"Advances in Targeted Therapies for Fibrodysplasia Ossificans Progressiva: From Molecular Pathogenesis to Clinical Trials"

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Abstract:- Fibrodysplasia Ossificans Progressiva (FOP) is an ultra-rare, disabling genetic disorder characterized by progressive heterotopic ossification (HO) in soft connective tissues, driven predominantly by a gain-of-function mutation in the *ACVR1* gene encoding the ALK2 receptor. Recent advances in the understanding of the molecular pathogenesis of FOP have highlighted dysregulated bone morphogenetic protein (BMP) signaling as the central mechanism underpinning ectopic bone formation. These insights have catalyzed the development of targeted therapies aimed at modulating the aberrant signaling pathways involved. Preclinical studies have demonstrated promising results for small-molecule inhibitors, monoclonal antibodies, and ligand traps that specifically interfere with ALK2 activity or its downstream effectors. Several of these agents have progressed into clinical trials, including palovarotene, garetosmab, and saracatinib, each targeting different components of the pathogenic cascade. This review provides a comprehensive overview of current therapeutic strategies under investigation, evaluates their mechanisms of action and clinical efficacy, and discusses ongoing challenges in translating molecular research into safe and effective treatments for FOP. The development of targeted therapies represents a transformative step in the management of this devastating condition, offering hope for disease-modifying interventions where none previously existed.

Keywords: Fibrodysplasia Ossificans Progressiva, palovarotene, *ACVR1,* BMP

I. **Overview of Fibrodysplasia Ossificans Progressiva (FOP)**: Fibrodysplasia ossificans progressiva is an uncommon autosomal dominant condition characterized by progressive ectopic ossification and distinctive skeletal abnormalities. Freke reported the first instances in 1739, and Patin in 1692. Up to 1918, Rosenstirn was able to locate 115 specific examples in the literature. By 1976, this number had increased to 470, and it currently surpasses 550. Thus, by personally assessing a sizable unselected series of patients from Great Britain, the current study aims to elucidate the clinical characteristics and natural history of fibrodysplasia ossificans progressive (1). About one in 1.5 to 2.0 million persons have fibrodysplasia ossificans progressiva (FOP), an autosomal dominant condition. It is marked by the emergence of bone in muscles ligaments, and tendons. Heterotopic ossification (HO) is the term adopted to signify this ectopic bone production(2). Progressive heterotopic endochondral ossification (HEO) is a hallmark of the extremely uncommon debilitating autosomal dominant genetic condition known as(FOP) fibrodysplasia ossificans progressive (3). Instead of being just mineralized calcium phosphate, the hard tissue that develops in affected patients is the result of osteoblasts creating new bone tissue using a cartilaginous template , a process that is also seen in routine skeletal tissues throughout regeneration and embryonic development. Additionally, the heterotopic bone tissue has bone marrow and is processed similarly to regular bone tissues by osteoblasts and osteoclasts . During

internal medicine operations carried out on patients with FOP, it is difficult to simply remove the heterotopic bone tissues because, although their locations can be used to differentiate them from normal bone tissues, their biochemical characteristics do not. Although most people with FOP can move their joints normally at birth, the heterotopic bones that originated in tendons, ligaments and skeletal muscle progressively integrate with one another and bridge with typical bones, strengthening the joints. This causes them to exhibit disability in a number of joints, including the jaw, once they reach their 30s. Furthermore, individuals with FOP experience rapid heterotopic bone growth as a result of soft tissue damage. As a result, people with FOP are not allowed to undergo invasive treatments like biopsy, surgery, or injection(4). Understanding conditions with high unmet medical needs, particularly rare conditions, requires the use of comprehensive natural history studies (NHSs). These studies describe the natural course of a disease, investigate diagnostic or monitoring methods, find potential biomarkers, create outcome measures, and link centres of expertise .FOP also exhibits signs of premature aging(5).Two kinds of benign heterotopic ossificans in soft tissues, including muscles, are known as myositis ossificans (MO): nonhereditary MO and fibrodysplasia ossificans progressiva (FOP). When soft tissues ossify after severe or repeated trauma, burns, or surgery, it is referred to as nonhereditary MO. Multiple ectopic ossifications across the body are a hallmark of FOP, a rare hereditary disease of bone morphogenetic protein (BMP). The majority of FOP patients have activin A receptor type I (ACVR1), a subtype of BMP type I receptors, with the same recurring single nucleotide alteration. The classic molecule (c.617G > A, p.R206H) is often associated with the typical clinical manifestations of FOP, such as significant heterotopic ossification at an early age and valgus deformity of the great toes(6). Prior to affecting the ventral, appendicular, caudal, and distal regions of the body, axial, cranial , the dorsal, and proximal anatomical sites are affected(7). In FOP, flare-ups—painful soft-tissue inflammatory episodes—often accompany the initiation of new lesion development that results in HO. Certain flare-ups can even be fatal, depending on where they occur. Therefore, a great deal of research is still needed to better understand flare-ups and their long-term effects, as well as to discover treatments that may lessen or even stop flare-ups from happening(8). Two studies, one from Germany and one from the USA, have proposed that the incidence of new mutations in this illness is influenced by the father's age. In addition to determining the frequency and mutation rates, the current study aimed to corroborate this in FOP patients from the United Kingdom(9).

1.2 Progression of heterotopic ossification

Frequently occurring gain-of-function mutations in the ACVR1 receptor result in a significant pro-osteogenic signalling cascade to be triggered, which results in FOP. Patients used to report flare-ups of excruciating swelling or painful lesions, which were frequently misdiagnosed as cancerous tumours. The fact that these false diagnoses suggested biopsies and the introduction of iatrogenic injuries that would encourage the development of HO was particularly worrisome. Additionally, creation of (HO) heterotopic ossification and flare-ups can be caused by situations that are usually innocuous for most

people, such as intramuscular vaccinations, dental procedures, small bumps, or even viral infections. In FOP patients, HO production usually begins in the dorsoaxial areas and gradually spreads outward(10).

1.3. Associated symptoms.

Its clinical appearance comprises a distinctive congenital defect of the great toes and growing (heterotopic ossification, or HO), extra-skeletal ossification which results in painful and

cumulative impairment. The phenotypic may be correlated with other skeletal abnormalities and symptoms, such as the fusion of cervical vertebrae , thumb deformity, or the existence of osteochondromas. With quiescent periods alternating with acute phases that cause bone neo-formation affecting , tendons, ligaments, skeletal muscles and joints, the course of FOP is very variable and episodic. Vaccinations, surgical and medical procedures, infections, trauma, or an unanticipated event without a known trigger can all result in flare-ups of FOP(11).

1.4. The rarity and complexity of FOP as a disorder.

In FOP, all irregular and family-related instances of classic Fibrodysplasia ossificans progressive(FOP) are resulting from a recurrent mutation in the (BMP) bone morphogenetic protein type I receptor, (ACVR1/ALK2). activin receptor IA/activin-like kinase 2. Today, drug research is predicated on this extremely conserved target(12)(13) .

1.5. The need for targeted therapies due to the severe consequences of the disease.

First Strategy: Mutant FOP receptor (mtACVR1) blocking action STIs, ligand traps, mutation allele-specific inhibitory RNA, blocking monoclonal antibodies against Activin A, and blocking monoclonal antibodies against ACVR1 are the five techniques under investigation.

Second strategy: Preventing the causes of inflammation

In the context of dysregulated BMP signalling, clinical observations and mice models of FOP offer compelling evidence of the immune system's involvement in initiating and intensifying HEO and FOP flare-ups. In animal models, targeted suppression of macrophages, mast cells and neuro-inflammatory pathways reduces HEO.

Third Strategy: suppressing progenitor cells in responsive connective tissue

HEO and chondrogenesis are inhibited by retinoid signaling pathway activation. By encouraging the breakdown of Smads unique to the BMP pathway, (RARγ) retinoic acid receptor-gamma agonists inhibit BMP signaling in prechondrogenic cells. A conditional FOP knock-in mouse model employs the RARγ agonist palovarotene to prevent both spontaneous and trauma-induced HEO

Fourth Strategy: suppressing the body's response to external stimuli that promote heterotopic ossification

In order for HEO to occur, skeletal muscle must first create an inflammatory and hypoxic milieu. Hypoxia-induced factor When mtACVR1 is present, 1-alpha enhances ligand-independent Smad1/5/8 signaling and integrates the cellular response to hypoxia and inflammation. HEO is eliminated in FOP animal models when HIF1-alpha is pharmacologically blocked with apigenin, PX-478, rapamycin or imatinib(14).

2. Molecular Pathogenesis of FOP

2.1. Genetic Basis of FOP:

A spontaneous novel mutation is the cause of the majority of FOP cases. Genetic transmission might be inherited from the father or the mother and is autosomal dominant when it is demonstrated. There is phenotypic heterogeneity. Environmental and genetic factors both affect the phenotype of FOP. Three pairs of identical twins with FOP were studied, and it was discovered that the congenital toe abnormalities in each pair were similar. However, environmental exposure to viral diseases, life history, and soft tissue trauma all had a significant impact on postnatal heterotopic ossification. Environmental variables have a significant impact on the postnatal course of (HO) heterotopic ossification, whereas genetic determinants have a significant impact on the disease phenotype during prenatal development.(15)

2.2 Description of the ACVR1 gene mutation and its role in pathogenesis.

The Activin A receptor, type I (ACVR1) gene which is a receptor for bone morphogenetic proteins (BMPs) and sometimes referred to as activin receptor-like kinase 2, or ALK2. Type I serine/threonine receptor kinase ACVR1 is a member of the seven receptors (ALKs 1–7) that make up the transforming growth factor-b receptor (TGFBR1) family (16).A conserved residue in the protein's GS domain is substituted in the ACVR1/ALK2 gene by the recurrent activating mutation (617G>A, R206H), which is present in about 97% of people with FOP(17).

2.3. Mechanism of the mutation: overactivation of the BMP signalling pathway.

It is the initial noteworthy finding in comprehending the molecular and genetic processes of HO in FOP(18). Two type I and two type II serine-threonine kinase receptor heterotetramer receptor complexes are activated by (BMPs)bone morphogenetic proteins ,which belong to the (TGFB) transforming growth factor beta family of extracellular signaling factors. To activate the receptor complex, type II receptors phosphorylate the (GS) glycine-serine cytoplasmic domain of type I receptors in response to ligand interaction. The BMP signaling pathway and transcriptional regulation are triggered by activated type I receptors via MAP kinase pathways and the phosphorylation of SMAD

proteins unique to the BMP pathway (SMADs 1, 5, 8). Apart from ACVR1, the BMPR1A (formerly known as ALK3), the BMP type I receptor that was altered in FOP BMPRIB (previously known as ALK6), and ACVRL1 (previously known as ALK1) type I receptors can also facilitate BMP signal transduction(19).

2.4. Molecular Consequences of ACVR1 Mutation:

With a distinct subcellular distribution and lower quantities of ACVR1 protein than the wild-type protein, the ACVR1 R206H mutation has molecular ramifications for the disease's pathophysiology(20).

2.5. Dysregulated bone formation and ectopic ossification.

Since trauma can enlarge the lesion and cause more ectopic bone formation, surgical removal of HO is not advised(21).

Prenatal development and postnatal skeletal repair are typically the only times bone production occurs. However, bone can grow outside of its typical physical and temporal contexts on account of severe damage or a particular genetic mutation after birth. Both endochondral and intramembranous ossification can result in the production of this extra-skeletal bone, also known as heterotopic ossification (HO)(22).

2.6. Role of other signalling pathways .

1. **ALK2 Receptor**
   In response to BMP ligands, mutant ALK2 proteins have a knack to develop into hypersensitive and improve basal receptor activity(23).
2. **Activin Receptor-Like Kinase**
   Both Fibrodysplasia ossificans progressiva and Diffuse Intrinsic Pontine Glioma share activating mutations in the gene ACVR1 that codes for ALK2, suggesting that both conditions may result from activated activin receptor-like kinase 2 (ALK2) signalling(24).
3. **Animal Models and Cellular Studies:**

3.1. Overview of FOP mouse models and their contribution to understanding the disease.

In Acvr1 R206H animal models, activin A has been demonstrated to stimulate heterotopic ossification of fibro/adipogenic precursors (FAPs)(25). The first stages of illness flare-ups in both FOP patients and mice models involve perivascular buildup of lymphocytes, mast cells, and macrophages in the afflicted skeletal muscle(26). The postnatal phenotype of mice chimeric for the Acvr1R206H mutation replicated nearly all features of classic FOP, despite the crucial and inexplicable difference between the human condition and FOP mouse models being the drastically different outcomes of embryonic ACVR1(R206H) expression(27). The in vivo consequences of ALK2 activating mutations have been studied using either a conditional gene expression model or chimeric/mosaic expression of mutant cells

since in mice, these mutations are fatal during embryonic development. Using a Cre-Lox inducible ALKQ207D transgene, the first such mouse model was created before ALK2 was found to be related to FOP(28).

3.2. Use of induced pluripotent stem cells (iPSCs) and other in vitro models to study FOP pathogenesis.

ESCs and induced pluripotent stem cells (iPSCs) are two examples of MSCs derived from pluripotent stem cells (PSCs) that may serve as such a source. Due to their limitless growth and differentiation capabilities, both may be avoided in long-term cultivation as MSCs(29).Drug development, regenerative medicine, and disease modelling all make extensive use of induced pluripotent stem cells(30).

4. Preclinical Research and Therapeutic Targets

4.1. Identifying Therapeutic Targets:

Palovarotene, a retinoic acid receptor gamma agonist, activin A inhibitors, and antibodies targeting ACVR1 are among the prospective treatment approaches that have been studied in clinical studies. Larger, well-controlled investigations are required to prove the efficacy and safety of these treatments, even if several of them have demonstrated promising outcomes in preclinical and early-phase clinical trials. considers clinical trial design factors and possible therapeutic targets for FOP(31). Clinical trials are now being conducted to investigate the several serotherapeutic drugs that have been shown to be useful in postponing or easing various age-related diseases in pre-clinical animals. Their prospective application in FOP presents a fresh treatment strategy for injury-induced flare-ups in FOP that warrants more investigation(32).

4.2. Potential role of inflammatory pathways and immune dysregulation in disease progression.

Adiponectin and leptin may control inflammatory pathways that reduce TNFα expression, which in turn lowers VCAM-1 and MMP3 expression in FOP, according to the IBM-WDD network study(33)**.** Muscle exhaustion, intramuscular vaccinations, mandibular blocks for dental procedures, and blunt muscle trauma from bumps, bruising, falls, or influenza-like diseases can all cause excruciating new flare-ups of FOP that develop to HO(34).

4.3. Targeted Therapeutic Strategies:

Discussions of contemporary FOP treatment possibilities include the difficulties in discovering new therapeutic targets and cutting-edge tactics like gene therapy, stem cell-based therapies, small chemical approaches, , and other creative techniques.(35)

4.3.1. Genetic Therapeutics for FOP

Research on FOP treatment has a bright future thanks to the development of genetic treatments. The main emphasis of these treatment approaches is the genetic cause of the illness, which is usually mutations in the ACVR1 gene. There is presently research being done on genetic techniques, such as gene insertion, gene editing, gene replacement, and gene silencing(36).

4.3.2. Stem-Cell Based Approaches

Beyond regenerative medicine, induced pluripotent stem cell (iPSC) technology may be applied to drug discovery research. The pluripotency of iPSCs allows diverse cell types that make up our body to differentiate and be employed for pharmacokinetic assays, medication safety, toxicity, and therapeutic treatment of FOP(37).

4.3.3. Immunotherapy

The immune system can be prevented from attacking healthy cells by suppressing its signaling pathways using chemicals called immune checkpoint inhibitors. With these immunotherapeutic medications, scientists intend to improve the immune system's ability to recognize and eradicate the abnormal cells that lead to FOP.(38)

4.3.4. Mesenchymal Stem Cells

Recently, rapamycin was discovered to be an intriguing medication for the treatment of FOP. FOP fibroblasts were used to create isogenic iPSCs, which were subsequently transformed into mesenchymal cells (MSCs) to provide an in vitro screening model. Using this approach, chemical compounds that might inhibit the enhanced chondrogenesis of FOP were screened for.(39)

5. BMP Pathway Inhibitors: Palovarotene

5.1. Description

The brand name for 4-[(E)-2-(5,5,8,8-tetramethyl-3-pyrazol-1-ylmethyl5,6,7,8-tetrahydronaphthalen-2-yl)-vinyl] is Palovarotene. Formerly known as R667, -benzoic acid is an oral bioavailable Retinoic Acid Receptor Gamma -selective agonist.(40)

5.2. Mechanism

Since closure affects some but not all growth plates, the mechanisms behind the premature epiphyseal closure linked to palovarotene are yet unresolved. (41)

5.3. Preclinical Efficacy

In mice models of FOP, preclinical research has shown that palovarotene is effective for minimizing heterotopic ossification. Recognizing the worries about palovarotene's harmful effects on young mice's bones is simultaneously crucial. (42)

6. Other small molecule inhibitors targeting the ALK2 receptor and BMP pathway.

prospective medications that target various BMP signaling cascade stages. These comprise ligand bioavailability-compromising compounds, BMPR expression inhibitors (such as kinase inhibitors and receptor antibodies) that inhibit BMPR activation, and intracellular inhibitors (such as SMAD inhibitors). BYL719, Saracatinib, Rapamycin, Palovarotene & are just a few of the substances that have been shown to block signaling downstream of BMPR, even though some of them were not initially thought of as BMPR antagonists. (43)

6.1. JAK Inhibitors in FOP

6.1.1. Examples-Tofacitinib, Ruxolitinib, Baricitinib, Upadacitinib.

6.1.2. Mechanism of Action- Suppress cascade of cytokines that are reliant on JAK-STAT.

6.1.3. Cellular Effect- Varies according on the particular cytokines that are inhibited.

6.1.4. Most Common Adverse Effects- Gastro intestinal side effects, Gastro intestinal perforation, hypercholesterolemia, infections, cytopenias, headache.Thrombosis, Black box warning for malignancies and severe infections.(44)

7. Gene Editing Approaches: Potential for CRISPR-Cas9 and other gene-editing techniques to correct the ACVR1 mutation.

A heterozygous ACVR1R206H mutant cell line was produced by selectively introducing the c.617G>A gene substitution into the endogenous ACVR1 locus in HEK 293T cells via CRISPR-Cas9 ribonucleoprotein (RNP) targeting. (45)

An alternate method to get around the potential drawbacks of directly reprogramming hiPSCs, such as impaired reprogramming ,low efficiency, and cell instability, is to introduce the CRISPR/Cas9 elements, the mutation-carrying single-stranded oligodeoxynucleotide (ssODN), and episomal reprogramming vectors into normal fibroblasts at the same time. Using this method, the ACVR1 R206H mutation was fixed and mutant ALK2/ACVR1-hiPSC lines were created.(46)

8. Challenges and limitations of gene therapy for FOP(47).

Table 1. Options for gene therapy in the in vivo treatment of fibrodysplasia ossificans progressiva

	Approach	Target	Effect
Replacement of genomes	**Expression of ALK2 in the wild type**	**mRNA**	**Mutant ALK2 receptors compete with normal ALK2.**
Silencing of genes	**ALK2-specific mutant RNAi**	**mRNA**	**suppression of expression of the mutant ALK2 receptor**
Silencing and gene replacement	**Combination of Expression of ALK2 in the wild type and ALK2-specific mutant RNAi**	**mRNA**	**Combined effect of Mutant ALK2 receptors compete with normal ALK2 and suppression of expression of the mutant ALK2 receptor**
Editing genes	**CRISPR/CAS-mediated correction of ALK2 mutation**	**DNA**	**Only normal ALK2 receptor is produced**

It is difficult to search for positive clones and get enough therapeutic material because of the induced DNs' overall constraint of continuous proliferation(48).

9. Clinical Trials (49)

Table 2 . FOP clinical phases.

	Clinical phases					
			Early/mild	Moderate	Profound	End-stage
The traits	Flare-ups	No previous history of flare-ups, or if they do occur, only on the neck ,back, or scalp	History of flare-ups generally related to the axial places and upper limbs	flare-up history in any place of the body	flare-up history in any place of the body	flare-up history in any place of the body
	Body parts that are impacted	back, Neck, upper limbs	Chest, Neck, back, lower limbs and upper limbs	jaw , Chest, Neck, back, lower limbs and upper limbs	jaw , Chest, Neck, back, lower limbs and upper limbs and distal limbs	Ankyloses of most or all joints
	Insufficiency of the The lungs		Limited chest expansion	No chest expansion, rigid chest wall, and diaphragmatic breathing	Right-sided heart failure and pulmonary hypertension are symptoms of thoracic insufficiency syndrome.	Right-sided heart failure and pulmonary hypertension are symptoms of thoracic insufficiency syndrome.
	The act of ambaulation	Unaffected or incapable of evaluating because of youthful age	Walks; in extreme situations (such as lengthy distances), a wheelchair may be used.	utilizes a wheelchair or an assistance device when walking.	Wheelchair-bound	Mostly bed-bound
	CAJIS	≤4	5–18	19–24	≥24	≥28

10. Emerging Drugs &other investigational agents and their potential to modify disease progression.(50)**.**

Table 3. FOP clinical trials were performed previously (by November 2021)

Name of the drug	Phase of clinical	Targeted Receptor	Number of NCT/UMIN
REGN2477(Garetosmab)	**Phase II**	**Nuclear**	**UMIN000028429**
Saracatinib	**Phase II**	**ACVR1**	**NCT05090891**
DS-6016a	**Phase I**	**ACVR1**	**NCT03858075**
INCB000928	**Phase I**	**ACVR1**	**NCT04818398**
BLU-782 (IPN60130)	**Phase II**	**Activin A**	**NCT03188666**
Saracatinib	**Phase II/III**	**mTORC1**	**NCT04307953**
Rapamycin	**Phase III**	**ACVR1**	**NCT03312634**
Palovarotene		**RARγ**	**NCT05027802**

V. Management of FOP

Controlling inflammation is the main goal of current clinical care of FOP since it sets off the series of events that result in HO. However, because triggering events can vary from serious physical harm to relatively little ones, handling them continues to be difficult. The three classes that make up the changing pharmaceutical landscape are: High-dose corticosteroids, (COX2) cyclo-oxygenase 2 inhibitors ,NSAIDs, aminobisphosphonates , mast cell inhibitors and muscle relaxants are examples of class I medicines that are used To deal with flare-ups; Class II drugs have potential but unproven uses in Fibrodysplasia ossificans progressiva, whereas Class III drugs are being studied clinically.(36)

Supportive care: The mainstay of FOP care is avoiding muscle and soft-tissue injuries in order to avoid inflammatory soft-tissue swellings and heterotopic ossification. In order to optimize function, lower problems, and enhance quality of life, supportive care is advised. Ideally, this entails comprehensive treatment from experts in pertinent domains.

Prevention of soft-tissue & muscle injury:-

1. Steer clear of intramuscular injections since regular DTP immunizations are especially dangerous.
2. Because venipuncture is a low-risk procedure, avoid arterial punctures.
3. It is probable that biopsies will result in heterotopic ossification.

Painful, recurrent soft-tissue swelling (flare-ups) :-

1. Prevent gastrointestinal issues caused by NSAIDs or COX-2 inhibitors by taking preventative measures.
2. Try to stay away from narcotic analgesia.

Mobility issues :- In order to prevent passive joint movement, use warm water hydrotherapy.

Depression:- Psychological support(51).

VI. Challenges and Barriers in Developing Targeted Therapies

The FOP community confronts several obstacles, such as low policymakers' and healthcare professionals' (HCPs') knowledge of FOP, A high percentage of inaccurate diagnoses globally, restricted accessibility specialized care of Fibrodysplasia ossificans progressiva, and a lack of More information and support for those who are separated from the worldwide Fibrodysplasia ossificans progressiva community(52).

VII. Future Directions

Future directions in targeted therapies for Fibrodysplasia Ossificans Progressiva (FOP) will likely center on refining molecular interventions that directly inhibit the aberrant ACVR1/ALK2 signaling pathway responsible for ectopic ossification. Advances in gene editing technologies, such as CRISPR-Cas9, hold promise for correcting the underlying genetic mutation at its source. Ongoing and future clinical trials will aim to optimize the safety and efficacy of small-molecule inhibitors, monoclonal antibodies, and RNA-based therapies, with a focus on minimizing side effects and preserving musculoskeletal function. Additionally, patient-specific models using induced pluripotent stem cells (iPSCs) may facilitate personalized treatment strategies. Collaborations between academic, clinical, and pharmaceutical sectors will be crucial to accelerating translational research and regulatory approval, ultimately improving quality of life for individuals affected by this rare and debilitating condition.

VIII. Conclusion

In conclusion, significant progress has been made in understanding the molecular mechanisms driving Fibrodysplasia Ossificans Progressiva, paving the way for the development of targeted therapies aimed at halting or reversing disease progression. Emerging treatments, including small-molecule inhibitors, biologics, and gene-editing approaches, offer renewed hope for patients, particularly as they advance through clinical trials. Continued research, collaboration, and innovation are essential to translating these scientific breakthroughs into effective, accessible treatments, ultimately transforming the outlook for individuals living with this devastating condition.

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