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Current Strategies and Future Prospects of Achondroplasia Treatment: A Systemic Review

Authors:

Daria Bednarczyk

ORCID https://orcid.org/0009-0007-1006-4955

daria.bednarczyk99@gmail.com

Central Clinical Hospital of Medical University of Warsaw

ul. Banacha 1A, 02-097; Warsaw; Poland

Wiktoria Pysiewicz

ORCID https://orcid.org/0009-0002-3245-8609

wiktoria.pysiewicz@gmail.com

Norbert Barlicki Memorial Teaching Hospital No. 1 of the Medical University of Lodz,

Lodz, Poland

ul. dr. Stefana Kopcińskiego 22, 90-153; Łódź; Poland

Wiktor Garbarczyk
ORCID https://orcid.org/0009-0001-4107-6795
wgarbarczyk@gmail.com
University Clinical Hospital No. 2 of Medical University of Łódź
ul. Żeromskiego 113; 90-549 Łódź; Poland

Agnieszka Napieralska
ORCID https://orcid.org/0009-0001-1163-8283
napieralskaa@gmail.com
University Clinical Hospital No. 2 of Medical University of Łódź
ul. Żeromskiego 113; 90-549 Łódź; Poland

Albert Kapla
ORCID https://orcid.org/0009-0004-0887-0825
albertkapla@wp.pl
NZOZ Gajda-Med Medical Group;ul.
ul. Teofila Kwiatkowskiego 19; 06-102; Pułtusk; Poland

Michalina Jurkiewicz
ORCID https://orcid.org/0009-0005-3318-121X
m.jurkiewicz86@gmail.com
Central Teaching Hospital of Medical University of Łódź
ul. Pomorska 25; 192-213 Łódź; Poland

Julia Białeta
ORCID https://orcid.org/0009-0009-3140-4060
bialetajulia@gmail.com
Central Teaching Hospital of Medical University of Łódź
ul. Pomorska 251; 92-213 Łódź; Poland

Katarzyna Rowińska
ORCID https://orcid.org/0009-0002-7921-7167
rowinska98@gmail.com
University Clinical Hospital No. 2 of Medical University of Łódź
ul. Żeromskiego 113; 90-549 Łódź; Poland

Karolina Siembab
https://orcid.org/0009-0000-9934-8741
kkaarolina75@gmail.com
Maria Skłodowska-Curie Regional Specialist Hospital in Zgierz
ul. Parzęczewska 35, 95-100 Zgierz; Poland

Alicja Černohorská
ORCID https://orcid.org/0009-0001-8230-2891
a.cernohor@gmail.com
Central Teaching Hospital of Medical University of Łódź
ul. Pomorska 251; 92-213 Łódź; Poland

Abstract

Introduction and Purpose:
Achondroplasia, the most common form of dwarfism, results from mutations in the FGFR3 gene and affects 1 in 25,000 people. The disorder causes disproportionate short stature due to a gain-of-function mutation in FGFR3, impacting bone growth. Patients often face various health challenges, including orthopedic, neurological, and respiratory issues. This review aims to analyze current treatment strategies, their limitations, and highlight promising new approaches for managing achondroplasia.

Materials and Methods:
This review synthesizes available literature on the clinical management of achondroplasia, focusing on treatment modalities such as growth hormone therapy, limb lengthening techniques, spinal surgery, and gene therapies. Emphasis is placed on understanding the efficacy, challenges, and emerging therapies for this genetic condition.

Results:
Current treatment approaches include recombinant human growth hormone (rhGH) therapy, which has shown modest success in increasing height but has limited long-term benefits. Limb lengthening remains a cornerstone for improving quality of life, with techniques like the Ilizarov method and PRECICE system, though complications and high costs persist. Spinal surgeries for foramen magnum stenosis and kyphosis provide relief but are complex and require individualized care. New treatments like Vosoritide,

a CNP analogue, show promise by promoting bone growth. Gene-editing techniques like CRISPR/Cas9 offer potential for correcting the underlying genetic mutations.

Conclusion:
Achondroplasia management continues to evolve with a combination of surgical, pharmacological, and genetic interventions. While limb lengthening and spinal surgeries significantly improve quality of life, new treatments like Vosoritide and CRISPR/Cas9 may revolutionize care by addressing the root cause of the condition. Ongoing research and clinical trials will likely refine these approaches, offering better outcomes for patients with achondroplasia.

Keywords

Achondroplasia, Achondroplasia treatment, Vosoritide, PRECICE, PRECICE system, Ilizarov apparatus, Short stature treatment, C-type natriuretic peptide, Growth hormone, Meclozine, Bowed legs, Spinal surgery, Surgical limb lengthening

Introduction:

Achondroplasia is the most common form of dwarfism caused by mutations in the FGFR3 gene (fibroblast growth factor receptor). Achondroplasia is estimated to have an incidence rate of 1 in 25,000. The disorder is a result of autosomal dominant inheritance. A gain-of-function type mutation in the transmembrane region of FGFR3 leads to insufficient bone growth. Because of the mutation, long bones develop in a limited way, contributing to a distinctive appearance. Individuals can reach a maximum height of 112-145 cm as adults. (1, 2, 3) The typical clinical presentation of the disease features disproportionally short stature and rhizomelic shortening of the limbs combined with an almost standard trunk. (4) Although patients with achondroplasia are leading a normal life, the disease is connected to various health issues, including orthopaedic and neurological difficulties, as well as ventilation and heart functioning problems. As a result, the patient requires comprehensive care.

Objective of the work:

The aim of this review is to analize and combine the available literature, present a summary of current treatment methods, asses the difficulties and negative aspects of various therapeutic strategies as well as emphasize new treatments for managing the genetic condition.

Materials and methods:

A search was performed in the PubMed database for this review article, utilizing the terms: achondroplasia, pharmacotherapy, vosoritide, growth hormone, surgical treatment of achondroplasia. These keywords were selected to identify pertinent scientific literature on the topic. In conclusion, 32 articles were referenced.

Description of the state of knowledge

Managing Growth and Bone Development :

Treating achondroplasia involves some major challenges. One of them is supporting bone development.

Treatment with recombinant human growth hormone rhGH :

Growth hormone, also known as somatotropin, is an anabolic hormone responsible for stimulating chondrogenesis and osteogenesis in growth cartilage. The stimulation occurs due to intermediating peptides and leads to weight gain and growth. Moreover, growth hormone regulates carbohydrate metabolism.

Recombinant human growth hormone injections play a significant role in the course of short-stature therapy for achondroplasia.

The mechanism of action is based on promoting the patients' growth through chondrocyte proliferation. The accomplishments of ten years of utilising this treatment method are significant, as they show a mean height increase of +2,8 cm in women and +3,5 cm in men. [5]

However, studies involving rats failed to demonstrate growth enhancement in the research group in comparison to the placebo-treated control group.

Short-term recombinant human growth hormone (r-hGH) treatment improved growth tempo, but no apparent advantage was found for long-term use. The impact on body disproportions is still unknown.

It is significant to note that the concentrations of growth hormone, insulin-like growth factor 1, and insulin-like growth factor binding protein 1 in the serum are within the standard range for children with achondroplasia. In this regard, r-GH is not typically recommended for treating achondroplasia. [2, 7]

Limb lengthening

Limb lengthening is the primary element of the multidirectional process of improving the quality of life in patients with achondroplasia. There are many possible ways of lengthening the limbs.

One of the first and most famous methods was the Ilizarow method. It involved an osteotomy and inserting rings connected with rods into bone fragments. The bone cells at the site of bone disruption multiply, forming new bone tissue. The Ilizarov apparatus enables precise control of the prolongation process. However, it can cause severe complications such as infections, difficulties with bone healing, and nerve and joint injuries. Pain can be a significant issue when dealing with this treatment. [7, 8, 9, 10]

The PRECICE system is an intramedullary lengthening implant. The device is placed inside the bone and then controlled via a remote control. An electromagnetic tool makes gradual elongation possible. This method of limb lengthening has a lower risk of infections than Ilizarow's apparatus. It also improves the comfort of life and aesthetics. On the other hand, the downside of this treatment is the high costs and the risk of complications. [11, 12]

The Present preferred (another) technique of limb lengthening is the 4-segment lengthening method. It allows the maximum total length gain to be achieved in the shortest time possible. Considering Schiedel and Rodl's metanalysis, only a few patients with achondroplasia can reach the lower limit of standard height for their sex and age.

It is worth mentioning that great benefit of limb lengthening is improvement of Quality Of Life (QOL) in patients with achondroplasia. [13, 14]

Spinal surgery:

Achondroplasia is linked to many spinal complications that significantly impact patients' quality of life. The underlying cause of this impairment is an excessive proliferation and differentiation of chondrocytes, which leads to abnormal bone growth and narrowing of the foramen magnum.

FMS - Foramen magnum stenosis :

The stenosis of the foramen magnum is commonly the first indication of spinal dysfunction in infants. Because of the spinal cord compression, central sleep apnea can develop. The development of compressive myelopathy is possible. Hydrocephalus is also a potential outcome. The severity of foramen magnum stenosis and the presence of neurological symptoms are the factors that determine the treatment of achondroplasia foramen magnum stenosis. In some instances, conservative treatment is feasible. It is centred around pain management and physical therapy. More advanced cases require decompression surgery. The upper cervical laminectomy is necessary to widen the foramen magnum. The procedure is based on removing the fragments of vertebrae or tissue around the spinal canal to relieve the spinal cord. If the hydrocephalus occurs, an endoscopic third ventriculostomy or ventriculoperitoneal shunt (VP) may be needed. [5, 15, 16, 17, 18]

TLK - Thoracolumbar kyphosis

Thoracolumbar kyphosis is typical for newborns with achondroplasia. Moreover, by 18 months, kyphosis is typically withdrawn in approximately 90% of cases. Kyphosis is more common in younger patients, as has been observed. It can lead to spinal stenosis. One of the main symptoms of TLK is trunk hypotonia. With increasing age, this condition has a high chance of spontaneous resolution. At first, it is important to restrict sitting without stabilisation in children under the age of one year.
Bracing may be required in some cases, such as thoracic spine deformity over 30 degrees. If sagittal plane deformation exceeds 60 degrees in 5-year-old children, anterior and posterior fusion can be performed. If there are significant neurological deficits or fixed kyphosis above 50 degrees, it is advisable to consider surgery. [15, 16]

Bowed legs :

Genu varum is characterised by an abnormal alignment of the lower limbs, in which the knees are displaced outward while the feet are brought closer together. The cause of this deformity is an internal tibial torsion. Proper examination of this structural deformity is required. It is crucial to emphasise the accelerated progression of the leg bowing problem with age. (It is essential to underscore the accelerated progression of the leg bowing condition with advancing age.) Some patients may develop symptoms, including lower limb pain or gait impairment, which could indicate the need for surgical intervention. Surgical treatment of genu varum in patients with achondroplasia should be based on hemiepiphysiodesis or tibial/fibular osteotomies with or without femoral osteotomies [14, 15, 16]

Hearing impairment :

Hearing impairment is a significant issue for individuals with achondroplasia. It originates from middle ear dysfunction, as evidenced by the analysis of abnormal tympanograms in achondroplastic patients. It is likely derived from improper development of the Eustachian tube. The prevalence of conductive hearing loss was more significant than sensorineural hearing loss.

Neglecting the issue may result in severe difficulties in speech development. For this reason, it is essential to follow an appropriate approach based on identifying the disease in children with achondroplasia and proper surgical treatment. Surgical management of hearing disorders relies on tympanostomy tube placement/ tympanostomy with tube insertion. [5, 16, 19]

C-Type Natriuretic Peptide CNP :

ANP, BNP and CNP are the main natriuretic peptides. They play an important role in the regulation of homeostasis of sodium, blood pressure and bone development. While ANP and BNP affect mainly the cardiovascular system and renal excretion, CNP concentrates on stimulating chondrocytes and promoting the growth of long bones. The mechanism of CNP action relies on the impact on NPR-B receptors that activate the cGMP signalling pathway, leading to the transformation of GTP (guanosine 5′-triphosphate) into cGMP (cyclic guanosine monophosphate) and activation of a variety of mediators, which support the development of the chondrocytes and proliferation of the cells in the growth plate cartilage. Due to gain-of-function mutations in FGFR3 in achondroplasia disease, excessive signalling has been made that alters chondrocyte proliferation and differentiation. [2, 20]

Vosoritide is a modified recombinant human C-type natriuretic peptide (CNP) analogue. It works by binding to NPR-B receptors, leading to inhibition of signalling pathways of the overactive FGFR3 gene. As a result, Vosoritide, similar to CNP, acts as a positive regulator of endochondral bone growth.

The treatment is dedicated to patients with achondroplasia aged at least >= 4 months whose epiphyses are not closed. The appropriate genetic testing should confirm the diagnosis of the disease. The product is administered daily with a subcutaneous injection. The dosage is based on the patient's body weight. [21]

Prolonged-Release C-Type Natriuretic Peptide: TransCon CNP :

Due to important structural modifications, TransCon (CNP 38) is a polypeptide with a longer half-life than Vosoritide. The biological half-life of Vosoritide is approximately 15-20 minutes, whereas

TransCon CNP is 90 hours. The primary purpose of developing this solution is to prevent high CNP blood levels and maintain a more stable CNP concentration. [22]

Gene editing and CRISPR/Cas9 technology - (Clustered Regularly Interspaced Short Palindromic Repeats)

CRISPR/Cas9 is a system widely used in biotechnology to deliberately modify genomes in precisely selected locations. The CRISPR system selectively binds to a dedicated DNA sequence known as Cas9, which is the basis for this tool's mechanism of action. Cas 9 is an endonuclease that can cut DNA near a particular sequence (acting as molecular scissors). Combining this method and DNA repair mechanisms, such as rendering specific genes inactive or inserting corrected sequences, can be utilised for gene therapy.

The application of CRISPR/CAS9 technology for treating achondroplasia is still in the preclinical stage of studies. Therapy is expected to have promising effects. [23, 25]

To study the CRISPR/Cas9 method, researchers used specially generated mice with mutations in the FGFR3-G374 gene. The mice obtained were representative of the individuals with achondroplasia. The study demonstrated that this technology can enable many repairs of the FGFR3 mutated genes. [24]

Meclozine

Meclozine is an antihistamine often used to treat motion sickness, dizziness (vertigo), or nausea. The mechanism of action of meclozine used in treating achondroplasia is based on blocking the activation of the ERK-MEK pathway. It allows for the inhibition of the enhanced activity of the FGFR3. [5, 20, 26]

A study has confirmed the effects of administering oral meclozine at a dose of 1-2 mg/kg/day in a mouse model of achondroplasia. The use of a drug has been demonstrated to promote the growth of long bones. The dosage is crucial for achieving these results, as 20 mg/kg/day is unsuccessful. [27]

Another study investigated the effect of long-term meclozine therapy in a mouse model of achondroplasia. The effect of meclozine on the reduction of paralysis resulting from spinal malformations and the increase in body length was observed. Moreover, the restoration of the hypertrophic zone in the growth plate was evident/noted in the mice. [28]

Tyrosine Kinase Inhibitor:

Infigratinib, an NVP-BGJ398 inhibitor, is a receptor tyrosine kinase inhibitor selective for FGFRs. It attaches to the ATP-binding site, inhibiting FGFR activity. Mouse-based studies have demonstrated that the drug induces an increase in limb length and restoration of cranial integrity. [32]

In addition, infigratinib can enhance mandibular abnormalities. Improving the structure of the mandible may have a secondary effect on the upper airway, potentially alleviating the symptoms of obstructive sleep apnea. Furthermore, the drug claims to enlarge the foramen magnum. However, dermatological side effects were observed during the oncological use of infigratinib, such as dry skin, nail plate damage, hair loss, and hand-foot syndrome. The potential use of this drug in treating achondroplasia is being evaluated through ongoing research. [5, 20, 29, 30]

Recifercept:

Recifercept is a soluble fibroblast growth factor receptor 3. This drug's mechanism of action involves competing with FGFR3 ligands like FGF9 or FGF18, which prevents their binding to FGFR3. It is presently undergoing clinical development to treat achondroplasia in pediatric patients.

Studies on mice with an FGFR3 mutation found that the drug supports bone growth, lowers the mortality rate, enhances body mass, and promotes bone development of the cranial base. The treatment improved skull length and the foramen magnum area and restored the cranium ratio and skull shape. Therefore, it may help address craniofacial issues, including midface hypoplasia, seen in achondroplasia patients.

In summary, Recifercept treatment resulted in significant improvements in Fgfr3 ach/+ mice; however, additional studies are required to confirm these findings. [31, 32]

Conclusion :

In conclusion, the management of achondroplasia represents a complex challenge. A comprehensive strategy is required to influence the neurological, skeletal, and orthopaedic problems related to the condition. Treatment methods such as limb lengthening techniques or recombinant human growth hormones have been applied until now and have demonstrated effectiveness. However, new ones are being studied due to their limitations and imperfections. Surgical interventions such as spinal or genu varum correcting procedures are extremely helpful in alleviating symptoms and improving quality of life. C-type natriuretic peptide analogues represent a promising therapy for achondroplasia, significantly influencing growth increase with potentially few side effects.CRISPR/Cas9 is an innovative treatment

method that can influence patients' disease at the genetic level. There are also other potential solutions in the treatment of achondroplasia that are currently being researched. These include tyrosine kinase inhibitors, meclosine, and recifercept, which require more extensive testing.

Disclosure

Author's contribution

Conceptualization: Daria Bednarczyk

Methodology: Wiktoria Pysiewicz

Software: Michalina Jurkiewicz

Check: Katarzyna Rowińska and Michalina Jurkiewicz

Formal analysis: Julia Białeta and Wiktor Garbarczyk

Investigation: Albert Kapla

Resources: Alicja Černohorská and Agnieszka Napieralska

Data curation: Karolina Siembab

Writing - rough preparation: Julia Białeta

Writing - review and editing: Albert Kapla

Visualization: Wiktoria Pysiewicz

Supervision: Alicja Černohorská

Project administration: Daria Bednarczyk

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In preparing this work, the authors used ChatGPT for the purpose of improving language and readability. After using this tool, the authors have reviewed and edited the content as needed and accept full responsibility for the substantive content of the publication.

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