International Journal of Innovative Technologies in Social Science

e-ISSN: 2544-9435

Scholarly Publisher
RS Global Sp. z O.O.
ISNI: 0000 0004 8495 2390

Dolna 17, Warsaw,
Poland 00-773
+48 226 0 227 03
editorial_office@rsglobal.pl

ARTICLE TITLE	CHANGING THE TRAJECTORY OF GROWTH: THE APPLICATION OF VOSORITIDE IN CHILDREN WITH ACHONDROPLASIA. A CHANCE FOR IMPROVED QUALITY OF LIFE?
DOI	https://doi.org/10.31435/ijitss.3(47).2025.3984
RECEIVED	10 August 2025
ACCEPTED	25 September 2025
PUBLISHED	29 September 2025
LICENSE	The article is licensed under a **Creative Commons Attribution 4.0 International License.**

© The author(s) 2025.
This article is published as open access under the Creative Commons Attribution 4.0 International License (CC BY 4.0), allowing the author to retain copyright. The CC BY 4.0 License permits the content to be copied, adapted, displayed, distributed, republished, or reused for any purpose, including adaptation and commercial use, as long as proper attribution is provided.

CHANGING THE TRAJECTORY OF GROWTH: THE APPLICATION OF VOSORITIDE IN CHILDREN WITH ACHONDROPLASIA. A CHANCE FOR IMPROVED QUALITY OF LIFE?

Marta Turek *(Corresponding Author, Email: martaturek74@gmail.com)*
Independent Public Clinical Hospital named Andrzej Mielęcki of the Silesian Medical University in Katowice, Katowice, Poland
ORCID ID: 0009-0005-7713-6875

Julia Szlążek
Medical University of Silesia, Katowice, Poland
ORCID ID: 0009-0007-6977-8856

Michalina Zagalska
Independent Public Clinical Hospital named Andrzej Mielęcki of the Silesian Medical University in Katowice, Katowice, Poland
ORCID ID: 0009-0002-7312-0065

Adam Jan Ząbek
Katowice Oncology Center, Katowice, Poland
ORCID ID: 0009-0003-6799-1814

Kamil Kerknawi
Zagłębie Oncology Center in Dąbrowa Górnicza, Dąbrowa Górnicza, Poland
ORCID ID: 0009-0009-9739-9954

Paulina Mikulec
Zagłębie Oncology Center in Dąbrowa Górnicza, Dąbrowa Górnicza, Poland
ORCID ID: 0009-0003-9900-3008

Marceli Mesyasz
Zagłębie Oncology Center in Dąbrowa Górnicza, Dąbrowa Górnicza, Poland
ORCID ID: 0009-0006-1917-4029

Tomasz Tamborski
County Hospital in Zawiercie, Zawiercie, Poland
ORCID ID: 0009-0003-6275-1010

Jakub Paweł Kuźniar
The Provincial Hospital in Bielsko-Biała, Bielsko-Biała, Poland
ORCID ID: 0009-0002-6716-7502

Emilia Gabriela Chrzanowska
Medical University of Silesia, Katowice, Poland
ORCID ID: 0009-0001-6228-1878

ABSTRACT

Achondroplasia (ACH) is the most common skeletal dysplasia and the leading genetic cause of dwarfism. It is characterized by disproportionate short stature and lifelong medical complications, with an estimated incidence of 1 in 25,000–30,000 live births. The condition results from a mutation in the fibroblast growth factor receptor 3 (FGFR3) gene, causing receptor overactivation and impaired bone growth at the growth plates. This review provides an overview of achondroplasia, including its pathophysiology, clinical features, diagnostic methods, and novel therapeutic options, with emphasis on vosoritide. Historically, management has focused on symptomatic treatment and surgical interventions to address complications such as foramen magnum stenosis, hydrocephalus, and postural deformities. Vosoritide (Voxzogo) marks a breakthrough as the first disease-modifying therapy targeting the underlying pathophysiology. It is a C-type natriuretic peptide (CNP) analog that inhibits the overactive MAPK pathway, thereby promoting chondrocyte proliferation and differentiation in growth plates and enabling endochondral bone growth. Phase 3 clinical trials demonstrated that vosoritide significantly increases annual growth velocity (by approximately 1.57 cm) and improves body proportions, with a favorable safety profile. Reported adverse effects were generally mild, including transient hypotension and injection site reactions. Despite these advances, vosoritide therapy does not eliminate the need for coordinated multidisciplinary care and psychological support. Patients require ongoing monitoring and management of associated complications, including neurological, orthopedic, respiratory, and developmental issues. In summary, achondroplasia remains the most frequent genetic form of dwarfism, traditionally managed through supportive care and surgery. The introduction of vosoritide represents a paradigm shift, offering the first targeted therapy that directly modifies disease progression and opens new perspectives for improving patients' quality of life.

KEYWORDS

Achondroplasia, Established Disease, New Treatment, Vosoritide FGFR3 Gene, C-Type Natriuretic Peptide (CNP) Analog

CITATION

Marta Turek, Julia Szlążek, Michalina Zagalska, Adam Jan Ząbek, Kamil Kerknawi, Paulina Mikulec, Marceli Mesyasz, Tomasz Tamborski, Jakub Paweł Kuźniar, Emilia Gabriela Chrzanowska. (2025) Changing the Trajectory of Growth: The Application of Vosoritide in Children With Achondroplasia. A Chance for Improved Quality of Life? *International Journal of Innovative Technologies in Social Science*. 3(47). doi: 10.31435/ijitss.3(47).2025.3984

COPYRIGHT

© The author(s) 2025. This article is published as open access under the **Creative Commons Attribution 4.0 International License (CC BY 4.0)**, allowing the author to retain copyright. The CC BY 4.0 License permits the content to be copied, adapted, displayed, distributed, republished, or reused for any purpose, including adaptation and commercial use, as long as proper attribution is provided.

Introduction

Achondroplasia (ACH) is the most common form of skeletal dysplasia, leading to disproportionate short stature, also known as dwarfism. It's also the most frequent genetic cause of dwarfism in humans, characterized by disproportionate short stature and significant, lifelong medical complications. This condition, recognized for millennia and evidenced by artifacts from various cultures, was first described under the name "achondroplasia" in the 19th century. Although considered a rare disease, its estimated incidence is approximately 1 in 25,000 to 30,000 live births.

This review aims to provide a comprehensive and up-to-date analysis of achondroplasia, with a particular focus on its pathophysiology, clinical presentation, diagnostic methods, and emerging innovative therapeutic options. This work seeks to compile and systematize knowledge regarding the epidemiology, genesis, and genetic basis of achondroplasia, to detail the spectrum of its characteristic clinical features and complications, to present current diagnostic methods, and to discuss new therapeutic perspectives and possibilities. Particular emphasis is placed on the introduction of vosoritide, the first disease-modifying drug. The purpose of this article is to increase awareness and understanding of achondroplasia, both as a well-established medical condition and as an area of dynamic therapeutic development, opening new hope for patients. The information presented was gathered as part of a narrative literature review, based on the PubMed database, using strictly defined inclusion criteria for articles from 2015-2025.

Aim

The primary objective of this review is to present a comprehensive and up-to-date analysis of achondroplasia, with a particular focus on its pathophysiology, clinical presentation, diagnostic methods, and emerging innovative therapeutic options. This work aims to compile and systematize knowledge regarding the epidemiology, genesis, and genetic basis of achondroplasia, to describe in detail the spectrum of distinctive clinical features and complications, to present current diagnostic methodologies, and to discuss new therapeutic perspectives and opportunities, with a special emphasis on the introduction of vosoritide. The content of this article seeks to enhance awareness and understanding of achondroplasia both as a disease with an established medical status and as an area of dynamic therapeutic development, opening new hope for patients.

Methods

This study is a narrative literature review on the new opportunities for treatment of achondroplasia. The authors used the PubMed database employing the terms 'achondroplasia'/'achondroplasia- new treatment'/'vosoritide resulting in 57 articles and science direct. Inclusion criteria such as years 2015-2025, english language text, full-text access and specific article types like reviews and randomized studies were applied, thereby minimizing the literature review to 15 articles. The authors conducted a personal review of the articles and due to inconsistency with the content of this work and thematic redundancy, content inappropriate for the article was removed.

Results:

A) Epidemiology, genesis, genetic

Achondroplasia (ACH) is the most common form of skeletal dysplasia, leading to disproportionate short stature (dwarfism). It is the most frequent genetic cause of dwarfism in humans, characterized by disproportional short stature and significant lifelong medical complications. Recognized for millennia, as evidenced by artifacts from various cultures, the term "achondroplasia" was first used in the 19th century, with its main features described shortly thereafter. Due to its characteristic chondrodysplastic phenotype, achondroplasia is typically diagnosed at birth [1, 2, 8, 9, 10, 13, 14]. While considered a rare disease, it is the most common form of dwarfism, with an estimated birth prevalence of approximately 1 in 25,000 to 30,000 live births [1, 2, 10]. Achondroplasia is inherited in an autosomal dominant manner with full penetrance [1, 2, 8, 10, 15]. This means that inheriting just one copy of the mutated gene from one parent is sufficient for the disease to develop. In the majority of cases (approximately 80%), achondroplasia results from *de novo* (sporadic) mutations, meaning the child's parents are of average height and unaffected by the condition. There is a strong association between achondroplasia and advanced paternal age, typically over 35 years [1, 2, 3, 8, 13, 14]. This phenomenon is attributed to a positive selective effect on spermatogonia, leading to an increased frequency of mutations in sperm with advancing paternal age. Achondroplasia belongs to a group of disorders known as RAMP disorders (Recurrent, Autosomal dominant, Male-biased, Paternal Age effect disorders). Other disorders with compelling evidence for similar effects include Apert syndrome, Noonan syndrome, and MEN2B [1, 8]. The recurrence risk for unaffected parents who already have an affected child is estimated at approximately 1% due to germline mosaicism. If one parent has achondroplasia, there is a 50% chance their child will also be affected. If both parents have achondroplasia, there is a 25% chance of having an unaffected child, a 50% chance of a child with achondroplasia, and a 25% chance of a lethal homozygous form. Homozygous achondroplasia leads to a very severe phenotype, significantly more pronounced than in heterozygous achondroplasia, and often results in death in early childhood. It is worth noting that other rarer, but allelic (resulting from mutations in the same *FGFR3* gene) dysplastic conditions can exhibit varying degrees of severity. The most significant of these include hypochondroplasia (a milder form), severe achondroplasia with developmental delay and acanthosis nigricans (SADDAN), and thanatophoric dysplasia (the most severe, often lethal). In cases where one parent has achondroplasia and the other has hypochondroplasia, there is a 25% risk of the child having double heterozygosity, resulting in a very severe phenotype that includes cognitive impairment and significant medical problems. Conversely, double heterozygosity with other, non-allelic bone dysplasias is rare and can lead to a very poor prognosis (e.g., achondroplasia-SEDC) or have a variable course (e.g., achondroplasia-pseudoachondroplasia). In some instances, a mitigating effect has even been observed [1, 2, 8, 13, 14, 15]. Achondroplasia is caused by a mutation in the fibroblast growth factor receptor 3 (*FGFR3*) gene. *FGFR3* is a crucial regulator of linear bone growth. It is primarily expressed in condensed mesenchyme, chondrocytes, and mature osteoblasts and

osteoclasts, where it regulates the formation, development, growth, and remodeling of the skeletal system. Mutations in the *FGFR3* gene lead to excessive, constitutive activation (gain-of-function) of the receptor. This abnormal activation of *FGFR3* signaling profoundly inhibits chondrocyte proliferation and maturation in the growth plates. This results in a significant reduction in growth plate size, decreased trabecular bone volume, and impaired bone elongation. Pathophysiologically, there is a reduction in hypertrophic chondrocytes, loss of extracellular matrix, and premature apoptosis [2, 10, 13, 15]. Downstream in the signaling cascade, *FGFR3* hyperactivity engages pathways such as MAPK (mitogen-activated protein kinase), STAT (e.g., STAT1, STAT5), Wnt/β-catenin, PI3K/AKT, and PLCγ. *FGFR3* activation leads to increased expression of Snail1, which is required for STAT1 and MAPK signal activation. The most common mutation is c.1138G>A (p.Gly380Arg), found in approximately 98% of individuals with achondroplasia, while the c.1138G>C mutation is found in about 1% of patients. These mutations are typically localized in the transmembrane domain of *FGFR3*. The severity of symptoms is a consequence of the degree of *FGFR3* activation. *FGFR3* expression in non-skeletal tissues (e.g., the brain) suggests its involvement in extra-skeletal manifestations of the disease [1, 2, 3, 8, 14, 15].

B) Symptoms

Achondroplasia (ACH) presents with a spectrum of distinctive clinical features and complications, necessitating lifelong multidisciplinary care. Individuals with achondroplasia exhibit short limbs, particularly their proximal segments (arms and thighs), a characteristic known as rhizomelia. The trunk is generally of relatively normal proportion but may be deformed by an exaggerated lumbar lordosis. The average adult height in Caucasian populations with achondroplasia is estimated to be 118–145 cm for men and 112–136 cm for women, although more recent studies suggest 123–143 cm for men and 115–134 cm for women. The average adult height is 129.9 cm for men and 122.4 cm for women. Final height typically represents -6 to -7 standard deviations below the mean for the unaffected population [1, 2, 4, 6, 8, 15]. Cranial features are dominated by macrocephaly, a prominent forehead, midfacial hypoplasia, and a flattened nasal bridge. Partial premature fusion of cranial sutures (craniosynostosis) may also occur, though it is uncommon [3, 6]. Hands and feet characteristically display a "trident hand" (excessive separation between the third and fourth fingers), brachydactyly (short fingers), and short, "bullet-shaped" phalanges [1, 3]. Foramen magnum stenosis (FMS) is a significant neurological concern, recognized as a cause of unexpected death in infants with achondroplasia. It can lead to spinal cord and brainstem compression, myelopathy, respiratory problems (including central sleep apnea), and high mortality if left untreated. FMS occurs in 5-10% of children. Symptomatic FMS is surgically managed in most cases within the first two years of life. Clinical signs include respiratory distress, snoring, apneas, cranial nerve dysfunction, swallowing difficulties, and neurological symptoms such as hyperreflexia, muscle weakness, or clonus. Decompression surgery leads to symptom resolution in 91% of patients, but a relatively high risk of complications (21%), reoperation (9%), and perioperative mortality (2%) persists [2, 3, 6, 15]. Spinal canal stenosis, particularly in the lumbar region, can cause pain, neurogenic claudication, and neurological deficits. It affects approximately 20% of adults by age 20 and 80% by age 60. Decompressive spinal surgeries are recommended for neurological symptoms. Postural abnormalities are also prevalent, including excessive lumbar lordosis (hyperlordosis) and thoracolumbar kyphosis. The latter is observed in 90-95% of patients in the first years of life. It typically improves with ambulation, but moderate kyphosis (20-40 degrees) may warrant orthopedic consultation. Megalencephaly with ventricular and fluid space enlargement is frequently observed; it is usually asymptomatic and requires no treatment. Approximately 6% of children develop hydrocephalus requiring neurosurgical intervention by age 5. For hydrocephalus, half of the patients were treated with endoscopic third ventriculostomy (ETV), and half received a shunt. No reoperations were noted after ETV, whereas shunt recipients averaged 1.5 reoperations per patient [1, 2, 3, 6, 11, 15]. Children with achondroplasia often experience developmental delays, particularly in gross motor skills. This delay is characterized by atypical movement patterns, such as "snowplowing" (pushing with feet while moving the head forward) or "reverse snowplowing" (supporting on heels and occiput) [1, 2, 3, 6, 11, 15]. Cognitive development is typically normal. Speech delays (especially expressive speech) can occur, often secondary to hearing loss. Orthopedic issues include joint hyperlaxity, particularly in younger children, genu varum (bowed legs), and restricted elbow range of motion (known as "elbow flexion contracture"). Fine motor difficulties may arise due to brachydactyly and joint hypermobility of the hand and wrist, impeding activities like writing [1, 7]. A high incidence of obstructive (OSA) and central sleep apnea (CSA) is observed. OSA is more common than CSA and can be attributed to adenotonsillar hypertrophy, midfacial hypoplasia, and pharyngolaryngeal hypotonia. CSA may result from brainstem compression due to foramen magnum stenosis

[2, 6, 15]. Middle ear infections leading to conductive hearing loss are also common. Obesity is a prevalent concern in children with achondroplasia, with early-onset predisposition, particularly for visceral obesity. It can exacerbate skeletal symptoms, worsen respiratory problems, and increase the risk of cardiovascular disease. Acanthosis nigricans, a skin manifestation characterized by dark, thickened skin areas (usually in the neck, axillae, and groin), is not uncommon. It is generally benign and harmless in this context. Dental problems, such as tooth crowding, mandibular prognathism, gothic palate, and macroglossia, can lead to malocclusion and articulation difficulties. Unfortunately, pain is a frequent companion for children with achondroplasia, both in childhood and adulthood [1, 2, 8, 13, 14, 15].

C) Diagnosis

The diagnosis of achondroplasia is primarily based on characteristic clinical and radiological features. Molecular confirmation, identifying mutations in the *FGFR3* gene (most commonly c.1138G>A, less frequently c.1138G>C), is possible and valuable in equivocal cases and for genetic counseling. Prenatal diagnosis can be challenging before 26 weeks of gestation, but ultrasonography may reveal characteristic features such as rhizomelia, brachydactyly, or macrocephaly. Non-invasive prenatal testing (NIPT) is increasingly available and can detect *FGFR3* mutations as early as the first trimester, provided the mother does not carry the same mutation. With the approval of vosoritide, a C-type natriuretic peptide (CNP) analog, which counteracts the overactivity of the *FGFR3* pathway and promotes bone growth, more families are seeking early diagnosis and treatment. Vosoritide, approved in Europe for children aged 2 years and older, and in the USA for children aged 5 years and older (expanded to 4 months in 2023), has demonstrated increased growth velocity and good tolerability [3, 4, 7, 8, 14].

D) Treatments and new chances

Traditional methods of treating Achondroplasia

Treatment for achondroplasia has primarily focused on symptomatic management and mitigating its health consequences, often requiring numerous surgical procedures and a multidisciplinary approach. Complications of this disease affect many systems. Neurosurgical interventions are present in the treatment of the conditions described later in the text. Cervicomedullary Compression (CMC) and Foramen Magnum Stenosis (FMS) occur in all infants with achondroplasia, but critical narrowing affects approximately 20% of infants, leading to compression of neural and vascular structures. This is one of the causes of sudden death in infants with achondroplasia. Clinical symptoms include breathing difficulties, snoring, apnea, cranial nerve dysfunction, swallowing problems, or neurological symptoms. Although most children develop normally, mortality due to FMS is reported in 2-5% of patients. Sleep studies and magnetic resonance imaging of the cranio-cervical junction are recommended immediately upon diagnosis of achondroplasia. The most frequently performed procedure is Foramen Magnum Decompression (FMD) in 99% of patients. Although 91% of patients experienced symptom resolution, 2% mortality, 9% reoperations, and 21% complications were reported. Spinal canal stenosis usually manifests in the second decade of life with lower back pain, weakness, radiculopathy, neurogenic claudication, and bowel/bladder dysfunction. Surgical treatment includes decompression (25%) or decompression with fusion (72%). After surgery, 95% of patients experienced symptom resolution, but 17% complications and 18% reoperations were reported. Reoperations may be caused by new stenosis, restenosis, or postoperative kyphosis. Hydrocephalus affects approximately 6% of children, requiring neurosurgical treatment by 5 years of age, and about 10% by adulthood. Half of the patients were treated with endoscopic third ventriculostomy (ETV), and the other half had a shunt implanted. Patients with shunts had 3% mortality and an average of 1.5 shunt revisions. Patients who underwent ETV as the first procedure did not require revision.[5,9,11,15]

As previously mentioned, orthopedic problems also occur in achondroplasia. Thoracolumbar kyphosis develops in most children in the first months of life and often corrects spontaneously. Unsupported sitting is associated with more severe kyphosis. In cases of progressive kyphosis, immobilization (orthosis) may be necessary, and less frequently, surgery. Genu Varum (bowed legs) affects 40-70% of patients. Surgical treatment is indicated depending on the severity of the deformity, symptoms, and functional limitations. Among the procedures, limb lengthening is also present, often using the Ilizarov method. There have also been attempts to administer growth hormone to improve growth rate. Studies have shown improvement, but long-term safety has not been fully explored.[3,5,8]

Sleep apnea is also very common, with a frequency of 10% to 87%. Untreated obstructive sleep apnea can have serious developmental consequences. Treatment may include adenoidectomy with or without

tonsillectomy, as well as the use of continuous positive airway pressure (CPAP, BiPAP). Additionally, middle ear problems, hearing loss, obesity, and developmental delay may occur, requiring care and maximum minimization of side effects.[1,15]

Vosoritide: a new era of therapy

Vosoritide (Voxzogo) is the first disease-modifying therapy for achondroplasia, directly targeting its pathophysiology. Achondroplasia is caused by gain-of-function mutations in the fibroblast growth factor receptor 3 (FGFR3) gene. These mutations lead to overactivation of FGFR3 signaling. Excessive FGFR3 signaling results in suppressed chondrocyte proliferation and maturation in the growth plate, significantly reducing its size, decreasing trabecular bone volume, and consequently shortening bones. FGFR3 activation promotes continuous activation of the mitogen-activated protein kinase (MAPK) pathway. Vosoritide, as a C-type natriuretic peptide (CNP) analog, is a modified recombinant human C-type natriuretic peptide (CNP) analog. Wild-type CNP is rapidly degraded by neutral endopeptidase (NEP) within just 2 minutes of entering the bloodstream. Vosoritide was designed to be resistant to this degradation, extending its half-life. Vosoritide acts by utilizing the CNP pathway. CNP and its receptor, natriuretic peptide receptor B (NPR-B), play a crucial role in regulating longitudinal bone growth. By binding to the NPR-B receptor, vosoritide inhibits the MAPK pathway. This occurs by facilitating the inhibitory phosphorylation of RAF-1 (rapidly accelerated fibrosarcoma proto-oncogene 1) via protein kinase G2 (PKG2). Through this action, vosoritide counteracts the overactivated FGFR3 signaling. Ultimately, vosoritide increases the proliferation and differentiation of chondrocytes in the growth plate (epiphyseal plate), thereby enabling endochondral bone growth. Studies have shown that CNP overexpression in chondrocytes rescues the achondroplasia phenotype via the MAPK-dependent pathway.[5,8,10,13,15]

The European Medicines Agency (EMA) approved vosoritide in 2021 for children with genetically confirmed achondroplasia aged 2 years and older, with open growth plates. Recently, the EMA extended the approval to children from 4 months of age. The U.S. Food and Drug Administration (FDA) approved vosoritide for children with achondroplasia aged 5 years and older in the USA, as well as for infants from birth. Vosoritide is also approved in Australia (as of May 2023, extended to infants from birth), Japan, and Brazil.[4,5,8,9,10,15]

Vosoritide is administered as daily subcutaneous injections. In a phase 3, placebo-controlled study, children treated with vosoritide grew an average of 1.57 cm more per year compared to the placebo group (in children aged 5-17 years). In open-label extension studies, sustained growth-promoting effects were observed, lasting up to 3.5 years, with no evidence of tachyphylaxis. The additional height gain over 2 years of treatment was 3.52 cm more than in untreated children. Phase 2 studies in younger children (3-59 months) also showed the effectiveness of vosoritide, as well as mild side effects and no negative impact on body proportions. Improvement in body proportions was demonstrated, reducing the upper-to-lower segment ratio.[5,8,10]

Vosoritide has a mild safety profile. The most common adverse effects were mild and transient injection site reactions, vomiting, and transient episodes of decreased blood pressure, which were usually asymptomatic and resolved without intervention. No harmful effects of the drug on bone maturation or children's body proportions have been reported. [5]

Initiating vosoritide therapy does not replace the need for coordinated multidisciplinary care. The team should include clinical geneticists, pediatric endocrinologists or pediatricians experienced in skeletal dysplasias, as well as specialists in pulmonology, neurosurgery, rehabilitation, and orthopedics. The patient should undergo genetic confirmation of the achondroplasia diagnosis. Serious complications of achondroplasia (e.g., cranio-cervical/spinal cord compression, spinal deformities, sleep-disordered breathing) or general health conditions that may affect growth or treatment should be ruled out. Infants should undergo a sleep study and magnetic resonance imaging of the cranio-cervical junction before starting treatment.[4,9,10]

The first dose should be administered under medical supervision, and patients monitored for reactions or adverse events. Regular growth assessments and evaluation of growth plate closure are essential for continued treatment. It's important to remember that there's no evidence that vosoritide changes the incidence of medical or orthopedic complications associated with achondroplasia. Psychological support is an important element, including providing information on the efficacy and safety of vosoritide to enable informed decision-making.[4,10]

Conclusions

Achondroplasia (ACH) remains the most common form of skeletal dysplasia and the most frequent genetic cause of dwarfism in humans, characterized by disproportionate short stature and numerous lifelong medical complications. This condition, known for millennia and formally described in the 19th century, has an estimated incidence of approximately 1 in 25,000 to 30,000 live births. Its genetic basis lies in a mutation of the fibroblast growth factor receptor 3 (FGFR3) gene, which leads to excessive, constitutive activation of this receptor, effectively inhibiting chondrocyte proliferation and maturation in the growth plates. The traditional approach to treating achondroplasia has focused on symptomatic management and alleviating health consequences, often requiring numerous surgical interventions and interdisciplinary care. Among the most serious complications requiring neurosurgical intervention are foramen magnum stenosis (FMS), which can lead to brainstem and spinal cord compression, and hydrocephalus. Orthopedic issues, such as excessive lumbar lordosis, thoracolumbar kyphosis, and genu varum (bowed legs), also frequently required treatment, including in some cases, limb lengthening. Additionally, patients with achondroplasia often contend with sleep apnea (obstructive and central), recurrent middle ear infections leading to hearing loss, obesity, and delays in motor development, underscoring the necessity of comprehensive, multispecialty care. The introduction of vosoritide (Voxzogo) marks a breakthrough in achondroplasia therapy, ushering in a new era in the treatment of this condition. It's the first disease-modifying therapy that directly targets the pathophysiology of achondroplasia. Vosoritide, a C-type natriuretic peptide (CNP) analog, works by inhibiting the excessively activated MAPK pathway, which is involved in FGFR3 signaling. This action allows vosoritide to increase chondrocyte proliferation and differentiation in the growth plate, enabling endochondral bone growth. Phase 3 clinical trials have shown that vosoritide significantly increases growth velocity (by an average of 1.57 cm per year in the study group) and improves body proportions, while demonstrating a mild safety profile with minimal side effects, such as injection site reactions or transient blood pressure drops. Vosoritide is approved in Europe for children with achondroplasia from 4 months of age, and in the USA from birth, provided there's genetic confirmation of the diagnosis and open growth plates. While vosoritide offers immense hope for patients, it's crucial to emphasize that initiating vosoritide therapy does not replace the need for coordinated, multidisciplinary medical care. Continued monitoring and management of achondroplasia complications by a team of specialists, along with psychological support, remain essential. This review, based on a systematic analysis of literature from 2015-2025, summarizes the current state of knowledge, highlighting both the established medical status of achondroplasia and the dynamic therapeutic developments that open new perspectives for improving patients' quality of life.

Disclosure

Authors do not report any disclosures.

Author's contribution:
All authors contributed to the article.
Project administration: Turek M
Conceptualization: Zagalska M
Methodology: Szlążek J, Turek M, Zagalska M
Software: Turek M, Zagalska M
Formal analysis: Tamborski T, Mesyasz M
Investigation: Ząbek A, Kuźniar J
Resources: Chrzanowska E, Mikulec P, Kerknawi K
Data curation: Turek M, Zagalska M
Writing - rough preparation: Mesyasz M, Mikulec P
Writing - review and editing: Tamborski T, Szlążek J
Visualization: Szlążek J , Turek M
Supervision: Tamborski T, Kerknawi K

All authors have read and agreed with the published version of the manuscript.

Funding statement: The study did not receive any external funding.
Institutional Review Board Statement: Not applicable.
Informed Consent Statement: Not applicable.
Data Availability Statement: Not applicable.
Acknowledgments: Not applicable.
Conflict of Interest Statement: The authors declare no conflict of interest.

REFERENCES

1. Pauli, R. M. (2019). Achondroplasia: A comprehensive clinical review. *Orphanet Journal of Rare Diseases, 14*(1), 1. https://doi.org/10.1186/s13023-018-0972-6
2. Ornitz, D. M., & Legeai-Mallet, L. (2017). Achondroplasia: Development, pathogenesis, and therapy. *Developmental Dynamics, 246*(4), 291–309. https://doi.org/10.1002/dvdy.24479
3. Wright, M. J., & Irving, M. D. (2012). Clinical management of achondroplasia. *Archives of Disease in Childhood, 97*(2), 129–134. https://doi.org/10.1136/adc.2010.189092
4. Tofts, L., Ireland, P., Tate, T., Raj, S., Carroll, T., Munns, C. F., Knipe, S., Langdon, K., McGregor, L., McKenzie, F., Zankl, A., & Savarirayan, R. (2024). Consensus guidelines for the use of vosoritide in children with achondroplasia in Australia. *Children, 11*(7), 789. https://doi.org/10.3390/children11070789
5. Wrobel, W., & Ben-Skowronek, I. (2024). Assessment of the efficacy of vosoritide therapy in children with achondroplasia in clinical trials. *Translational Pediatrics, 13*(9), 1515–1516. https://doi.org/10.21037/tp-24-249
6. Kubota, T., Adachi, M., Kitaoka, T., Hasegawa, K., Ohata, Y., Fujiwara, M., Michigami, T., Mochizuki, H., & Ozono, K. (2020). Clinical practice guidelines for achondroplasia. *Clinical Pediatric Endocrinology, 29*(1), 25–42. https://doi.org/10.1297/cpe.29.25
7. Okenfuss, E., Moghaddam, B., & Avins, A. L. (2020). Natural history of achondroplasia: A retrospective review of longitudinal clinical data. *American Journal of Medical Genetics Part A, 182*(11), 2540–2551. https://doi.org/10.1002/ajmg.a.61825
8. Leiva-Gea, A., Martos Lirio, M. F., Barreda Bonis, A. C., Marín del Barrio, S., Heath, K. E., Marín Reina, P., Guillén-Navarro, E., Santos Simarro, F., Riaño-Galán, I., Yeste Fernández, D., & Leiva-Gea, I. (2022). Achondroplasia: An update on diagnosis, follow-up, and treatment. *Anales de Pediatría, 97*(6), 423–423.e10. https://doi.org/10.1016/j.anpedi.2022.10.004
9. Merchant, N., Hoover-Fong, J., & Carroll, R. S. (2025). Approach to the patient with achondroplasia: New considerations for diagnosis, management, and treatment. *Journal of Clinical Endocrinology & Metabolism, 110*(7), e2309–e2316. https://doi.org/10.1210/clinem/dgaf017
10. Semler, O., Cormier-Daire, V., Lausch, E., Bober, M. B., Carroll, R., Sousa, S. B., Deyle, D., Faden, M., Hartmann, G., Huser, A. J., Legare, J. M., Mohnike, K., Rohrer, T. R., Rutsch, F., Smith, P., Travessa, A. M., Verardo, A., White, K. K., Wilcox, W. R., & Hoover-Fong, J. (2024). Vosoritide therapy in children with achondroplasia: Early experience and practical considerations for clinical practice. *Advances in Therapy, 41*(1), 198–214. https://doi.org/10.1007/s12325-023-02705-9
11. Akinnusotu, O., Isaacs, A. M., Stone, M., & Bonfield, C. M. (2023). Neurosurgical management of cervicomedullary compression, spinal stenosis, and hydrocephalus in pediatric achondroplasia: A systematic review. *Journal of Neurosurgery: Pediatrics, 32*(5), 597–606. https://doi.org/10.3171/2023.6.PEDS23162
12. Feller, C., & Senthilvel, E. (2024). Sleep-disordered breathing in an infant with achondroplasia and foramen magnum stenosis. *Cureus, 16*(3), e56291. https://doi.org/10.7759/cureus.56291
13. Chen, H., Zhang, R., Jin, M., Yang, J., Chen, L., & Xie, Y. (2024). Advances in the mechanism and therapies of achondroplasia. *Genes & Diseases, 12*(4), 101436. https://doi.org/10.1016/j.gendis.2024.101436
14. Bucerzan, S., Alkhzouz, C., Crisan, M., Miclea, D., Asavoaie, C., Ilies, R., & Grigorescu-Sido, P. (2021). Diagnostic, treatment and outcome possibilities in achondroplasia. *Medical Pharmacy Reports, 94*(Suppl 1), S22–S24. https://doi.org/10.15386/mpr-2222
15. Mindler, G. T., Stauffer, A., Chiari, C., Mladenov, K., & Horn, J. (2024). Achondroplasia: Current concept of orthopaedic management. *Journal of Children's Orthopaedics, 18*(5), 461–476. https://doi.org/10.1007/s11832-024-00728-7