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Review Article

How do we Treat Aberrant Excessive Signaling in FGF3 Receptor Pathway to Cure Achondroplasia in Childhood?

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Abstract

In 1878, a French physician named Joseph Marie Jules Parrot coined the term achondrodysplasia. This term is purely historical and does not explain the cause or symptoms of the disorder. Other names that were once used but are now obsolete include chondrodystrophy, chondrodystrophia fetalis, Parrot syndrome, and Kaufmann syndrome, named after the German pathologist Eduard Kaufmann. Achondroplasia is the most common form of genetic short stature, occurring in 1 out of every 20,000 births. It is considered a rare disease. Achondroplasia is caused by a specific mutation in the fibroblast growth factor receptor gene FGFR-3. This gene is located on chromosome 4p 16.3. The mutation in achondroplasia leads to an overexpression of the FGFR3 receptor, inhibiting the proliferation of chondrocytes, which are cells responsible for cartilage formation. In 96% of cases, there is a specific G (1138) A point mutation in the FGFR-3 gene. Researchers are currently focusing on developing targets that can reduce the overexpression of the FGF3 receptor and inhibit chondrocyte formation. This mutation disrupts cartilage formation, causing the growth plates in bones to ossify prematurely. This results in restricted growth, particularly in the arms and legs, leading to a disproportionate short stature where the trunk and head are relatively longer than the extremities. This article provides an overview of achondroplasia, with a special focus on current therapies and future treatment options for pediatric patients. Various targets in the FGFR3 signaling pathway are being studied in clinical research, and their potential for treating achondroplasia will be analyzed in detail. The ultimate goal is to find a cure by targeting the aberrant excessive FGF3 receptor signaling pathways. The article will discuss the FGFR3 receptor pathways in detail and mention possible clues for curing the disease.

Keywords: Achondroplasia, Children, Aberrant signaling, FGFR3 receptor, Treatment

Introduction

Achondroplasia is the most common of the approximately 650 forms of short stature [1,2,5,7,15-17, 24,25,30,43,44,48,49,58,66,68]. A dominantly inherited FGFR3 gain of function mutation permanently activates the FGFR3 and downstream MAPK, mitogen-activated protein kinase signaling cascade [1-68]. This inhibits chondrocyte differentiation, slows down growth plate activity, and additionally triggers serious complications, such as stenosis of the foramen magnum and spinal canal, and narrowing of the upper airway. Increasing knowledge of complications of FGFR3 activation has led to the development of treatment recommendations aimed at reducing morbidity and mortality from this condition, particularly deaths from spinal cord compression and sleep apnea in infants and young children [1,2,5,7,15-17, 24,25,30,43,44,48,49,58,66,68]. It is a genetic developmental disorder of cartilage and bone tissue, a gene defect of FGF3 receptor gene which induces overexpression at the FGF 3 receptor [1-68]. The cause has been known since 1996 [1,2,5,7,15-17, 24,25,30,43,44, 48,49,58,66,68]. Achondroplasia is a skeletal dysplasia (developmental disorder of the skeleton) and affects approximately one in 20,000 births [1-68]. With over 250,000 people affected worldwide, it is a rare condition [1-68]. In

Germany, 40-45 children are born with achondroplasia each year. External symptoms of achondroplasia are short upper arms and thighs, small, often broader hands and feet, and in relation, a long trunk. Hip and elbow joints cannot be fully extended, while finger, knee and ankle joints are hyperextended. Because of the reduced size of the chest, breathing is often impaired [18,38,39]. The narrowness of the nasopharynx often causes infections, especially of the upper respiratory tract [18,38,39]. Middle ear infections may also occur. The cerebrospinal fluid flows poorly or hardly at all due to the narrowness of the spinal canal. Attention should be paid to hearing disorders in early childhood, as these can impair speech development. Due to the narrow spinal canal, back complaints and delayed and slower physical development occur more frequently [19,45,53,62]. The shorter arms and the reduced extensibility of the elbows result in a significantly smaller grasping radius. The children can also tire more quickly. Apart from this, however, they develop completely normally and their intelligence is not affected. Leg axis changes of varying severity occur. The bending of the spine leads in some people to an outward curvature of the spine (kyphosis) and at the same time with hyper lordosis. Growth usually ends at approximately 120-140 cm [1-68]. It was suspected early on that achondroplasia is due to the mutation of a gene. Achondroplasia is inherited in an autosomal dominant manner [1-68].

Molecular Background of Achondroplasia

FGF-3 Receptor

Fibroblast growth factor receptor 3, or FGFR3, is a cellular receptor that binds various fibroblast growth factors. FGFR3 is associated with the cluster of differentiation and is also called CD333. FGFR3 is a receptor tyrosine kinase with a extracellular, intracellular and transmembrane domain. Binding of growth factors on the extracellular side induces dimerization of two receptors, activating them. As a result, various signaling pathways are induced, these control proliferation, differentiation and migration of the cell. It is known that FGFR3 is particularly involved in the ossification of long bones and regulates the remodeling of cartilage into bone substance. FGFR3 is produced in different isoforms (FGFRIIIb and -c) and the expression of the individual forms is tissue-specific and differs in molecular weight. FGFR3IIIb was present to be activated by FGF-1 and FGF-9 [69]. FGFR3IIIc was activated by FGF 1, -2,-4,-8- and -9 [69]. Six available recombinant FGFs (-1, -2,-4,-5,-6,-7) activate 2 isoforms of human FGFR3 [69]. In achondroplasia, an aberrant, overactive FGFR3 signaling pathway is present. The stimulation of FGFR3 has a variety of functional effects with regulation of epithelial cell growth and its differentiation.

The FGFR3 signaling pathway plays a role in regulating cell growth. In this study, L6 cells that lacked FGFR3 were genetically modified to express two different isoforms of FGFR3, known as FGFR3 Illb and FGFR3 Illc. These isoforms are produced through alternative splicing of exon Ill of the FGFR3 gene, which encodes the ligand binding domain. The expression of FGFR3 Illc in the modified L6 cells led to growth responses when exposed to various members of the FGF (Fibroblast Growth Factor) family, including FGF-1, FGF-2, FGF-4, and FGF-6. On the other hand, cells expressing FGFR3 Illb only responded to FGF-1. When FGFR3 was activated by binding to its ligand, it triggered the activation of the Mitogen-Activated Protein Kinase (MAPK) pathway. FGFR3 interacts with two different pools of adapter proteins, primarily GRB2, which then links to Ras. The activated FGFR3 mainly interacts with a complex consisting of GRB2, Sos (son of sevenless), and a previously identified 90-kDa protein called protein 80K-H. This complex was also found to contain a novel 66-kDa protein. The 66-kDa protein's tyrosine phosphorylation was dependent on ligand activation of FGFR3, suggesting its importance in FGFR3-specific signaling.

In addition to this unique pathway, FGFR3 also links to the GRB2-Sos complex through the adapter protein She. However, activated FGFR3 was unable to induce the dissociation of the GRB2-Sos complex after Sos phosphorylation. In summary, the FGFR3 signaling pathway involves two GRB2-containing complexes: She-GRB2-Sos and 80K-Hpp66-GRB2-Sos. These complexes may alternatively link FGFR3 to the MAPK pathway. Activated FGFR3 was also found to phosphorylate phospholipase C-y but reduce the phosphorylation of c-Src.

FGF-Receptor 3 Signaling Pathways

The STAT pathway is another signaling pathway activated by FGFR kinase. In this pathway, FGFR kinase phosphorylates STAT1, STAT3, and STAT5. Specifically, STAT3 interacts with a phosphorylated tyrosine residue at position 677, which is part of a specific motif known as pYxxQ. This phosphorylation event leads to the activation of STAT proteins, which then translocate to the nucleus and regulate gene expression. The STAT pathway plays a role in various cellular processes, including cell growth, differentiation, and immune response. In addition to regulating gene expression in the nucleus activated pathways also play a role in inhibiting FGFR signaling. The interaction between SPRY and GRB2 inhibits the RAS-MAPK pathway and regulates the PI3K-AKT pathway. GRB2 dimers attach to the c-terminus of FGFR2 inhibiting SHP2 and allowing for low levels of receptor kinase activity. Molecules shaded in red generally function to inhibit FGFR signaling. The dimerization of the FGFR1 kinase domain leads to sequential phosphorylation of tyrosine residues, resulting in increased FGFR kinase activity and phosphorylation of tyrosine substrates for CRKL, STAT, GRB14, and PLCγ binding. The first phase of activation involves the phosphorylation of Y653 (1P) in the activation loop leading to a significant increase in kinase activity. In addition to regulating gene expression in the nucleus, activated pathways also play a role in inhibiting FGFR signaling. The interaction between SPRY and GRB2 inhibits the RAS-MAPK pathway and regulates the PI3K-AKT pathway. GRB2 dimers attach to the c-terminus of FGFR2, inhibiting SHP2 and allowing for low levels of receptor kinase activity. Molecules shaded in red generally function to inhibit FGFR signaling. The dimerization of the FGFR1 kinase domain leads to sequential phosphorylation of tyrosine residues, resulting in increased FGFR kinase activity and phosphorylation of tyrosine substrates for CRKL, STAT, GRB14, and PLCγ binding. The first phase of activation involves the pho-

sphorylation of Y653 (1P) in the activation loop, leading to a significant increase in kinase activity.

FGF-Receptor 3 Signaling Interference and Interactions

BMP, bone morphogenetic protein, and PTHrP, known as parathyroid hormone related peptide/receptor/Indian Hedge-Hog (IHH), play an important role in morphogenetics of the disease. Several interactions of FGFR3 signaling with other pathways were described, which contribute to the pathological effect of FGFR3 mutations in cartilage. These involve the FGFR3-mediated inhibition of the cytokine signaling, including the LIF-STAT3 pathwav important for skeletal growth. Aberrant FGFR3 signaling suppresses chondrocyte differentiation, by dysregulated SOX9 expression, increased degradation of BMP type 1 receptor, and ectopic activation of WNT/B-catenin pathway, via ERK MAP kinase-mediated phosphorylation of WNT co-receptor. The FGFR3 signaling interferes with the Indian Hedgehog (Ihh)/ Parathyroid Hormone-Related Protein (PTHrP) signaling, essential for regulation of both chondrocyte proliferation and differentiation. This is mediated by downregulation of PTHrP expression, and by FGFR3 effect on the length of the primary cilia, which affects cilia-based Ihh signaling. Moreover, activation of STAT-1-transcryptional regulator and inactivation of PI3K-AKT-pathway influence chrondrocyte growth. FGF3 interacts moreover with autophagosome ATG5-proteins leading to decreased chondrocyte viability.

Molecular Background of Different Options to Treat Achondroplasia

Present therapeutical molecular options to cure the disease "achondroplasia" are described as following in six groups: (group 1) prevention of ligand-induced receptor activation by ligand antagonists or neutralizing antibodies; (group 2) prevention of receptor dimerization by specific antibodies; (group 3) the prevention of receptor phosphorylation or receptor activation by receptor tyrosine kinase inhibitors; (group 4) acting on FGFR3 signal transduction by appropriate inhibitors or by modulation towards alternative path-ways; (group 5) acting on FGFR3 gene expression at the DNA or mRNA level, by RNAi technology and (group 6) blocking of the MAP-Kinase signaling pathway through the action of C-type Natriuretic Peptide (CNP) via guanylyl cyclase (GC-B) by providing cyclic GMP (cGMP) as a messenger.

Therapeutical Targets to Treat Achondroplasia

Different clinical research was introduced to find a target to treat and cure the disease [3,4,9,11,26,27,31,32,37] (Table 1).

Table 1: Therapeutical targets, mode effects, side effects and application in the treatment of achondroplasia.

Therapeutical Target	Effect	Side effects	Application
CNP Analogon:	Antagonist of MAPK signaling pathway in growth plate	Only 15min in blood; short HWZ	s.c. once daily
Binding to NPR-B receptor			(Vosoritide)
Vosoritide (BMN111) [8,13,21-23,28-29,50]	Catching FGFR3 ligands by FGFR2 aptamer	in patients 2 years of age and older in whom the epiphyses have not yet closed	s.c. once weekly
Trans Con CNP (35)	(neutralization)		(Trans Con CNP)
(Drugs that modulate growth plate homeostasis)			
FGFR3-Antibody:	Anti FGF3 Antibody;	action of sequestering extracellular FGF	Phase 2 randomized, 3 arm (3 active doses of Recifercept), parallel group dose finding study of safety, tolerability, PK and efficacy, total number of participants is 63 in 2 age straified cohorts of 0-2 years and 6-10 years old. The study will enroll approximately 54 children with achondroplasia aged 2-10 years (inclusive) who will be enrolled and randomized to receive one of three doses of recifercept.
TA-46/Recicercept (soluble FGFR3 as a decoy receptor) (57)	Binding to extracellular domain of FGFR3, block ligand binding, interfere with co-factor receptor interaction, inhibiting dimerization of the receptor		
B-701/Vofatamab			
Tyrosine Kinase Inhibitor: (nearly 15 different targets in clinical study)	Small Molecule Inhibitor of intracellular tyrosine kinase, several TKI are known, infigratinib in clinical development in phase ½	Common side effects of Erdafitinib reported in clinical studies include stomatitis (inflammation of the mouth), diarrhea, abdominal pain, nausea, constipation, and dysgeusia (altered sense of taste).	

Infigratinib/Erdafitinib	Oral application		
80 K-H-Antiserum	Inhibitor of (GRB2 adapter-protein/nucleoside exchange factor/80K-H-protein)-complex; Inhibitor of 80 K-H protein		Research is in childhood shoes and a possible new target in achondroplasia research.
Histamin receptor antagonist:	Direct inhibition of FGFR3-RAS-ERK-pathway, preclinical studies were performed in transgenic FGFR3 -ACH/+mice	Because it is a first-generation antihistamine that crosses the blood-brain barrier, it not only has an antiemetic effect but also makes patients drowsy.	Only a few studies to date [42,56], application unclear
Meclozine (42,56)			
Recombinant somatotropin	Recombinant growth hormone, insufficient safety and efficacy, statins correct skeletal phenotype, reduce the expression of key regulators of growth plate cartilage	Lack of energy substrate (hypoglycemia, fasting, physical activity), increase in serum levels of certain amino acids (e.g., by high-protein diet), fever, and psychological stress represent secretion stimuli for somatropin. Somatropin is negatively regulated by somatostatin, an inhibitory hormone (growth hormone-inhibitory hormone, GHIH) produced in the pancreas and hypothalamus. Somatropin is the quantitatively most significant hormone of the pituitary gland. It makes up about ten percent by weight of the dried gland [10,61,63].	Efficacy in achondroplasia patients are clearly ruled out [10,61,63].,

Vosoritide (BMN111)

Vosoritide (BMN111) is an analogon of C-type Natriuretic Peptide (CNP) used to treat achondroplasia in patients 2 years of age and older in whom the epiphyses have not yet closed. Vosoritide has been on the German market under the trade name Voxzogo since October 1, 2021, and is indicated for the treatment of achondroplasia in patients 2 years of age and older in whom the epiphyses have not yet closed. The diagnosis of achondroplasia must be verified by an appropriate genetic test. Voxzogo is marketed in the dosage form of powder and solvent for the preparation of a solution for injection: 0.4mg powder in 0.5ml solution (0.8mg/ml after reconstitution), 0.56mg powder in 0.7ml solution (0.8mg/ml after reconstitution) and 1.2 mg powder in 0.6 ml solution (1.2mg/ml after reconstitution). Treatment with Vosoritide must be initiated and directed by a physician appropriately qualified in the management of such growth disorders or skeletal dysplasias. C-natriuretic Peptide (CNP) and its receptor, natriuretic peptide receptor B (NPR-B), are considered key regulators of longitudinal bone growth. CNP signaling promotes bone growth by inhibiting the MAPK pathway.

Vosoritide is a modified analog of CNP that acts as an agonist of NPR-B. By binding to NPR-B, Vosoritide inhibits the fibroblast growth factor receptor 3 signaling cascade, which is negatively regulated by a gain-of-function mutation in achondroplasia. In this context, extracellular signal-regulated kinases 1 and 2 (ERK1/2) in the overlapping MAP kinase (MAPK) signaling pathway are inhibited as a consequence of inhibition of the serine/threonine kinase rapid-accelerated fibrosarcoma (RAF-1). Thus, like physiological CNP, the CNP analogue vosoritide serves as a positive regulator of endochondral bone growth by stimulating chondrocyte proliferation and differentiation.

Vosoritide is absorbed after a median of 15 minutes. The mean Cmax and AUC (± SA) from time zero to the last measurable concentration observed after 52 weeks of treatment were 5 800 (± 3680) and 290000 (±235000) pg-min/ml, respectively. The mean (± SA) apparent volume of distribution after 52 weeks of treatment was 2910 (± 1660) ml/kg. Metabolism is most likely via catabolic pathways. Mean (± SA) apparent clearance was 79.4 (53.0) ml/min/kg after 52 weeks of treatment. The mean (± SA) half-life is 27.9 (9.9) minutes. Patient-to-patient variability (coefficient of variation) in apparent clearance was 33.6%. The increase in plasma exposure (AUC and Cmax) with dose was greater than dose-proportional over the dose range of 2.5 (0.17 times the recommended dose) to 30.0μg/kg/day (twice the licensed dose). Body weight is the only significant covariate for the clearance or volume of distribution of vosoritide. Clearance and volume of distribution of vosoritide increased with increasing body weight in patients with achondroplasia (9 to 74.5kg). The recommended dosage takes this variation into account and recommends the use of doses above (in patients weighing between 10 and 16kg) or below (in patients weighing greater than 44kg) the "standard dose" of 15μg/kg to achieve similar levels of exposure in all weight classes. The most common side effects that may occur during therapy with vosoritide are: injection site re-

actions, vomiting, hypotension, dizziness and syncope. The drug is also marked with the black triangle and accordingly it is constantly monitored for other emerging side effects. Studies to date indicate that CYP- or transporter-related interactions are unlikely with the use of vosoritide. In addition, because Vosoritide is a recombinant peptide, drug-drug interactions are generally unlikely to occur.

TransCon CNP

Trans Con-CNP is a medication being developed for the treatment of conditions related to achondroplasia, a type of dwarfism. It is a modified form of C-type natriuretic peptide (CNP-38) that is attached to a carrier molecule called polyethylene glycol. This design allows for sustained release of CNP in the body when administered once a week through subcutaneous injections. Studies conducted on mice and cynomolgus monkeys have shown that TransCon CNP, with its continuous exposure to CNP, is more effective in promoting bone growth compared to intermittent exposure to CNP. Additionally, TransCon CNP has been well tolerated in these animal models, with no adverse effects on the cardiovascular system even at exposure levels higher than expected in clinical use. In comparison, the unconjugated CNP-38 molecule or a daily CNP-39 molecule (which has the same amino acid sequence as Vosoritide, a drug used to treat achondroplasia) resulted in reductions in blood pressure and/or an increase in heart rate when administered at equivalent doses.

The half-life of the daily CNP-39 molecule in cynomolgus monkeys was estimated to be 20 minutes, while CNP-38 released from TransCon CNP had a half-life of 90 hours. The peak concentration of CNP-39 was approximately 100 times higher than that achieved with TransCon CNP. Furthermore, CNP-39 exposure was only detectable for up to 2 hours after administration, whereas TransCon CNP provided systemic exposure to CNP-38 for at least 7 days. The prolonged exposure to CNP and the controlled peak serum concentrations achieved with TransCon CNP are believed to enhance its efficacy compared to short-lived CNP molecules. This is due to better coverage of therapeutic drug levels and a reduced risk of hypotension (low blood pressure). TransCon CNP is a promising medication that utilizes the TransCon Technology to provide sustained levels of CNP in the body. It has shown potential as an effective and well-tolerated treatment option for achondroplasia, offering the convenience of once-weekly dosing while minimizing the risk of cardiovascular side effects associated with high CNP concentrations.

Recifercept

Recifercept is a drug that binds to certain proteins in the body to treat achondroplasia, a genetic disorder that affects bone growth. It specifically targets a defective receptor called FGFGR3 and limits its activation by competing with other proteins in the FGF family. This helps to restore normal bone growth and improve skeletal development. The drug works by downregulating certain signaling pathways in the body, specifically the MAPK and phospholipase C pathways. However, it does not affect the STAT1 pathway. Preclinical studies in mice have shown several benefits of recifercept, including increased bone growth, improved bone structure, elongation of long bones, and better skeletal development of the thorax. In addition to these skeletal improvements, recifercept has also been found to have positive effects on the skull and reproductive capacity. It prevents premature closure of the synchondroses, which are cartilaginous joints in the skull, leading to improved skull proportions. It also increases the size of the pelvic bone, which could potentially reduce the need for cesarean sections in women with achondroplasia. Furthermore, recifercept has been shown to have a beneficial effect on atypical visceral obesity in achondroplasia. Mutations in the Fgfr3 gene, which is associated with achondroplasia, have been linked to an increased predisposition to adipogenesis (the formation of fat cells) in mesenchymal stem cells. However, treatment with recifercept eliminates this phenomenon in animal models. Overall, recifercept shows promise as a potential treatment for achondroplasia, with positive effects on bone growth, skeletal development, skull proportions, reproductive capacity, and obesity. Further research and clinical trials are needed to fully understand its efficacy and safety in humans.

Vofatamab (Anti-FGF3 Antibody)

Vofatamab is a Monoclonal Antibody (mAb) that specifically targets FGFR3, a protein involved in cell signaling. It has been studied as a potential treatment for urothelial carcinoma, a type of bladder cancer, both as a standalone therapy and in combination with other drugs such as docetaxel or pembrolizumab. Clinical trials (NCT02401542, NCT03123055, NCT02925533) have been conducted to evaluate its effectiveness in these settings. Vofatamab is a human-derived antibody that binds to the external portion of FGFR3, preventing the attachment of ligands from the FGF family. By blocking this interaction, it aims to inhibit the growth and spread of cancer cells. Currently, it is being investigated in clinical trials for the treatment of urothelial neoplasms and multiple myeloma. In addition to its potential use in cancer treatment, vofatamab has also been considered as a potential therapeutic option for achondroplasia, a genetic disorder that affects bone growth. However, no preclinical studies have been initiated to explore this possibility further. One potential challenge with vofatamab is its large size as an antibody. This may pose difficulties in terms of its ability to penetrate the growth plate, where the extracellular matrix is dense. Further research is needed to determine its effectiveness and potential limitations in different clinical settings.

Tyrosine Kinase Inhibitors

Erdafitinib is a type of medication known as an antineoplastic tyrosine kinase inhibitor. It belongs to a subgroup of drugs called FGFR inhibitors. In clinical studies, another FGFR inhibitor called Infigratinib has shown promising effects in treating certain types of cancer. Erdafitinib works by binding to a receptor called Fibroblast Growth Factor Receptor (FGFR), which is involved in controlling various cellular processes such as cell differentiation and proliferation. In certain tumors, this receptor becomes dysregulated and constantly activated, leading to uncontrolled tumor growth. By binding to FGFR subtypes FGFR1-FGFR4, Erdafitinib inhibits the enzymatic activity of these receptors and stops the subsequent signaling

pathways. This ultimately leads to apoptosis (cell death) of tumor cells and slows down tumor growth. In addition to FGFR, Erdafitinib also inhibits other tyrosine kinases, which are enzymes involved in cell signaling. This makes Erdafitinib a potential treatment option for patients with metastatic or locally advanced urothelial carcinoma who have not responded to first-line therapy and have specific mutations or amplifications of the FGFR2 or FGFR3 genes. Common side effects of Erdafitinib reported in clinical studies include stomatitis (inflammation of the mouth), diarrhea, abdominal pain, nausea, constipation, and dysgeusia (altered sense of taste). Erdafitinib was approved by the US Food and Drug Administration (FDA) in April 2019. The drug was discovered by Astex Pharmaceuticals and is licensed by Janssen.

Somatotropins

Growth hormones are involved in the synthesis of nucleic acids and proteins, cell division, and carbohydrate metabolism, which leads to organ and bone growth and weight gain. Short-term growth hormone therapy has been found to be more effective than long-term treatment in increasing growth velocity, with the greatest height gain typically observed in the first year of treatment. Studies have shown that 10 years of growth hormone treatment can result in a mean growth gain of 3.5cm in men and 2.8cm in women. Combining growth hormone treatment with other methods, such as l-thyroxine or surgical elongation of the tibia and/or femur, can further increase final height. However, growth hormone treatment has been found to be ineffective in patients with lower limb and spine deformities. Studies in rats have shown that growth hormone treatment leads to greater weight gain but no significant difference in height gain compared to a placebo.

The text also mentions that a variable growth hormone treatment model, similar to the natural secretion rhythm, may be more effective than continuous daily administration. It is unclear whether growth hormone administration negatively affects spinal cord pressure or the severity of foramen narrowing, and no symptoms of acromegaly have been observed in treated patients. A meta-analysis of growth hormone treatment in achondroplasia shows ambiguous data regarding body disproportion. Somatropin is produced in the α-cells of the anterior pituitary. Its surge-like release is regulated by the hypothalamus with its somatropin-releasing factor (SRF, GHRH growth hormone-releasing hormone, GRF, somatoliberin) and somatostatin. During sleep, somatropin is produced the most. Puberty is the age with the most pronounced somatropin production.

Lack of energy substrate (hypoglycemia, fasting, physical activity), increase in serum levels of certain amino acids (e.g., by high-protein diet), fever, and psychological stress represent secretion stimuli for somatropin. Somatropin is negatively regulated by somatostatin, an inhibitory hormone (growth hormone-inhibitory hormone, GHIH) produced in the pancreas and hypothalamus. Somatropin is the quantitatively most significant hormone of the pituitary gland. It makes up about ten percent of the weight of the dried gland.

Meclozine (Meclizine)

Meclozine is a drug from the group of systemic H1 antihistamines. It is effective against nausea and vomiting and has been shown to be safe to use during pregnancy. In other EU countries, preparations are or were known under the names Postafene or Agyrax. The synthesis of meclozine starts from (4-chlorophenyl)-phenylmethanol, which is first reacted after halogenation by thionyl chloride and reaction with acetylpiperazine to give a 4-chlorophenyl-phenylpiperazinylmethane intermediate compound. Acid cleavage of the acetyl group is followed by N-alkylation on the piperazine ring with 3-methylbenzyl chloride to give the racemic target molecule. Alternatively, the last synthesis step can be carried out as a reductive N-alkylation on the piperazine ring with 3-methylbenzaldehyde. The synthesis yields the racemate. For pharmaceutical applications, the compound is converted to dihydrochloride. Meclozine is used to treat nausea and vomiting, especially motion sickness and pregnancy vomiting. Its safety for use during pregnancy is well established; it is even considered the drug of choice for pregnancy vomiting. Alternatives include doxylamine. Meclozine acts by competitive inhibition at histamine H1 receptors. Because it is a first-generation antihistamine that crosses the blood-brain barrier, it not only has an antiemetic effect but also makes patients drowsy.

Discussion

Achondroplasia is a genetic disorder characterized by short stature due to abnormal bone growth. It is caused by mutations in the FGFR3 gene, which leads to dysregulation of bone development. The prevalence of achondroplasia is relatively low, affecting about one in every 26,000-28,000 live births. While some cases are inherited, the majority are due to spontaneous mutations. The specific mutation in the FGFR3 gene that causes achondroplasia is a substitution of glycine with arginine at codon 380. This mutation disrupts the normal process of bone formation, resulting in disproportionate short stature. Interestingly, this region of the gene has a significantly higher mutation rate compared to other regions of the human genome. Therapeutic strategies for achondroplasia aim to decrease the excessive signals and impulses from the FGFR3 gene. Several approaches have been studied, including the use of C-Type Natriuretic Peptide (CNP), FGFR3-binding peptides, soluble FGFR3, meclizine, statin, and FGFR inhibitors. These treatments have shown promising results in cell and animal models, with some increasing bone length. One potential therapy for achondroplasia is the use of a stable form of CNP called vosoritide or BMN-111. CNP can attenuate the signals activated by FGFR3, leading to increased growth velocity. Clinical trials have shown positive effects of vosoritide on growth in patients with achondroplasia. However, the treatment requires subcutaneous injections and may need to be administered for an extended period of time. Another therapeutic strategy is to target FGFR3 with a Tyrosine Kinase Inhibitor (TKI). These inhibitors have been investigated for FGFR3-driven cancers and could potentially be repurposed for the treatment of achondroplasia. However, current FGFR inhibitors are not specific to FGFR3 and inhibit all FGFRs.

In conclusion, achondroplasia is a genetic disorder characterized by short stature due to abnormal bone growth. The disease is caused by mutations in the FGFR3 gene, and therapeutic strategies aim to decrease excessive FGFR3 signals. Promising treatments include stable CNP and FGFR inhibitors, although further research is needed to develop more specific inhibitors for FGFR3. The research on finding a cure for achondroplasia is being conducted by teams worldwide, with investigations into rhGH and vosoritide being the most advanced. However, even if these treatments are approved for widespread use, they will not cure all the symptoms associated with achondroplasia. Important aspects such as disproportionality, the axial skeleton, and the foramen magnum have not been confirmed to be affected by these treatments. These aspects pose further complications in the daily lives of achondroplasia patients. The ideal drug for achondroplasia should be small in size, specific for FGFR3, and effectively inhibit its signaling pathway. It should also have low production costs, be easy to administer to pediatric patients, and minimize side effects. Currently, recombinant human growth hormone meets these criteria, and vosoritide may potentially meet them in the future. Other drugs are still in the early stages of clinical trials. Treating achondroplasia in childhood is crucial as some organs are still developing, and long-term treatment is often necessary. However, this therapy is costly and compliance-dependent, and it does not provide a cure for the condition.

Moreover, Achondroplasia is caused by a specific mutation in the fibroblast growth factor receptor gene FGFR-3. This gene is located on chromosome 4p 16.3. In 96% of cases, there is a specific G (1138) A point mutation in the FGFR-3 gene. Future research must focus on gene editing therapies like CRISP-CAS 9 endonuclease therapy in early life to correct the gene defect in a one-time approach. Then, no long-life therapy with targets like vosoritide and others are necessary.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

Acknowledgement

SB wrote the article, LB made suggestions and corrections of the references, GV checked the information details and references, EL worked-on manuscript, and EMA checked the references in detail.

Conflict of Interest

None.

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