Recent Advancement Therapies in the Treatment of Fibrodysplasia Ossificans Progressiva – Overview

Spurti Awatimath[1], Jincy Thomas[1]*, Prajna T K[1] ,

[1] Department of Pharmacology, College of Pharmaceutical Sciences, Dayananda Sagar University, Bengaluru, Karnataka

Corresponding Author: *

Ms. Jincy Thomas

Assistant Professor

Department of Pharmacology

College of Pharmaceutical Sciences

Dayananda Sagar University

Bengaluru - 560078

Karnataka, India

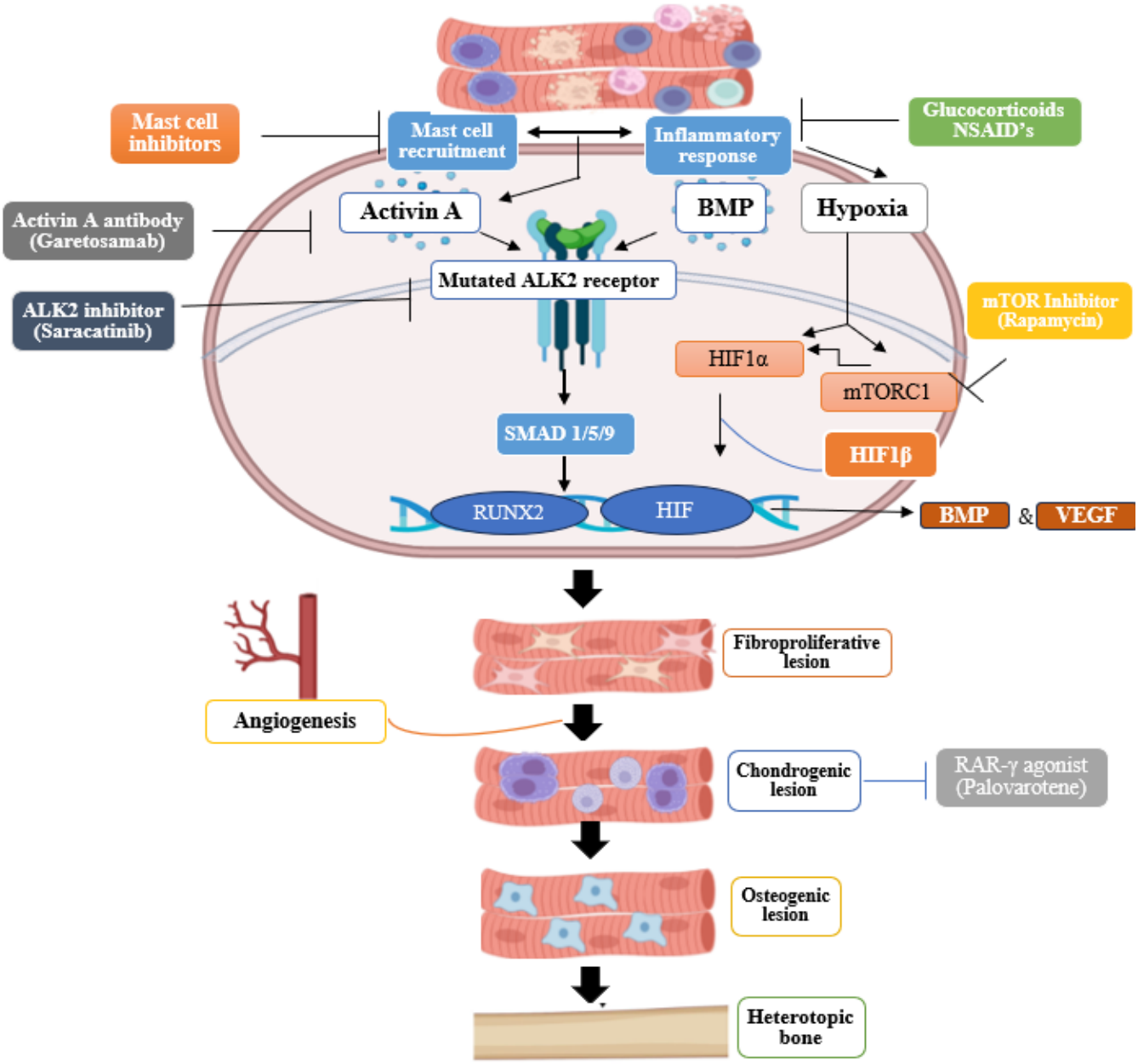
Email id: jincypharmacology@gmail.com

ABSTRACT:

Fibrodysplasia ossificans progressiva (FOP), colloquially termed Stone Man's disease, is an infrequent and incapacitating hereditary condition distinguished by anomalous bone development within muscles, tendons, and ligaments. This condition leads to progressive ossification, resulting in immobility and severe disability for affected individuals. A variant in the ACVR1 genome causes an overabundance of BMP signalling, which is the primary biological component responsible for the FOP. FOP is often diagnosed based on clinical indicators that are supported by molecular investigation. As of right now, there is no confirmed cure for FOP; instead, therapy focuses on managing symptoms and preventing acute flare-ups. Various therapeutic approaches are being explored, including gene therapy, enzyme and transcriptional target modifiers, antibody interventions, and immune checkpoint blockers. Collaboration between researchers, patient communities, and regulators is crucial to accelerate drug development and improve outcomes for individuals with FOP. To improve our knowledge and management of this uncommon ailment, more research and clinical trials are necessary.

Keywords: FOP, Stone Man’s disease, ACVR1 genome, BMP signalling, Gene therapy

Graphical Abstract



1. INTRODUCTION:

The rare inherited condition known as fibrodysplasia ossificans progressiva (FOP) is caused by alterations in the ACVR1/ALK2 genetic material, which codes for the Activin A receptor type 1/Activin-like kinase 2 receptor. This particular receptor is essential to the bone morphogenetic protein (BMP) signalling cascade. FOP causes aberrant bone growth outside of the bone matrix and presents with a wide range of indicators, some of which resemble premature ageing [1]. Fibrodysplasia ossificans progressiva (FOP), popularly referred to as "stone man syndrome," is an inheritable condition affecting connective tissues that is extremely debilitating. In addition to the progressive production of bone cells within the muscles of the skeleton, the disorder is further defined by congenital anomalies in the palms and big toes [2]. Non-skeletal aberrant bone production is a feature of FOP, a connective tissue condition. It is inherited dominantly and associated with hyperproliferative BMP production and aberrant bone development due to abnormalities in a gene that normally inhibits BMP4 [3]. Worldwide, fibrodysplasia ossificans progressiva affects about 1 in every 2 million babies born. Regretfully, around 90% of people with this illness receive incorrect diagnoses and treatments, which results in needless interventions [4]. The erratic, intermittent ossification of bone in multiple soft tissue sites usually causes edoema in the afflicted areas, limited motion, and ultimately the fusion of the afflicted joints (spine, arms, thighs, elbows, knees, hands, jawline, and ankle joints), often in a predictable fashion [5]. The disease progresses and gets more complex with reduced movement at the associated sites, respiratory distress, and infections in the lungs. Deep limitation of chest wall motions is the primary reason of death in this illness, resulting mainly in breathing problems and cardiac arrest [6]. Imaging results show a variety of unusual findings, such as elongated thin vertebral body parts, shortened and extended hip bone necks, fusion of joints in the neck spinal vertebrae (C2-C7), shortened first bones of the hand and foot, deviations of both big toes towards the outer side, single-phalanx structure of the big toes, inappropriate bone formation in muscles and tendons, and enlarged rear structures [7]. FOP stands as the inaugural documented instance in medical history where an organ system undergoes transformation into another. It is hailed as a quintessential model for unravelling the disruption of cellular destiny determination and the equilibrium of tissue upkeep [8]. The ramifications of FOP transcend mere skeletal concerns, encompassing challenges in articulation, swallowing, and respiratory capacity, frequently culminating in untimely mortality [9]. The term "Fibrodysplasia Ossificans Progressiva" was first used in the 1970s by Dr. Victor

McKusick of the Johns Hopkins University School of Medicine to more fully describe the ossification ability of different soft tissue components, including ligaments and tendons [10].

2. INNOVATIVE AND EXPLORATORY APPROACHES TO TREATING FOP

Numerous experimental and potential approaches are being explored to address various aspects of the wider FOP pathophysiology or the disturbed BMP pathway [11]. These tactics fall into four main categories: stem cell-based therapies, genetic interventions, immunomodulatory treatments, and modulators that target transcriptional and enzymatic processes. Additionally, continuous efforts have been made to repurpose currently available medications for the treatment of FOP [12].

2.1 GENE THERAPY

a. CRISPR-Cas9

Gene therapy, which makes use of cutting-edge gene-editing technologies such as CRISPR-Cas9, has great potential as a FOP treatment. With the use of this innovative method, researchers can precisely alter the targeted genes' DNA sequences, potentially correcting genetic defects linked to the disorder [13]. The CRISPR-Cas9 complex is commonly transported by viruses like as lipid nanoparticles (LNPs) and adeno-associated virus (AAV). The vector selection ensures tissue specificity by rewording the complex using specific terms [14]. Two essential components of the CRISPR/Cas-9 system are proteins (Cas-9) and RNA that guides transcription (gRNA). The Cas-9 protein, the pioneering enzyme employed in genome editing, was initially extracted from Streptococcus pyogenes (SpCas-9) [15]. RNA directs target viral DNA in prokaryotes. Synthetic guide RNA (sgRNA), used in gene editing, combines tracrRNA (Trans-activating CRISPR RNA) and crRNA (CRISPR RNA) to accurately target genes for modification [16]. Opting for a vector tailored to the targeted tissue guarantees that gene editing exclusively affects the designated cells. Despite its widespread adoption in clinical contexts, lauded for its exceptional accuracy and enduring impact on the genome, CRISPR-Cas gene editing treatments for fibrodysplasia ossificans progressiva (FOP) encounter challenges such as off-target genetic alterations, ethical dilemmas, and a complex regulatory authorization process [17]. CRISPR-Cas9, a genetic modification tool, employs RNA guides to pinpoint DNA segments and the Cas9 enzyme to induce dual-strand fractures

at designated sites. These fractures are subject to repair via NHEJ or HDR mechanisms, leading to either gene mutations or exact modifications, respectively [18].

The genetic approaches to treating FOP are compiled in **Table 1**. Gene editing utilizes methodologies like CRISPR-Cas9 to directly rectify mutations in the ACVR1/ALK2 gene at the DNA level. The process of introducing functional copies of the ACVR1 gene into cells is referred to as gene supplementation. Whether to completely silence the ACVR1 gene or to suppress the mutant allele only, this is the subject of gene silencing research. A comprehensive therapeutic approach is achieved by combining gene silencing and gene insertion approaches through the gene replacement method.

Therapeutic Strategy	Objective	Molecular Target	Anticipated Outcome
Gene editing	employing CRISPR-Cas9 technology to modify mutations within the ACVR1 gene.	DNA	The exclusive generation of the corrected ACVR1 ALK2 protein.
Gene addition	the ACVR1 gene being inserted in functional, undamaged copies	DNA, mRNA	the conflict between the mutant versions that have long existed and the recently introduced functioning ACVR1/ALK2
Gene silencing	Total deactivation or selective suppression of particular ACVR1 alleles	mRNA	While allele-specific suppression specifically reduces the expression of the mutant ACVRI gene, overall inactivation could lead to unforeseen physiological consequences.
Gene replacement	Coordinating the incorporation of genes and the inhibition of gene expression simultaneously	mRNA	Expression of the mutant ACVR1 is selectively suppressed at the allele level, while the lack of functional ACVR1/ALK2 is compensated for by introducing functional ACVR1.

b. Ribonucleic acid-based interventions

Another approach in gene therapy exploration for FOP involves RNA interference (RNAi). RNAi, a natural biological mechanism, regulates gene expression by suppressing specific target genes. To inhibit the expression of the mutant ACVR1 genes associated with FOP, researchers are investigating the use of RNA interference (RNAi). This strategy can reduce the synthesis of the mutant ACVR1 protein, which can prevent the aberrant bone growth characteristic of FOP [19]. Initial findings of targeted inhibition of caACVR1 have been reported by Kaplan et al. and Takahashi et al. in Gene Therapy. In both investigations, caACVR1 mRNA is degraded but normal ACVR1 expression is preserved through the use of allele-specific RNA interference (ASP-RNAi). Because of this thoughtful design, cells from FOP patients—who usually show higher levels of BMP signalling than control cells—can have their normal BMP signalling levels restored. These findings demonstrate the growing potential of ASP-RNAi in the management of illnesses in humans [20]. Research has produced allele-specific siRNA (ASP-RNAi) duplexes that are intended to specifically inhibit the expression of the mutant c.617A allele in the mesenchymal progenitor cells of patients with familial orthopaedic syndrome. With the use of ASP-RNAi techniques, patient cells' high BMP signalling was reduced to levels akin to those of control cells, and their accelerated osteogenic differentiation was brought back to control levels. The findings offer information in favour of the theory that ASP-RNAi may be an appropriate therapy for FOP [21]. According to recent research by Maruyama et al., gapmers showed a propensity to maintain the majority of normal products while decreasing the expression of ACVR1R206H and the related protein level. In vitro osteogenic development was inhibited as a result of this focused action [22].

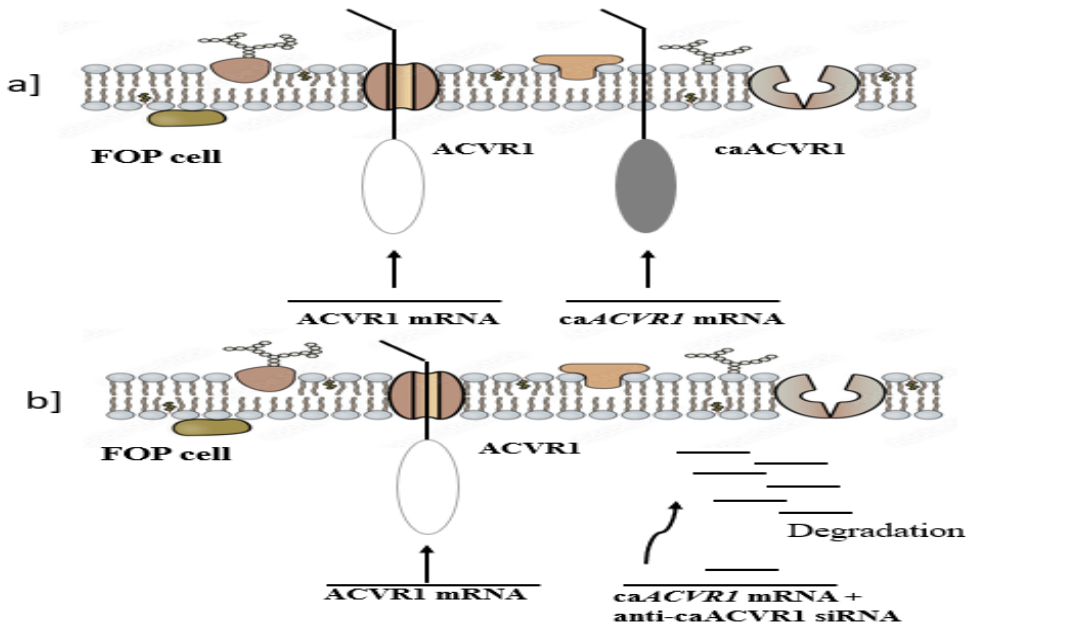


Fig 1 [a] Both normal ACVR1 and mutant ACVR1 (caACVR1) are seen in FOP patients. [b] By targeting caACVR1 mRNA precisely, allele-specific siRNA preserves normal ACVR1.

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c. Adeno-associated Virus (AAV) Vectors

AAV vectors are often utilised in gene therapy endeavours to introduce therapeutic genes into targeted cells. Researchers are exploring the potential of introducing intact copies of the ACVR1 gene into cells affected by FOP using AAV vectors. By giving these cells functional ACVR1 genes, normal bone formation will be restored and the progression of FOP will be stopped. Originating from a benign virus, AAV vectors have proven to be safe and effective in infecting cells that are dividing as well as those that are not, which makes them attractive options for introducing therapeutic genes [23][24][25].

2.2 Gene Therapies

Given the encouraging results of genetic treatments for monogenic ailments such as lipoprotein lipase deficiencies, inherited retinal dystrophy, and atrophy of the spinal muscles, it is reasonable to assume that fibrodysplasia ossificans progressiva (FOP) could benefit from a similar strategy. Existing gene therapies show promise in treating FOP because the disease arises from a single-gene mutation in ACVR1 that leads to enhanced function [26]. In addition, with the suppressive protein FKBP12, the region inside ACVRI identified as the glycine-serine

(GS)-rich domain is essential for attachment and triggering through ligand-activated BMP type 2 receptors. The R206H mutation in missense occurs at this exact position. According to computational modelling, this mutation causes a structural change in the receptor that may interfere with FKBP12 binding. As a result, this modification may improve responsiveness to non-traditional ligands and avoid the requirement for ligand binding. The downstream signalling pathways in fibrodysplasia ossificans progressiva (FOP) may then be affected by these changes [27][28]. Scientists reintroduced the normal form of the mutant ACVR1R206H gene while simultaneously suppressing it using an AAV vector. This approach effectively thwarted and addressed trauma-induced heterotopic ossification (HO) in a mouse model of fibrodysplasia ossificans progressiva (FOP) by efficiently reinstating the disturbed BMP signalling pathways. Gene therapies provide enormous potential benefits, but they also present considerable challenges [29].

UPCOMING OPPORTUNITIES FOR GENETIC STRATEGIES IN FOP

Research opportunity to explore the fundamental mechanisms of FOP appeared with the recent discovery of ACVR1 as the causative genes. Generally, ACVR1 functions as a BMP type I transmitter when BMP ligands activate it. Both the unconventional BMP signalling routes, which involve MAPK, and the traditional Smad1/5/8 transmission route are started by ACVR1 in conjunction with BMP type II domains [30].

2.3 Enzymatic and Transcriptional Target Modifiers

The discovery of transcriptional and enzymatic target modulators is gradually changing the FOP therapeutic landscape. By specifically affecting important signalling channels and gene expression mechanisms, these therapies seek to attenuate or reverse the disease. The main types of modulators that are being examined are described in this part along with their potential therapeutic benefits, which are supported by preclinical studies and current research initiatives. Improving our technical ability to anticipate long-term results and overcome obstacles like off-target effects and treatment resistance is crucial if we are to fully realise the therapeutic promise of these modulators in clinical settings. This calls for ongoing preclinical research initiatives as well as extensive clinical studies [31].

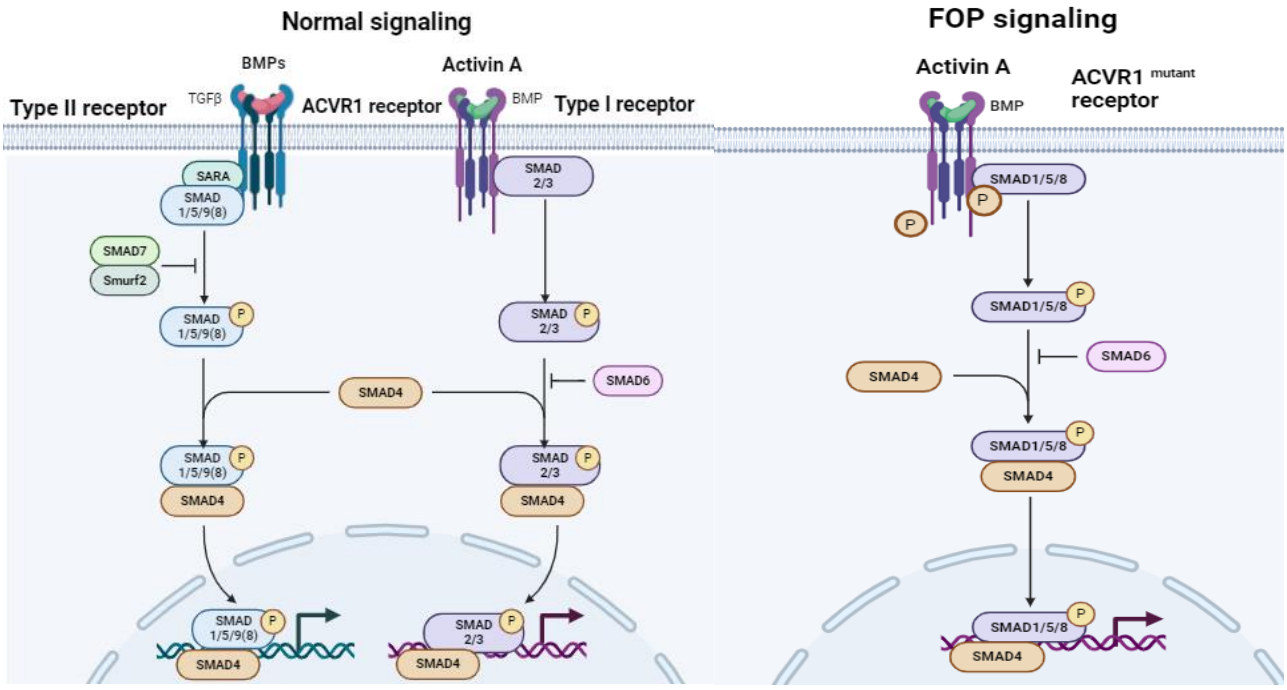

Fig 2: Mutant ALK2 receptors cause an aberrant form of BMP signalling in FOP, upsetting the regular route. Generally, type II and type I receptors work together to form a receptor complex, which is coordinated by BMP or activin A molecules. across phosphorylation processes set off by this complex, signals are eventually sent across the BMP and TGF-β pathways by activating downstream SMAD proteins such as SMAD1/5/9 for BMP and SMAD2/3 for activin A. But in FOP, aberrant activin A signalling results in aberrant BMP signalling activation through mutant ALK2 receptors. The onset of FOP symptoms is significantly influenced by this deviation from the standard procedure. Furthermore, the disease is made worse by these mutant ALK2 receptors, which increase overall signalling activity.

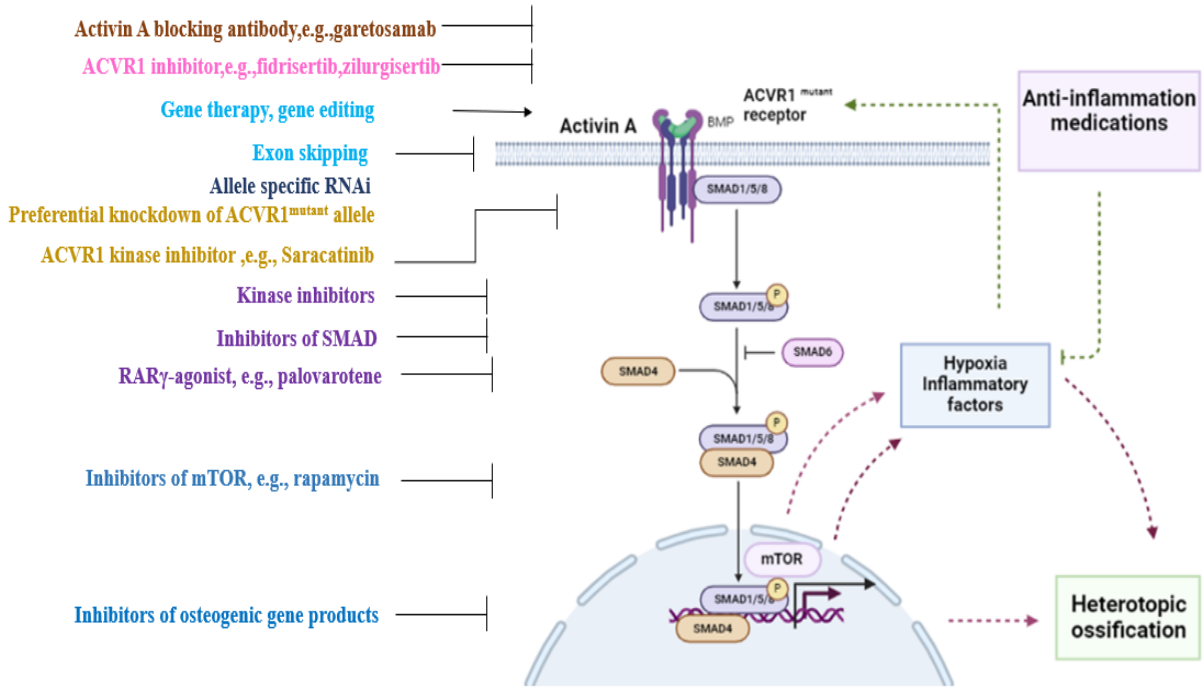

Fig 3: The aberrant BMP signalling route in FOP is illustrated in this picture, which also identifies the precise points at which the pathway is modulated by therapeutic therapies. For example, garetosamab and other activin A blocking antibodies disrupt activin A-driven signalling. ZILURISERTIB and Fidrisertib, two ACVR1 inhibitors, block the action of mutant ACVR1 receptors. The objective of genetic therapies, such as, allele-specific RNA interference, exon skipping, and selective stimuli of mutant variants of ACVR1, is to diminish the generation of faulty ACVR1 receptors. Saracatinib is one of the ACVR1 kinase inhibitors that prevents the ACVR1 receptor from acting as a kinase. SMAD inhibitors and agents that target SMAD kinase interfere with the BMP pathway's downstream signalling. Palovarotene, a RARγ-agonist, increases the efficiency of proteasomes in breaking down the SMAD1/5/9(8) proteins. Bone morphogenetic protein products and mTOR inhibitors influence how cells react to BMP signalling. Furthermore, innovative tactics.

Robust growth factors that belong to the Transforming Growth Factor Beta group are called bone morphogenetic proteins (BMPs). More than 20 different BMP members are known to exist in human biology, and they all play specialised roles in vital developmental processes such, bones creation, red blood cell formation, and nervous system formation. The predominant mode of operation for the BMP signalling cascade is the canonical Smad's-dependent pathway. Initially, a heterotetrametric complex is formed by a homodimer of type II receptors and a homodimer of type 1 receptors, which is then activated by BMPs. Subsequently, the type I

receptors undergo phosphorylation and activation facilitated by the type II receptors, which in turn phosphorylate Smad1/5/9 (also referred to as Smad1/5/8). Following their phosphorylation, Smad1/5/9 and Smad4 combine to create a complex that moves into the nucleus. Target genes controlled by BMPs are transcriptionally triggered when this complex attaches to BMP response sites inside the nucleus [31]. An increased risk of cancer has been linked to dysfunctions in four type I receptors (ALK1, ALK2, ALK3, and ALK6) that are involved in BMP signalling. Within the intracellular glycine-serine-rich (GS) region of ALK2, the often-occurring mutation R206H causes FOP. In order to control ALK2 activation when BMP ligands are not present, the FKBP12 protein, sometimes referred to as FKBP1A, binds to ALK2 at this mutation location. Despite the lack of BMP ligands, it has been shown that the ALK2R206H mutation causes baseline abnormal BMP signalling. Initially, BMP ligand stimulation was believed to contribute to the progression of ectopic endochondral ossification in FOP. Later, further mutations associated with FOP were found in the ALK2 kinase and GS domains, which were found to correlate with the ages at which the disease manifests and the degree of aberrant bone production [32][33][34].

Under normal circumstances, TGF-B signalling is typically mediated by activin A. However, recent research has indicated that in FOP, activin A triggers BMP signalling abnormally. In regular conditions, BMPs activate type I receptors ALK1, ALK2, ALK3, and ALK6 to initiate BMP signalling, which relies on Smad 1, Smad 5, and Smad 9. On the other hand, activin A utilizes type I receptors ALK4 and ALK7 to initiate TGF-B signalling, which is reliant on Smad 2 and Smad 3. It is noteworthy that activin A usually does not trigger BMP signalling that is dependent on Smad1/5/9. In vitro investigations on cells expressing ALK2R206H have demonstrated that activin A can, in fact, stimulate BMP signalling that is dependent on Smad1/5/9 but not otherwise. Furthermore, studies utilising a conditional knock-in rat model to investigate FOP in living organisms have demonstrated that activin A promotes aberrant bone growth. Notably, antibodies that specifically target activin A can halt the abnormal ossification seen in the FOP animal model. This supports the hypothesis that mutant ALK2 is the means by which activin A interacts with the BMP cascade [35][36][37].

2.4 Receptor targeting:

a. Inhibition of Glycogen Synthase Kinase-3 (GSK-3) β

New competitors in this area are GSK-3β inhibitors, which act as BMP signalling cascade downstream regulators, and PPARγ agonists in order which primarily stimulate the creation of fat cells rather than bone cells. While the latter promotes the expression of adipogenic genes to counteract osteogenesis, the former aims to prevent pluripotent stem cells from undergoing the osteogenic change [38]. GSK-3 is a crucial component of the BMP signalling system, and compounds that target it block its action. By doing this, they impede the process by which cells change into entities that make bones, hence impeding heterotopic ossification (HO) [39]. The first seeks to inhibit the transformation of pluripotent stem cells into bone-forming cells, whereas the latter combats bone formation by boosting the expression of genes responsible for fat cell development.

b. Stem cells

Innovative therapeutic opportunities have been made possible by the development of stem cell innovations, most notably MSCs and iPSCs. Mesenchymal stem cells (MSCs), which possess multipotent characteristics enabling their transformation into adipocytes, chondrocytes, and osteoblasts, originate from both bone marrow and adipose tissue. Their effectiveness has been demonstrated in addressing abnormal bone formation in models of Fibrodysplasia Ossificans Progressiva (FOP) [40].

c. Mesenchymal Stem Cells (MSCs)

Preclinical investigations have yielded promising results, demonstrating that mesenchymal stem cells (MSCs) possess the capability to restrain bone formation in models of FOP [41]. Mesenchymal stem cells (MSCs) can be extracted from a number of sources that include bone marrow, blood from the umbilical cord, and fatty tissue. Furthermore, MSCs may experience genetic changes that improve their efficacy as therapeutic agents [42]. However, using MSCs has a unique set of challenges of its own. Research findings highlight several intrinsic challenges associated with MSC therapies, such as reactions occurring at the injection site, the potential for uncontrolled proliferation or migration of cells from their original locations and their differentiation into unforeseen cell types, the inconsistency in yielding anticipated results among cells, and the risk of tumour development [43][44].

d. Induced Pluripotent Stem Cells (iPSCs)

The development of induced pluripotent stem cells (iPSCs) from mature, differentiated cells represents a highly promising advancement in regenerative medicine. This breakthrough makes it easier to create customised induced pluripotent stem cells (iPSCs), which provides a large pool of adaptable cells that can be genetically modified and differentiated into specific cell lineages to treat a range of genetic and degenerative diseases. Upon transplantation, this approach helps mitigate the risk of graft versus host disease [45]. First, it was demonstrated that Oct4/Sox2/Klf4/c-Myc or Oct4/Sox2/Nanog/LIN28, four important factors, having increased expression, could induce fibroblast cells to reprogramme into iPS cells via viral integration. This was followed by the discovery that fibroblasts may be used to generate iPS cells by the integration of Oct4/Sox2/Klf4, without the need for c-Myc [46]. Theoretically, patients with FOP may benefit from having these reprogrammed cells replace damaged bone-forming cells. iPSCs are essential for both therapeutic and scientific applications related to FOP research because of their capacity to grow cells specific to individual patients or disorders. However, there are particular difficulties with iPSCs. An important technical hurdle in the reprogramming of cells, such as MSCs, lies in their intricate and complex nature. Similar to MSCs, there exists a slight yet notable risk of tumorigenesis associated with PSCs. The difficulties encompass the intricacy of technical procedures and the efficiency of cell reprogramming. By developing improved reprogramming processes and investigating ways to reduce financial obligations, these problems could be lessened [47].

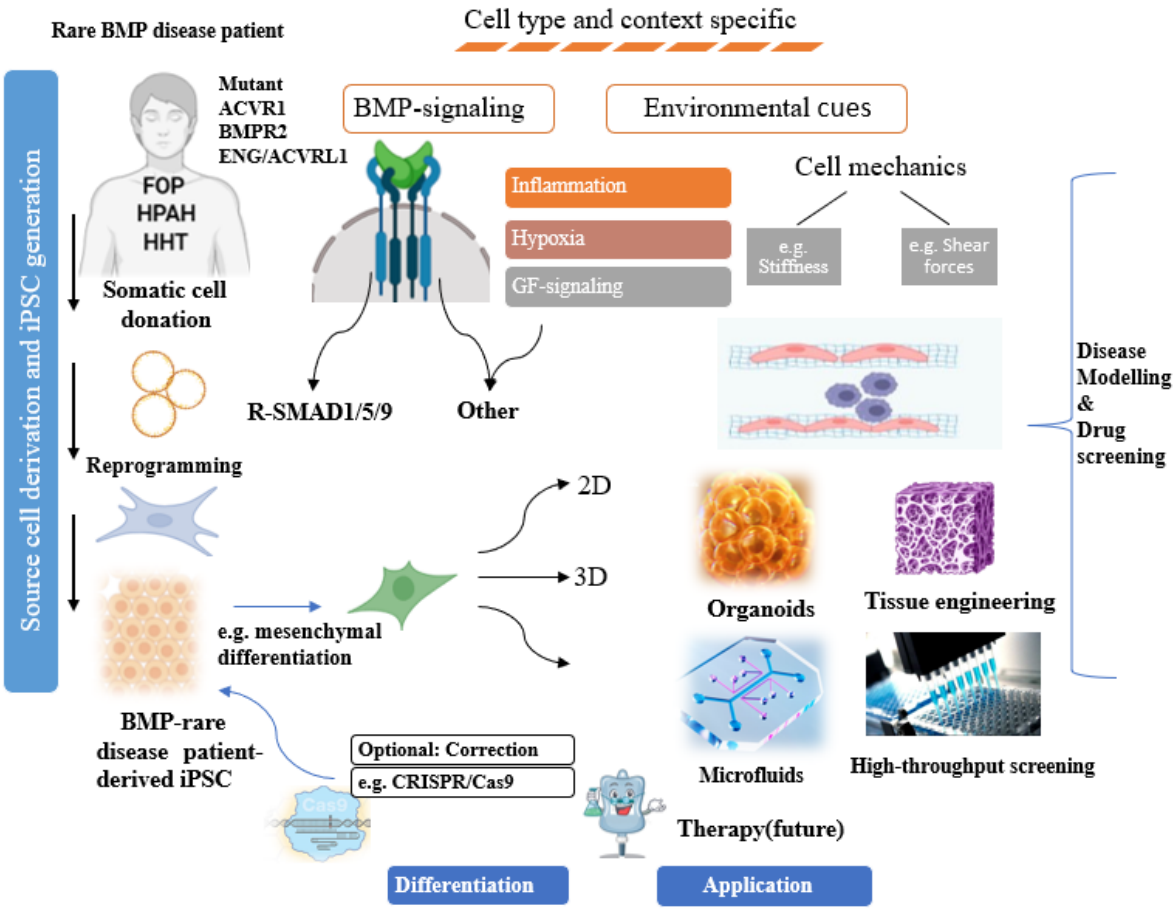

Fig 4: Progress in Modelling BMP-Related Rare Diseases using Human iPSCs

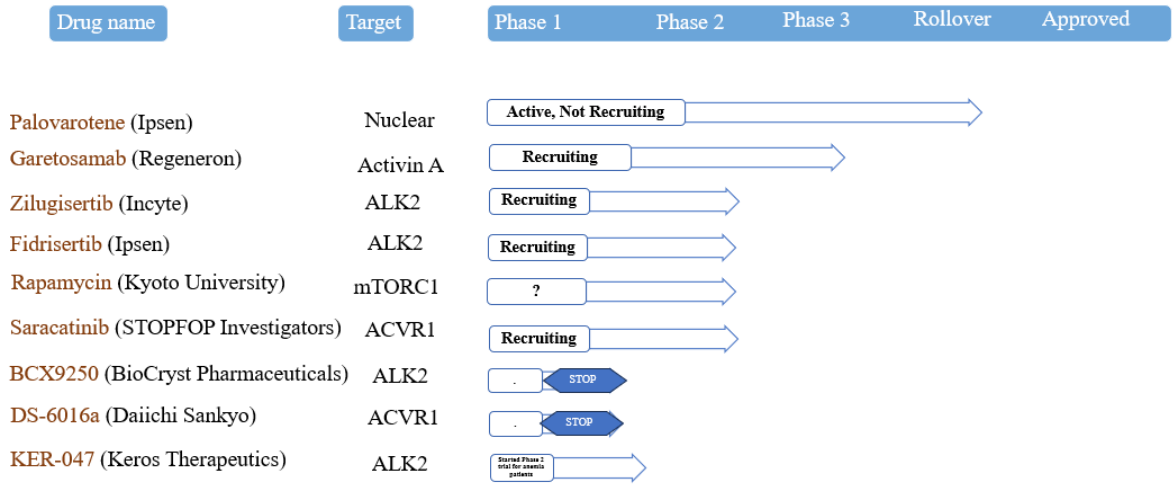

Table 2: Current clinical trials targeting therapeutic interventions for FOP are underway, aiming to advance treatment options. These trials focus on interventional approaches to manage the condition.

2.5 Focusing on BMP signalling: Inhibitors and Allosteric Modulation

In order for FOP to form, the BMP signalling pathway is essential. Intracellular signalling requires conformational changes generated by ligands, which are obstructed by transcriptional modulators such as BMP receptor antagonists. In animal models, allosteric inhibitors like dorsomorphin effectively block aberrant bone formation by selectively targeting BMP type I receptors, particularly ACVR1. Novel ligand traps that use fusion proteins that fuse the extracellular region of ACVR2A or ACVR2B with the Fc portion of IgG1 have been created to capture BMP receptors. These traps indirectly impede BMP signalling. Palovarotene, currently the sole FDA-approved medication for FOP, emerges as a promising avenue for further investigation due to its mode of action. Additional strategies include BMP signalling downstream inhibitors like fendiline and perhexiline, BMP receptor kinase blockers such dorsomorphin, and compounds generated from fungi that impede bone formation like NG-393, and trichocyalide A/B, NG-391 [48][49][50][51].

2.6 Simultaneous Targeting through mTOR Pathway Suppression

A popular immunosuppressive drug, rapamycin inhibits mechanistic target of rapamycin complex 1 (mTORC1) by binding to FKBP12 and creating a complex. The serine-threonine protein kinase mTORC1 is essential in initiating intracellular signalling pathways linked to cellular proliferation, one of which involves HIF1α [52]. It has its effect by blocking mTORC1, which obstructs the as well as osteogenesis pathways that are activated by activin A. In FOP therapy, PI3Kα inhibitors, specifically BYL719, represent a promising alternative to rapamycin. Particularly in cells with ACVR1 mutations associated with FOP, these inhibitors have shown notable effectiveness in preclinical conditions. Together with the mTOR pathway, they work by simultaneously suppressing other important signalling pathways such as SMAD and AKT. Their ability to successfully treat FOP is demonstrated by their diverse strategy [53][54][55].

Palovarotene

Retinoid signalling, facilitated by retinoic acid receptors (RARs), holds significant sway over chondrogenesis and skeletal development. Research underscores an antagonistic dynamic between retinoid signalling and chondrogenesis, where retinoid intervention dampens chondrogenesis. This insight fuels exploration into targeting the retinoid pathway for conditions like Fibrodysplasia Ossificans Progressiva (FOP). While direct retinoid therapy faces constraints due to broad effects, selective RAR agonists, such as palovarotene, exhibit promise in thwarting heterotopic ossification in both animal models and clinical trials. Palovarotene's Phase 3 trials showcase reductions in ossification volume, flare-up duration, and pain among FOP patients. Despite its potential, palovarotene bears risks, including teratogenicity and mucocutaneous side effects, necessitating vigilant monitoring during clinical application [56][57][58].

2.7 Counteracting Overactive Activin A Signalling with Antibody Intervention

Our knowledge of FOP biology was drastically altered in 2015 when Hatsell et al. discovered that the unusual ligand for ACVR1, activin A, stimulates signalling through the SMAD 1/5/8 pathway in the mutant ACVR1R206H receptor. Aberrant activin A signalling in cells harbouring the ACVR1R206H mutation has been effectively regulated through the use of neutralizing antibodies. These antibodies function by blocking the interaction between the ligand and receptor, thus interrupting subsequent signalling pathways and ultimately diminishing the occurrence of heterotopic ossification. Hino et al. provided support for this result by showing that mice injected with activin A and stem cells obtained from FOP patients underwent heterotopic ossification induction. Further investigations using genetically modified mice models verified activin A's involvement in the pathophysiology of FOP. By using a particular antibody to block activin A, heterotopic bone growth was avoided. As a result, Phase 2 trials for the treatment of FOP are being conducted on an anti-activin A antibody (REGN2477), which has demonstrated promise in preventing aberrant bone production. However, as activin A is essential for many biological functions, such as immunology, inflammation, and tissue growth, close observation of its inhibition's effects is essential [59][60][61][62].

2.8 Immunotherapy

The innate immune system is implicated in FOP, according to evidence from a variety of study levels. Results show that early FOP lesions contain mast cells, lymphocytes, and macrophages; muscle cell death associated with these cells; viral infections cause flare-ups; and the timing of these events is significant. Corticosteroids also have a positive effect on early flare-ups. The innate immune system is also thought to be responsible for the initialization of heterotopic ossification, according to recent investigations on mice [63][64][65]. Immunocheckpoint inhibitors and monoclonal antibodies are examples of novel therapeutic approaches that show promise for patient care [66].

2.9 Precision Antigen Targeting with Monoclonal Antibodies

The precision of monoclonal antibodies (mAbs) is being praised, and they are becoming a viable treatment option for FOP. mAbs are designed to attach to particular antigens on abnormal cells, designating them for immune-mediated eradication. For the specific removal of cells, they can also be used with cytotoxic agents. mAbs need substantial preclinical and clinical research to prove safety and efficacy. They are specifically made to target pathways implicated in FOP, such as aberrant BMP signalling and increased cytokine production. It is necessary to investigate combination therapy and cost-reduction measures in order to address issues such as resistance and excessive costs [67][68].

3. REGULATING IMMUNE REACTIONS WITH IMMUNE CHECKPOINT BLOCKERS

In addition to monoclonal antibodies, immune checkpoint inhibitors (ICIs) are being investigated as possible FOP therapies. ICIs function by blocking signals that prevent immune systems from identifying aberrant cells, which may help with more focused cell removal in FOP. Preclinical investigations have demonstrated their potential through the modification of immune responses and the reduction of activation of key molecules implicated in the pathogenesis of FOP. To guarantee safety and efficacy, however, extensive assessments are required before to clinical use, taking into account difficulties such immune-related adverse events and off-target effects. Progressing this treatment strategy for FOP requires creating highly targeted inhibitors and carrying out thorough clinical studies [69][70].

3.1 Infiltrating Cells

A build-up of mast cells, monocytes, and macrophages is frequently seen in FOP inflammatory lesions. These infiltrating cells drive heightened secretion of cytokines and chemokines, such as IL-3, IL-7, IL-8, IL-10, CCL5, CCR7, and CXCL10. These cells produce a variety of chemokines and cytokines that exacerbate the inflammatory response. There may be a therapy option available if studies employing mice models are correct and fewer of these invading cells can considerably lessen heterotopic ossification. Targeting these cellular infiltrates as a treatment approach for FOP, however, may not be as successful without comprehensive preclinical and clinical investigations. Concerns include immune cell depletion, which can have detrimental effects and necessitates close monitoring and the creation of mitigation plans like to those used in oncology [71][72][73].

4. REUTILIZED MEDICATIONS FOR FOP: A RAY OF HOPE

Creating new drugs for exceedingly rare conditions like FOP is quite difficult. Repurposing already-approved medications is an alternate strategy that provides speedier, less expensive, and less dangerous paths. This strategy, known as pharmaceutical repositioning, is especially effective for uncommon conditions such as FOP, which encounter distinctive hurdles in the process of therapeutic advancement. Through repurposing, medications like thalidomide and sildenafil have in the past revealed new uses. Currently, medications that target the HIF1α and PI3Kα pathways, corticosteroids, and inhibitors show promise in treating FOP because they target important pathways like BMP signalling and inflammation, which prevent heterotopic ossification. Saracatinib was originally developed to treat cancer, and in preclinical models, it shows encouraging suppression of ACVR1, indicating that more clinical research is necessary. Comprehensive trials are necessary, even if initial clinical studies of repurposed medicines for FOP seem promising. This process can be accelerated by state-of-the-art methods like as computational biology and patient-derived cell models. In order to expedite drug approval and provide a successful and promising path for comprehending and treating FOP, cooperation between researchers, patient communities, and regulators is essential [74][75][76][77].

Saracatinib

Saracatinib exhibited promising pharmacokinetic characteristics, demonstrating favourable oral absorption and an extended half-life of approximately 40 hours. It was first created by AstraZeneca UK Limited as a strong kinase inhibitor that targeted Src/Abl kinases for the

treatment of cancer. AstraZeneca worked with research organisations such as the Medical Research Council, Europe's Innovative Medicines Initiative, and the National Institutes of Health to repurpose Saracatinib for experimental medicine studies, even though the drug's initial trials in different cancers showed insufficient efficacy for further investigation. Recent phase II trials have explored the possibility of using Saracatinib as a therapy for cognitive impairment and lymphangioleiomyomatosis. The trials used lower daily doses for longer treatment periods. Saracatinib has also been found in recent research to be a strong ALK2 inhibitor, which may be useful in the treatment of fibrodysplasia ossificans progressiva (FOP). In preclinical animals, Saracatinib successfully inhibited heterotopic ossification without affecting processes related to development. Notably, a phase II clinical research supported by Europe's Innovative Pharmaceuticals Initiative and headed by an investigator was started in 2020 with the purpose of assessing Saracatinib's safety as well as effectiveness in adult individuals with FOP. Participants in STOPFOP, a six-month double-blind randomised controlled study, are observed using low-dose whole-body computed tomography (CT) to evaluate changes in heterotopic bone volume. An open-label augmentation phase then follows [78][79][80][81][82][83][84].

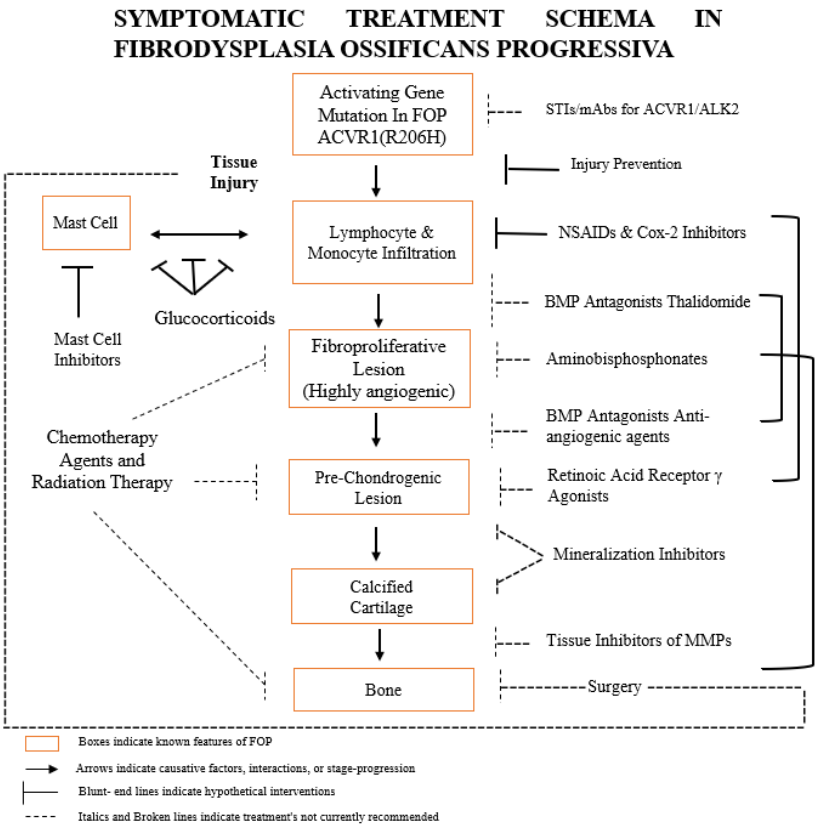

Fig 5: Symptomatic Treatment of FOP

CONCLUSION

The development of novel therapeutic targets for Fibrodysplasia Ossificans Progressive (FOP) holds considerable promise for better symptom management, altering disease progression, and providing personalized treatment options for those affected. Innovative strategies such as gene therapy, small molecule treatments, stem cell-based methods, immunotherapy, and nanoparticle delivery systems are currently under investigation to address the root causes of FOP and prevent abnormal bone growth.

Nevertheless, several obstacles impede the development of new therapies for FOP. These include difficulties in patient recruitment due to the disease's rarity, variability in how the disease manifests, a shortage of reliable biomarkers, and ethical issues related to placebo-controlled trials. Despite these challenges, ongoing research and clinical trials offer hope for enhanced management strategies and therapeutic options.

Looking ahead, priorities include the further identification and validation of therapeutic targets, comprehensive safety and efficacy assessments, optimization of delivery techniques, and better patient selection and stratification. Additionally, exploring combination therapies is promising. By decoding the intricate mechanisms of FOP and creating targeted treatments, the objectives of improved patient outcomes, disease modification, and ultimately finding a cure for FOP can be actively pursued.

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