third percentile of the reference range and the "collar hoop" sign is present (rounded overgrowth of periosteum between the epiphysis and metaphysis, and a wider angle for the metaphyseal diaphyseal junction), routine ultrasound during pregnancy, especially in the third trimester, may suggest achondroplasia [30, 31].

Short stature can also be detected with three-dimensional helical computed tomography, which can reveal more specific symptoms such as rhizomelia and spinal canal stenosis in the lumbar vertebrae, or allow for better imaging of the "collar hoop" sign [31]. The use of MRI in the prenatal diagnosis of skeletal dysplasia has also been studied, with results indicating that it confirms the diagnosis in 82 percent of cases. During the examination, the image of the brain, spinal cord, spine and lung volume are all given special attention. Fetal MRI may be effective in detecting many kinds of skeletal dysplasia, although the examiner's ability is a factor. Magnetic resonance imaging (MRI) can be a useful addition to an ultrasound examination, especially when the results of the ultrasound are inconclusive [32].

Because it avoids the need for invasive amniocentesis, cell-free foetal DNA testing of the mother's blood is becoming increasingly popular for the identification of congenital disorders. Achondro-plasia can be detected by next-generation foetal DNA sequencing, however this method is not as extensively used as aneuploidy detection [33, 34]. All prenatal study results must be confirmed by the postnatal examination of the child.

Diagnosis after Birth: Recognition of achondroplasia in neonates is based on the presence of distinctive clinical manifestations in combination with radiological findings, with no need for a molecular examination. Evidence of a heterozygous FGFR3 gene mutation in a proband is required if there is ambiguity due to unclear illness signs. The detection of the two most common alterations, c.1138G>A and c.1138G>C, is the most common test used to confirm achondroplasia. A multigene panel, which can identify further mutations in the FGFR3 gene, is the next step in the diagnostic process, followed by a differential diagnosis [35].

Methods of Treatment: Surgical and pharmacological therapies are two types of treatments for achondroplasia. The Ilizarov apparatus or monolateral external fixator is used to lengthen the lower limbs, which includes many treatments and the risk of catastrophic consequences [36].

Recombinant Human Growth Hormone (rhGH): Growth hormone (somatotropin) is an anabolic hormone that plays a role in the synthesis of nucleic acids and proteins, cell division stimulation, and glucose metabolism regulation, resulting in organ and bone growth as well as weight gain [36]. Recombinant somatotropin is one of the symptomatic treatments for achondroplasia short stature and it seeks to improve the patients' growth through direct action or the influence of IGF-1 on chondrocyte proliferation [37]. Short-term GH therapy is more beneficial than long-term treatment in improving growth velocity, according to several studies. The most significant increase in height occurs during the first year of treatment [38, 39]. A 10-year treatment with human recombinant growth hormone (rhGH) resulted in a mean growth gain of +3.5 cm in men and +2.8 cm in women. The use of rhGH and L-thyroxine together resulted in a final growth gain of 10.0 cm in males and 9.8 cm in females. In boys and females, using this approach in combination with surgical tibial and/or femoral elongation raised final height by +17.2 cm and +17.3 cm, respectively [40]. In rat studies, there was no significant difference in height gain between the growth hormone and placebo groups, although the treated group gained much more weight. The authors also suggested that using a variable GH treatment paradigm (one that mimics natural secretion rhythms) could be more beneficial. Than continuous daily administration, but this requires further examination [41].

CONCLUSIONS: All of the information shown above shows that finding a cure for achondroplasia is a top priority for researchers around the world. The most advanced research is currently focused on rhGH and vosoritide. Even if these treatments are approved for broad use, they will not eliminate all of the symptoms of achondroplasia. Despite the fact that they increase bone length, their effects on critical elements including disproportionality, the axial skeleton, and the foramen magnum have yet to be verified. Each of these factors has its own set of difficulties that affect patients with achondroplasia on a daily basis. The ideal treatment for achondroplasia should be small enough to easily penetrate the growth plate, selective for FGFR3, and inhibit the signalling pathway it activates. Because the therapy is long-term, the cost of manufacture should be as low as possible and the drug administration method should be simple and agreeable to a juvenile patient. In addition, adverse effects should be kept to a minimum to ensure dose tolerance. Recombinant human growth hormone currently meets the best requirements for a successful achondroplasia treatment, and vosoritide may meet them in the future, while the rest of the drugs are still in the early stages of clinical testing.

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