

Monitoring and Management of Fibrodysplasia Ossificans Progressiva: Current Perspectives

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Abstract: Fibrodysplasia ossificans progressiva (FOP), sometimes known as myositis ossificans progressiva, is an ultra-rare disease in which bone is formed in muscular tissue, tendons and ligaments. This is known as heterotopic ossification (HO). FOP is caused by a heterozygous mutation in the highly conserved ACVR1/ALK2 gene which affects about 1 in 1.5–2 million individuals. At birth, patients with the predominant R206H mutation only exhibit a bilateral hallux valgus. During childhood, heterotopic bone formation develops in a typical pattern, affecting the axial muscles first before appendicular body parts are involved. HO can start spontaneously but is often elicited by soft tissue trauma or medical procedures. After soft tissue injury, an inflammatory process called a flare-up can start, followed by the formation of HO. HO leads to a limited range of motion, culminating in complete ankylosis of nearly all joints. As a result of HO surrounding the thorax, patients often suffer from thoracic insufficiency syndrome (TIS). TIS is the most common cause of a limited life expectancy for FOP patients, with a median life expectancy of 56 years. Management is focused on preventing soft-tissue injury that can provoke flare-ups. This includes prevention of iatrogenic damage by biopsies, intramuscular injections and surgery. Anti-inflammatory medication is often started when a flare-up occurs but has a poor basis of evidence. Several forms of potential treatment for FOP are being researched in clinical trials. Progression of the disease is monitored using CT and 18F-NaF PET/CT combined with functional assessments. Patients are regularly evaluated for frequently occurring complications such as restrictive lung disease. Here, we review the current management, monitoring and treatment of FOP.

Keywords: fibrodysplasia ossificans progressiva, heterotopic ossification, activin A receptor type 1, treatment strategies

Introduction

Fibrodysplasia ossificans progressiva (FOP) is an autosomal dominant disease with a prevalence of around 1 per 1.5–2.0 million people.¹⁻³ It is characterised by the formation of bone in muscles, tendons and ligaments. This ectopic bone formation is known as heterotopic ossification (HO).

Clinical Presentation

Patients with FOP are often born with a monophalangeal great toe with hallux valgus deformity (Figure 1). Although always present in patients carrying the classic FOP mutation (R206H), this malformation can vary in severity and might not be present in patients with variant mutations of FOP.^{4,5} Other skeletal abnormalities like exostosis can also be found, but are less consistently present.^{6,7} HO is often preceded by local inflammatory symptoms (swelling, pain, loss of function, warmth, redness) at the site where heterotopic bone will develop, the so-called flare-up. Flare-ups and subsequent HO formation can be triggered by muscular trauma (falls, intramuscular injections, surgical interventions)

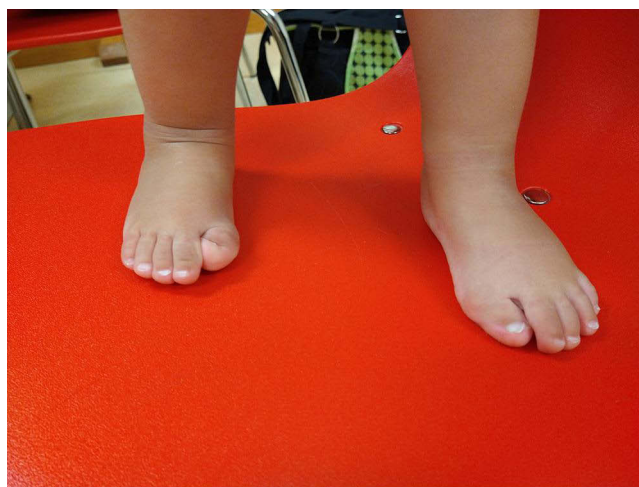


Figure 1 Bilateral, congenitally malformed great toes in a 2-year-old child with fibrodysplasia ossificans progressiva. Both great toes show typical shortening and are angled inward (hallux valgus).

but can also occur spontaneously.⁸ However, it should be noted that not all flare-ups induce HO. The first episodes of HO and flare-ups often start around the age of 5, though there is great variation in the age of onset between patients.^{8–10}

Due to its rarity the diagnosis is often delayed by 5–6 years.⁹ Devastating stories are known of patients with undiagnosed FOP undergoing surgical procedures to remove the ectopic bone, resulting in even worse heterotopic bone formation at the surgical site.¹¹ If FOP is suspected, based on the abnormal short toe or signs of a flare-up or heterotopic ossification, mutation analysis is recommended to confirm the diagnosis. Heterotopic bone formation follows a characteristic pattern of development throughout the body: the first HO typically occurs in the neck and upper back, with aging, distal body parts are also progressively affected. Eventually, almost all joints of the body are functionally ankylosed making patients wheel chair dependent, usually before the age of 30.^{9,12}

The extent of heterotopic bone in these patients causes a radiological image that resembles the formation of a second skeleton (Figure 2). Interestingly, the diaphragm, tongue, eye and heart muscle are unaffected by HO in patients with FOP, though it is unclear why.

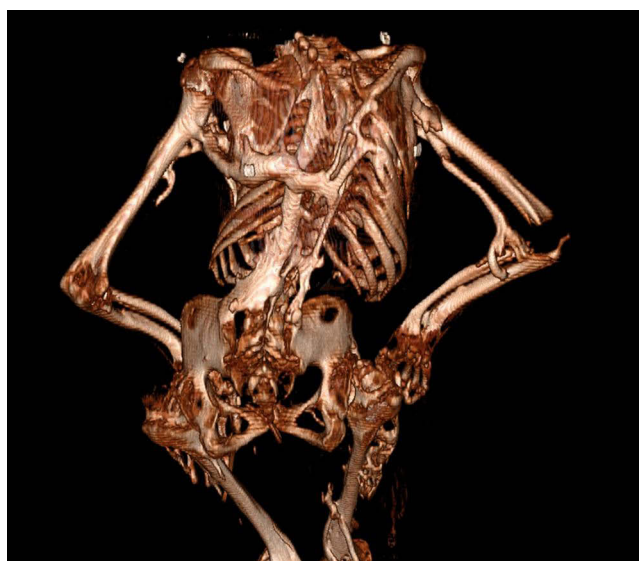


Figure 2 3D reconstruction of low-dose whole-body computed tomography scan of an adult patient with advanced FOP. There are prominent ossifications across the back, neck and chest, surrounding both hips and along the humeri leading to an altered stature and almost complete ankylosis of the joints.

Cardiopulmonary complications often occur in FOP.^{13–16} A high incidence of conduction abnormalities has been reported, but most are non-specific and it is unclear whether they are clinically relevant.¹⁷ HO around the thoracic cage and ribs becoming ankylosed causes pulmonary restriction and eventually thoracic insufficiency syndrome (TIS).^{13–16,18} This makes patients particularly susceptible to viral and bacterial pneumonia. TIS, pneumonia and trauma are the main causes of mortality in these patients¹³ at a median age of 56 years.^{9,13}

Pathophysiology

In recent years, knowledge of the pathophysiology of FOP has grown considerably, especially since the discovery of the causative missense mutations (R206H) in the ACVR1 (activin receptor type 1)-gene.¹⁹ This autosomal dominant, often *de novo* mutation is responsible for 97% of all FOP cases.¹⁹ Despite having the same mutation, there is a great variation in age of onset and speed of progression of disease between patients, for unknown reasons. Several other mutations have been described, with a variant/atypical phenotype ranging from very mild to more severe with atypical features such as cerebellar abnormalities and cataracts, but all affect the ACVR1 gene.²⁰ The mutation causes a gain of function of the activin receptor type 1 /activin receptor-like kinase 2 (ACVR1/ALK2,) making it sensitive to activin A, hypersensitive to BMP-ligands and “leaky signaling” in absence of stimulation (Figure 3).^{19,21}

The stimulation of ACVR1/ALK2 causes phosphorylation of SMAD 1/5/9, which in turn causes activation of transcription factors ultimately leading to heterotopic bone formation. This process is aggravated through an only partially understood process of inflammation and hypoxia, which involves HIF, mast cells and several inflammatory factors (Figure 3).²²

Monitoring

Monitoring FOP activity is a major challenge. No blood tests exist to evaluate disease activity. A plethora of potential markers such as C-reactive protein (CRP), alkaline phosphatase (ALP) and multiple interleukins have been investigated to assess disease activity, but were incapable of predicting or measuring flare-up activity or severity consistently.^{23–25} Therefore, other techniques to monitor disease progression had to be sought, as monitoring is pivotal to evaluate the efficacy of, for instance, study drugs. Kaplan et al developed a scoring system – the cumulative analogue joint involvement scale (CAJIS) – to evaluate and monitor the decrease of a patients’ functional mobility.²⁶ It is a quick and easy method wherein fifteen major joints are roughly classified into either being functional, partially functional and non-functional, culminating in an overall score estimating the patients’ overall mobility. As heterotopic bone also forms outside these fifteen major joints and especially in the thoracic cage, imaging techniques can be performed to evaluate, monitor – and more importantly – measure HO volumes throughout the body (Figure 2). Head-to-toe low dose CT-scan can accurately measure heterotopic bone volume in FOP. Sequential CT-scan can be used to evaluate heterotopic bone volume increase, providing an objective outcome measure for therapeutic interventions.^{9,27} The evaluation of a CT-scan in FOP patients is often challenging because of the disrupted anatomy due to the ankyloses and deformities. In FOP a CT-scan can be used to measure bone when it has been fully formed, but it does not contribute to finding bone which is still being formed and less calcified. If. An alternative imaging modality that could be used in the setting of a flare-up is the 18F-NaF PET-scan. The 18F-NaF that is administered prior to the PET-scan, incorporates into newly formed bone. Therefore, the fate of a flare-up – ossifying or non-ossifying – can be identified using this modality.^{9,28} Furthermore, chronic activity of FOP disease has been described in which existing heterotopic bone has the tendency to slowly expand without inflammatory symptoms.^{8,28} Labelled sodium fluoride will also incorporate in chronically active HO, and will thus be visible on the 18F-NaF PET/CT. The 18F-NaF nuclear tracer might not be available in all hospitals, and – as with the CT - analysis of the images is challenging. Therefore, we recommend that this is performed in collaboration with an FOP expert centre. Other imaging techniques that are more widely available (eg ultrasound, MRI) have thus far not shown to be of value for monitoring disease activity but further studies are necessary.

A known complication of the formation of HO is loss of mobility. But, as described earlier, the most threatening complication is cardio-pulmonary failure due to HO that has formed around the thoracic cage. It is therefore recommended to perform a pulmonary function test, ECG and echocardiography regularly to follow up on pulmonary and cardiac function and yearly in more severely affected patients.

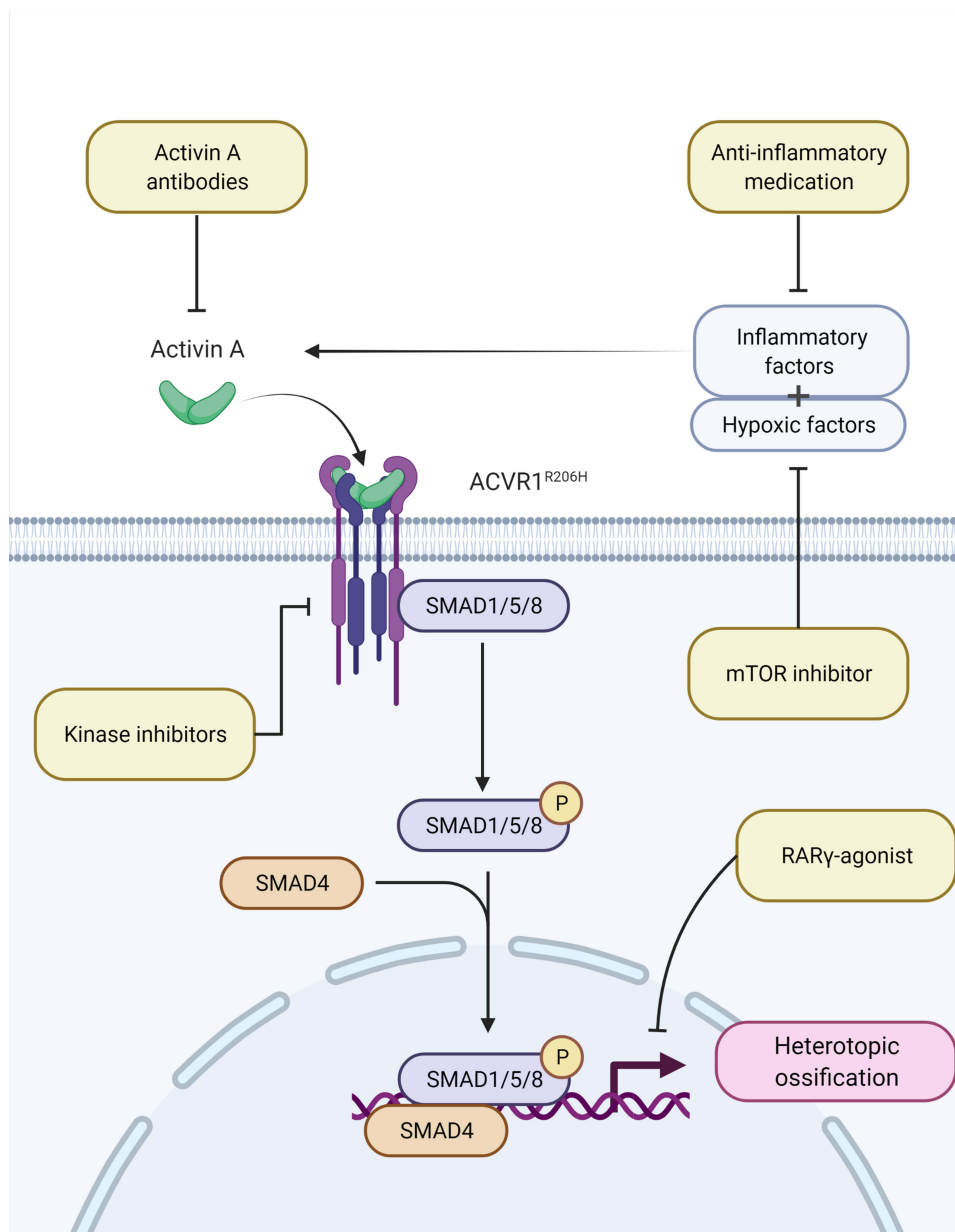


Figure 3 Pathological pathway leading to heterotopic ossification and possible treatment strategies.

Note: Created with Biorender.com.

Abbreviations: ACVR1, activin receptor type 1; RAR γ , retinoic acid receptor gamma; mTOR, mammalian target of rapamycin; P, phosphorylated.

Current Management and Treatment

Medical management and treatment of individuals with FOP is complex, requires specific care and is therefore usually performed in ultra-specialised centres in which physicians from different disciplines with FOP-specific knowledge are able to coordinate treatment.²⁹ Although the amount of knowledge and scientific publications about FOP has increased significantly in the last years, many of the current treatment recommendations are still based on expert opinion rather than conclusive evidence.

Measures to prevent soft-tissue injuries are crucial in the guidance of FOP patients. It is recommended that FOP patients avoid contact sports and other physical activities that might cause soft-tissue injury. Likewise, precautions must be taken to prevent falls that can occur more frequently as mobility declines. These precautions, such as handrails or

adapted toilets, can be supplied by experienced occupational therapists. They can also provide custom made adaptations to (wheel) chairs to reduce the chance of ulcers by bony protrusions.

Malnutrition can develop in FOP patients as a result of jaw ankylosis. If jaw ankylosis occurs, patients should be referred to a dietician in order to maintain an adequate nutritional status.

To delay loss of pulmonary function, FOP patients are encouraged to exercise as much as their mobility allows. Specific recommendations for improving/maintaining pulmonary health include singing and the regular use of a spirometer.³⁰

Venipuncture is possible but should be done by an experienced phlebotomist with cold packs applied locally afterwards. Muscle biopsies and intramuscular injections must be avoided since they can cause a flare-up.³¹ An adapted childhood immunization program is necessary, as intramuscular immunisation should not be given and some vaccines have been found to induce a flare-up, even when administered subcutaneously.³⁰ Therefore, the guidelines from the International Clinical Council on FOP (ICC-FOP) should be consulted prior to the administration of vaccines. All currently FDA-authorized vaccines against SARS-CoV-2 are given intramuscularly. Despite a report on a small number of FOP patients that received the vaccine intramuscularly,³² vaccination against SARS-CoV-2 is therefore currently not routinely recommended by the ICC-FOP. Risks and benefits have to be weighed on an individual basis by patients and physicians.

Although surgery is relatively contraindicated in FOP patients, as it almost always results in development of additional heterotopic bone,³³ there are some exceptions. Potentially life-saving surgery should not be avoided and has been done with positive outcomes³³ Some cases have been described in which heterotopic bone recurred more extensively than before surgery to remove it, but with a better functional outcome.³⁴ Minor surgery, such as removal of molars to increase the possibility of solid food intake or relief of an abscess, can be considered but only with precautions mentioned below.

If surgery is performed in an FOP patient, it should always occur in specialised FOP centres. Both the surgical procedures as the anaesthetic procedures are challenging. General anaesthesia requiring airway management is highly complex in FOP patients due to jaw and cervical ankylosis and restricted thoracic excursion. Even when the mouth opening is still normal, direct laryngoscopy should be avoided because overstretching the temporomandibular joint may cause ankylosis.³⁵ To address these problems, awake fiberoptic nasotracheal intubation is generally recommended, but subsequent ventilation can still be complicated due to pulmonary restriction present in FOP.^{13–16,18} Weaning from mechanical ventilation can also be challenging, and patients are at risk of developing postoperative pulmonary complications such as pneumonia, atelectasis or respiratory failure. To mitigate the risk of such complications, perioperative respiratory physiotherapy is commonly recommended.³⁶ To prevent additional heterotopic ossification, care should be taken that muscle trauma is limited during and after surgery. While locoregional anaesthesia has generally been regarded as contraindicated due to tissue trauma by needle passes, ultrasound-guided regional anaesthesia techniques not requiring needle penetration through muscle and connective tissue, such as ankle blocks, can be considered to avoid the FOP-specific risks associated with general anaesthesia.^{33,37} It should also be noted that positioning of the patient for surgery can be difficult due to restricted joint mobility but must be performed with utmost care to avoid pressure and tissue injury.³⁸ These challenges require specialised team members in every stage of the pre-, peri- and post-operative period. Peri-operative pharmaceutical therapy as described below can be considered.

Pharmaceutical Treatment

There is no FDA-approved drug available for the indication FOP.

The cornerstone of current expert-based treatment of flare-ups are anti-inflammatory drugs. A high-dose course of corticosteroids (1–2 mg/kg, max 100 mg) should be started as soon as possible (within 24 hours) after the first appearance of a flare-up in a major joint and should be continued for at least 4 days.³⁰ This treatment can also be considered as a preventative measure after traumatic injury or before non-avoidable surgery. Flare-ups in the neck and back are less susceptible to corticosteroid therapy and in these cases, corticosteroids are not recommended.^{8,30} The duration of corticosteroid treatment can be extended based on the response to therapy, but a short duration (under four days) is preferred due to risks of side-effects of long-term corticosteroid use. It should be noted that evidence for

treatment with corticosteroids is anecdotal. In a global study on the natural history of FOP flare-ups, 31% of patients reported improvement of symptoms with corticosteroids and only 12% reported that corticoid therapy resulted in a complete resolution of symptoms.⁸ Whether or not corticosteroids have an effect on objective measurements, such as heterotopic bone volume, has not been established.

NSAIDs are frequently used as both anti-inflammatory and analgesic drugs in FOP patients. Prostaglandins have been found to be elevated in FOP patients experiencing a flare-up, marking a potential mode of actions for NSAIDs.³⁹ They can be applied both systemically and topically. There have been no clinical trials that investigate their potential to prevent heterotopic bone formation in FOP.

Several other classes of medication have been prescribed off-label as treatment of FOP. Bisphosphonates have a prominent effect on bone metabolism and might influence FOP through several pathways.^{30,40,41} Mast cell inhibitors are thought to be effective due to the presence of mast-cells in early FOP lesions.⁴⁰ Treatment with imatinib, which affect multiple pathways implicated in FOP, has been shown to reduce subjective intensity of flare-ups, but inhibition of HO was not investigated in patients.⁴² Furthermore, antiangiogenic drugs, chemotherapeutic therapy and other anti-inflammatory medications have been suggested for treatment.⁴³ However, evidence for these medications is anecdotal and usage is usually restricted to last-resort situations, as many of these drugs have severe side-effects.

Pain management in patients with FOP aligns with standard pain management guidelines. Referral to a chronic pain management specialist can be considered in patients who suffer from more long term pain problems, since this can substantially affect Quality of Life in these patients.^{44,45}

Treatments in Development

In recent years, promising efforts have been made to develop effective medication to prevent HO in FOP. Although the first Phase 3 trial for medication in FOP started in 2017 (NCT03312634), no results have yet been published in peer-reviewed journals. We have summarised the working mechanisms of therapies currently in clinical Phase 2 or 3 trials in Figure 3.

Firstly, blocking retinoid signaling required for chondrogenic differentiation. The only drug in development for FOP in this medication class is Palovarotene, a retinoic acid-gamma (RAR- γ) antagonist. Palovarotene notably suppresses HO in FOP mouse models⁴⁶ and has been investigated in phase 2 and 3 trials (NCT02190747 and NCT03312634), but no peer-reviewed results have been published at time of writing.

Secondly, blocking the stimulation of the ALK2 by activin A. This strategy has been adopted by several companies, one of which has been clinically tested (NCT03188666). A phase 3 trial of this compound, Garetosmab, has recently been announced.

Thirdly, influencing the inflammatory and hypoxic pathways that aggravate FOP through mTOR inhibition. Preclinical evidence suggests that mTOR plays a significant role in the early pathophysiology of FOP.⁴⁷ After promising experiments in mice,⁴⁸ a clinical trial has been set up in Japan to evaluate efficacy and safety in FOP patients (UMIN000028429).

Finally, direct inhibition of the ALK2. Both existing and newly developed kinase inhibitors have been identified as potent inhibitors of ALK2 and these have shown efficacy in preclinical models.^{49,50} Of these, Saracatinib is currently being tested in a phase 2 clinical trial (NCT04307953), with the significant benefit of an existing body of safety data. Several other, newly developed, kinase inhibitors are expected to move on into the clinical trial phase in the near future.

All of the potential therapies focus on preventing HO. Further research is needed to determine which of these medications can be used in the different stages of FOP activity.⁵¹ If these drugs are found to be effective, future trials might also investigate the removal of existing heterotopic bone.

Conclusion

FOP causes progressive immobility and reduced life-expectancy due to the development of a large volume of heterotopic bone in skeletal muscles. Although there are numerous treatments in development, prevention of soft-tissue injury remains the cornerstone of clinical practice. Despite numerous advancements in FOP research within the past decade, much still remains unknown about this severe and disabling disease.

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Disclosure

The authors report no conflicts of interest in this work.

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