

Fibrodysplasia Ossificans Progressiva: Genetic Basis, Clinical Features, And Treatment

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Abstract:

Fibrodysplasia ossificans progressiva (FOP) is an uncommon but serious genetic disorder in which soft tissues such as muscles, tendons, and other connective tissues are progressively transformed into bone. A mutation in the ACVR1 gene, which encodes a bone morphogenetic protein (BMP) receptor necessary for the normal development and growth of bone, causes FOP. FOP typically begins to show signs and symptoms during early childhood, with episodes of accelerated bone development due to inflammation, minor trauma, or stress. As the disease progresses, individuals with FOP develop extensive heterotopic ossification, resulting in joint fusion and ultimately loss of mobility. Commonly affected joints include the knees, hips, shoulders, and spine, leading to severe disability and respiratory problems. Currently, there is no proven or effective treatment for FOP, and medical care is focused on managing pain and preventing complications. However, studies aimed at improving the understanding of how FOP develops at the molecular level have led to new avenues for potential therapies, including gene-based therapies and small-molecule inhibitors targeting the ACVR1 receptor.

Keywords: Fibrodysplasia ossificans progressiva, ACVR1 mutation, Heterotopic ossification, Bone morphogenetic proteins, Rare genetic disorder

I. INTRODUCTION:

Fibrodysplasia ossificans progressiva (FOP) is a genetic disorder that causes progressive disability due to ongoing heterotopic ossification; this is the process of bone forming in connective tissue that should otherwise be replaced with new muscle, tendon, or ligament. As soft tissue continues to become bone, the body becomes restricted in movement through the development of skeletal deformities and a decrease in overall quality of life. FOP is primarily caused by mutations in the ACVR1

gene that lead to unusual activation of BMP signaling pathways, which result in improper formation of bone in soft tissue, mostly in response to relatively minor injuries, inflammatory changes, or viral infections. Despite advances in our understanding of FOP's genetic and molecular basis, no definitive cure currently exists. Therefore, current treatment focuses on symptom management and prevention of flare-ups. Ongoing research aims to identify targeted therapies. This article reviews and summarizes the genetic basis, molecular mechanisms, clinical presentation, and current treatment modalities of fibrodysplasia ossificans progressiva.

Pathophysiology and Disease Progression:

Fibrodysplasia ossificans progressiva (FOP) is a rare genetic disorder that may occur in association with bacterial and viral infections and is classified as an autosomal-dominant disorder.² FOP leads to irregular bone formation in tendons, muscles, and ligaments through heterotopic ossification, resulting in unusual bone growth at sites where bone normally forms through endochondral ossification (i.e., with cartilage used as a template).

FOP is a genetically based disorder caused by a mutation in the receptor for activin A in the ACVR1 gene, which alters bone morphogenetic protein (BMP) signaling. These proteins regulate growth and development, and their dysregulation creates an unusual environment in which muscles, tendons, and ligaments are replaced by bone, leading to joint immobility and skeletal deformities. The disorder causes structural and functional changes through a series of pathological processes: first through endochondral ossification, followed by dysregulated growth signals that result:

- (i) Malformed articulation of bones (bone formation at irregular joint sites),
- (ii) Abnormal calcification of muscle, and

- (iii) Disorganized connective tissue leading to restricted movement of affected limbs or joints.

There is no known cure for fibrodysplasia ossificans progressiva. While most patients remain relatively symptom-free in early life, many develop progressive limitations in mobility. After the age of 30, extensive heterotopic bone formation may lead to complete joint fusion.^{1,3,4,5}

Clinical Features, Flare-ups, and Disease Progression

Flare-ups of Fibrodysplasia Ossificans Progressiva (FOP) and the follow-up growth of heterotopic ossification (HO) can be caused by mild trauma related to intramuscular vaccinations, muscle fatigue, mandibular blocks for dental procedures, blunt muscle trauma, bruising, falls, bumps, and illnesses such as flu-like viral infections. The cause of classic forms of FOP is a recurrent activating mutation (617G>A; R206H) in the ACVR1/ALK2 gene, which is responsible for the type I BMP receptor Activin-like Kinase 2/Activin A receptor. While definitive information representing HO at this time had not been established, there were no known analytical markers for the disease in either peripheral blood or urine. Likewise, understanding the molecular pathways of the pathophysiology of FOP patients has become increasingly difficult. Accessing tissue samples from patients through invasive procedures has not been recommended to date. In 1965, BMP was first characterized and identified as a unique class of molecule within the bone matrix that stimulates the formation of heterotopic bone from skeletal muscle.⁶

The Bone Morphogenetic Proteins (BMP) and ALK2 as a transmembrane kinase have the closest direct link to Fibrodysplasia ossificans progressiva (FOP). There are either inherited or spontaneous cases of FOP; both types are being studied in the context of the ACVR1/ALK2 gene. There are also five type I BMP receptors and two type II BMP receptors that interact with BMP, which are extracellular ligands belonging to TGF β superfamily. The type II receptors are ACTR2A, ACTR2B, and BMPR2; the type I receptors are ALK1 (ACVR1), ALK3 (BMPR1), ALK6 (BMPR1B), and ALK1 (ACVR1L). These receptors allow for the regulation and improvement of signal transduction.⁸

The GS domain of type I receptor is phosphorylated by type II receptor. Phosphorylation of members of the mitogen-activated protein kinase (MAPK) pathway by type II receptor and BMP-

specific Smads (Smad1, Smad5, and Smad8) is the basis of gene transcription. Through these phosphorylation actions, type II receptor phosphorylation activates a protein kinase domain response, which initiates further downstream signal transduction. Changes in FKBP12 interactions caused by the mutation of ALK2R206H in patients with FOP destabilize tertiary protein configuration.⁹

The entirety of mortality information was examined by the International Fibrodysplasia Ossificans Progressiva Association (IFOPA) for the years 1988-2006 as well as from 1973-2006 by the International Fibrodysplasia Ossificans Progressiva Clinic at the University of Pennsylvania. For each individual, the sex, birthdate, the date of passing, and the cause of death were extracted from their medical records. During the 33-year interval from 1973-2006, 30 male & 30 female patients belonging to the cohort of patients with fibrodysplasia ossificans progressiva died. At the time of death, the median ages of all 60 patients ranged from 3 years to 77 years.¹⁰

Using the IFOPA membership list, on individuals still living (as of January 2006), the median estimated lifetime was 56 years (95% CI 51 to 60 years). The main underlying condition leading to death in patients with FOP was pneumonia (15%; median age at death 40 years) and heart and respiration failure (54%; median age at death 42 years) due to thoracic insufficiency syndrome.⁹ Each patient who died had a medical history that indicated they had fibrodysplasia ossificans progressiva as characterized by a history of progressive heterotopic ossification that follows a pattern across the skeleton, along with congenital deformity of the great toe. Many also had shorter, broader necks of the femur than are normal as well as osteochondromas of the proximal medial tibia, shortening of the thumbs, and abnormalities in the cervical spine.^{11,12}

EPIDEMIOLOGY OF FOP

Fibrodysplasia ossificans progressiva (FOP) is the most severe and life-altering extra-skeletal bone formation disorder. It is a hereditary disease characterized by progressive, extra-skeletal ossification. It affects an estimated 1 in 2 million people worldwide. This condition appears to have no known geographic, racial, gender or ethnic predisposition; therefore making it very difficult to get a true and accurate prevalence of the Condition.¹¹ The fact that the prevalence of this condition may be much greater than was initially thought (0.5/million) would indicate that this is

much more prevalent (yet still rare) than currently recorded.¹³ As there is such a large and varied group of similar conditions along with the fact that there are many unique and individual clinical expressions of this disorder, it is very challenging to estimate the number of people who have been diagnosed with FOP and as such are currently prevalent in the world.¹⁴ The range of confirmatory diagnosed patients with FOP, once registered, varies widely from region to region. In North America, the prevalence of FOP was found to be 0.65/million; in Western Europe, 0.47/million; in Latin America, 0.27/million; and in Africa, 0.05/million. The study by Connor and Evans in 1982 showed the prevalence of FOP in the UK to be 0.61/million among 44 patients diagnosed with the disorder.¹⁵

CLASSIC CLINICAL FEATURES OF FOP

Classic FOP is described by two clinical characteristics: (1) abnormality of the great toe, and (2) distinctive anatomical patterns of progressive heterotopic ossification (HO). FOP patients will appear normal at birth, except for the abnormalities of the great toes, which are present in all affected individuals (regardless of classification). Children with FOP will develop frontotemporal swelling and painful, highly inflamed soft tissues throughout their first decade of life.

Skeletal muscles, tendons, ligaments, fascia, and associated bone-like tissue structures comprise a protective casing surrounding the bones of the limb. A painful new Heterotopic Ossification (HO) flare-up may occur due to any of the following minor traumatic events: muscle weakness due to an intramuscular vaccine, "Mandibular block" associated with a dental procedure, and the sharp muscle trauma associated with

sudden impact (i.e., bump or fall, etc.), or due to a flu-like illness. A painful, rapid development of new HO from surgically removing previous HO usually occurs in individuals who have had surgery to remove strange bone growth from other parts.¹⁶

In FOP, the development of heterotopic ossification follows a path similar to normal skeletal development in embryos. FOP usually impacts the lower, far, front, and limb areas, along with the upper, rear, main, and back parts of the body. The skeletal muscles that remain unaffected by FOP include the tongue, diaphragm, and extraocular muscles. The FOP process does not involve smooth muscle or the heart. All patients with classic FOP show big toe anomalies. Joint abnormalities can vary and can be detected through skeletal surveys.

Even before heterotopic ossification occurs, newborns with congenital cervical spine issues may have moderate limits on their movements. Most neonates with FOP generally have typical movements, so only a few functional impairments are seen.¹⁷

Most FOP patients need assistance with daily living activities throughout their lives. By their thirties, they usually rely on wheelchairs. Jaw stiffness can lead to significant weight loss. Pneumonia or right-sided heart failure can also complicate the rigid fixation of the chest wall. With a median survival age of about 45 years, the consequences of thoracic insufficiency syndrome (TIS) are a major cause of death. Bilateral hallux valgus deformities and early-onset heterotopic ossification are typical features of fibrodysplasia ossificans progressiva (FOP).

Short metatarsals, monophalangism, and delta-shaped dysplastic proximal phalanges are hallux valgus abnormalities that are present at birth and can be detected on prenatal imaging. These conditions are usually bilateral, but they may sometimes be unilateral or absent. This finding is present in individuals with the classic phenotype and the common c.617G>A mutation, which often appears as the first clinical sign. Nearly all patients develop heterotopic ossification, an age-related, episodic disorder that may be triggered by vaccinations or other soft-tissue injuries.¹⁸

Extrasosseous bone formation refers to unusual bone development in soft connective tissues. It often appears as a hard lump or mass. One form, heterotopic ossification, can occur spontaneously or after soft-tissue damage. This condition may affect joint mobility and swallowing, especially near the axial skeleton. Thoracic insufficiency syndrome, a significant cause of death, may arise from the impact of ossification on the respiratory system and airways. It may be misdiagnosed as solitary osteochondromas or tumors. Nearly 100% of individuals may develop inflammatory soft-tissue swellings, which can result from trauma or occur spontaneously.¹⁹

Approximately 40% of newborns and infants develop large, firm, sensitive, immobile nodules on their scalps. These often resolve spontaneously without medical intervention and may indicate localized soft-tissue swelling. About 90% of individuals have other skeletal abnormalities, such as osteochondromas. Around 80% have cervical spine fusions, which can restrict their range of motion. A short, wide femoral neck is present in about 70% of individuals. Scoliosis

affects approximately 65% of adults and may worsen thoracic insufficiency syndrome. About half of the patients may have thumb abnormalities, such as hypoplasia and dysplastic phalanges.

MOLECULAR MECHANISM OF PATHOGENESIS IN FOP

In conjunction with type II receptors such as BMP receptor type II (BMPR-II), activin receptor type IIA (ActR-IIA), and activin receptor type IIB (ActR-IIB), the extracellular part of ALK2 (a type I receptor) binds to various ligands in the TGF- β

family, including BMP-6, BMP-7, BMP-9, and activin B. ALK2 is phosphorylated in a ternary complex that forms when ligands bind at the cell membrane because type II receptors are constitutively active Ser/Thr kinases. Research shows that type II receptors phosphorylate the GS domain, which consists of glycine and serine residues. Similar to Smad1, Smad5, and Smad8/9, phosphorylated ALK2 promotes kinase activity and phosphorylates serine residues along with other downstream substrates.²⁰

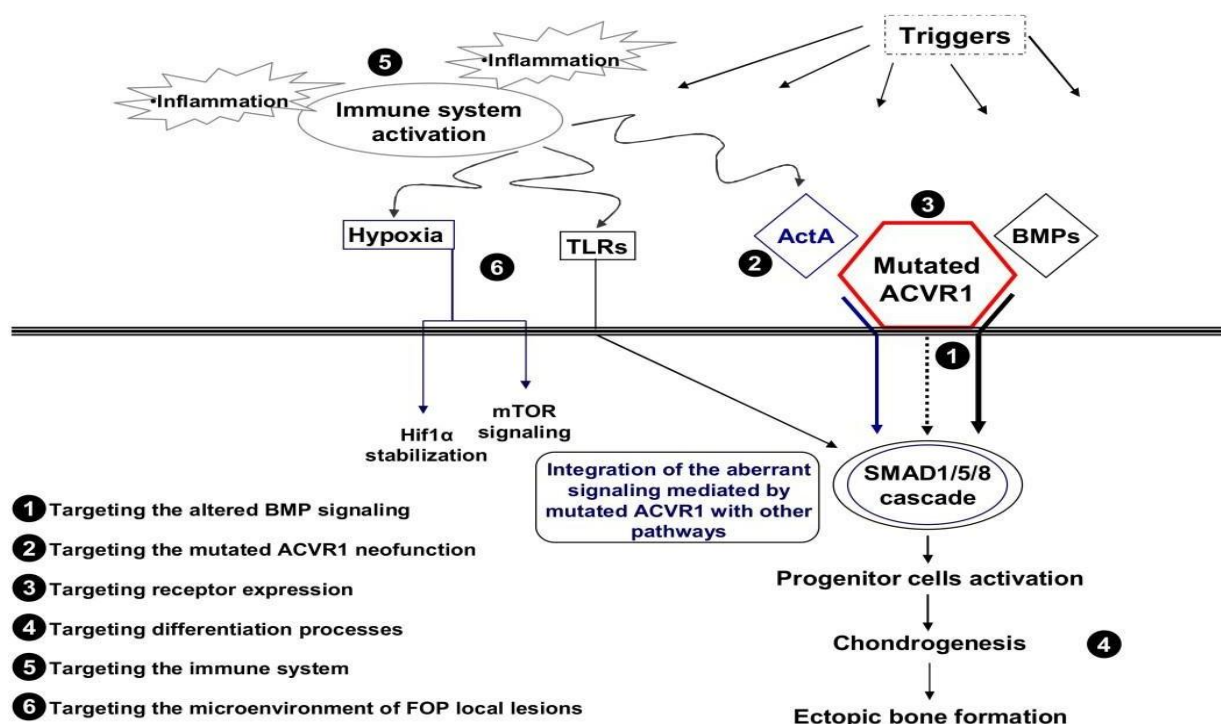


Figure 1: Molecular mechanism of FOP

Target gene transcription is controlled by phosphorylated Smad proteins in the nucleus. Without the addition of exogenous ligands, overexpression of the mutant ALK2 linked to FOP triggers intracellular signaling, whereas wild-type ALK2 does not. This indicates that these are gain-of-function changes. The kinase activity of the type II receptors makes the mutant ALK2 more sensitive.

The 12 kDa FK506-binding protein, FKBP12, attaches to the unphosphorylated regions of type I receptors in the TGF- β family, including ALK2, and represses their kinase activity. Mutations in the intracellular regions of ALK2 may lower the binding affinity to FKBP12 and, in some cases, trigger downstream intracellular signaling.

One of the ALK2 mutants, delP197_F198insL, resists suppression by FKBP12 because it loses the interaction site for FKBP12. However, when the mutant ALK2 and FKBP12 are coexpressed in vitro, intracellular signaling by ALK2 decreases. The clinical characteristics of a patient with the delP197_F198insL mutation appear similar to those observed in typical FOP cases, if not more severe.²¹

ETIOLOGIES OF FOP

Fibrodysplasia ossificans progressiva is a genetic disorder caused by a recurrent mutation in the ACVR1/ALK2 gene on chromosome 2. This mutation can occur through inheritance or

spontaneously. It affects the bone morphogenetic protein (BMP) signaling pathway.²¹

Skeletal muscle forms unusual bone due to these changes in fibrodysplasia ossificans progressiva (FOP). Most cases arise from a specific nucleotide change in the ACVR1/ALK2 gene at position 617 (guanine to adenine). This leads to a substitution at position 206 (arginine to histidine) in the ALK2 protein. Other mutations in exons 4 to 7 of the ACVR1/ALK2 gene alter the expression of BMP receptors and kinase domains, which are vital for cell signaling. Signal transduction involves three type II receptors (ACTR2A, ACTR2B, and BMPR2) and four type I receptors (ALK2 (ACVR1), ALK3 (BMPR1A), ALK6 (BMPR1B), and ALK1 (ACVR1L)).

Recent years have provided greater insight into the underlying mechanisms of FOP. Mutations in the ACVR1/ALK2 gene and BMP type I receptors are involved in the condition. This understanding has improved, especially after identifying the critical missense mutation (617G>A, R206H) in the GS or kinase domain of the ACVR1/ALK2 gene. These mutations are inherited in an autosomal-dominant manner, while new mutations account for about 97% of FOP cases. The mutation increases the sensitivity of activin receptor type 1/activin receptor-like kinase 2 to activin A, decreases its sensitivity to BMP ligands, and allows unwanted signaling without stimulation.

Unique clinical characteristics of variant or atypical FOP phenotypes include more or less severe great toe deformities. BMPs cause skeletal muscle to form heterotopic bone in vivo and also induce myoblasts to differentiate into osteoblastic cells in vitro. BMP receptors (BMPRs) belong to the TGF- β superfamily. BMP signaling activates heteromeric receptor complexes composed of type I (BMPR-I) and type II (BMPR-II) receptors. The BMPR-II receptor activates the BMPR-I receptor by transphosphorylating its GS domain. This process initiates an intracellular signaling cascade through phosphorylation of SMAD proteins. The mutant ACVR1 receptor may become abnormally activated, resulting in excessive stimulation of the SMAD1/5/8 signaling pathway and activation of transcription factors. This ultimately leads to heterotopic bone formation. Inflammation and hypoxia may worsen this process, involving HIF, mast cells, and inflammatory mediators.

Furthermore, mutations appear to alter ACVR1 receptor signaling. Both the non-osteogenic ligand activin A and BMP ligands cause the mutant receptor to exhibit hyperresponsiveness. When

activin A binds to the mutant ACVR1 receptor, it initiates signaling through the SMAD1/5/8 pathway. However, when it binds to wild-type ACVR1 receptors, SMAD signaling does not occur. This dysregulation of BMP signaling is believed to trigger ectopic chondrogenesis, osteogenesis, and joint fusion in FOP. Most ACVR1 mutations associated with enhanced BMP signaling are gain-of-function variants.

DIAGNOSIS

Mutations seem to change how the ACVR1 receptor signals. Both the non-osteogenic ligand Activin A and the BMP ligands allow the mutant receptor to show hyperresponsiveness. When Activin A binds to a mutant ACVR1 receptor, it can start signaling through the SMAD1/5/8 pathway. In contrast, when it binds to wild-type ACVR1 receptors, SMAD signaling does not start. The disruption of the BMP signaling system is thought to trigger ectopic chondrogenesis, osteogenesis, and joint fusion in fibrodysplasia ossificans progressiva (FOP). Most of the ACVR1 mutations that have been studied to enhance BMP signaling are gain-of-function.

There are no official diagnostic standards for FOP. In addition to having a heterozygous pathogenic mutation in the ACVR1/ALK2 gene, the person with heterotopic ossification and hallux deformities was suspected of having FOP. However, anyone showing any of the following radiological and clinical features should be suspected of having FOP: congenital hallux valgus deformity, progressive heterotopic ossification, and painful scalp nodules in infancy caused by soft tissue trauma and repeated soft-tissue swelling (flare-ups).²²

This condition should recognize that a lack of suspicion can lead to delays or errors in diagnosis. This, in turn, may result in unnecessary tests and intrusive biopsies, which can trigger flare-ups. In 50% of cases, these flare-ups can cause heterotopic ossification (HO), permanent injury, and lifelong disability. Osteochondromas (HMO), fibrodysplasia ossificans progressiva (FOP) without hallux, hereditary progressive multiple osseous heteroplasia (POH), metachondromatosis (METCDS), and brachydactyly type B1 (BDB1) are some of the malformations that can be identified. Hallux anomalies may present as tumor-like swellings or isolated congenital malformations.

FOP can be diagnosed through imaging, but it must be used correctly. Basic radiography only shows skeletal abnormalities and heterotopic

ossification. Early lesions have been identified with Positron Emission Tomography (PET), magnetic resonance imaging (MRI), and computed tomography (CT). MRI can detect pre-osseous inflammatory lesions in the muscle, which may reduce the need for further testing, such as a biopsy, and provide an accurate genetic diagnosis. It can also help in recommending specific treatment methods.

CNS abnormalities that previously lacked attention include isolated inflammatory changes, demyelinated lesions, and structural deformities. MRI scans reveal these issues. The left longissimus thoracic muscle, bilateral latissimus dorsi, and right pectoral muscle showed multifocal ossification in the 3D computed tomography (CT) reconstruction. The MRI and CT scan results are similar, and no other spine abnormalities are found. However, biochemical tests provide a clearer understanding of the disease process. DNA sequence analysis can confirm a diagnosis by identifying the underlying mutation.

The development of the embryonic skeleton and bone healing relies on the ACVR1 protein, which plays a key role in bone growth and development. While there are no known treatments for FOP at this time, it is crucial to identify the issue early and seek treatment to avoid unnecessary trauma. This includes intramuscular vaccines or procedures that could trigger a flare-up.²²

PREVENTION OF FLARE-UPS

To reduce flare-ups, experts recommend avoiding blunt muscle stress, muscle exhaustion, and joint strain. Customized lifestyle plans based on age, mobility, and cultural norms should be considered. High-risk activities like jogging, cycling, and contact sports should be avoided. In cases of significant impact injuries, oral prednisone should be used to prevent flare-ups. Even without strong clinical evidence, experts agreed that a short course of oral corticosteroids (prednisone at 2 mg/kg/day), started within the first 24 hours after major trauma, had a good preventive effect.

Since major dental treatments and surgeries can trigger flare-ups, taking a course of oral steroids before and after these procedures could be a helpful preventative step. Patients with FOP should not receive intramuscular injections because these can lead to flare-ups and cause heterotopic ossification at the injection site. All specialists agreed that vaccinations should not be given during flare-ups, and when a vaccine is provided, it should be done subcutaneously to reduce the risk of flare-ups. While

there are discussions about the long-term use of current medications such as NSAIDs, the FOP Treatment Guidelines suggest that doctors use their judgment when prescribing treatments for individual patients to manage symptoms.²³

II. MANAGEMENT

Clinical therapy

Since tissue damage and the resulting inflammation trigger HO, its foundation relies on preventing and managing inflammation. However, triggering events vary widely. They can range from minor incidents like intramuscular injections to severe injuries such as knocks, bruises, falls, influenza-like infections, and basic muscle fatigue. This variety makes prevention difficult. It is unclear how each of these events impacts HO, primarily because they are not recognized until symptoms flare up. Nevertheless, the main goal of clinical therapy is to reduce inflammation to alleviate symptoms, as inflammation usually follows a triggering event. Currently, there is no effective treatment for FOP.

Pharmacological therapies for treating FOP fall into three classes, according to Kaplan et al. Class I medications treat the acute inflammation of flare-ups. These include nonsteroidal anti-inflammatory drugs and corticosteroids. A strong corticosteroid, prednisolone, increases blood vessel permeability during inflammation, reduces blood vessel widening, and lowers the recruitment of inflammatory mediators by activating the glucocorticoid receptor. While this drug has systemic side effects, it effectively addresses the initial inflammatory response, especially when taken within 24 hours of the flare-up starting and for up to 4 days. Additionally, NSAIDs like indomethacin and ibuprofen block the synthesis of prostaglandins, which cause fever, inflammation, and pain. Other NSAIDs, such as Celecoxib, specifically inhibit COX-2 and have pain-relieving, anti-inflammatory, and fever-reducing effects; however, they should be used carefully.

Although class II drugs might help treat FOP, there is currently little evidence supporting their use. Montelukast is a leukotriene receptor antagonist that works with COX inhibitors to treat asthma. For it to be effective, the medicine must be taken for a long time. Typically, Cromolyn is used for allergies, but it can also help prevent inflammation in FOP by blocking histamine and related mediators. Imatinib is a strong chemotherapy drug that specifically targets tyrosine kinases, suppresses HIF1- α , PDGFR α , and c-KIT, and leads

to mast cell death. Pamidronate is an amino bisphosphonate that suppresses calcification, changes bone mineralization, and has immunomodulating effects at high doses. However, it is not suitable for hypocalcemia or kidney problems, and it decreases bone density.

Class III drugs are currently being studied in clinical settings. These medications target the ACVR1R206H gene's BMP signaling, both outside and inside the cell. Inhibitors of the mammalian target of rapamycin (mTOR) block chondrocytes' non-canonical signaling of the ACVR1 signal. The monoclonal antibody against activin A, REGN 2477 (Garetosmab), is in a phase III clinical study after completing phase II. In a phase III clinical trial, the retinoic acid receptor gamma (RAR γ) agonist palovarotene blocks downstream SMAD signaling, promotes SMAD degradation, and encourages chondrogenesis.

While traditional physiotherapy should be avoided because it can cause overstretching and soft tissue injuries, physical therapy to prevent muscle wasting from limited movement is recommended. Light physical activity, like swimming, reduces the risk of muscle trauma or overstretching, allowing patients to engage in active range of motion exercises. FOP patients can enhance their daily activities and improve their quality of life with occupational therapy.²⁴

III. GENE THERAPY

CRISPR-Cas9

By modifying the ACVR1 gene, researchers are exploring CRISPR-Cas9 technology as a potential treatment for FOP. This gene-editing method allows precise alterations to the DNA sequence, which could stop the abnormal bone growth associated with FOP. The system consists of a Cas9 enzyme and a guide RNA molecule, enabling specific modifications to the genomes of living cells.²⁵

RNA interference therapy

Researchers are looking into RNA interference (RNAi) as a different approach to gene therapy. RNA interference (RNAi) is a biological process that controls gene expression. It can inhibit the expression of the mutant ACVR1 gene in FOP. This may help prevent abnormal bone growth by lowering the production of the mutated ACVR1 protein.²⁵

Adeno-associated virus vectors

To stop the progression of FOP, researchers are studying how to use adeno-associated virus (AAV) vectors to transfer healthy ACVR1 genes to cells

affected by the disease. This helps regular bone development continue. AAV vectors can infect both dividing and non-dividing cells; they are safe. AAV vectors are better than other viral vectors because they can target many types of tissues, provide long-lasting expression, cause little immune response, and can carry up to 5 kilobases of DNA, which includes most therapeutic genes.²⁵

IV. CONCLUSION

Fibrodysplasia ossificans progressiva (FOP), a rare and progressive genetic disorder, is characterized by unusual ossification of soft tissues, leading to severe functional impairment and decreased quality of life. Mutations in the ACVR1 gene are the primary cause of FOP, resulting in dysregulated bone morphogenetic protein (BMP) signaling and inappropriate bone formation. While significant advances have been made in understanding the molecular and genetic basis of FOP, no definitive cure currently exists, and treatment remains primarily supportive.

Recent studies have demonstrated several promising therapeutic strategies, including small-molecule inhibitors targeting ACVR1 receptors as well as gene-based approaches. However, numerous challenges remain, such as identifying reliable biomarkers, understanding disease progression, and developing safe and effective therapies for the prevention or reversal of heterotopic ossification. Interdisciplinary research and collaboration will be critical for translating molecular insights into effective treatments and improving outcomes and quality of life for individuals living with this debilitating condition.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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