REVIEW ARTICLE

Navigating Fibrodysplasia Ossificans Progressiva (FOP): Insights into Diagnosis, Management and Therapeutic Advancements

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ABSTRACT

Fibrodysplasia ossificans progressiva(FOP), famously known as stoneman syndrome is a lesser-known clinical entity. This condition begins its clinical presentation at birth. Delay in diagnosis or wrong diagnosis leads to unnecessary procedures which leads to worsening of the condition. The goal of this article is to review the existing literature on epidemiology, clinical presentation and relevant aspects for the diagnosis and treatment options for FOP. In addition, we also briefed about the ongoing research activities on this condition. FOP classically presents as congenital bilateral great toe deformity and early onset progressive heterotrophic ossification that can result in a deformed secondary skeleton. There occur several flare-ups during lifetime that can be triggered by seemingly minor trauma such as intramuscular immunisation, influenza-like viral illnesses, pulmonary infections, blunt muscle trauma, muscle fatigue, etc. There are no known predilection or risk factors for occurrence of this disease. Since August 2023, Sohonos (palovarotene) capsules have been approved by the U.S. Food and Drug Administration (FDA) to reduce the volume of extra-skeletal bone formation, or new heterotopic ossification, in adults and children with FOP who are 8 years of age or older for females and 10 years of age or older for males. Ongoing clinical trials are evaluating additional therapies, such as Garetosmab and Saracatinib, for their potential to manage flare-ups and prevent new heterotopic ossification.

KEY WORDS: Stoneman syndrome, Sohonos, Palovarotene, Heterotopic ossification, BMP signalling pathway, ACVR1

Introduction

Despite affecting a relatively small population, rare diseases present major problems to both individuals and society. Only a small portion of the vast list of uncommon diseases that exist are acknowledged, most of them are yet to be discovered. Due to the low prevalence of such conditions, there is very less information available about the nature, progression, and management of them. As a result, rare diseases have become a crucial worldwide health issue. Only a small number of these illnesses can be treated effectively. Any patient suffering from such conditions must deal with a range of issues as accurate diagnosis and effective treatment are difficult. In addition to the physical challenges of managing a rare ailment, patients and their families may also face financial hardships.

One such condition is Fibrodysplasia ossificans progressiva (FOP), also known as Stoneman Syndrome, it is an ultra-rare entity with 1 case per 2 million population globally, and it is the most disabling condition of extra skeletal ossification known in humans. It does not have any racial, ethnic, gender, or geographic predilection [1-3].

It is caused by activating mutations in the activin A receptor, type 1/activin-like kinase-2 (ACVR1/ALK2), a bone morphogenetic protein (BMP) type 1 receptor. These mutations drive abnormal bone formation, leading to progressive disability [4, 5]. FOP's complex clinical presentation and diagnostic challenges often result in misdiagnosis, which can exacerbate the condition through inappropriate interventions [1, 3]. Significant advances in treatment, including the 2023 FDA approval of palovarotene (Sohonos), have improved management options, while ongoing research explores novel therapies like gene editing and targeted inhibitors to alleviate symptoms and reduce disability [6].

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The aim of this article is to review the literature on the main characteristics of FOP, the relevant aspects for the diagnosis, treatment options for this pathology (highlighting the recently approved drug palovarotene), and to briefly discuss ongoing research activities on FOP.

Methods And Materials

The literature review was searched on databases: PubMed, including Medline and Google Scholar, using keywords: Fibrodysplasia ossificans progressiva, Stoneman syndrome, progressive heterotopic ossification, BMP signaling pathway, ACVR1, ALK2.

Epidemiology

FOP is a remarkably uncommon hereditary disorder characterized by its remarkable scarcity in the world. With an approximate prevalence of around 1 case for every 2 million people, FOP stands as perhaps of the most uncommon genetic condition experienced in clinical practice [1-3]. This rarity has contributed to its relatively less recognition within the medical community which led to potential challenges in diagnosis and appropriate management [3]. FOP does not express any distinct racial, geographic, ethical, or gender predilection, making it a condition that can affect individuals from varied backgrounds [3, 7].

FOP prevalence varies: ~0.65/million in North America, 0.47 in Western Europe, 0.27 in Latin America, 0.05 in Africa, and 0.04 in Asia-Pacific [8].

Etiopathogenesis

FOP is inherited in an autosomal dominant pattern though most cases occur sporadically [3]. After a fetus's bones begin to form in the womb, an inhibitory protein typically deactivates the protein that induces ossification, but in patients with FOP, the protein continues to function [3, 4]. When injured muscle or connective tissue cells at the sites of injury or growth incorrectly express a bone repair enzyme during apoptosis (self-regulated cell death), excess bone morphogenetic protein 4 (BMP4) produced by the immune system response results in abnormal bone formation in patients with FOP. BMP type I receptor ACVR1/ALK2 activating mutations are to blame [4, 5]. As a result of the abnormal ACVR1/ALK2 receptor-FKBP1A connection caused by these activating mutations, downstream bone morphogenetic protein (BMP) signalling is amplified [5]. Inflammatory processes and hypoxia play a significant role in triggering the flare ups [3]. Following trauma or other triggers, the resulting bone forms its own distinct skeletal components independently of the rest of the skeleton [3, 5]. Heterotopic ossification often begins in cervical paraspinal muscles, progressing axial to appendicular, cranial to caudal, and proximal to distal. These ossified tissues can fuse with normal bone. Asymmetric trunk–pelvis fusion frequently leads to scoliosis [3].

Clinical Features

FOP is classically characterized by congenital bilateral hallux valgus malformation and early onset heterotopic ossification [9, 10]. FOP causes episodic flare-ups, often beginning in the first decade, triggered spontaneously or by trauma. During flare-ups, soft tissues (muscles, tendons, fascia, ligaments, aponeuroses) undergo endochondral ossification, leading to permanent immobilization [9, 10].

Scalp nodules, commonly appearing in childhood, are often the first postnatal manifestations of FOP. Notably, a stiff neck often precedes cervical bone ankylosis, and if any residual movement is left, that may lead to chronic headaches and arthritic symptoms [9, 10]. The heterotopic ossification progresses in a characteristic anatomical and temporal pattern, initially affecting dorsal, axial, cranial, and proximal regions of the body before extending to ventral, appendicular, caudal, and distal regions. Atypical FOP features include short thumbs and clinodactyly [9, 10].

Though the flare-ups are episodic, the disability they cause is cumulative. As a result, most patients become wheelchair-bound and unable to perform daily activities by their third decade of life [11]. Flare-ups can be triggered by seemingly minor events, such as intramuscular immunisation, muscle fatigue, blunt muscle trauma, bruises, falls, or influenza-like viral illnesses [11]. Even surgical procedures like biopsies have the potential to induce explosive flare-ups [12]

Interestingly, some areas in the body, like smooth muscles, cardiac muscles, diaphragm, tongue, and extraocular muscles, remain unaffected by the ossification process [9].

Complications

One common complication associated with this condition includes frequent catastrophic falls [13]. According to a study 54% percent of all falls suffered by the patients with FOP led to permanent disability compared with 4% of all falls led to permanent disability in the normal people [13]. Weight loss might occur due to the ankylosis of the jaw. In some cases, weight loss might also occur due to superior mesenteric artery syndrome, adding to the challenges faced by those affected [14]. Cardiorespiratory failure and death in early age can occur due thoracic insufficiency syndrome from fixation and immobility of the chest wall [13].

Table 1: Summary of clinical features of FOP

1. Congenital bilateral hallux valgus malformation and early onset heterotrophic ossification.
2. Soft tissue swellings which transform into mature heterotrophic bone, causing immobilisation (flare-ups).
3. Stiff neck and cervical bone ankylosis.
4. Flare-ups triggered by seemingly minor events like intramuscular immunisation, muscle fatigue, blunt muscle trauma, bruises, falls, or influenza-like viral illnesses.
5. Atypical FOP features: short thumbs, clinodactyly.
6. Frequent falls due to gait incoordination and immobilisation, which are often catastrophic.
7. Increased risk of fractures due to immobilisation and chronic prednisone usage.
8. Increased risk of head injuries especially due to immobilisation of upper limbs.
9. Neurological symptoms: focal demyelination, CNS dysgenesis, brainstem hamartomatous lesions, and dysmorphisms.
10. Cumulative disability by third decade of life, leading to wheelchair use and limited activities.
11. Progeroid features.
12. Complications: weight loss due to jaw ankylosis, cardiorespiratory failure and sometimes death from thoracic insufficiency.

The immobilisation and the use of prednisone during flare-ups can increase the risk of fractures [15]. Deficiencies in gait coordination and loss of protective function by hands likely accounted for the severity of injuries, especially to the head, in people with FOP. Additionally, the effects may extend to the central nervous system (CNS) in the form of brainstem hamartomatous lesions and dysmorphisms [13]. These CNS manifestations may be variably associated with dental nuclei and/or calcification. Furthermore, neurological symptoms due to focal demyelination and CNS dysgenesis have been reported [13]. Progeroid features associated with mutations in ACVR1 might occur, which include osteoarthritis, hearing loss, alopecia, myelination defects, heightened inflammation, subcutaneous lipodystrophy, menstrual abnormalities, and nephrolithiasis [13, 16]. Progeroid features may secondarily be related to immobilization from progressive heterotopic ossification, including decreased vital capacity, osteoporosis, fractures, sarcopenia, and predisposition to respiratory infections. Clinical features are summarised in [Table. 1] [13, 16].

In addition, a significant deterioration in the quality of life secondary to progressive deterioration in physical abilities was observed in FOP. Studies showed that many of them also experienced anxiety, depression, or irritability during a flare-up as it can signal a worsening of the condition [11]. FOP presents a complex clinical picture, severely impacting mobility and quality of life. Recognizing its diverse features is key to effective management and care.

Diagnosis

The diagnosis of FOP demands a multi-faceted approach, including clinical evaluation, radiological imaging, and genetic testing. The clinical presentation of FOP is clear, with characteristic features such as congenital malformation of the great toes, which is considered a hallmark of the condition. However, the clinical presentation can fluctuate, making early diagnosis difficult [9]. Flare-ups are a chief diagnostic clue and must be carefully differentiated from other inflammatory conditions and soft tissue tumors to prevent unnecessary procedures that can worsen the disease [9].

Radiological imaging like X-rays, computed tomography (CT), and magnetic resonance imaging (MRI) are required to confirm the presence and extent of heterotopic ossification in those affected individuals [9, 14]. The classic anatomical patterns of heterotopic ossification have been well-documented in various studies, particularly in the neck, spine, shoulders, hips, and proximal limbs [9, 14].

Another way of diagnosing is via genetic testing which plays an important role in proving the diagnosis of FOP. Nearly all individuals with FOP have a particular heterozygous missense mutation (c.617G>A; p.R206H) in the ACVR1 gene, which encodes the activin A type I receptor [17]. This mutation is known to dysregulate bone morphogenetic protein (BMP) signalling, leading to the unusual formation of bone in soft tissues [17].Genetic testing, clinical assessment, and radiological imaging assume pivotal parts of diagnosis.

Differential diagnosis of FOP includes recognizing it from different symptoms along with comparing it to other diseases as a way of precise diagnosis would help to stay away from misdiagnosis and improper clinical intercessions. One of the essential differential diagnoses is progressive osseous heteroplasia (POH), a related problem that includes heterotopic solidification but basically affects subcutaneous fat instead of muscles and ligaments [9, 14]. Other differentials include aggressive juvenile fibromatosis, myositis ossificans, and soft tissue sarcomas, which may at first manifest as soft tissue swellings and can be confused with FOP in its initial phases [9, 14].

The uniqueness of FOP and the variability in its clinical presentation pose challenges to timely diagnosis. Misdiagnosis remains a concern, and studies have highlighted the importance of raising awareness among healthcare professionals to prevent procedures and interventions that are unnecessary [18]. Early and accurate diagnosis is pivotal to optimizing patient care, halting exacerbation of the condition, and providing

appropriate counselling for affected individuals and their families [9, 18].

Table 2: FDA recommendations in use of Palovarotene for FOP [6]

Manufacturing company / trade name	Composition / recommended dosage	Warnings and precautions	Common adverse effects	Remarks
Ipsen / Sohonos	Palovarotene / Adults and paediatric patients aged 14 years and older should take 5 mg of Sohonos once daily, with an increase in dose at the time of a flare-up to 20 mg once daily for 4 weeks, followed by 10 mg once daily for 8 weeks for a total of 12 weeks (20/10 mg flare-up treatment). Patients under 14 years, based on their body weight, should take from 2.5 to 5 mg of Sohonos	Skin-related Issues: Dry skin, lip dryness, itching, rashes, hair loss, redness, skin peeling, and dry eyes are linked to Sohonos. Some patients might need skin moisturisers, sunscreen, and eye drops, or a dose reduction. Metabolic Bone Disorders: Sohonos can impact bone health, potentially leading to reduced bone mineral content and density, increasing the risk of spinal fractures. Periodic radiologic assessment of spinal fractures is advised. Mood and Mental Health Effects: Sohonos may contribute to depression, anxiety, mood changes, and even thoughts of self-harm. Patients experiencing new or worsening symptoms should reach out to their healthcare provider. Night-Blindness and Driving: Sohonos can cause night-blindness, posing risks for nighttime driving.	Frequently observed side effects of Sohonos include dry skin, lip dryness, joint pain, itching, extremity pain, rashes, hair loss, redness, headaches, back pain, skin peeling, nausea, musculoskeletal pain, muscle aches, dry eyes, hypersensitivity, swelling in limbs, and fatigue	Sohonos carries a boxed caution for potential harm to embryos and foetuses, along with the risk of premature closure of bone growth in children. Medical professionals must confirm the non-pregnant status of individuals capable of pregnancy before starting treatment, and regularly during the course of therapy. It's advised to track the height development of growing paediatric patients. Prior to initiating Sohonos, all such patients should have their baseline skeletal maturity assessed. Ongoing observation is suggested every 6 to 12 months until patients attain full skeletal maturity or reach their adult height.

Treatment

Current Guidelines

Since August 16, 2023, the FDA has approved palovarotene (Sohonos) for FOP treatment in adults and children—females ≥8 years, males ≥10 years [6]. Palovarotene is an orally bioavailable selective retinoic acid receptor (RAR)γ agonist. This compound binds to RARγ and inhibits BMP (bone morphogenetic protein), SMAD (small mothers against decapentaplegic), and NF-κB (nuclear factor kappa B) signalling pathways [6]. It prevents chondrogenesis, hindering heterotopic ossification and allowing normal muscle repair. Recommended dosing for adults and those ≥14 years: 5 mg daily; during flare-ups, 20 mg daily for 4 weeks, then 10 mg daily for 8 weeks [6, 15]. For patients under 14 years, dosing is weight-based (2.5 to 5 mg daily).

Palovarotene carries a boxed warning for embryo-fetal toxicity and premature epiphyseal closure in growing pediatric patients [6].

Early inflammatory flare-ups affecting major joints of the appendicular skeleton and the jaw could be managed with high-dose glucocorticoids [9, 15]. Early glucocorticoid use (within 24 hrs) is beneficial but not advised for major joint, chest, or back flares unless critical, due to limited efficacy [9, 15]. Prednisone is typically dosed at 2 mg/kg once daily for 4 days in acute flare-ups, or 1-2 mg/kg once daily for 3-4 days to prevent flare-ups after soft tissue injury (maximum 100 mg/day). Intravenous methylprednisolone (7-15 mg/kg) or prednisolone (20-30 mg/kg) for 3 consecutive days (maximum 1000 mg/day) is used for severe cases [9,

[15]. Indomethacin and other nonsteroidal anti-inflammatory drugs are helpful, acting by mechanisms of prostaglandin inhibition and direct suppression of osteoblast cell cycle progression [14, 19].

For chronic pain and disease management, options include COX-2 inhibitors (e.g., celecoxib), mast cell stabilizers, leukotriene inhibitors, and occasional aminobisphosphonates [9, 15]. Celecoxib (100-200 mg twice daily for maintenance, 6 mg/kg twice daily for flare-ups, max 600 mg/day) is contraindicated in patients allergic to sulfonamides or with aspirin-sensitive asthma [15, 19]. Montelukast (4 mg for 2-14 years, 10 mg for >14 years, once daily at bedtime) requires monitoring for behavioral changes [15, 19]. Cromolyn (5 mg/kg four times daily for <2 years, 100 mg four times daily for 2-12 years, 200 mg four times daily for adults) has limited evidence for efficacy in FOP and should be used cautiously [9, 15]. Aminobisphosphonates, such as pamidronate (0.75 mg/kg/day for 3 days) or zoledronate (5 mg IV over 30 minutes, adults only), are contraindicated in renal dysfunction and have limited efficacy, requiring cautious use [14, 15]. Tofacitinib, a JAK inhibitor, has shown promise in reducing flare-ups in refractory FOP cases at 5-10 mg twice daily, though it is off-label and requires further study for efficacy and safety [9, 15]. Imatinib has been used off-label in children with uncontrolled FOP flare-ups but lacks proven efficacy. The ICC advises reviewing active clinical trials first, as off-label use may disqualify trial eligibility [15]. A summary of pharmacological interventions for FOP is given in [Table. 3].

Table 3: Pharmacological interventions for FOP symptomatic management

Drug	Mechanism	Remarks	Dosage
Corticosteroid (Prednisone, Methylprednisolone)	Decreases lymphocyte and macrophage recruitment and tissue infiltration; anti-inflammatory	Not recommended for flare-ups involving major joints, chest, or back unless critical, due to limited efficacy in these areas	Orally (Prednisone): 2 mg/kg once daily for 4 days in acute flare-ups; 1-2 mg/kg once daily for 3-4 days to prevent flare-up after soft tissue injury (Max dose=100 mg/day). IV: 7-15 mg/kg of methylprednisolone or 20-30 mg/kg of prednisolone for 3 consecutive days (Max dose=1000 mg/day).
NSAIDs (Non-specific COX-1 and COX-2 inhibitors)	Anti-inflammatory and anti-angiogenic, useful during flare-up		Ibuprofen: 4-10 mg/kg PO every 6 hrs, as needed. Indomethacin: 2-4 mg/kg/day PO divided in three doses (Max 150 mg/day).
Selective COX-2 inhibitor (Celecoxib)	Anti-inflammatory and potent anti-angiogenic	Not in patients allergic to sulfonamides or in ones with aspirin-sensitive asthma	100-200 mg BD for maintenance and 6 mg/kg PO BD for flare-ups (Max 600 mg/day).
Montelukast	Blocks inflammatory mediators (leukotrienes)	Should be monitored for change in behaviour and mood	(2-14 yo) 4 mg PO HS (>14 yo) 10 mg PO HS.
Cromolyn	Reduces mast cell degranulation	Limited evidence for efficacy in FOP; use with caution	(<2 yo) 5 mg/kg QID (2-12 yo) 100 mg PO QID (Adult) 200 mg PO QID.
Aminobisphosphonates	Anti-angiogenic, protects normotrophic bone from osteopenic effects of high dose glucocorticoids	Contraindicated in renal dysfunction; limited efficacy, use cautiously	Pamidronate: 0.75 mg/kg/day for 3 days. Zoledronate: Only adults (18 yo) 5 mg IV slow infusion over 30 minutes.
Tofacitinib	JAK inhibitor; reduces inflammatory signaling in refractory FOP cases	Off-label use; requires further study for efficacy and safety; may disqualify patients from clinical trials	5-10 mg PO BD (off-label, dosing based on case reports)

Prophylactic Strategies

Measures like implementing prophylactic dental strategies, avoiding intramuscular injections, preventing muscle fatigue, and minimizing passive movements are essential [15]. Similarly, proactive measures are vital to prevent falls, influenza, pulmonary infections, and complications arising from restrictive chest wall disease. Wearing a helmet to prevent head injuries and adapting toilet seats for comfort can be considered [15]. Other interventions like hearing aids for conductive hearing impairment, hydration promotion, dietary guidance, occupational therapy, warm water hydrotherapy, lower limb elevation, DVT prophylaxis, supportive stockings for lymphedema, and psychological support collectively contribute to the management of various aspects of FOP and enhance the overall well-being of patients with FOP [15]. Non-operative fracture stabilization is recommended [19].

Research by Hirotsugu et al. demonstrated the potential of Rapamycin, a mammalian target of rapamycin (mTOR) inhibitor, as a prophylactic therapy, effectively inhibiting Activin-A-induced heterotopic ossification in preclinical models. However, its inhibitory effects on angiogenesis should be considered when used in younger patients, and clinical efficacy remains unconfirmed [20].

Ongoing Research

Ongoing research efforts encompass a spectrum of targeted strategies for FOP. Notably, clustered regularly interspaced short palindromic repeats and CRISPR-associated protein 9 (CRISPR-Cas9) gene therapy involves precise editing of the ACVR1 gene mutation using guide RNA and the Cas9 enzyme, effectively halting abnormal bone growth by modifying the gene's DNA [21].

Studies exploring the therapeutic potential of Transforming Growth Factor beta (TGF beta) as targeted therapy in FOP are in progress [21]. Several researchers reported that allele-specific RNA interference (ASP-RNAi) could be used to create modified small interfering RNAs (siRNAs), which are capable of selectively silencing disease-causing ALK2 mutants linked to FOP while preserving the normal ALK2 allele [15, 21]. Significant progress has been made with small-molecule inhibitors targeting glycogen synthase kinase-3 beta and the bone morphogenetic protein signalling pathway [21]. Stem cell-based strategies, including mesenchymal stromal cells and induced pluripotent stem cells, offer potential for tissue regeneration and suppression of abnormal bone formation. Particularly noteworthy are induced pluripotent stem cells derived from urine cells [21].

In several studies, inhibition of the Casein kinase 2 (CK2)/herpesvirus-associated ubiquitin-specific protease (HAUSP)/RUNX2 pathway has demonstrated efficacy in blocking heterotrophic ossification [15, 16, 21]. Yeon-Suk Yang et al. reported that recombinant adeno-associated virus serotype 9 (AAV9) serotype transduction significantly reduces spontaneous heterotopic ossification in major cells of origin in animal models [15]. A phase 2 LUMINA-1 trial by Baujat et al. indicated that Garetosmab, a fully human monoclonal antibody inhibiting Activin A, prevented new heterotopic ossification lesions in FOP patients, though it did not significantly reduce lesion activity in pre-existing lesions ($P = 0.0741$) [15, 21].

Bernad J. Smilde et al.'s STOPFOP trial (NCT04307953) demonstrated that Saracatinib, a potent inhibitor of ALK2/ACVR1 kinase and Src kinase, reduced heterotopic ossification formation in animal models, with ongoing phase 2/3 trials evaluating efficacy and safety in humans [15, 21]. A phase 2/3 trial (NCT05628714, ASH-FOP-201) is recruiting to evaluate andecaliximab, a monoclonal antibody targeting matrix metalloproteinase 9, for safety and efficacy in reducing new heterotopic ossification and flare-ups in pediatric (≥2 years) and adult FOP patients, including a lead-in phase for participants aged 12 years and older [15].

An observational study at UCSF is recruiting to assess off-label use of anti-IL1 therapies (anakinra or canakinumab) in severe FOP cases to block ACVR1-induced flare activity and heterotopic ossification, with preliminary data suggesting reduced flare frequency [15]. These advancements hold potential as innovative therapeutic agents for FOP and may offer a path toward revolutionary FOP treatment and symptom alleviation. Information about ongoing clinical trials is briefed in [Table. 4].

Role Of Public Health Organizations

Regional and international organizations play an important role in improving the quality of life of those they reach in the global FOP community. However, globally, fundamental issues remain around raising awareness of FOP among healthcare professionals, identifying individuals with FOP, reducing time to diagnosis, and ensuring access to best practices in care, support, and clinical research [22].

The FOP Connection Registry (https://classic.clinicaltrials.gov/ct2/show/record/NCT02745158) serves as a comprehensive database to bring together information from FOP patients, caregivers, and physicians. Its purpose is to enhance collaboration, support research, and contribute to the advancement of knowledge and treatment options for FOP. As of 2025, the registry continues to expand, facilitating global collaboration and data sharing to accelerate FOP research.

Table 4: Ongoing clinical trials in the treatment of FOP

Clinical trial	Status	Intervention	Phase	Mechanism of action
https://clinicaltrials.gov/ct2/show/NCT04307953	Recruiting	Saracatinib + placebo	Phase 2/3	Inhibits Src kinase and ALK2 activity, reducing heterotopic ossification formation.
https://clinicaltrials.gov/ct2/show/NCT05039515	Active, not recruiting	IPN60130 (Fidricertib) + Placebo	Phase 2	Inhibit the activity of an enzyme ALK2, which is thought to play a crucial role in promoting the formation of heterotopic ossification.
https://clinicaltrials.gov/ct2/show/NCT05394116	Active, not recruiting	Garetosmab + Placebo	Phase 3 (LUMINA-1 trial showed prevention of new HO lesions but no significant effect on pre-existing lesions, P = 0.0741)	Monoclonal antibody inhibiting Activin A.
https://clinicaltrials.gov/ct2/show/NCT05090891	recruiting	INCB000928 + Placebo	Phase 2	Inhibits the activity of the mutant ACVR1 protein.
https://clinicaltrials.gov/ct2/show/NCT05628714	Recruiting	Andecaliximab + Placebo	Phase 2/3	Monoclonal antibody targeting matrix metalloproteinase 9 to reduce heterotopic ossification and flare-ups.
ASH-FOP-201 (NCT number pending)	Recruiting	Andecaliximab + Placebo	Phase 2/3	Monoclonal antibody targeting matrix metalloproteinase 9 to reduce heterotopic ossification and flare-ups.
UCSF Observational Study (no NCT number)	Recruiting	Anakinra or Canakinumab (off-label)	Observational	Anti-IL1 therapies to block ACVR1-induced flare activity and heterotopic ossification.

Conclusion

Fibrodysplasia Ossificans Progressiva (FOP) poses significant diagnostic and therapeutic challenges due to its rarity and progressive heterotopic ossification. The 2023 FDA approval of palovarotene marks a critical advancement in managing flare-ups. Current treatments include cautious glucocorticoid use, NSAIDs, and off-label tofacitinib and imatinib, while trials like Garetosmab (NCT05394116), Saracatinib (NCT04307953), andecaliximab (ASH-FOP-201), and anti-IL1 therapies (UCSF observational study) explore novel therapies. Ongoing preclinical research into gene and stem cell therapies offers hope for future treatments. Continued efforts are needed to improve diagnostics and develop effective interventions for this devastating condition.

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