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Fibrodysplasia ossificans progressiva: a comprehensive review

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ABSTRACT

Fibrodysplasia ossificans progressiva (FOP) is a rare genetic disorder that causes heterotopic ossification of soft tissues, leading to abnormal bone growth in muscles, tendons, and ligaments. First identified in the 17th century, FOP was classified in 1968 and is linked to a mutation in the Activin A receptor type I gene (ACVR1) which affects bone morphogenetic protein (BMP). The autosomal dominant condition FOP has the potential to lead to aberrant bone development. At birth, FOP individuals appear normal, except for characteristic malformations of the great toes. FOP patients develop painful, inflammatory soft tissue swellings during the first decade of life, often precipitated by soft tissue injury. Minor trauma can trigger new flare-ups and leads to progressive heterotopic ossification. Most FOP sufferers are wheelchair-bound by their third decade and needs lifelong assistance with daily living tasks. Bone morphogenetic proteins (BMPs) are bound by the transmembrane kinase receptor ALK2, which is encoded by the (ACVR1/ALK2 gene). FOPs induce heterotopic bone formation in skeletal muscle and can be caused by mutations in the activin A receptor type I (ACVR1) and activin-like kinase 2 (ALK2) gene. Clinical therapy focuses on preventing and controlling inflammation, with ongoing research focusing on specific therapies targeting receptor activity, aberrant pathways, or cellular components influencing bone neo-formation.

Keywords: Fibrodysplasia ossificans progressive, Heterotopic ossification, Bone morphogenetic protein, Activin A receptor type I gene, Activin like kinase 2

INTRODUCTION

Fibrodysplasia ossificans progressiva (FOP) is a rare hereditary disorder which causes heterotopic ossification of delicate tissues and leads to irregular bone development in muscles, ligaments, and tendons. The other names are munchmeyer's disease, stoneman's disease, myositis ossificans progressiva. A mutation in the Activin A receptor type I gene (ACVR1 gene), which impacts bone morphogenetic protein (BMP), triggers signaling, and results in the aberrant bone growth therefore it is associated with FOP.[1] Fibroid dysplasia ossificans progressiva (FOP) is one kind of autosomal dominant disorder. In FOP, the tissues are not formed by mineralized calcium phosphate in the patient, but it resembles the new bone formation by osteoblast cells through the cartilaginous template known as endochondral ossification and also the same process is observed in the normal skeletal tissues during embryonic development and regeneration.[2,5] Most people with fibrodysplasia ossificans progressive are able to move their joints normally when they are born, but later on, several joints become disabled. After reaching above 30 years, the heterotopic bones are gradually fused resulting in the formation of a bridge with the normal bone.[2] At birth, FOP sufferers appear normal, with the exception of the distinctive deformities of the great toes that are evident in all traditionally affected persons. The sporadic episode of painful soft tissue swellings such as flare-ups occurs during the first decade of life and are often precipitated by soft tissue injury.

New flare-ups of FOP and the development of progressive heterotopic ossification (HO) can be brought on by mild trauma from intramuscular vaccinations, muscle exhaustion, mandibular blocks for dental work, blunt muscle trauma, bruising, falls, bumps, or influenza-like viral infections.[3]

As the second decade of life comes to an end, the majority of patients are wheelchair-bound and experience greater immobility.4 Most patients are immobilized in a standing position or permanently in a wheelchair in the third decade of life and need lifelong assistance with activities of daily living. The estimated period of lifespan is 56 years and death often results due to the complications of thoracic insufficiency syndrome. Heterozygous missense mutations have been identified in all affected patients like activin receptor A, type I (ACVR1) and bone morphogenetic protein (BMP) type I receptors. The standard-of-care medical management is based on the prevention of complications and is supportive currently. However definitive cures and treatments are not available yet.[3]

Classic FOP is caused due to the recurrent activating mutation (617G>A; R206H) in the gene ACVR1/ALK2 encoding Activin A receptor type I/Activin-like kinase 2, a bone morphogenetic protein (BMP) type I receptor.[4] The heterotopic ossification was initially challenging for a significant period. FOP was diagnosed since there were no trustworthy biomarkers for the illness that could be found in peripheral blood or urine. It is making it difficult to determine the molecular pathways underlying the pathogenesis reported in FOP patients. Because the tissue samples were inaccessible, so invasive procedures were contraindicated. BMP was originally found in the year of 1965 and found as a unique molecule in the bone matrix that induces heterotopic bone to develop in the skeletal muscle.

The ACVR1/ALK2 gene encodes a receptor of transmembrane kinase, ALK2 and binds to the bone morphogenetic proteins (BMPs). The ACVR1/ALK2 gene is linked to the BMP and FOP, hence research fields are sporadic and inherited cases of FOP. 5 BMPs are extracellular ligands from the TGFβ superfamily, that interact with type I and type II transmembrane serine/threonine kinase BMP receptors to exert their effects. Four type I receptors (ALK1(ACVR1), ALK3(BMPR1), ALK6(BMPR1B), and ALK1(ACVR1L)) and three type II receptors (ACTR2A, ACTR2B, and BMPR2) enhance the signal transduction.

The type II receptor phosphorylates the type I receptor GS domain. This promotes the activating of the protein kinase domain response and triggers downstream signal transduction by phosphorylating components of the mitogen-activated protein kinase (MAPK) pathway and BMP-specific Smads (Smad1, Smad5, and Smad8) to regulate the gene transcription. The ALK2R206H mutation in FOP alters interactions with FKBP12 leading to destabilization of tertiary protein structure.[6] The International Fibrodysplasia Ossificans Progressiva Clinic at the University of Pennsylvania from 1973 to 2006 and the International Fibrodysplasia Ossificans Progressiva Association (IFOPA) from 1988 to 2006 analyzed the complete mortality statistics.

Medical records were examined to determine each person's sex, date of birth, death and its cause of death. Thirty male and thirty female patients died throughout the course of the 33-year period from 1973 to 2006; these individuals belonged to the fibrodysplasia ossificans progressiva group. The median age of all sixty patients was forty years of age at the time of death (over 3 to 77 years). When including data from living individuals (as of January 2006) in the IFOPA membership list, the median estimated lifespan was found to be 56 years (95% confidence interval 51 to 60 years).

The most frequent causes of mortality for patients with FOP were pneumonia (15%, median age of 40 years) and cardiorespiratory failure due to thoracic insufficiency syndrome (54%, median age of 42 years).[9] All patients had a confirmed fibrodysplasia ossificans progressiva history, characterized by congenital malformations of the great toes and progressive heterotopic ossification in characteristic anatomic patterns. Additionally, patients with FOP have shortened thumbs, modifications of the cervical spine, short, broad femoral necks, distal femora, and proximal medial tibial osteochondromas.[9,10]

HISTORICAL BACKGROUND OF FOP

FOP cases may have existed in antiquity. It was first found in the 17th century and categorized in 1968. It was reported by French physician Guy Patin in 1692. Over 250 years ago, the London physician also provided a detailed description of FOP. In the 20th century, the modern understanding of FOP began to take shape. In 1938, Dr. R. Adams provided a thorough explanation of the illness, it was not until the late 20th and early 21st centuries that significant genetic insights were gained. In 2006, researchers identified the specific genetic mutation in the ACVR1 gene responsible for FOP.[7,8]

London physician John Freke of Saint Bartholomew's Hospital wrote to The Royal Society of Medicine on April 14, 1736, and it was published in 1740. A 14-year-old boy with a healthy appearance visited the hospital to treat swellings on his back, which have grown in the past three years ago, specifically on the left side. These swellings originating from the neck, vertebrae and ribs, form a fixed pair of bone bodices in his back.[8]

EPIDEMIOLOGY OF FOP

Fibrodysplasia ossificans progressiva, the most severe and debilitating extra skeletal ossification disorder in humans is a genetic disorder characterized by progressive heterotopic ossification followed by certain anatomic

patterns and congenital abnormalities of the big toe. The global prevalence of this condition is approximately one in two million individuals. There is no ethnic, racial, gender, or geographic predisposition.[11-13] The true prevalence of Fop can be evaluated, and recent study information shows the prevalence gets higher than the already mentioned 0.5 per million.

The highly unusual characteristics of FOP and the wide range of diseases make it difficult to measure prevalence. There was a significantly different region in the prevalence of FOP patients who were both registered and confirmed. It was found that the disease was prevalent in North America at 0.65 per million, Western Europe at 0.47 per million, Latin America at 0.27 per million, and Africa at 0.05 per million. The study by Connor and Evans was published in 1982 observed 44 patients with FOP and estimated the prevalence to be 0.61 per million people in the UK.

The study focused on a survey of relevant physician specializations and used multimethod case ascertainment. According to a 2017 study by Baujat et al, which found 89 patients with FOP on January 1, 2012, the prevalence of FOP in France is 1.36 (95% confidence interval 1.1 to 1.7) per million persons, which is more than twice as high as the study from 1982. The Baujat study's reported prevalence of FOP in France is believed to be close to but still lower than the true biological prevalence.[10]

It has been demonstrated that fibrodysplasia ossificans progressiva displays phenotypic variability, with the disease's phenotype being influenced by both hereditary and environmental variables. Three sets of monozygotic twins were examined, and it was found that all three sets had the same congenital toe abnormalities. However, the postnatal heterotopic ossification varied considerably depending on life history, environmental exposure to viral infections, and soft tissue trauma.

The Genetic determinants greatly influence of disease phenotype during prenatal development while environmental factors greatly influence postnatal progression of heterotopic ossification. Misdiagnosis involving fibrodysplasia ossificans progressiva are common. The majority of patients receive misdiagnosis before heterotopic ossification developing, and they are exposed to unnecessary diagnostic and treatment procedures that affect the disease's normal development and cause irreversible damage.

Fibrodysplasia ossificans progressiva's genetic cause has recently been found and providing the hope to improve the management of the condition. After the identification of a link between chromosomal region 2q23–24 and fibrodysplasia ossificans progressive. A recurrent mutation in the gene encoding activin A receptor type I (ACVR1), a BMP type I receptor, has been identified as the cause of all classically occurring inherited and sporadic cases.[11,12] There's ongoing research into understanding FOP better and developing potential treatments.

CLASSIC CLINICAL FEATURES OF FOP

Two clinical features define classic FOP: The deformities of the great toes and the typical anatomic patterns of increasing heterotopic ossification (HO). At birth, FOP sufferers appear normal, With the exception of the distinctive deformities of the great toes that are evident in all traditionally affected persons. During the first decade of life, Children with FOP develop frontotemporal palsy and experience painful, highly inflammatory soft tissue.

These swellings include skeletal muscles, ligaments, tendons, fascia, and aponeuroses, which form an armament-like surround of bone. These swellings are referred to as flare-ups. Minor trauma includes muscle weakness, intramuscular immunizations mandibular blocks for dental work and sharp muscle trauma from bumps, bruising, falls, influenza-like illness can trigger the painful new flare-ups of FOP that proceed to progressive HO. Whenever heterotopic bone is surgically removed to cause painful and rapidly growth of new bone is frequently the outcome.[8,13,17]

In typical conditions, the morphological and chronological progression of HO in FOP mimics the pattern of typical embryonic skeletal development. The ventral, appendicular, caudal, and distal regions are usually affected by FOP. In addition to the dorsal, axial, cranial, and proximal regions of the body. The tongue, diaphragm, and extra-ocular muscles are among the skeletal muscles that are mysteriously spared from FOP. There is no cardiac or smooth muscle involved in the FOP process.[8]

All patients with classic FOP have abnormalities in their big toes. Screening skeletal surveys can detect the variable joint abnormalities. The Congenital cervical spine abnormalities can cause the mild mobility restrictions in infants even prior to the development of heterotopic ossification. Although the majority of newborns with FOP movements are normal but very few functional abnormalities only for noted.[14,15] By the third decade of life, the majority of FOP sufferers are confined to wheelchairs and need lifetime assistance with everyday living tasks. Significant weight loss due to ankylosis of the jaw may occur, and rigid fixation of the chest wall may be more challenging in cases of pneumonia or right-sided heart failure. The complications from thoracic insufficiency syndrome (TIS) are a common cause of mortality, with a median age of survival of about 45 years.[8,17]

Fibrodysplasia ossificans progressiva (FOP) is typified by early-onset heterotopic ossification and congenital bilateral hallux valgus deformities. The latter may arise spontaneously or be triggered by trauma, such as intramuscular immunizations. It has been reported that over 800 individuals had over 20 harmful mutations in

ACVR1. These observations, along with reports of the characteristic FOP phenotype in people without molecular genetic testing, provide as the basis for the phenotypic traits associated with this disorder can be described below.

Bilateral congenital hallux valgus malformations are common, affecting more than 97% of individuals. The Hallux valgus malformations are present from birth and identifiable on prenatal imaging, include short metatarsals, monophalangisms, and delta-shaped dysplastic proximal phalanxes, often bilateral but can be unilateral or absent in some cases. It contains a 100% of individuals with common c.617G>A variant and classic phenotype, often present as the first clinical feature.

Heterotopic ossification the condition affecting approximately 100% of the individuals, is age-dependent and episodic, potentially triggered by soft-tissue injury, including vaccinations. An abnormal bone formation in soft connective tissues is formed the condition is extraosseous bone formation, and it frequently appears as a hard lump or mass. Heterotopic ossification, a type of bone formation, can occur spontaneously or due to soft-tissue trauma. It can affect areas near the axial skeleton, affecting joint mobility and swallowing. Ossification can also impact the airway and respiratory function, leading to thoracic insufficiency syndrome, a leading cause of mortality. It may be misdiagnosed as tumors or isolated osteochondromas.

Inflammatory soft-tissue swellings, which can be spontaneous or triggered by trauma, follow an injury can occur approximately 100% of individuals. Scalp nodules are, large, firm, immobile, and tender, appear in 40% of neonates and infants, often regressing spontaneously without treatment, possibly a localized manifestation of soft-tissue swellings.

Other skeletal abnormalities like, Osteochondromas occur in ~90% of individuals, cervical spine fusions, can cause mobility limitations can affect ~80% of individuals. Short broad femoral neck occurs ~70% of individuals. Scoliosis: About 65% of people have scoliosis, which may aggravate thoracic insufficiency syndrome. Variable thumb malformations, such as hypoplasia and dysplastic phalanges, can affect ~50% individuals. Distal limb reduction defects can affect <3% of individuals.[16] FOP often leads to skeletal abnormalities such as short thumb malformations, temporomandibular joint malformations, osteochondromas, and asymmetric fusions of costovertebral and costotransverse joints.

ETIOPATHOGESIS OF FOP

The ACVR1/ALK2 gene plays a crucial role in both the development of the embryo's skeleton and its subsequent repair after birth. A recurrent mutation in the ACVR1/ALK2 gene, which is located on chromosome 2, is the characteristic of the monogenic condition fibrodysplasia ossificans progressiva. This mutation can impact the BMP (bone morphogenetic proteins) signaling system in both inherited and spontaneous cases. These FOPs cause the production of heterotopic bones in the skeletal muscle. The genetic mutation responsible for the majority of cases of typical fibrodysplasia ossificans progressiva is a nucleotide modification in the codon of the ACVR1/ALK2 gene at position 617 (guanine->adenine). It causes a substitution mutation in the codon of ALK2 proteins at position 206 (arginine->histidine). Some additional mutations in exons 4-7 of the ACVR1/ALK2 gene alter the expression of two domins including, Ser/Thr kinase and glycine/serine-rich domains, are crucial for intracellular signaling are the BMP receptors.2 Four type I receptors (ALK2 (ACVR1), ALK3 (BMPR1A), ALK6 (BMPR1B), and ALK1 (ACVR1L) and three type II receptors (ACTR2A, ACTR2B, and BMPR2) facilitate signal transduction.

In recent years, knowledge of the pathophysiology of FOP has grown considerably, FOP is a condition characterized by mutations of gene encoding the ACVR1 / ALK2 and bone morphogenetic protein (BMP) type I receptor. Particularly after the causative missense mutations (617G>A, R206H) in the GS or protein kinase domains of the ACVR1/ALK2 gene were discovered. These are autosomal dominant; 97% of FOP cases are frequently caused by a de novo mutation. The mutation enhances the function of the activin receptor type 1 /activin receptor-like kinase 2, making it sensitive to activin A, hypersensitive to BMP-ligands and “leaky signaling” in absence of stimulation.[18]

Few patients with rare mutations in the same gene exhibits unusual clinical features for FOP (variant/ atypical phenotype) ranging from notably greater or lesser severity of great toe malformations. In vivo, BMPs trigger heterotopic bone development in skeletal muscle, and in vitro, they trigger the differentiation process that myoblasts use to change into osteoblastic cells. BMP receptors (BMPR) are part of the TGF-β superfamily.[20] Type I (BMPR-I) and type II (BMPR-II) receptors combine to form heteromeric receptor complexes that are activated by BMP signaling. The BMPR-II activates the BMPR-I by trans phosphorylating their GS domain, the mechanism starts an intracellular signaling cascade through the phosphorylating SMAD proteins.

It's possible that the mutant ACVR1 receptor is active, which would cause abnormal signaling through the kinase receptor and excessive stimulation of the SMAD1/5/8 signaling pathway downstream to cause the activating transcription factors can lead to heterotopic bone formation and exacerbated by inflammation and hypoxia which involves HIF, mast cells, and inflammatory factors. Furthermore, mutations appear to change the ACVR1 receptor's signaling selectivity. Both the non-osteogenic ligand Activin A and BMP ligands enable the mutant receptor to exhibit hyperresponsive. When activin A binds to a mutant ACVR1 receptor, it can initiate signaling through the SMAD1/5/8 pathway; however, when it

attaches to wild type ACVR1 receptors, SMAD signaling is not initiated. The dysregulation of the BMP signaling system is believed to initiate ectopic chondrogenesis, osteogenesis, and joint fusion of FOP. Most of the ACVR1 mutations that have been evaluated to improve the BMP signaling are gain-of-function variants.[12,18,19]

DIAGNOSIS

There are no formal diagnostic criteria for FOP. Proband with heterotopic ossification and hallux deformities was suspected to have diagnosis of FOP and confirmed to detect the heterozygous pathogenic mutation in the ACVR1/ALK2 gene. However, the FOP should be suspected in individuals are exhibit any of the following radiological and clinical characteristics should be congenital hallux valgus deformity, progressive heterotopic ossification, and painful, scalp nodules in infancy due to recurrent soft-tissue swelling (flare-ups), and soft tissue trauma.

This condition should keep in mind that a lack of suspicion can leads to delayed or misdiagnosed conditions, potentially causing inappropriate and unnecessary testing and invasive biopsy to cause flare-ups can trigger HO, permanent harm, and lifelong disability in 50% of cases. Differential diagnosis for FOP lacking hallux malformations includes Hereditary multiple osteochondromas (HMO), progressive osseous heteroplasia (POH), metachondromatosis (METCDS), and brachydactyly type B1 (BDB1), with hallux anomalies potentially representing isolated congenital malformations or tumor-like swellings.

Imaging can be helpful in diagnosing FOP, but it must be appropriately. The simple radiographs are used to identify heterotopic ossification and skeletal anomalies only. Computed tomography (CT), magnetic resonance imaging (MRI) and Positron Emission Tomography (PET) scans of early lesions have been described. Magnetic resonance imaging (MRI) can detect pre-osseous inflammatory lesions in the muscle, avoiding the further tests (such as biopsy), leads to the accurate genetic diagnosis, and potentially recommended for particular treatment interventions.

MRI studies reveal CNS anomalies such as structural malformations, demyelinated lesions, or focal inflammatory changes, which have been underexplored in previous research. The 3D computerized tomography (CT) reconstruction showed multifocal ossification on soft tissue including right pectoral muscle, bilateral latissimus dorsi, and left longisimus thoracic muscle. An MRI and CT scan reveal similar results, with no additional spine abnormalities found.[28] However, the radiological and biochemical tests are used to provide valuable information into the disease process, DNA sequence analysis ultimately can provide to confirm a diagnosis by identifying the underlying mutation.[21] Genetic testing confirms the diagnosis of FOP. When child or adult presents with soft-tissue swellings, deformed great toes, and heterotopic ossification can exhibit the same mutation in the ACVR1/ALK2 gene. The ACVR1 protein involved in bone growth and development is crucial for bone healing and embryonic skeleton development. Even though there aren't any recognized therapies for FOP at the moment, it's crucial to identify the condition early on and get treated to avoid needless trauma like intramuscular vaccinations or surgeries that could cause the condition to flare up.[22]

PREVENTION OF FLARE-UPS

Experts recommend to avoiding the blunt muscle trauma, muscle fatigue, and stretching joints to prevent flare-ups. High-risk activities like running, bicycling, and contact sports should be avoided, while individualized lifestyle plans should be considered based on age, mobility, and cultural norms. In case of clinically significant impact injuries, oral prednisone should be administered is possible to prevent flare-ups. Experts agreed that a short (3-4 day) treatment of oral corticosteroids (prednisone at 2 mg/kg/day), initiated within the first 24 hours after significant trauma, had an acceptable preventive effect, even in the absence of strict clinical evidence.

A course of oral steroids before and after significant dental work or surgery could have a good preventive effect because these procedures are high-risk triggers for flare-ups. Patients with FOP should avoid intramuscular injections as they may trigger flare-ups and develop heterotopic ossification at the injection site. To prevent the flare-ups administered vaccine for subcutaneous route only and all expert agreed for no immunization should be administered during flare-ups. The FOP Treatment Guidelines advise physician discretion in using medications to control disease symptoms in individual patients and despite disagreements about chronic treatment with existing medication such as NSAIDS.[23]

MANAGEMENT

Clinical therapy

It is based on the prevention and control of inflammation, since tissue injury and subsequent inflammation leads to trigger the HO. But it can be very challenging to prevent a triggering event because they can vary widely in nature, from little events such as intramuscular injections to serious trauma such as knocks, bruising, falls, influenza-like infections, and simple muscle tiredness (Kaplan et al). How each of these events influence HO is not fully understood, mainly because they remain unnoticed until a flare-up occurs. Nonetheless, since inflammation always follows a trigger, the major goal of clinical therapy is to reduce inflammation in order to reduce symptoms. Currently the proper treatment for FOP does not exist. According to Kaplan et al, categorize pharmacological agents for managing FOP into three classes.

Class I medication to manage the acute inflammation of flare-ups. These including corticosteroid and nonsteroidal anti-inflammatory drugs. Prednisolone is a potent corticosteroid activates the glucocorticoid receptor, decreasing inflammatory mediator recruitment, inhibit vasodilation and increasing vascular permeability during inflammation, the medication is highly effective against the initial inflammatory response, especially when administered within 24 hours of flare-up onset and upto 4 days, should be considered the systemic side effects. Furthermore, NSAIDs like ibuprofen and indomethacin block the production of prostaglandin, which is what causes pain, inflammation, and fever. They have analgesic, anti-inflammatory, and antipyretic properties and other NSAIDS like Celecoxib specifically inhibits COX-2, but should be used cautiously. The NSAIDS should be taken after discontinuing the corticosteroid medication.

Class II medication, although these medications can theoretically be used to treat FOP, there is currently little data to support their usage. Montelukast is a leucotriene receptor antagonist, is used for asthma treatment and has complementary action to COX inhibitors and prolonged use the drug needed to achieve therapeutic effects. Cromolyn, a mast cell stabilizer, to prevent the histamine and related mediators and normally used for allergies and may be used to prevent inflammation of FOP. Imatinib, a selective thyrosine kinase inhibitor, inhibits HIF1-α, PDGFRα, c-KIT and induces mast cell apoptosis and is a potent chemotherapy agent. Pamidronate is a amino bisphosphonates group to produce the immunomodulating effects and affecting the bone mineralization, and suppressing calcification at high doses, but not suitable for renal dysfunction or hypocalcaemia and decrease bone density.[24]

Class III medication, which are currently under clinical investigation for effective treatment. These drugs target both extracellular and intracellular for BMP signalling from ACVR1R206H gene. Mammalian target of rapamycin (mTOR) inhibitors to block the non-canonical ACVR1 signal transduction in chondrocytes. Under phase II clinical trial, Monoclonal antibody against activin A REGN 2477(Garetosmab), under phase III clinical trial. Retinoic acid receptor gamma (RARγ) agonists Palovarotene to inhibits downstream SMAD signalling, promotes SMAD destruction and prevents chondrogenesis, under phase III clinical trial.[24,26]

Some more pre-clinical strategies to prevent mutant ACVR1-dependent bone induction include the use of nucleic acid-based inhibitors, exon-skipping oligonucleotides or allele-specific RNA interference, BMP receptor kinase inhibitors like dorsomorphin, downstream BMP signaling inhibitors like Fendiline and Perhexiline, and inhibitors of fungal metabolites that promote osteoblast differentiation, like NG-391, NG-393, and trichocyalide A/B.[24] FOP lacks an etiologic treatment, but ongoing research focuses on specific therapies targeting receptor activity, aberrant pathways, or cellular components influencing bone neo-formation.[27] Surgical therapy aimed at enhancing the patient's range of movement has been found to induce further ossification. The same patient were local recurrences detected at four months after surgery.

Four months following surgery, local recurrences were found in the same patient. Medications like leukotriene inhibitors and new drugs may show promise. Early clinical diagnosis and patient education are crucial for therapy prevention. surgical release is unsuccessful because induced by new trauma. For FOP patients, radiation therapy may be explored as a postoperative measure to prevent recurrence, however its efficacy is not well documented.[28]

Physical therapy to prevent muscle atrophy due to mobility limitations and light physical activity reduce the risk of muscle trauma or stretching (swimming) that allows patients to perform active range of motion exercise is recommended, while traditional physiotherapy should be avoided due to over-stretching and soft tissue injuries. Occupational therapy is used to help FOP patients have better lives and enhance their everyday activities.[23,25]

Gene therapy

CRISPR-Cas9

The CRISPR-Cas9 system is being explored as a potential treatment for FOP, specifically by editing the ACVR1 gene. This gene-editing tool allows for precise DNA sequence alteration, potentially stopping bone growth associated with FOP. The system consists of a guide RNA molecule and a Cas9 enzyme, allowing specific changes in living cell genomes.[29,30]

RNA interference therapy

It is alternative gene therapy the researchers are exploring the use of RNA interference (RNAi). One biological mechanism that regulates gene expression is called RNA interference (RNAi), and it helps to prevent the expression of the mutant ACVR1 gene in FOP. By decreasing the production of the mutant ACVR1 protein, this may prevent aberrant bone development.[30]

Adeno-associated virus vectors

Researchers are looking at using adeno-associated virus (AAV) vectors to deliver healthy ACVR1 genes to FOP-affected cells to stop the disease's progress. Then return normal bone formation. AAV vectors are safe, can infect both dividing and non-dividing cells. Most therapeutic genes can fit in a payload of up to 5 kilobases of DNA that AAV vectors can transport and offer minimal immunogenicity, prolonged expression, and broad tissue tropism, making them superior to other viral vectors.[30,31]

CONCLUSION

FOP is a rare and progressive condition that causes abnormal bone formation in soft tissues, severely impacting patients' lives. While current treatments are limited and mainly focus on managing symptoms, advances in genetic research and emerging gene therapies offer hope for future improvements in care. Continued research is crucial to developing effective treatment and improving the quality of life for individuals with FOP. This review mainly focuses on the disease (fibrodysplasia-ossificans progressiva) including clinical manifestations, etiopathogenesis, diagnosis, prevention and different treatment options. These techniques are used in clinical settings including pharmacological management and gene therapy.

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