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Advances in the treatment of achondroplasia

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Abstract: Achondroplasia is a condition resulting from a missense mutation in the FGFR3 (fibroblast growth factor receptor 3) gene, representing the predominant etiology of short height in humans. Physical phenotypic characteristics encompass small stature, macrocephaly with frontal bossing, midface hypoplasia, rhizomelic shortening of the limbs, brachydactyly, and genu varum. Untreated cases result in several orthopedic and neurological issues that ultimately lead to impairment. Treatment techniques for achondroplasia can be categorized into surgical and pharmaceutical therapy. Enhanced comprehension of the etiology of this disease has prompted efforts to create causative pharmaceutical treatments. This review introduces innovative possible pharmacological therapies for achondroplasia including vosoritide, which received approval for patient usage in 2021, as well as TransCON CNP, meclozine, infigratinib, and recifercept, all now undergoing clinical trials.

Aim of the study: The main aim of this study is to elucidate the most recent treatment methodologies for patients with achondroplasia. This article presents groundbreaking advancements and new therapies designed to enhance the quality of life for patients with achondroplasia, while also raising awareness of available treatment choices and fostering optimism for future developments in this domain. In 2021, vosoritide (Voxzogo), a C-type natriuretic peptide (CNP) analogue, was approved by the US FDA and EMA for use in children with achondroplasia. As of January 2025, vosoritide therapy has been available in Poland for patients with achondroplasia under the drug program, which is a response to the unmet therapeutic need in patients with achondroplasia.

Materials and methods: A review of the literature available in the PubMed and Google Scholar databases was performed, using the key words: „achondroplasia", „FGFR3", „skeletal dysplasia", „vosoritide", „short stature".

Keywords: achondroplasia, FGFR3, skeletal dysplasia, vosoritide, short stature

1. Introduction

Achondroplasia is the most prevalent condition within the category of primary skeletal dysplasias. It accounts for about 90% of instances in patients with excessively small stature [1]. It impacts almost 250,000 individuals globally. Achondroplasia manifests in roughly 1 in 20,000 to 1 in 30,000 live births annually [2].

The condition is genetically determined, inherited in an autosomal dominant manner, and results from a point mutation in the gene encoding the transmembrane portion of fibroblast growth factor receptor 3 (FGFR3). The gene is located on the short arm of chromosome 4. This condition results in abnormal endochondral ossification, thereby impairing the formation of certain bones in the affected individual. It is estimated that more than 80% of mutation cases arise spontaneously. Owing to the mechanism of inheritance, there are no disparities in the prevalence of achondroplasia between genders. Advanced paternal age during conception is a recognized risk factor for achondroplasia. This mutation is thought to arise during spermatogenesis [3].

The phenotypic of an individual with achondroplasia is characteristic. Distinctive traits encompass macrocephaly, pronounced frontal bones, hypoplastic midface, rhizomelic limb shortening, brachydactyly, and valgus lower limbs. The intellectual development of patients with achondroplasia typically falls within the normal range. The life expectancy in this demographic is statistically 10 years less than that of the overall population. Patients with achondroplasia experience medical issues throughout their life. Increased mortality is noted in infants, whereas older children encounter various laryngological issues. Adults with achondroplasia, conversely, exhibit a heightened risk of obesity development. Particular emphasis must be placed on the various orthopedic diseases present in these patients. Joint laxity is prevalent, thoracolumbar kyphosis is evident, and spinal stenosis poses a significant difficulty. Functional and psychosocial difficulties are essential considerations in the care of a patient with achondroplasia.

2. Clinical presentation and diagnosis

The clinical presentation of achondroplasia is distinctive. The symptoms related to development problems are the most conspicuous. Typically, there is **reduced stature**, **macrocephaly** accompanied by midfacial hypoplasia and a prominent, broad forehead, as well as **rhizomelic disproportion**, wherein the proximal segment of the limb is shorter than the distal segment. Furthermore, there exist skeletal abnormalities in both the upper and lower extremities, pronounced joint laxity, and thoracolumbar kyphosis.

At delivery, the newborn's body length may fall within the normal range; nonetheless, subsequent linear growth is significantly limited. The average terminal height of patients with achondroplasia is 130 cm for men and 125 cm for women. The growth trajectory of persons with achondroplasia resembles that of children of typical height until the onset of puberty. The extent of this rise is diminished across all age demographics. The most significant variation in height from the average occurs within the initial five years of life. Children with achondroplasia experience little or no growth surge during puberty [4] [5]. The trunk size is typically average, indicating that the seated height of the patient is comparable to that of healthy individuals [6]. At the age of 2, the arm span and leg length of children with achondroplasia are typically approximately 10 cm shorter than those of children of average height at the same age. In adulthood, the average arm span is reduced by 64 cm in both genders, while leg length is diminished by approximately 44 cm in men and 40 cm in women [7].

Upper limb abnormalities encompass developmental diseases of the hand, such as brachydactyly, characterized by the shortening of the fingers. The defining feature is the space between the ring and middle fingers, referred to in literature as a "trident hand". Furthermore, individuals with achondroplasia may encounter radial head subluxation and posterior angulation of the humerus, potentially leading to limited extension in the elbow joints.

Among the typical **deformations of the lower limbs**, it is necessary to indicate primarily the shortening of the limbs and the deviation of the axis, which occur in every patient with achondroplasia. The bending of the lower limbs in a varus character (genu varum) is present not only at the level of the knees, but also at the level of the ankles. These deformations have a very complex etiology, they are the result of internal torsion of the tibia, lateral bending and instability of the knee ligaments. These disorders cause many orthopedic problems with the joints of the lower limbs and gait abnormalities in later life [8].

Characteristic of achondroplasia are **sagittal spinal abnormalities**, particularly thoracolumbar kyphosis (TLK). This characteristic is apparent at birth and may subsequently intensify due to macrocephaly and diminished trunk muscular tone. This abnormality is prevalent in children up to two years old, with a dramatic decline in its prevalence in later life. As the infant matures and acquires the capacity to stand and walk, lumbar sacral hyperlordosis and heightened sacral inclination may emerge. Imaging investigations of the spine may disclose diverse bone abnormalities of the vertebrae and numerous alterations in the adjacent soft tissues [9] .

The defining feature of the condition is **the stenosis of the foramen magnum** (FMS), posing a significant risk of spinal cord compression at this location. The etiology of this symptom arises from the disruption of endochondral ossification in the skull base, caused by the FGFR3 mutation. The manifestation of apneas during sleep is frequently noted as symptoms originating from the spinal cord. Additional symptoms linked to FMS encompass dysphagia, hyperreflexia, and widespread hypotonia. As a secondary consequence of FMS, certain infants may experience hydrocephalus, which endangers the child's life and development. Cervical spinal compression in the foramen magnum may be linked to a heightened risk of sudden infant death syndrome. The foramen magnum is believed to be anatomically most restricted when a kid with achondroplasia reaches roughly 1 year of age. Research suggests that 2-7.5% of neonates succumb to abrupt mortality attributable to foramen magnum stenosis [6].

In adulthood, individuals with achondroplasia frequently experience several distressing conditions stemming from spinal stenosis and compression of the nerve roots or spinal cord, including pseudo claudication and paresthesia in the legs.

The preliminary **diagnosis** of achondroplasia relies on clinical manifestations and distinct radiological observations. The condition is confirmed through molecular genetic testing. A constellation of phenotypic traits can be detected during standard prenatal ultrasound examinations in pregnant women (shortened long bones in the fetus). Presently, prenatal diagnostics may encompass non-invasive fetal DNA testing derived from maternal blood.

Individuals with achondroplasia must also contend with other non-orthopedic issues. **Obesity** is prevalent among these people, thereby exacerbating joint and lower back issues. Obesity is associated with various problems, including hypertension, type 2 diabetes, and obstructive sleep apnea. Regrettably, hypertension and other circulatory system disorders frequently manifest in adult patients with achondroplasia [10]. Obesity is a risk factor for **obstructive sleep apnea**, and in patients with achondroplasia, the facial anatomical structure further predisposes them to this issue. The hypoplastic midface and hypertrophied pharyngeal and palatine tonsils constrict the airway space. Obstructive sleep apnea in children may lead to diminished academic performance and behavioral issues. Sleep apnea, as previously mentioned, may also be associated with cervicospinal compression at the foramen magnum.

3. Standard therapy for individuals with achondroplasia

Treatment for achondroplasia has been restricted to surgical intervention or expectant management. Therapeutic interventions that target the underlying disease have been a persistent and unfulfilled requirement. Recent advancements in the understanding of the disease's etiology have led to the initiation of clinical trials for novel medicines in pediatric patients with achondroplasia. This part will succinctly examine conventional treatments for people with achondroplasia, while contemporary advancements including novel pharmaceuticals will be addressed in a separate chapter.

The management of achondroplasia is unequivocally an interdisciplinary endeavor. It concentrates on particular issues that arise during the progression of the disease. Individuals with achondroplasia necessitate management from a pediatrician, neurologist, orthopedist, pediatric endocrinologist and frequently an otolaryngologist, cardiologist, psychologist, and physiotherapist, as well as specialized anesthetic evaluation during the perioperative phase.

The primary management of patients with achondroplasia is optimizing functional ability while monitoring, preventing, and addressing problems.

During each follow-up appointment for a kid with achondroplasia, **height and head circumference** must be measured and recorded on the relevant growth charts for the condition. It is crucial to differentiate between "normal" macrocephaly (enlarged ventricles with normal pressure) and clinically severe hydrocephalus. For instance, charting the skull circumference of a kid with achondroplasia against the general population of children of the same age may lead to numerous unnecessary imaging procedures and neurosurgical evaluations. Routine measurements of skull circumference in children should be conducted till the age of 6 years because of the delayed closure of cranial sutures. Intervention-requiring hydrocephalus occurs in approximately 5% of cases. **Foramen magnum stenosis** plays a significant role in the etiology of hydrocephalus. Surgical intervention for hydrocephalus can be achieved through endoscopic third ventriculostomy, ventricular shunting, or decompression of the posterior cerebral fossa. It is important to highlight that, despite the constriction of the foramen magnum, the majority of children with achondroplasia do not necessitate surgical intervention for this condition. In patients with FMS, it is essential to do a sleep study followed by MRI imaging of the craniocervical junction. Should any of these tests yield an aberrant result, a neurosurgical consultation is warranted to assess eligibility for surgical intervention, including surgical expansion of the foramen magnum and upper cervical laminectomy. Children exhibiting symptoms FMS are often treated within the initial 24 months of life. Furthermore, if cervical spinal compression is evident, the patient is recommended to refrain from contact sports, trampoline use, diving, gymnastics, and other physical activities that may exacerbate spinal cord compression. Regrettably, FMS symptoms may manifest later in a patient's life, rather than exclusively during childhood [11].

Thoracolumbar kyphosis (TLK) is a prevalent manifestation in neonates with achondroplasia. It is recommended that parents restrict unsupported sitting for their children until they reach 12 months of age, as this often halts the advancement of kyphosis. This ailment typically fades autonomously by 18 months of age, coinciding with the child's capacity to walk at that stage. In instances of persistent TLK over 50 degrees Cobb beyond the age of five, and in the presence of spinal compression symptoms, surgical intervention is advised to enhance or preserve the existing neurological state, rectify the deformity, and prevent further advancement of kyphosis. Circumferential decompression typically necessitates subtractive osteotomy of the vertebral body and resection of the spine. In juvenile patients exhibiting mild to moderate

thoracolumbar kyphosis with Cobb angles ranging from 20 to 40 degrees and without neurological abnormalities, careful monitoring is conducted. In certain youngsters, the usage of orthoses until they are able to walk independently is justified, but the benefits of such treatment have not been firmly shown. It is noted that TLK lasting beyond 18 months of age may spontaneously ameliorate prior to the age of three. Post the age of three, the compensatory mechanism of hyperlordosis commences its function in mitigating kyphosis.

Lumbar spinal stenosis is the predominant cause of disability in adults. Upon the manifestation of symptoms, the patient must be referred for neurosurgery and orthopedic assessment [9]. Multilevel laminectomy with lateral hilar decompression and instrumented posterior spinal stabilization may be required to enhance patients' quality of life and prevent post-laminectomy instability [12]. This treatment is deemed highly beneficial, with enhanced function seen in over 90% of patients [11].

Bowed legs are a prominent sign of achondroplasia. The evaluation of the kid to determine the degree of this deformity should be an integral component of any physical development assessment. The criteria for surgical intervention are challenging to ascertain, and no definitive recommendations exist in this domain [13]. In instances when bowed legs advance and result in distressing symptoms (e.g., lower limb pain, alterations in gait), treatment options encompass hemiepiphysiodesis (guided growth) feasible during childhood, as well as more intrusive procedures: tibial or fibular osteotomy, with or without femoral osteotomy [14].

Historically, **bone lengthening operations** for achondroplasia have involved the surgical elongation of long bones followed by the insertion of external fixators. The intervention is referred to as the Ilizarov surgery [15]. New procedures for limb lengthening in patients with achondroplasia have recently evolved; nonetheless, these treatments remain linked with significant risks of complications, as well as substantial financial and societal expenditures. Contemporary surgical limb lengthening employs rod technology, utilizing limb distraction succeeded by the implantation of intramedullary magnetic nails. The rods can be elongated utilizing powerful external magnets.

These approaches continue to be contentious, particularly as the significance of height for physical functioning and quality of life in individuals with achondroplasia has not been definitively determined. Literature presents evidence of enhanced physical quality of life and more freedom in everyday activities; nonetheless, it has been posited that the study employed overly general questionnaires [16] [17].

Notwithstanding various abnormalities in the upper limbs, surgical procedures in this domain are infrequently performed. The sole exception is surgical intervention to elongate the humerus, necessitated by patients' difficulties in reaching, which constrains their autonomy, particularly concerning personal hygiene [6]. This procedure carries a significant risk of problems; yet, it is crucial for enhancing the self-esteem of patients with achondroplasia[18].

Access to **physical therapy** is essential for the effective care of patients with achondroplasia. Rehabilitation is crucial for enhancing function, mobility, and attaining maximum independence. Physical therapy is particularly beneficial in cases of delayed milestone attainment throughout early development, as well as in the perioperative or postoperative phases.

In patients with achondroplasia, it is imperative to enhance knowledge regarding the significance of sustaining an optimal body weight and **preventing obesity**, which poses a substantial health risk to this population. Atypical visceral obesity, frequently seen in this demographic, exacerbates skeletal system symptoms and contributes to the onset of circulatory system diseases; thus, early identification and suitable management of this chronic condition are critically important [13][19]. Research indicates a rise in mortality from cardiovascular events among adult patients aged 25 years [13]. An essential strategy to avert obesity is enough physical activity; thus, it is imperative that uniform guidelines about physical activity and sports engagement for individuals with achondroplasia are established.

In youngsters with achondroplasia, monitoring by **otolaryngologist** specialists and audiological assessments are crucial. Ear infections, to which these children are susceptible, must be meticulously prevented and treated well. Consistent intervention and vigilant oversight are essential to prevent issues with speech development [20].

The prompt identification and management of obstructive sleep apnea are equally crucial. Patients with achondroplasia experience sleep breathing difficulties throughout their lives.

Individuals with achondroplasia exhibit a heightened risk of **perioperative complications** attributable to upper airway anomalies, thoracic and spinal malformations, as well as challenges in intubation and airway management. Guidelines exist for the perioperative management of patients with skeletal dysplasia [21]. Approximately 70-80% of individuals with achondroplasia have undergone at least one surgical intervention associated with the condition [5][22].

The contemporary management of patients with achondroplasia should be interdisciplinary from birth, emphasizing optimal quality of life, maintaining overall health, fostering

independence in daily activities, preventing chronic illnesses, and offering ongoing psychological support.

4. Novel pharmaceuticals - hope to patients with achondroplasia

Notwithstanding a distinct unmet need, pharmaceutical therapeutic alternatives for achondroplasia have, thus far, been exceedingly restricted. Until recently, **growth hormone (GH) therapy** was the sole treatment suggested for achondroplasia and is exclusively approved for use in Japan. The enduring efficacy of GH remains a subject of contention [23][24].

New promising pharmaceutical therapy for achondroplasia have emerged only in recent years. In 2021, vosoritide (Voxzogo), a C-type natriuretic peptide (CNP) analogue, received approval from the United States Food and Drug Administration (US FDA) for administration to children with achondroplasia. The medication has received approval from the European Medicines Agency (EMA). Since January 2025, vosoritide therapy has been accessible in Poland for patients with achondroplasia under the medication program.

While vosoritide is presently the sole medicine sanctioned by health authorities, numerous more investigational drugs are under development for the same use. Multiple other medicines are under development, including infigratinib, a FGFR1-3 inhibitor, TA-46 (Recifercept), a FGFR3 decoy and Transcon-CNP, a CNP.

4.1.Prospective Targets for Novel Pharmacological Interventions in Achondroplasia

To elucidate the mechanism of action of these medications, we must consider the influence of the CNP protein (C-type natriuretic peptide) on bone development and ossification in humans [25]. This process involves distinguishing the stages of chondrocyte proliferation, hypertrophy, and subsequent apoptosis, as well as the emergence of osteoclasts, bone marrow cells, and ultimately osteoblasts, which convert cartilage tissue into bone. Endochondral ossification is modulated by various substances, including growth hormone (GH), thyroid hormones, insulin-like growth factor 1 (IGF-1), insulin-like growth factor 2 (IGF-2), parathyroid hormone (PTH), and fibroblast growth factors [26]. Among the natriuretic peptides that contribute to human

physiology, four primary subtypes may be identified: ANP, BNP, CNP, and DNP, which activate three receptor subtypes: NPR-A, NPR-B, and NPR-C. The initial two natriuretic peptides perform various roles within the circulatory system and are not the focus of this study. CNP primarily exerts a stimulatory impact on chondrocytes and affects the formation of long bones. The function of DNP remains inadequately delineated; nonetheless, it is thought to possess regulatory qualities within the cardiovascular system [27]. CNP influences the growth plate via the NPR-B receptor. It facilitates the transformation of GTP (guanosine-5'-triphosphate) into cGMP (cyclic guanosine monophosphate) and activates mediators (phosphodiesterases and cGKI and cGKII - cGMP-dependent protein kinases). Kinases obstruct the MAPK pathway by inhibiting RAF-1, which subsequently affects MEK-1, MEK-2, ERK-1, and ERK-2. This mechanism results in gene expression within the chondrocyte nucleus, promotes chondrocyte proliferation and differentiation, ultimately enhancing the development of the extracellular matrix [28].

In achondroplasia, the mutated FGFR3 gene is constantly activated. FGF receptors undergo persistent autophosphorylation, thus activating intracellular signaling pathways Raf/MEK/ERK and Stat1, which limit chondrocyte differentiation and promote the formation and proliferation of cartilage matrix. Consequently, endochondral ossification, the process through which bones develop from cartilage, is compromised, leading to minor elongation of long bones. This finally results in dwarfism (reduced limb length) [29]. Research on transgenic mice revealed that the overexpression of the CNP peptide resulted in enhanced endochondral ossification in chondrocytes and increased body length in these transgenic specimens relative to their littermates [30]. Natural CNP is swiftly destroyed by endopeptidases and possesses an insufficient half-life for successful treatment of achondroplasia, prompting clinical experiments with other formulations of this molecule.

New pharmaceuticals for achondroplasia target the dysregulated FGFR3 pathway by neutralizing FGF ligands (recifercept, RBM-007), inhibiting FGFR3 catalytic activity (infigratinib), and directly (meclozine) or indirectly (stable C-natriuretic peptide (CNP) ligands) suppressing the RAS-ERK pathway [29].

4.2.Vosoritide

Vosoritide is analogous to C-type natriuretic peptide (CNP). It binds to the Natriuretic Peptide Receptor B (NPR-B), activates it, and reinstates chondrogenesis, the process of cartilage development. The activation of NPR-B results in the suppression of the downstream

signaling of the FGFR-3 gene. The downstream signaling of the FGFR-3 gene suppresses proliferation and differentiation in bones, resulting in dwarfism. Vosoritide inhibits Rapidly Accelerated Fibrosarcoma Kinase-1, hence promoting proliferation and differentiation in bones, which leads to the treatment of achondroplasia.

Vosoritide is a medication approved for individuals with achondroplasia starting at 4 months of age. The administration may be continued until the growth plates fuse and the growth velocity falls below 1.5 cm per year. These are evidence indicating the patient possesses no additional development potential. The method of administration is subcutaneous. Subcutaneous administration facilitates home-based medicine intake and offers a convenient method for patients. Suggested injection locations on the body comprise the anterior mid-thigh, the lower abdomen excluding the 2 inches (about 5 centimeters) surrounding the navel, the superior buttocks, or the posterior aspect of the upper arms. The identical injection site must not be utilized on two successive days. Vosoritide is administered once daily. It should be administered at around the same time daily, if feasible [31]. The advised dosage is 15-30 μg/kg of body weight, although it may fluctuate based on the drug's volume of distribution relative to body weight [32].

Vosoritide enhances linear height by an average of 1.57 cm annually, exhibiting a more pronounced increase in males compared to females (1.98 cm/year versus 1.55 cm/year). This expected rise in final height may yield advantageous functional consequences [33].

Administration of vosoritide must be commenced and overseen by a physician suitably equipped to manage growth problems or bone dysplasia.

The therapy response may differ among patients. Evaluating treatment response necessitates ongoing anthropometric measures for a minimum of 1-2 years following the commencement of medication. Patients must be observed and evaluated consistently every 3-6 months to check body weight and physical growth. The dosage must be modified based on the patient's body weight.

Currently, there is no evidence of enhancement in areas beyond linear growth due to vosoritide treatment; nonetheless, it seems to correlate with a positive trend in the disproportion between upper and lower body segments [31]. In vosoritide studies, bone age was shown to advance regularly, suggesting that vosoritide does not induce premature bone aging in children with achondroplasia [32].

The medication is well tolerated by patients. The majority of the documented adverse effects were modest. The most reported adverse effects included injection site responses, vomiting and hypotension.

Vosoritide is anticipated to enhance the quality of life and autonomy of patients by reinstating normal endochondral bone development and consequently accelerating growth rate, while also diminishing the occurrence and severity of lifetime problems. It is acceptable to assert that vosoritide, as the first disease-modifying drug, represents a significant advancement in the treatment of patients with achondroplasia [34].

4.3.Other CNP-variants

As previously stated, vosoritide is the sole medication authorized for the treatment of achondroplasia. Alongside vosoritide, two more CNP variants, **TrancCon CNP and ASB20123**, have been created and are presently undergoing clinical testing. TransCon CNP, conjugated to a PEG carrier, maintains consistent systemic levels of CNP in the patient, hence facilitating enhanced stimulation of bone development in a murine model compared to intermittent elevations in CNP levels. This preparation is delivered weekly. The extended-release formulation of the medication will mitigate elevated CNP levels in the bloodstream and the concomitant detrimental effects on the cardiovascular system. The second CNP variant, ASB 20123, likewise promotes skeletal growth in mice and has demonstrated a more advantageous plasma half-life and retention in vascular cartilage compared to wild-type CNP [35].

4.4.Other pharmaceuticals undergoing clinical trials

Meclozine, a histamine receptor antagonist, is another medication evaluated in clinical studies. This is a recognized medication utilized for the management of symptomatic motion sickness. It inhibits the activation of ERK in the FGFR3-RAS-ERK pathway through MAP kinase [36]. A study on mice shown that meclozine enhanced bone volume and the quality of metaphyseal trabecular bone, resulting in increased body length and a reduction in anomalies of long bones, skull, and vertebrae [35]. Although meclizine is easily accessible and commonly utilized, its administration for the treatment of achondroplasia must be conducted periodically, particularly throughout the growth phase in children. Clinical investigations indicate that the

medicine is well tolerated, with no evidence of toxic buildup leading to observable adverse effects [37].

Infigratinib, a FGFR3 tyrosine kinase inhibitor, disrupts ATP binding, hence inhibiting FGFR3 catalytic activity. This drug's potential application in achondroplasia is currently being investigation in clinical trials [35].

Recifercept (formerly known as TA-46) is a recombinant soluble FGFR3 (sFGFR3) that selectively associates with fibroblast growth factor (FGF) family members, including FGF2, FGF9, and FGF18, thereby inhibiting the activation of the malfunctioning receptor in achondroplasia [38].

The approval of vosoritide as the inaugural precision therapy for achondroplasia represents a significant advancement for affected youngsters. Alongside altering their natural growth trajectory, it is anticipated that it will diminish medical issues and enhance functionality. It is anticipated that soon families will have the option to evaluate a variety of effective targeted therapies tailored to their kid with achondroplasia, commencing from birth, should they opt for such interventions.

It is essential to underscore that therapy with vosoritide and any future growth regulation does not eliminate the necessity for vigilant monitoring of any problems associated with achondroplasia, which are inherent to its natural history.

5. Summary

Achondroplasia is a prevalent condition affecting almost 250,000 individuals worldwide, affecting 90% of cases in patients with excessively small stature. It is genetically determined and inherited in an autosomal dominant manner, resulting from a point mutation in the gene encoding the transmembrane portion of fibroblast growth factor receptor 3 (FGFR3). The condition results in abnormal endochondral ossification, impairing the formation of certain bones in the affected individual. Advanced paternal age during conception is a recognized risk factor for achondroplasia.

The clinical presentation of achondroplasia is distinctive. Symptoms include reduced stature, macrocephaly, midfacial hypoplasia, a prominent, broad forehead, rhizomelic disproportion, skeletal abnormalities in both the upper and lower extremities, pronounced joint laxity, thoracolumbar kyphosis the stenosis of the foramen magnum (FMS), which increases the risk of spinal cord compression. The intellectual development of patients with

achondroplasia typically falls within the normal range, and their life expectancy is statistically 10 years less than that of the overall population.

Prenatal diagnosis relies on clinical manifestations and radiological observations, and the condition is confirmed through molecular genetic testing. Prenatal diagnostics may include non-invasive fetal DNA testing derived from maternal blood. Obesity is a common issue among individuals with achondroplasia, exacerbating joint and lower back issues and associated with hypertension, type 2 diabetes, and obstructive sleep apnea.

Treatment for achondroplasia is an interdisciplinary endeavor, involving pediatrician, neurologist, orthopedist, pediatric endocrinologist, otolaryngologist, cardiologist, psychologist, and physiotherapist. Primary management involves optimizing functional ability while monitoring, preventing, and addressing problems.

Thoracolumbar kyphosis (TLK) is a common manifestation in neonates with achondroplasia, and it is recommended that parents restrict unsupported sitting until they reach 12 months of age. In cases of persistent TLK over 50 degrees Cobb beyond the age of five, surgical intervention is advised to enhance or preserve the existing neurological state, rectify the deformity, and prevent further advancement of kyphosis. Lumbar spinal stenosis is the predominant cause of disability in adults, and multilevel laminectomy with lateral hilar decompression and instrumented posterior spinal stabilization may be required to enhance patients' quality of life and prevent post-laminectomy instability. Bowed legs are a prominent sign of achondroplasia, and the criteria for surgical intervention are challenging to ascertain.
Surgical limb lengthening operations for achondroplasia have evolved, but new procedures have been developed, such as rod technology and intramedullary magnetic nails. Physical therapy is essential for the effective care of patients with achondroplasia, and early identification and appropriate management of obesity are crucial. In children with achondroplasia, it is essential to conduct surveillance by otolaryngology specialists and do audiological evaluations. Ear infections must be prevented and treated well, and consistent intervention and vigilant oversight are essential to prevent speech development issues. Prompt identification and management of obstructive sleep apnea are equally crucial. Individuals with achondroplasia exhibit a heightened risk of perioperative complications due to upper airway anomalies, thoracic and spinal malformations, and challenges in intubation and airway management. The contemporary management of patients with achondroplasia should be interdisciplinary from birth, emphasizing optimal quality of life, maintaining overall health,

fostering independence in daily activities, preventing chronic illnesses, and offering ongoing psychological support.

New pharmaceuticals have emerged for achondroplasia. Vosoritide, a C-type natriuretic peptide (CNP) analogue, has received approval from the US FDA and the European Medicines Agency (EMA) for administration to children with achondroplasia. The mechanism of action of these drugs is to promote chondrocyte proliferation and differentiation by blocking the persistently active kinase pathway resulting from the mutant FGFR3 gene in this condition. Vosoritide is approved for individuals with achondroplasia starting at 4 months of age and can be continued until the growth plates fuse and the growth velocity falls below 1.5 cm per year. It is administered once daily, with the recommended dosage of 15-30 μg/kg of body weight. Vosoritide enhances linear height by an average of 1.57 cm annually, with more pronounced increases in males. Vosoritide is well tolerated by patients and is expected to enhance the quality of life and autonomy of patients by reinstating normal endochondral bone development and accelerating growth rate while diminishing the occurrence and severity of lifetime problems. Two more CNP versions, TrancCon CNP and ASB20123, have been created and are presently undergoing clinical testing. Meclozine, a histamine receptor antagonist, is another medication evaluated in clinical studies. It inhibits the activation of ERK in the FGFR3-RAS-ERK pathway through MAP kinase, enhancing bone volume and the quality of metaphyseal trabecular bone, resulting in increased body length and reduced anomalies of long bones, skull, and vertebrae. Infigratinib, a FGFR3 tyrosine kinase inhibitor, is currently being investigated in clinical trials.

Disclosure

Author'scontribution: Patrycja Jędrzejewska-Rzezak
Conceptualisation: Patrycja Jędrzejewska-Rzezak
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