JBMR Plus, 2025, **9**, ziaf150
https://doi.org/10.1093/jbmrpl/ziaf150
Advance access publication: September 19, 2025
Guidelines

Medical guidelines for fibrodysplasia ossificans progressiva

Frederick S. Kaplan[1,†,*], Mona Al Mukaddam[2,†], Genevieve Baujat[3,†], Alberto Hidalgo Bravo[4,†], Matthew Brown[5,†,‡], Amanda Cali[6,‡], Tae-Joon Cho[7,†], Corrie Crowe[8,‡], Carmen L. De Cunto[9,†], Patricia L.R. Delai[10,†], Robert J. Diecidue[11,†], Elisabeth Marelise W. Eekhoff[12,†], Lisa Friedlander[13,‡], Clive S. Friedman[14,†], Zvi Grunwald[15,†], Nobuhiko Haga[16,†], Edward C. Hsiao[17,†], Richard Keen[18,†], Joseph A. Kitterman[19,‡], Charles Levy[20,‡], Vrisha Madhuri[21,†], Rolf Morhart[22,†], J. Coen Netelenbos[23,†], Christiaan Scott[24,†], Eileen M. Shore[25,‡], Michael Zasloff[26,†], Keqin Zhang[27,†], Robert J. Pignolo[28,†]

[1]Departments of Orthopaedic Surgery, Medicine, and the Center for Research in FOP and Related Disorders, The Perelman School of Medicine at The University of Pennsylvania, Penn Medicine University City, Philadelphia, PA 19104, United States
[2]Departments of Medicine (Division of Endocrinology, Diabetes and Metabolism), Orthopaedic Surgery and the Center for Research in FOP and Related Disorders, The Perelman School of Medicine at the University of Pennsylvania, Penn Medicine University City, Philadelphia, PA 19104, United States
[3]Departement de Génétique, Centre de Référence Maladies Osseuses Constitutionnelles, Hôpital Necker-Enfants Malades, Paris, France
[4]Department of Genomic Medicine, Instituto Nacional de Rehabilitación, Mexico City 14389, Mexico
[5]Department of Medicine, King's College London, Guy's Hospital, London SE1 9RT, United Kingdom.
[6]Radiant Hope Foundation, Mountain Lakes, NJ 07046, United States
[7]Division of Pediatric Orthopaedics, Seoul National University Children's Hospital, Seoul 110-744, Republic of Korea
[8]1793 Springdale Road, Cherry Hill, NJ 08003, United States
[9]Department of Pediatrics, Pediatric Rheumatology Section, Hospital Italiano de Buenos Aires, Ciudad Autónoma de Buenos Aires, Gascon 450, 1181, Argentina
[10]Hospital Israelita Albert Einstein, Instituto de Ensino e Pesquisa, São Paulo, Brazil
[11]Department of Oral and Maxillofacial Surgery, Sidney Kimmel Medical College, Thomas Jefferson University, Philadelphia, PA 19107, United States
[12]Department of Internal Medicine/Endocrinology and Metabolism, Amsterdam University Medical Center (Amsterdam UMC), 1081 HV Amsterdam, The Netherlands
[13]Department of Oral Prosthodontic Rehabilitation, Université de Paris Cité, Reference Center for Rare Oral and Dental Diseases-Service Odontology Group, Hospitalier Pitié Salpetriere-Charles Foix, Inserm UMR 1123, Lab Eceve, Institut Imagine, Paris, France
[14]Schulich School of Medicine and Dentistry, Imagine Dentistry, London, ON N6H OK1, Canada
[15]Department of Anesthesiology, Thomas Jefferson University, Philadelphia, PA 19107, United States
[16]National Rehabilitation Center for Persons with Disabilities, Saitama 359-8555, Japan
[17]Division of Endocrinology and Metabolism, Department of Medicine, University of California-San Francisco, San Francisco, CA 94143, United States
[18]Department of Medicine, The Royal National Orthopaedic Hospital, Division of Rheumatology, Stanmore HA7 4LP, United Kingdom
[19]Department of Pediatrics and Cardiovascular Research Institute, University of California San Francisco, San Francisco, CA 94143, United States
[20]Department of Physical Therapy, University of Florida, Gainesville, FL 32607, United States
[21]Department Paediatric Orthopaedics, Ida Scudder Chair for Clinical Research, Christian Medical College Hospital, Vellore 632004, India
[22]Department of Pediatrics, Klinikum Garmisch-Partenkirchen, D-82467 Garmisch-Partenkirchen, Germany
[23]Department of Internal Medicine; Section of Endocrinology, Amsterdam University Medical Center (Amsterdam UMC), Location VU University Medical Center (VUMC) Amsterdam, University Hospital Vrije Universiteit, 1081 HV Amsterdam, The Netherlands
[24]Division of Dermatology and Rheumatology, Department of Pediatrics, University of Ottawa, Ottawa, ON K1H 8L1, Canada
[25]Departments of Orthopaedic Surgery, Genetics, and the Center for Research in FOP and Related Disorders, The Perelman School of Medicine at The University of Pennsylvania, Philadelphia, PA 19104, United States
[26]Departments of Surgery and Pediatrics, Georgetown University, Washington, DC 20007, United States
[27]Department of Endocrinology, Tongji Hospital, Shanghai Tongji University, Shanghai 200065, P.R. China
[28]Department of Medicine, Mayo Clinic College of Medicine, Rochester, MN 55905, United States

Received: August 4, 2025. **Revised:** September 5, 2025. **Accepted:** September 9, 2025

*Corresponding author: Frederick S. Kaplan, Isaac and Rose Nassau Professor of Orthopaedic Molecular Medicine, The Perelman School of Medicine at the University of Pennsylvania, Department of Orthopaedic Surgery, 3737 Market Street – Sixth Floor, Philadelphia, PA 19104, United States (frederick.kaplan@pennmedicine.upenn.edu).
†Member of the ICC
‡Consultant to the ICC
Post-Publication Inquiries: frederick.kaplan@pennmedicine.upenn.edu or pignolo.robert@mayo.edu
From The International Clinical Council on FOP (ICC) & Consultants

Abstract

Fibrodysplasia ossificans progressiva (FOP) is an ultra-rare genetic condition characterized by congenital malformations of the great toes and progressive heterotopic ossification (HO) in specific anatomic patterns. Present management summarized here is focused on early diagnosis, assiduous avoidance of injury and iatrogenic harm, symptomatic amelioration of painful flare-ups, and optimization of residual function. Twenty-one members of the International Clinical Council on FOP (ICC) and seven consultants from 15 countries, chosen for their clinical expertise in FOP, developed this summary statement. Further advances in therapeutics will be based on rigorous clinical trials to assess novel and emerging treatment and prevention strategies. A detailed and updated exploration of the topics outlined in this brief perspective can be found in "The Medical Management of Fibrodysplasia Ossificans Progressiva: Current Treatment Considerations" which can be found on the International Clinical Council on FOP (ICC) website (www.iccfop.org).

Keywords: fibrodysplasia ossificans progressiva, heterotopic ossification, BMP signaling pathway, ACVR1, guidelines

Lay Summary

Fibrodysplasia ossificans progressiva (FOP) is a very rare genetic condition of bone formation in muscles, tendons, and ligaments. Currently, medical efforts focus on early diagnosis, avoidance of injury, symptomatic treatment of painful flare-ups, and maintenance of function. The International Clinical Council on FOP (ICC) developed these brief guidelines for managing FOP. Further advances will be based on clinical trials to assess new medications for FOP. A detailed exploration of the topics outlined in these guidelines can be found in "The Medical Management of Fibrodysplasia Ossificans Progressiva: Current Treatment Considerations" which can be found on the following website (www.iccfop.org).

Introduction

Fibrodysplasia ossificans progressiva (FOP; MIM# 135100) is an ultra-rare, disabling, fully penetrant, autosomal dominant, genetic condition characterized by congenital malformations of the great toes and progressive, heterotopic ossification (HO) in specific anatomic patterns.[1–4] Fibrodysplasia ossificans progressiva is the most catastrophic disorder of HO in humans and has a dramatic impact on patients and family.[5] However, there is great variability among individuals in terms of course and severity. Flare-ups that often lead to HO are episodic and may be misdiagnosed as tumors; immobility is cumulative.[6,7] Joint degeneration and ankylosis often occur independently of HO.[8]

Most children with FOP develop episodic, painful, inflammatory soft tissue swellings called flare-ups during the first decade of life. While some flare-ups regress spontaneously, most transform soft connective tissues into mature heterotopic bone through a process of endochondral ossification. Minor trauma, such as intramuscular (IM) immunizations, mandibular blocks for dental work, muscle fatigue, blunt muscle trauma, or influenza-like viral illnesses, can trigger new flare-ups of FOP leading to progressive HO. Attempts to surgically remove heterotopic bone often provoke explosive and painful new episodes of HO.[2,9]

Most patients with FOP are confined to a wheelchair by the third decade of life and require lifelong assistance with activities of daily living. The median estimated life expectancy is 56 yr. Death often results from complications of thoracic insufficiency syndrome.[10]

A common gain-of-function, missense pathogenic variant in activin receptor IA (ACVR1, also known as ALK2), encoding a bone morphogenetic protein (BMP) type I receptor, occurs in all sporadic and familial cases with a classic presentation of FOP.[11] An estimated 97% of individuals with FOP have this recurrent variant ($ACVR1^{R206H}$). Approximately 3% of affected individuals have different pathogenic variants in ACVR1—some with more severe phenotypes, and some with less.[12] However, all known individuals with FOP have gain-of-function, heterozygous, pathogenic variants in the gene encoding ACVR1.

The discovery of the genetic variants in ACVR1 that cause FOP established a critical milestone in understanding FOP, revealed a highly conserved therapeutic target in the BMP signaling pathway, and propelled the development of novel inhibitors of ACVR1-mediated BMP pathway signaling. Effective therapies for FOP will likely be based on the results of clinical trial interventions that modulate overactive ACVR1 signaling. However, present management is focused on early diagnosis, assiduous avoidance of injury and iatrogenic harm, symptomatic amelioration of painful flare-ups, optimization of residual function, and monitoring and treating co-morbidities.[1,9,11–20]

Here, we summarize the medical guidelines on FOP based upon currently available knowledge. This report is not intended to present a specific approach for managing the symptoms of FOP, but rather is intended to present views, statements, or opinions of the authors that may be helpful to others who face similar challenges.

Further advances in therapeutics will be based on knowledge of disease mechanisms at the molecular and cellular level, the refinement of genetically based animal models for drug testing, and rigorous clinical trials to assess novel and emerging treatment and prevention strategies.[9,15,21–25]

Although there are common physical features shared by every person who has FOP, there are differences among individuals that may alter the potential benefits or risks of any medication or class of medications discussed here. The decision to use or withhold a particular medication must ultimately rest with an individual patient and his or her physician. We emphasize that this report reflects the authors' experience and opinions on the various classes of symptom-modifying medications and is meant only as a guide to this controversial area of therapeutics.

Materials and methods

All twenty-one members of the International Clinical Council on FOP (ICC; www.iccfop.org), as well as 7 consultants from 15 countries, chosen for their expertise in FOP, developed this summary statement. Participants included

anesthesiologists, endocrinologists, rheumatologists, orthopedic surgeons, clinical geneticists, molecular geneticists, neonatologists, pediatricians, internists, physiatrists, geriatricians, dermatologists, dentists, oral surgeons, and a non-voting representative from a parent support group. All participants completed a conflict-of-interest declaration. The consensus was supported without pharmaceutical industry support or funding.

A modified Delphi-like consensus methodology was adopted. A comprehensive literature search was conducted using PubMed and the search terms "fibrodysplasia ossificans progressiva." Additional relevant articles on FOP were also identified by PubMed searches when supplementary information was necessary. A comprehensive review of >2900 articles formed the basis of discussion by the Publications Committee of the ICC. As FOP is an ultra-rare condition, evidence-based statements are generally moderate to low. If published data were unavailable or insufficient, experts' clinical experiences and opinions were considered.

Perspective and discussion

Executive summary of key practice points

General recommendations

1) The diagnosis of FOP is clinical (malformed great toes and progressive HO) but requires genetic confirmation of a pathogenic *ACVR1* gene variant.[1,2,11,12,26]
2) If FOP is suspected, all elective procedures such as surgeries, biopsies, and IM immunizations should be deferred until a definitive diagnosis is confirmed.[1]
3) Each patient should have a primary physician who is willing to consult with an FOP expert and help coordinate a local care team.[27]
4) Patients and their families should be informed about the International Clinical Council on FOP (ICC; www.iccfop.org), the International FOP Association (IFOPA; www.ifopa.org), and country-specific support groups at the time of diagnosis.
5) Emergent medical care should be provided (See *Emergency Guidelines for First Responders, Physicians & Dentists* in this report).

Physical activities

Activity is encouraged at all ages, but passive range of motion to restore or improve joint mobility (motion performed by someone other than the patient—in other words, a movement of a joint carried out by an operator without aid of the patient's muscles) must be avoided. Singing, water exercises, and activities for respiratory health are strongly encouraged. Avoid soft tissue injuries, contact sports, overstretching of soft tissues, and muscle fatigue.[1]

Anesthesia

An expert anesthesiologist experienced in general anesthesia for FOP patients must be consulted pre-operatively in all cases. If general anesthesia is required, an awake intubation by nasotracheal fiber-optic technique should be performed because of cervical spine fusions, jaw motion limitations, sensitive airway, and risk of inducing an obstructing neck flare-up. Highly skilled FOP-aware anesthesiologists should be present for all elective intubations.[28]

Chronic pain

Chronic pain syndromes are common in FOP and may be related to neuropathies (eg, entrapment, nerve damage, allodynia), musculoskeletal origin (eg, back pain, myofascial pain), inflammation, or mechanical/compressive causes (eg, from expanding HO, especially late in the course of a flare-up). General principles of management include identification of the type of pain (neuropathic versus nociceptive), use of multiple non-invasive treatment modalities coordinated by multidisciplinary pain specialists, use of adjuvant non-pharmacologic modalities, and treatment of depression (which may provide pain relief independent from correction of any mood disorder). Suboptimal seating and positioning (ie, wheelchairs), poorly fitting shoes, or improperly adjusted ambulatory aids may play a role in persistent pain. Referral to a rehabilitation specialist may be indicated.[29] Please see the ICC website (www.iccfop.org) for latest updates.

COVID-19

Please see section on COVID-19 as well as ICC and IFOPA websites (www.iccfop.org and www.ifopa.org) for latest updates.

Dental emergencies

It is always advisable to obtain a complete dental examination if a patient has swelling or pain of the oral-facial region, as it can be difficult to distinguish a swelling of dental origin from a flare-up of FOP. If the dental radiographs and/or pulpal testing (vitality of the nerve of the tooth) indicate no obvious dental origin to the swelling, it is prudent to assume an FOP flare-up and initiate prednisone flare-up dosing. If it is not possible to get a dental radiograph or do pulpal testing, then empirically prescribing an appropriate antibiotic together with prednisone is warranted until a definitive diagnosis can be made. Any dental surgery should be delayed until 8 wk after flare-ups resolve. Good oral hygiene and routine dental exams/check-ups are imperative to prevent dental caries. See the full ICC recommendations at www.iccfop.org.

Falls

Locked upper limbs may accentuate head and neck trauma from falls. Epidural hematomas are common (surgical emergencies). Consider protective headgear in children who have upper limb involvement and in adults who remain ambulatory. All head and neck injuries should be evaluated emergently.[30]

Flare-ups: (back/chest)

Consider non-steroidal anti-inflammatory medications (NSAIDs) or cyclooxygenase-2 (COX-2) inhibitors (oral or topical) with assiduous gastrointestinal (GI) precautions. Use analgesics, muscle relaxants, and local applications of ice packs, as needed. Avoid narcotic analgesia. Corticosteroids may be used in severe cases, but do not appear to be as effective for controlling back/chest flare-ups as with other types of flare-ups.[1,16]

Flare-ups: (limbs/throat/submandibular)

Patients can present with inflammatory flare-ups with significant swelling and inflammation. These symptoms can be highly variable between patients and events. Prednisone—2 mg/kg once daily (up to a total of 100 mg daily) in AM (per oral) for 4 d (or equivalent corticosteroid); begin as early as possible after the onset of flare-up signs and symptoms.

However, early detection can be subtle, especially with flare-ups in the lower limbs. Keep prednisone on-hand as "pill-in-pocket" approach for emergencies. Alternatively, pulse intravenous (IV) corticosteroids of the equivalent prednisone dose may be used as directed. Avoid corticosteroids, if possible, for axial flares. Use oral and/or topical NSAID analgesics and/or muscle relaxants, as needed, with assiduous GI precautions. Local application of cool packs may also be helpful. Avoid narcotic analgesia whenever possible. Fibrodysplasia ossificans progressiva experts should be consulted with all submandibular flare-ups, and the detailed guidelines should be assiduously followed.[16,31,32]

Flare-ups (prophylaxis)

Flare-ups often result from soft tissue injuries. Prednisone [1-2 mg/kg (per oral)] once daily (maximum of 100 mg/d) for 3-4 d can be given to help prevent flare-ups after severe soft-tissue injury. Do not use after minor bumps or bruises. Use prednisone prophylactically as directed for dental or surgical procedures.[1,16]

Fractures

Fractures can occur in both normotopic and heterotopic bone and usually heal well without much heterotopic bone if treated conservatively. A brief course of prednisone is suggested. An FOP expert in fracture management should be consulted in all cases.[33]

Gastrointestinal issues

Many patients with FOP report frequent nausea and vomiting. The cause and significance of this is unknown. Gastrointestinal complaints should be investigated to rule out more serious conditions. Significant weight loss or very low body mass index in the setting of severe scoliosis can be associated with bowel obstruction and superior mesenteric artery syndrome. Treatment would include weight gain. See the full ICC recommendations at www.iccfop.org.

Hearing

Conductive hearing impairment is common in FOP through various mechanisms. Fibrodysplasia ossificans progressiva patients should be screened in childhood by audiometry for hearing impairment. Hearing aids may improve severe conductive hearing loss.[34]

Immunizations

Immunization by subcutaneous administration is recommended for all vaccines that can be administered by that route. Avoid all IM immunizations and intranasal influenza immunizations with live vaccines as they may precipitate flare-ups of FOP. There have been no reported cases of flare-ups following subcutaneous immunization with the Measles, Mumps, Rebella (MMR) or the Measles, Mumps, Rubella, and Varicella (MMRV) vaccines despite the fact that they contain attenuated viruses.[35] Immunizations should not be given during flare-ups and should be avoided until 8 wk after flare-ups resolve. All household contacts should be immunized against influenza, pertussis, and COVID-19. Consult detailed immunization guidelines and updates on the ICC website (www.iccfop.org).

Influenza

Administer influenza vaccines subcutaneously, but never during flare-ups. Wait until 6-8 wk after a flare-up has resolved before administering influenza vaccine. Avoid live attenuated influenza vaccine as it may cause flu-like symptoms and precipitate flare-ups of FOP. Household contacts of FOP patients should be immunized annually. Consider anti-viral therapy if flu symptoms occur.[36] Consult detailed influenza immunization guidelines on the ICC website, as recommendations may change annually (www.iccfop.org).

Injuries

The prevention of flare-ups and heterotopic bone formation involves multimodal approaches. This includes the recognition and avoidance of known causes of flare-ups: contact sports, soft tissue injuries, blunt muscle trauma, muscle fatigue, muscle stretching, IM injections and immunizations, biopsies, removal of heterotopic bone, all non-emergent surgical procedures, and viral illnesses.[1,16]

IVs

Patients with FOP can tolerate peripheral blood collection and IV access when performed by an experienced phlebotomist. It is critical that the procedure be performed in as gentle and minimally-invasive manner as possible. Tourniquet time should be minimized. Consultation with clinicians who are familiar with the care of FOP patients is essential. Superficial IV access and venipuncture are acceptable. Traumatic IVs must be avoided. Central lines, PICC lines, and arterial punctures may cause HO and should be avoided unless critical for the patient's medical management.[1,16]

Kidney stones

There is a 3-fold greater risk of kidney stones in FOP. Encourage fluid intake (preferably water) of 1.5-2 L/d, and avoidance of high protein and high salt diets. Age- and sex-based recommended daily allowances for calcium should be maintained.[37]

Limb swelling

Lymphedema and transient neuropathy may occur with flare-ups of limbs. Elevate legs while sleeping and recumbent, whenever possible. Take 1 low-dose aspirin daily with food for deep venous thrombosis (DVT) prophylaxis, if indicated. Rule out deep vein thrombosis with Doppler ultrasound. Use fitted support stockings for chronic lymphedema (but avoid traumatic compression). Lymphedema therapy may be helpful for chronic lymphedema.[38]

Medications

Consult detailed medication guidelines and updates on the ICC website (www.iccfop.org).

Approved therapies in FOP

Palovarotene, an RAR-γ agonist, has been approved in the United States, Canada, UAE, Australia, and Russia but not approved in Europe.[18,39]

Corticosteroids

1) Corticosteroid prophylaxis is recommended for significant blunt muscle trauma, as prophylaxis for a potential flare or as treatment of an active flare. The usual recommended dose is prednisone 2 mg/kg/d per oral × 4 d, with a maximum dose of 100 mg/d.
2) Corticosteroid prophylaxis is recommended for dental and surgical procedures.

3) Corticosteroid treatment should be considered for the symptomatic relief of emergent flare-ups of the limbs, jaw, or submandibular area.

COX-2 inhibitors and NSAIDs

There is no definitive evidence that chronic treatment with COX-2 inhibitors or NSAIDs prevents or ameliorates flare-ups in FOP. However, COX-2 inhibitors or oral/topical NSAIDs may be helpful for symptomatic management of flare-ups and chronic arthropathy when corticosteroids are not indicated.

Bisphosphonates

There is no definitive evidence that bisphosphonates prevent or ameliorate flare-ups in FOP. However, IV bisphosphonates may be considered for the prevention of corticosteroid-associated bone loss. Dentists should be made aware of any prior bisphosphonate use. Bisphosphonates may be considered for treating osteoporosis of the native skeleton, as guided by standard-of-care.

Off-label medications (imatinib, tofacitinib, canakinumab, anakinra, and so on)

There is no definitive evidence that these medications prevent or ameliorate HO after flare-ups in FOP. These medications may be considered for patients with severe, intractable FOP flare-ups. Importantly, pharmacological testing of orally available drugs that target MMP-9 has just begun, and it would be premature to make any recommendations regarding their use without human data. See the full ICC recommendations at www.iccfop.org regarding off-label medication use.

Chemotherapy agents and radiation therapy

There is no evidence of efficacy with these agents. The use of these approaches is contraindicated in the management of FOP.

Miscellaneous agents in FOP

The chronic use of antiangiogenic agents, calcium binders, colchicine, fluoroquinolone antibiotics, propranolol, mineralization inhibitors, PPAR-γ antagonists, and TNF-α inhibitors currently has no role in the management of FOP.

Mental health

Patients with any chronic illness are at risk of mental health complications. If there is suspicion of depression or anxiety, psychological support is recommended. Family therapy may be helpful.[5]

Neurological issues

Patients with FOP have reported a higher incidence of neurological symptoms, including pain both during and after an FOP flare-up. The sources of pain should be carefully explored and may be due to poor positioning or suboptimal equipment. Some individuals with FOP report chronic headaches. If headaches persist, patients should be referred to a neurologist who can make recommendations for treatment. See the full ICC recommendations at www.iccfop.org.

Nutrition

In cases of ankylosis of the jaw, a dietician should be consulted to ensure adequate nutrition. See the full ICC recommendations at www.iccfop.org.

Occupational therapy

Occupational therapy (OT), focused on enhancing activities of daily living, may be useful to improve the quality of life of FOP patients. Perform periodic OT evaluations for assistive devices, as activities of daily living are likely to change over time. Other health professionals (recreational therapists, orthotists, speech language pathologists, vocational specialists, audiologists, creative arts therapists, psychologists, etc.) may play a role in maintaining or improving health, function, and quality of life. See the full ICC recommendations at www.iccfop.org.

Orthodontics

Routine orthodontic care has not been reported to cause flare-ups of FOP. However, all FOP patients seeking orthodontic care should consult with an FOP dental expert. See the full ICC recommendations at www.iccfop.org.

Physical therapy

Passive range of motion to restore or improve joint range of motion is strictly prohibited. An assessment of ambulatory aids may be indicated. Warm water hydrotherapy may be helpful.[1]

Pregnancy

Although pregnancy with FOP is possible, FOP poses major life-threatening risks to mother and child as well as life-altering consequences to the entire family. Pregnancy in FOP should never be undertaken without serious consideration and family planning. Unwanted pregnancies should be assiduously avoided. Any pregnancy should be avoided during clinical trials. Independent genetic counseling is available, if desired. Should a pregnancy occur, guidance and care at a high-risk pregnancy center are imperative.[40]

Pressure ulcers

In patients with limited motion, prevention of pressure ulcers by appropriate methods or devices is recommended. A wound care team should be involved in patient care if pressure ulcers are at risk of developing or exist. A rehabilitation equipment evaluation may also add value. See the full ICC recommendations at www.iccfop.org.

Respiratory health

Singing, swimming, and incentive spirometry are strongly encouraged to maintain lung function. Perform baseline pulmonary function tests (PFTs), echocardiogram, chest X-ray, and pulse oximetry after 4 yr of age. Pulmonary consultation should be instituted by the end of the second decade. Sleep studies may be helpful in directing specific respiratory therapies, including noninvasive overnight ventilation with a soft mask. Supplemental oxygen should not be used in an unmonitored setting. In patients with respiratory insufficiency, immunization for influenza and pneumococcal pneumonia should be considered. Please follow immunization guidelines above.[10,41]

Scalp flare-ups

Scalp flare-ups are common, especially in young children with FOP, and represent early flare-ups of the condition. Flare-ups of the scalp can appear as prominent swellings and may be initially disfiguring. A conservative approach without steroid use, if possible, should be taken with scalp flare-ups, with monitoring and pain control if necessary. Scalp flare-ups will resolve spontaneously over time and disfigurement will be minimal as new ossifications are incorporated into the growing skull. Although they can be alarming in size, scalp flare-ups often spontaneously regress and are of minimal clinical significance.[42]

School

Children with disabilities may be entitled to Individual Educational Programs (IEPs) to help students succeed in school. Use school aides to protect and assist children. Preschool evaluation is helpful. School nurses, staff, and teachers should be aware of the limitations of FOP, and protocols for managing injuries and flare-ups, as well as special adaptive needs. See the full ICC recommendations at www.iccfop.org.

Skin

Careful skin management is critical for individuals with FOP. Chronic maceration or minor trauma, especially over a bony prominence, can predispose the skin to fungal or bacterial infection, while immobility and prominent bony masses increase the risk of pressure ulcers, lymphedema-related blistering, and ingrown toenails—all of which may provide a portal of entry for pathogens and progress to sepsis.

Spinal deformity

Spinal deformity is common in FOP and can occur independently of flare-ups. Rapid progression of spinal deformity—especially in childhood or adolescence—should be evaluated by an expert in FOP.[41,43]

Surgery

Avoid surgery, except in emergencies. Always avoid surgery to remove heterotopic bone.[1–3]

Teeth

Preventive dental care is essential and should begin in early childhood. Avoid sugary sweets and drinks. Avoid mandibular blocks, over-stretching of the jaw, and muscle fatigue. Consult FOP dental experts before any procedure. See the full ICC recommendations at www.iccfop.org.

Current treatment considerations

At present, there are limited treatments for FOP. The disorder's rarity, variable severity, and fluctuating clinical course pose substantial uncertainties when evaluating experimental therapies. The ultimate treatment of FOP will likely be based on integrated knowledge of the cellular and molecular pathophysiology of the condition.[9,20] A schema of our current knowledge is presented in Figure 1.

In evaluating each treatment or prospective treatment, we have focused on the known mechanism of action of the drug as it relates to the proposed pathogenesis of FOP. Consideration for use of each medication was made based on current regulatory approval, or if no approval, balancing the clinical uncertainty of each agent when used to treat FOP against the compassionate need to control the disabling symptoms of the disease adequately and safely, especially during flare-ups.

Each pharmacologic agent was classified into 1 of 4 categories based on Phase 3 clinical trial results and approved use, experimental or anecdotal experience with the drug, as well as knowledge of each drug's safety profile (Tables 1-4). For dosing and major side effects of commonly prescribed medications for other indications, where they are the same in FOP, refer to our complete online guidelines (www.iccfop.org).

We emphasize that this report reflects the authors' experience and opinions on the various classes of symptom-modifying medications and is meant only as a guide to this controversial area of therapeutics. Although there are common physical features shared by every person who has FOP, there are differences among individuals that may alter the potential benefits or risks of any medication or class of medications discussed here. We emphasize that the decision to use or withhold a particular medication must ultimately rest with an individual patient and his or her physician.

Regulatory-approved medications have been approved by at least 1 regulatory authority (eg, US Federal Drug Administration, or FDA). Currently, only chronic and episodic use of palovarotene (Sohonos) has received limited regulatory approval.

Class I medications can be considered for acute flare-ups involving the major joints of the appendicular skeleton. The immediate use of prednisone at a dose of 2 mg/kg/d (up to 100 mg) can be considered as a single daily dose for a maximum of 4 d. For maximum beneficial effect, the prednisone should be started within 24 h of the onset of a flare-up, which corresponds to the earliest phase of acute inflammatory infiltration into skeletal muscle. If the flare-up is more than 2 days old, prednisone is generally less effective. If the flare-up responds to the medication but recurs when the prednisone is discontinued, a repeat 4-d course with a subsequent 10-d taper can be considered. Taper by approximately 10%/day over 10 d, as guided by clinical judgment. Consult an endocrinologist if there are questions or concerns. Prednisone should generally not be used for flare-ups on the chest or trunk, as it is difficult to judge the exact onset of a new flare-up. Prolonged or chronic use of corticosteroids is of no benefit, is harmful systemically, and should not be considered. Furthermore, suppression of the pituitary-adrenal axis is likely to occur with chronic or long-term use and can have long-term harmful effects. The use of prednisone is meant only to suppress or abort the early inflammatory events of an acute FOP flare-up and potentially suppress the subsequent death of skeletal muscle in the earliest stages of an FOP flare-up.

When prednisone is discontinued (or if a flare-up existing for more than 48 h is being considered for treatment), symptomatic treatment may be considered with a non-steroidal anti-inflammatory agent (NSAID). A COX-2 inhibitor can be used instead of a traditional NSAID (Table 1). As with all NSAIDs, GI precautions should prevail. If long-term use of a COX-2 inhibitor is considered, serum liver and kidney function tests should be monitored. COX-2 inhibitors should be used with caution in FOP patients with a history of cardiovascular disease or in older FOP patients who are severely immobilized or completely non-ambulatory.

Class II Medications can be considered on off-label use with caution, at the physician's discretion.

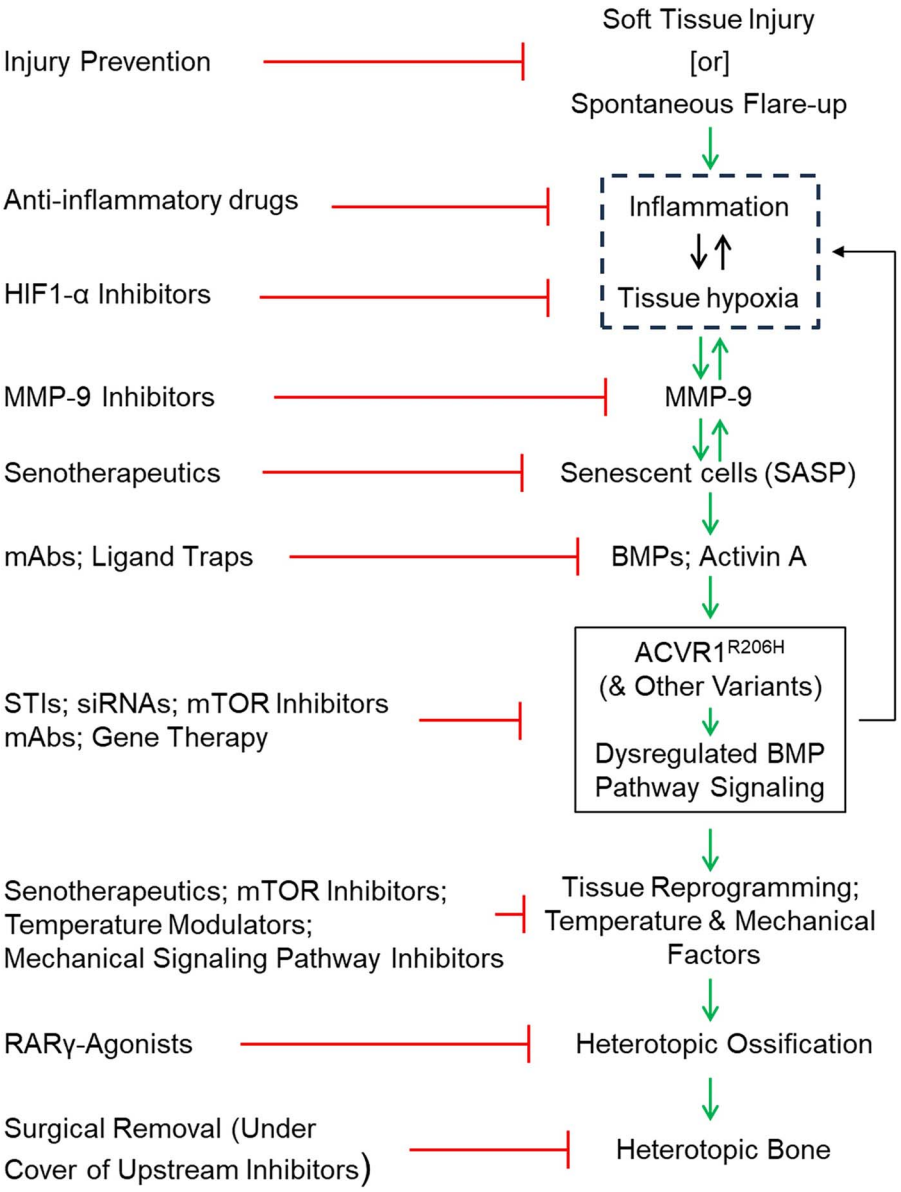

Figure 1. Targets and potential therapies for fibrodysplasia ossificans progressiva.

Class III Agents are compounds under development, being tested in clinical trials, and are not yet available for general use.

Emergency guidelines for first responders, physicians, and dentists (see ICCFOP.org)

1) Avoid all IM injections unless necessary for survival of the patient. IM injections may cause flare-ups and subsequent ossification.
2) Peripheral IV access is permissible. Use smallest needle possible with brief tourniquet time. Avoid repeated tourniquet use or over-inflation of blood pressure cuffs.
3) Avoid central venous access unless necessary for survival of the patient.
4) In case of major trauma, administer corticosteroids immediately (oral) or IV equivalent of oral Prednisone: 1-2 mg/kg once daily for 4 d.
5) Pad all bony prominences to prevent pressure ulcers and skin breakdown.
6) The cervical spine is often partially or completely ankylosed from FOP. Do not manipulate.
7) With head injury, always brace the neck.
8) Flare-ups of the anterior neck beneath the chin (submandibular) can compromise breathing and swallowing and should be considered a medical emergency. Submandibular flare-ups require early identification. Provide high-dose steroids immediately (Solumedrol 80 mg intravenously or Dexamethasone 15 mg intravenously). Avoid additional trauma with lesional manipulation. Airway monitoring, aspiration precautions, nutritional support, and immediate use of corticosteroids are mandatory.
9) Acute and often severe limb swelling can be seen with flare-ups of FOP, especially of the lower extremities. Due to intense inflammation, angiogenesis, and capillary leakage, this swelling may grow to an extraordinary and alarming size and lead to extravascular compression of nerves and tissue lymphatics. After excluding

Table 1. Regulatory-approved medications for fibrodysplasia ossificans progressiva.

Generic (trade)	Class	Mechanism of action	Dosing	Major side-effects
Palovarotene (Sohonos) in the United States, Canada, and Australia Sohonos Educational Program and must be completed by any healthcare professional who wants to prescribe Sohonos. Educational materials can be found at: SOH-US-000215-SOHONOS-Educational-Program-Materials-for-Prescribers-and-Pharmacists.pdf	RAR-γ Agonist	Inhibits Ectopic Chondrogenesis	**For adults and pediatric patients 14 yr and older:** 5 mg daily. Stop daily dosing when flare-up dosing begins. Flare-up dosage for adults and pediatric patients 14 yr and older is 20 mg daily for 4 wk, followed by 10 mg daily for 8 wk (for a total of 12 wk of flare-up treatment), even if symptoms resolve earlier. Then return to daily dosing of 5 mg. If, during a flare-up treatment, the patient experiences marked worsening of the original flare-up site or another flare-up at a new location, restart the 12-wk flare-up dosing at 20 mg daily. For flare-up symptoms that have not resolved at the end of the 12-wk period, the 10 mg daily dosage may be extended in 4-wk intervals and continued until the flare-up symptoms resolve. If new flare-up symptoms occur after the 5 mg daily dosing is resumed, flare-up dosing may be restarted. **For patients under 14 yr of age (8-13 yr for females and 10-13 yr for males):** Dosage is weight-based for both prophylactic and flare-up dosing. See prescribing information at: Microsoft Word - pi-mg-fda-comments-15aug2023-combined-rev 17Aug2023 (d2rkmuse97gwnh.cloudfront.net)	**FDA black-box warning: teratogenicity and premature epiphyseal closure** Prescribing information can be found at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/215559s000lbl.pdf The medication guide (for patients) can be found on the IpsenCares website (ipsencares.com): https://d2rkmuse97gwnh.cloudfront.net/a88aa6d6-3ca0-4362-a711-d53c45ae33ff/1e0071ea-de05-46be-8b8d-90d92765c70f/1e0071ea-de05-46be-8b8d-90d92765c70f_source__v.pdf **Premature epiphyseal closure:** Premature epiphyseal closure occurred with SOHONOS. Assess baseline skeletal maturity before SOHONOS therapy and monitor linear growth in growing pediatric patients. Growing pediatric patients are recommended to undergo baseline assessment of growth and skeletal maturity before starting treatment and continued clinical and radiographic monitoring every 6-12 mo until patients reach skeletal maturity or final adult height. **Mucocutaneous adverse reactions:** Dry skin, lip dry, pruritus, rash, alopecia, erythema, skin exfoliation, and dry eye occurred with SOHONOS. Prevent or treat with skin emollients, sunscreen, artificial tears. Dosage reduction may be required in some patients. **Metabolic bone disorders:** Decreased vertebral bone mineral content and bone density may occur. Assess for vertebral fracture periodically using radiologic method. **Psychiatric Disorders:** Depression, anxiety, mood alterations and suicidal thoughts and behaviors occurred with SOHONOS. Contact healthcare provider if new or worsening symptoms develop in patients treated with SOHONOS. **Night Blindness:** May occur and make driving at night hazardous **Pregnancy:** May cause fetal harm.

a possible deep vein thrombosis, the swelling should be treated conservatively with adequate pain control, elevation, and ultimately with safe lymphedema manipulations. Although signs and symptoms of compartment syndrome may prompt consideration of emergent surgical release of pressure (eg, fasciotomy), this will exacerbate the flare-up and MUST be avoided. If clinical suspicion of compartment syndrome is high, consider the use of mannitol.

10) In the case of limb swelling that prompts concern for deep vein thrombosis, Doppler ultrasound evaluation of the venous system may be indicated. In the rare situation that deep vein thrombosis is detected, appropriate therapy should be instituted and monitored.
11) Head and neck injuries are common from falls, as the arms are rigid from ankylosis of the shoulders early in life and cannot be used to protect the head in case of falls.
12) With any head injury, even without loss of consciousness, a head CT is mandatory to rule out intracranial bleeding due to the high likelihood of an unprotected impact.
13) The jaw is likely limited in movement or functionally ankylosed. Even if it is mobile, it is extremely susceptible

Table 2. Class I medications: generally accepted for use in fibrodysplasia ossificans progressiva.

Generic (trade)	Class	Mechanism of action
Prednisone, tablet form[a–g] **Prednisolone, liquid form (deltasone)**[a–g]	Corticosteroid	Decreases lymphocyte and macrophage recruitment and tissue infiltration; potent anti-inflammatory drug: Decreases inflammation, swelling, and edema, especially when involving jaw, throat, and major joints
Ibuprofen (advil/motrin)	Non-steroidal anti-inflammatory medication (non-specific COX-1 and COX-2 inhibitor)	Anti-inflammatory and anti-angiogenic; symptomatic relief during a flare-up; Potential use in prevention by inhibiting production of inflammatory prostaglandins
Indomethacin (indocin)	Non-steroidal anti-inflammatory medication (non-specific COX-1 and COX-2 inhibitor)	Anti-inflammatory and anti-angiogenic; symptomatic relief during a flare-up; Potential use in prevention by inhibiting production of inflammatory prostaglandins
Celecoxib (Celebrex)	COX-2 inhibitor	Anti-inflammatory and anti-angiogenic; symptomatic relief during a flare-up; Potential use in prevention by inhibiting production of inflammatory prostaglandins

[a]Do not use after minor bumps or bruises. Do not use for flare-ups involving chest or back (see text). Use prednisone prophylactically as directed for dental or surgical procedures. (Medication should be taken with food). The protocol for IV corticosteroid therapy is as follows: 7-15 mg/kg of methylprednisolone or 20-30 mg/kg of prednisolone sodium IV daily on 3 consecutive days. Some prefer to administer it on alternate days as some patients tolerate it better. 2 mg/kg once daily in AM by oral administration (PO) × 4 d for acute flare-ups involving major joints (maximum of 100 mg/d). Flare-ups often result from over-use and soft tissue injuries. Prednisone—1-2 mgs/kg (per oral) once daily for 3-4 d to prevent flare-up after severe soft-tissue injury.[2] May repeat for 4 d and then taper for as long as 2 wk. [b]May also use longer treatment with taper for flare-ups in the submandibular region, especially those that affect breathing or swallowing. [c]Prednisone or prednisolone should be started within 24 h of the onset of a flare-up for maximal effectiveness. [d]For patients with frequent flare-ups requiring prolonged steroid treatments, consider a bisphosphonate to prevent steroid-induced osteoporosis (see text). [e]For patients in endemic regions, anti-parasitic precautions may be needed. [f]Alternatively, high dose intravenous corticosteroid (methylprednisolone or prednisolone sodium) therapy may be considered but must be performed during an inpatient hospitalization to monitor for potential side effects of hypertension. [g]Total daily dose of methylprednisolone or prednisolone sodium should not exceed 1000 mg.

to trauma. Do not passively manipulate. Over-stretching of the jaw and mandibular blocks is forbidden as they will cause flare-ups.

14) It is always advisable to obtain a complete dental examination for swelling or pain of the oral-facial region, as it can be difficult to distinguish a swelling of dental origin from a flare-up of FOP. If the dental radiographs and/or pulpal testing (vitality of the nerve of the tooth) indicate no obvious dental origin to the swelling, it is prudent to assume an FOP flare-up and initiate prednisone flare-up dosing. If it is not possible to get a dental radiograph or do pulpal testing, then prescribing an appropriate antibiotic together with prednisone is warranted until a definitive diagnosis can be made. Any dental surgery should be delayed until 8 wk after flare-ups resolve.
15) Dental pain is a common issue in FOP patients and must be evaluated and treated promptly, but only after thorough consultation with an FOP dental expert. Over-stretching of the jaw and mandibular blocks is forbidden.
16) Facial swelling due to scalp flare-ups in FOP is uncommon but may occur. Other etiologies for facial swelling should be considered, such as drug reactions and cavernous sinus thrombosis. A brief course of an antihistamine should be considered to exclude allergies in FOP patients who present with facial swelling.
17) For "dirty" or contaminated wounds, use tetanus hyperimmune globulin. Avoid tetanus immunization as IM or subcutaneous immunization unless necessary, as this has a high likelihood of inciting a flare-up.
18) Hearing impairment is common in FOP. Speak loudly and clearly when appropriate.
19) Although stable hearing loss is a common feature of FOP in children, acute hearing loss and ear pain are not common and should be evaluated and treated as in any child.
20) Kidney stones are very common in adults with FOP but may occur at any age. Keep well hydrated.
21) Fractures are common in normotopic as well as heterotopic bone. Closed immobilization with splinting and bracing is recommended. Open reduction is contraindicated unless thoroughly discussed with an FOP specialist.
22) With nausea and vomiting in individuals with an ankylosed jaw, cover empirically with antibiotics for aspiration pneumonia.
23) Ask if patient is enrolled in any FOP Clinical Trials and communicate with principal investigator and regional FOP specialist.
24) In the case of choking and failure to clear throat manually, perform Heimlich maneuver if there is no evidence for abdominal heterotopic bone that would prevent attempts.
25) Chest compressions will likely be futile. The chest wall is rigid and immobile in adults with advanced stages of classic FOP.
26) Intubation must be through an awake, fiberoptic nasotracheal approach by an experienced anesthesiologist.
27) If an emergency tracheotomy is necessary in an individual with anterior neck ossifications, a dental or other drill may be necessary to create an airway.
28) In emergency situations where patients have difficulty clearing secretions, use bronchodilators, mucolytics, and guaifenesin, with a low threshold for mechanical insufflation-exsufflation devices. Hydration should be optimized with IV fluids.
29) Avoid unmonitored use of supplemental oxygen to minimize the chance of respiratory failure and death.

Table 3. Class II medications: off-label use for fibrodysplasia ossificans progressiva.

Generic	Trade	Class	Proposed mechanism of action as it relates to fibrodysplasia ossificans progressiva
Montelukast	Singulair	Leukotriene receptor antagonist	Blocks inflammatory mediators; complementary action to cyclo-oxygenase inhibitors.
Cromolyn	Gastrocrom	Mast cell stabilizer	Reduces mast cell degranulation but poorly absorbed from GI tract. May be more effective if used chronically
Pamidronate[a]	Aredia	Aminobisphosphonate	Anti-angiogenic; possibly anti-inflammatory; potential inhibition of early angiogenic fibroproliferative lesion; well-established effects on decreasing bone remodeling in normotopic skeleton and in protecting normotopic skeleton from profound osteopenic effects of chronic intermittent high dose glucocorticoids.
Zoledronate	Zometa	Aminobisphosphonate	Anti-angiogenic; possibly anti-inflammatory; potential inhibition of early angiogenic fibroproliferative lesion; well-established effects on decreasing bone remodeling in normotopic skeleton and in protecting normotopic skeleton from profound osteopenic effects of chronic intermittent high dose glucocorticoids.
Imatinib	Gleevec	Selective Tyrosine Kinase inhibitor	Off-target effects of blocking c-Kit, HIF-1α, PDGFRα, and multiple MAP kinases[44,45]
[b]**Tofacitinib**	Xeljanz	Janus kinase inhibitor	Janus kinase inhibitor, representing a new class of disease-modifying antirheumatic drugs (DMARDs), with anti-inflammatory properties and FDA approved for juvenile idiopathic arthritis, as well as other rheumatologic conditions and ulcerative colitis. In an FOP case series by Nikishina et al. 2023, levels of IL-1RA decreased in 4/5 individuals (80%) and increased in 1/5 (20%), suggesting that at least part of the mechanism of action in FOP is related to suppression of inflammatory cytokines.
[c]**Canakinumab**	Ilaris	IL-1β inhibitor	Antibody that blocks the IL-1β pro-inflammatory cytokine. This is FDA approved in children > = 4 yr of age for treatment of CAPS, Muckel-Well's syndrome, and FCAS. In an FOP uncontrolled case series of 4 patients by Haviv et al. 2024, flare activity was reduced by 61%-89%.

[a] Peds (2-3 yr): 0.75 mg/kg/d by slow IV infusion for 3 days; For children older than 3 yr and for adolescents and adults: 1.0 mg/kg/d for 3 days. Medication should be infused slowly each day over 4-5 h. On the first day of the first cycle of treatment, the patient must receive half the dose. In case of fever, give standard acetaminophen treatment. The 3-d cycle of treatment should be repeated no more than 4 times annually. For dilution instructions, see complete guidelines at icconfop.org. Patients should have the following blood tests checked prior to pamidronate treatment: serum calcium, phosphate albumin, alkaline phosphatase, 25-hydroxyvitamin D, BUN, creatinine, CBC. All patients should receive adequate supplemental dietary calcium and vitamin D daily during and indefinitely following pamidronate treatment. [b] 5mg twice daily (oral dosing) was found to be beneficial in an FOP case series by Nikishina, et al., Pediatric Rheumatology 21:1-9, 2023. https://doi.org/10.1186/s12969-023-00856-1. Also available as an extended release formulation (XR) at 11 mg once daily and higher induction doses of 10 mg twice daily or 22 mg once daily (XR) for 8 wk. An oral solution is also available at 1 mg/mL. [c] Follow Familial Mediterranean fever (FMF) dosing regimen: At <40 kg weight, start at 2 mg/kg every 4 wk. Can increase to 4 mg/kg. For >40 kg, start at 150 mg every 4 wk. Maximum dose 300 mg sq every 4 wk (maximum dose used for FMF).

Conclusions

We hope that these guidelines are useful to patients with FOP and their caretakers. The physician caring for a patient with FOP must constantly review evolving scientific information and chart the safest, most compassionate, and most responsible course for the patient. In the absence of clear evidence-based research from controlled clinical trials, it is difficult to advocate a particular therapy with enthusiasm. Carefully designed and well-controlled clinical trials are the safest bridge across the troubled waters of FOP. Such an approach is ongoing and will require the patience of the entire FOP community.

A detailed and updated exploration of the topics outlined in this brief review can be found in "The Medical Management of Fibrodysplasia Ossificans Progressiva: Current Treatment Considerations." The full guidelines and references can be found on the International Clinical Council for FOP (ICC) website (www.iccfop.org).

Acknowledgments

We gratefully acknowledge The Center for Research in FOP and Related Disorders at The University of Pennsylvania, The Isaac & Rose Nassau Professorship of Orthopaedic Molecular Medicine at the University of Pennsylvania (to F.S.K.), The Robert & Arlene Kogod Professorship (to R.J.P.) at The Mayo Clinic, and the Radiant Hope Foundation for their support. No funds were received for this work.

Author contributions

Frederick Kaplan (Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing—original draft, Writing—review & editing), Mona Al Mukaddam (Data curation, Formal analysis, Investigation, Methodology, Validation, Writing—review & editing), Genevieve Baujat (Data curation, Formal analysis, Investigation, Methodology, Validation, Writing—review & editing), Alberto Hidalgo-Bravo (Data curation, Formal analysis, Investigation, Methodology, Validation, Writing—review & editing), Matthew A. Brown (Data curation, Formal analysis, Investigation, Methodology, Validation, Writing—review & editing), Amanda Cali (Data curation, Formal analysis, Investigation, Methodology, Validation, Writing—review & editing), Tae-Joon Cho (Data curation, Formal analysis, Investigation, Methodology, Validation, Writing—review & editing), Corrie Crowe (Data curation, Formal analysis, Investigation, Methodology, Validation, Writing—review & editing), Carmen De Cunto (Data curation, Formal analysis, Investigation, Methodology, Validation, Writing—review & editing), Patricia Delai (Data curation, Formal analysis, Investigation, Methodology, Validation, Writing—review & editing), Robert Diecidue (Data curation, Formal analysis, Investigation, Methodology, Validation, Writing—review & editing), Elisabeth M.W. Eekhoff (Data curation, Formal analysis, Investigation, Methodology, Validation, Writing—review & editing), Lisa Friedlander (Data curation, Formal analysis, Investigation, Methodology, Validation, Writing—review & editing), Clive Friedman (Data curation, Formal analysis, Investigation, Methodology, Validation, Writing—review & editing), Zvi Grunwald (Data curation, Formal analysis, Investigation, Methodology, Validation, Writing—review & editing), Nobuhiko Haga

Table 4. Class III agents: compounds for investigational use in fibrodysplasia ossificans progressiva.

Generic [sponsor; trial]	Class	Proposed mechanism of action as it relates to FOP	Dosing (research phase)	Major side effects
ACVR1/ALK2 Signal Transduction Inhibitor, STI (Saracatinib) [Astra Zeneca; STOPFOP]	Signal Transduction Inhibitor	Blocks ACVR1/ALK2 signal transduction	Not applicable at present time; Ongoing Phase II clinical trial	See: www.clinicaltrials.gov; www.ifopa.org/ongoing_clinical_trials_in_fop
ACVR1/ALK2 Signal Transduction Inhibitor, STI (Fidrisertib; IPN60130) [Ipsen; FALKON]	Signal Transduction Inhibitor	Blocks ACVR1/ALK2 signal transduction	Not applicable at present time; Ongoing Phase II clinical trial	See: www.clinicaltrials.gov; www.ifopa.org/ongoing_clinical_trials_in_fop
ACVR1/ALK2 Signal Transduction Inhibitor, STI (Zilurgisertib; INCB000928) [Incyte; PROGRESS]	Signal Transduction Inhibitor	Blocks ACVR1/ALK2 signal transduction	Not applicable at present time; Ongoing Phase II clinical trial	See: www.clinicaltrials.gov; www.ifopa.org/ongoing_clinical_trials_in_fop
mTOR Inhibitors (eg, Sirolimus) [Kyoto University]	mTOR Inhibitor	Inhibits ACVR1/ALK2 signal transduction	Not applicable at present time; Ongoing Phase II clinical trial	Common side effects include rash, stomatitis, metabolic abnormalities like hyperlipidemia and hyperglycemia, anemia, leukopenia, thrombocytopenia, fatigue, increased risk of infections and pneumonitis See, for example: Arena, C, et al. Internat J Oncol 59: 54, 2021. https://doi.org/10.3892/ijo.2021.5234
Monoclonal Antibody Against Activin A (Garetosmab) [Regeneron; Lumina/Optima]	Activin A Antibody	Blocks Activin A signaling through mutant ACVR1/ALK2	Not applicable at Present time; Ongoing Phase III clinical trial	See: www.clinicaltrials.gov; www.ifopa.org/ongoing_clinical_trials_in_fop
Monoclonal Antibody Against MMP-9 (Andecaliximab) [ās*hi**bio***; ANDECAL]	MMP-9 Antibody	Reduces Activin-A release from macrophages and matrix stores; likely multimodal actions on all HO factors	Not applicable at Present time; Phase II/III clinical trial	See: Sandborn WJ, et al. Aliment Pharmacol Ther. 2016; 44(2): 157-69; Gossage DL, et al. Clin Ther. 2018; 40(1): 156-65; Sanborn WJ, et al. J Crohn's Colitis. 2018; 12(9): 1021-9

(Data curation, Formal analysis, Investigation, Methodology, Validation, Writing—review & editing), Edward C. Hsiao (Data curation, Formal analysis, Investigation, Methodology, Validation, Writing—review & editing), Richard Keen (Data curation, Formal analysis, Investigation, Methodology, Validation, Writing—review & editing), Joseph A. Kitterman (Data curation, Formal analysis, Investigation, Methodology, Validation, Writing—review & editing), Charles Levy (Data curation, Formal analysis, Investigation, Methodology, Validation, Writing—review & editing), Vrisha Madhuri (Data curation, Formal analysis, Investigation, Methodology, Validation, Writing—review & editing), Rolf Morhart (Data curation, Formal analysis, Investigation, Methodology, Validation, Writing—review & editing), J. Coen Netelenbos (Data curation, Formal analysis, Investigation, Methodology, Validation, Writing—review & editing), Christiaan Scott (Data curation, Formal analysis, Investigation, Methodology, Validation, Writing—review & editing), Eileen M. Shore (Data curation, Formal analysis, Investigation, Methodology, Validation, Writing—review & editing), Michael Zasloff (Data curation, Formal analysis, Investigation, Methodology, Validation, Writing—review & editing), Keqin Zhang (Data curation, Formal analysis, Investigation, Methodology, Validation, Writing—review & editing), and Robert Pignolo (Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing—original draft, Writing—review & editing)

Funding

No funds were received for this work.

Conflicts of interest

F.S.K. is a clinical trial investigator for Ashibio, Incyte, Ipsen, and Regeneron and serves in an unpaid capacity on the Medical Registry Advisory Board of the International Fibrodysplasia Ossificans Progressiva Association, the International Clinical Council on FOP, and Tin Soldiers. M.A.M. is a clinical trial investigator for Ashibio, Incyte, Ipsen, and Regeneron, and serves in an unpaid capacity on the Medical Registry Advisory Board of the International Fibrodysplasia Ossificans Progressiva Association, the International Clinical Council on FOP, and Tin Soldiers. G.B. has research grants and conference support from FOP France and Ipsen, is a clinical trial investigator for Incyte, Ipsen, and Regeneron, is a member of the Medical Registry Advisory Board of the IFOPA, of the European Reference Network on rare bone diseases (BOND), of the scientific committee of FOP France, and a representative to the European FOP consortium. A.H.B. is a clinical trial investigator for Incyte, Ipsen, and Regeneron. M.B. is a clinical trial investigator for Incyte, Ipsen, and Regeneron. A.C. is a trustee of The Radiant Hope Foundation. T-J.C. is a clinical trial investigator for Incyte and Ipsen. C.C.: None declared. C.L.D.C. is a clinical trial investigator for Incyte and Ipsen and a member of the Medical Registry Advisory Board of the IFOPA. P.D. is a consultant for Ipsen, a clinical trial investigator for Incyte, Ipsen, and Regeneron, and a member of the Board of Directors of Tin Soldiers Global and the Noi Ci Siamo Association in Switzerland. R.J.D.: None declared. E.M.W.E. is a clinical trial investigator for STOPFOP, Regeneron, Ipsen, and Incyte, a member of the Medical Registry Advisory Board of the IFOPA, the steering committee of the Amsterdam Bone Center, the European Reference Network on rare bone diseases, a representative to the European FOP consortium, Chair of the NVE BoNe, and Chair of the Rare Bone Disease Center Amsterdam UMC. L.F.: None declared. C.F. is a consultant for Ipsen, Clinical Director for The Special Olympics, a member of the Board of Directors of Tin Soldiers Global, and has received an honorarium from Springer for a presentation. Z.G. is a consultant for the Axdev Group. N.H. was a clinical investigator for Ipsen. E.C.H. serves in an unpaid capacity on the Medical Registry Advisory Board of the International Fibrodysplasia Ossificans Progressiva Association; the Fibrous Dysplasia Foundation

Medical and Scientific Advisory Boards; and the International Clinical Council on FOP. ECH receives support for clinical trials through his institution from Clementia Pharmaceuticals, an Ipsen Company; Ipsen Pharmaceuticals; Ascendis; and āshibio. R.K. is a consultant for Ipsen, Alexion, Kyowa Kirin, UCB, Amgen, and Richter, a member of the Advisory Board of Alexion, Kyowa Kirin, Theramex, a clinical investigator for Alexion, Kyowa Kirin, Incyte, Ipsen, and Regeneron, and a member of the Advisory Board of The Brittle Bone Society and the National Health Service (NHS) of England. J.K.: None declared. C.E.L.: None declared. V.M.: None declared. R.M. is a consultant for Ipsen. J.C.N.: None declared. C.S. is a consultant for Ipsen and was a previous clinical trial investigator for Ipsen and Regeneron. E.M.S.: None declared. M.A.Z. was a member of the Clementia/Ipsen Data Safety Monitoring Board (DSMB) during the Palovarotene clinical trials and is currently on the Incyte DSMB. K.Z. is a clinical trial investigator for Incyte, Ipsen, and Regeneron. R.J.P. is a clinical trial investigator for Ashibio, Incyte, Ipsen, and Regeneron, a member of the Medical Registry Advisory Board of the IFOPA, and a consultant for Incyte, Ipsen, and Regeneron. RJP is a co-inventor for the use of Andecaliximab in conditions of heterotopic ossification.

Data availability

Not applicable.

References

1. Pignolo RJ, Shore EM, Kaplan FS. Fibrodysplasia ossificans progressiva: diagnosis, management, and therapeutic horizons. *Pediatr Endocrinol Rev*. 2013;10 Suppl 2(02):437-448.
2. Hüning I, Gillessen-Kaesbach G. Fibrodysplasia ossificans progressiva: clinical course, genetic mutations and genotype-phenotype correlation. *Mol Syndromol*. 2014;5(5):201-211. https://doi.org/10.1159/000365770
3. Pignolo RJ, Bedford-Gay C, Liljesthröm M, et al. The natural history of flare-ups in fibrodysplasia ossificans progressiva (FOP): a comprehensive global assessment. *J Bone Miner Res*. 2016;31(3):650-656. https://doi.org/10.1002/jbmr.2728
4. Pignolo RJ, Baujat G, Brown MA, et al. The natural history of fibrodysplasia ossificans progressiva: a prospective, global 36-month study. *Genet Med*. 2022;24(12):2422-2433. https://doi.org/10.1016/j.gim.2022.08.013
5. Al Mukaddam M, Toder KS, Davis M, et al. The impact of fibrodysplasia ossificans progressiva (FOP) on patients and their family members: results from an international burden of illness survey. *Expert Rev Pharmacoecon Outcomes Res*. 2022;22(8):1199-1213. https://doi.org/10.1080/14737167.2022.2115360
6. Kitterman JA, Kantanie S, Rocke DM, Kaplan FS. Iatrogenic harm caused by diagnostic errors in fibrodysplasia ossificans progressiva. *Pediatrics*. 2005;116(5):e654-e661. https://doi.org/10.1542/peds.2005-0469
7. Pignolo RJ, Durbin-Johnson BP, Rocke DM, Kaplan FS. Joint-specific risk of impaired function in fibrodysplasia ossificans progressiva (FOP). *Bone*. 2018;109:124-133. https://doi.org/10.1016/j.bone.2017.06.009
8. Towler OW, Shore EM, Kaplan FS. Skeletal malformations and developmental arthropathy in individuals who have fibrodysplasia ossificans progressiva. *Bone*. 2020;130:115116. https://doi.org/10.1016/j.bone.2019.115116
9. Kaplan FS, Shore EM, Pignolo RJ. Fibrodysplasia ossificans progressiva emerges from obscurity. *Trends Mol Med*. 2025;31(2):106-116. https://doi.org/10.1016/j.molmed.2024.08.010
10. Kaplan FS, Zasloff MA, Kitterman JA, Shore EM, Hong CC, Rocke DM. Early mortality and cardiorespiratory failure in patients with fibrodysplasia ossificans progressiva. *J Bone Joint Surg Am*. 2010;92(3):686-691. https://doi.org/10.2106/JBJS.I.00705
11. Shore EM, Xu M, Feldman GJ, et al. A recurrent mutation in the BMP type I receptor ACVR1 causes inherited and sporadic fibrodysplasia ossificans progressiva. *Nat Genet*. 2006;38(5):525-527. https://doi.org/10.1038/ng1783
12. Kaplan FS, Xu M, Seemann P, et al. Classic and atypical fibrodysplasia ossificans progressiva (FOP) phenotypes are caused by mutations in the bone morphogenetic protein (BMP) type I receptor ACVR1. *Hum Mutat*. 2009;30(3):379-390. https://doi.org/10.1002/humu.20868
13. Brennan TA, Lindborg CM, Bergbauer CR, Wang H, Kaplan FS, Pignolo RJ. Mast cell inhibition as a therapeutic approach in fibrodysplasia ossificans progressiva (FOP). *Bone*. 2018;109:259-266. https://doi.org/10.1016/j.bone.2017.08.023
14. Barruet E, Morales BM, Cain CJ, et al. NF-κB/MAPK activation underlies ACVR1-mediated inflammation in human heterotopic ossification. *JCI Insight*. 2018;3(22):e122958Published 2018 Nov 15. https://doi.org/10.1172/jci.insight.122958
15. Hsiao EC, Di Rocco M, Cali A, et al. Special considerations for clinical trials in fibrodysplasia ossificans progressiva (FOP). *Br J Clin Pharmacol*. 2019;85(6):1199-1207. https://doi.org/10.1111/bcp.13777
16. Pignolo RJ, Kaplan FS. Druggable targets, clinical trial design and proposed pharmacological management in fibrodysplasia ossificans progressiva. *Expert Opinion on Orphan Drugs*. 2020;8(4):101-109. https://doi.org/10.1080/21678707.2020.1751122
17. Di Rocco M, Forleo-Neto E, Pignolo RJ, et al. Garetosmab in fibrodysplasia ossificans progressiva: a randomized, double-blind, placebo-controlled phase 2 trial. *Nat Med*. 2023;29(10):2615-2624. https://doi.org/10.1038/s41591-023-02561-8
18. Pignolo RJ, Hsiao EC, Al Mukaddam M, et al. Reduction of new heterotopic ossification (HO) in the open-label, phase 3 MOVE trial of Palovarotene for fibrodysplasia ossificans progressiva (FOP). *J Bone Miner Res*. 2023;38(3):381-394. https://doi.org/10.1002/jbmr.4762
19. Lounev V, Groppe JC, Brewer N, et al. Matrix metalloproteinase-9 deficiency confers resilience in fibrodysplasia ossificans progressiva in a man and mice. *J Bone Miner Res*. 2024;39(4):382-398. https://doi.org/10.1093/jbmr/zjae029
20. Kaplan FS, Al Mukaddam M, Baujat G, et al. The Medical Management of Fibrodysplasia Ossificans Progressiva: Current Treatment Considerations. *Proc Intl Clin Council FOP*. 2024;3:1-159. https://www.iccfop.org/dvlp/wp-content/uploads/2024/07/FOP-GUIDELINES-FINAL-2024.pdf
21. Chakkalakal SA, Zhang D, Culbert AL, et al. An Acvr1 R206H knock-in mouse has fibrodysplasia ossificans progressiva. *J Bone Miner Res*. 2012;27(8):1746-1756. https://doi.org/10.1002/jbmr.1637
22. Hatsell SJ, Idone V, Wolken DM, et al. ACVR1R206H receptor mutation causes fibrodysplasia ossificans progressiva by imparting responsiveness to activin a. *Sci Transl Med*. 2015;7(303):303ra137. https://doi.org/10.1126/scitranslmed.aac4358
23. Hino K, Ikeya M, Horigome K, et al. Neofunction of ACVR1 in fibrodysplasia ossificans progressiva. *Proc Natl Acad Sci USA*. 2015;112(50):15438-15443. https://doi.org/10.1073/pnas.1510540112
24. Wang H, Lindborg C, Lounev V, et al. Cellular hypoxia promotes heterotopic ossification by amplifying BMP Signaling. *J Bone Miner Res*. 2016;31(9):1652-1665. https://doi.org/10.1002/jbmr.2848
25. Lees-Shepard JB, Yamamoto M, Biswas AA, et al. Activin-dependent signaling in fibro/adipogenic progenitors causes fibrodysplasia ossificans progressiva. *Nat Commun*. 2018;9(1):471. Published 2018 Feb 2. https://doi.org/10.1038/s41467-018-02872-2
26. Kaplan FS, Xu M, Glaser DL, et al. Early diagnosis of fibrodysplasia ossificans progressiva. *Pediatrics*. 2008;121(5):e1295-e1300. https://doi.org/10.1542/peds.2007-1980

27. Pignolo RJ, Bedford-Gay C, Cali A, et al. Current challenges and opportunities in the care of patients with fibrodysplasia ossificans progressiva (FOP): an international, multistakeholder perspective. *Orphanet J Rare Dis*. 2022;17(1):168. Published 2022 Apr 18. https://doi.org/10.1186/s13023-022-02224-w
28. Kilmartin E, Grunwald Z, Kaplan FS, Nussbaum BL. General anesthesia for dental procedures in patients with fibrodysplasia ossificans progressiva: a review of 42 cases in 30 patients. *Anesth Analg*. 2014;118(2):298-301. https://doi.org/10.1213/ANE.0000000000000021
29. Levy CE, Berner TF, Bendixen R. Rehabilitation for individuals with fibrodysplasia ossificans progressiva. *Clin Rev Bone Min Metabolism*. 2005;3:251-256.
30. Glaser DL, Rocke DM, Kaplan FS. Catastrophic falls in patients who have fibrodysplasia ossificans progressiva. *Clin Orthop Relat Res*. 1998;346:110-116. https://doi.org/10.1097/00003086-199801000-00016
31. Janoff HB, Zasloff MA, Kaplan FS. Submandibular swelling in patients with fibrodysplasia ossificans progressiva. *Otolaryngol Head Neck Surg*. 1996;114(4):599-604. https://doi.org/10.1016/S0194-59989670253-X
32. Luchetti W, Cohen RB, Hahn GV, et al. Severe restriction in jaw movement after routine injection of local anesthetic in patients who have fibrodysplasia ossificans progressiva. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 1996;81(1):21-25. https://doi.org/10.1016/s1079-2104(96)80141-7
33. Lindborg CM, Al Mukaddam M, Baujat G, et al. Most fractures treated nonoperatively in individuals with Fibrodysplasia Ossificans Progressiva heal with a paucity of flareups, heterotopic ossification, and loss of mobility. *Clin Orthop Relat Res*. 2023;481(12):2447-2458. https://doi.org/10.1097/CORR.0000000000002672
34. Levy CE, Lash AT, Janoff HB, Kaplan FS. Conductive hearing loss in individuals with fibrodysplasia ossificans progressiva. *Am J Audiol*. 1999;8(1):29-33. https://doi.org/10.1044/1059-0889(1999/011)
35. Lanchoney TF, Cohen RB, Rocke DM, Zasloff MA, Kaplan FS. Permanent heterotopic ossification at the injection site after diphtheria-tetanus-pertussis immunizations in children who have fibrodysplasia ossificans progressiva. *J Pediatr*. 1995;126(5 Pt 1):762-764. https://doi.org/10.1016/s0022-3476(95)70408-6
36. Scarlett RF, Rocke DM, Kantanie S, Patel JB, Shore EM, Kaplan FS. Influenza-like viral illnesses and flare-ups of fibrodysplasia ossificans progressiva. *Clin Orthop Relat Res*. 2004;423:275-279. https://doi.org/10.1097/01.blo.0000129557.38803.26
37. Gupta RR, Delai PLR, Glaser DL, et al. Prevalence and risk factors for kidney stones in fibrodysplasia ossificans progressiva. *Bone*. 2018;109:120-123. https://doi.org/10.1016/j.bone.2017.12.010
38. Moriatis JM, Gannon FH, Shore EM, Bilker W, Zasloff MA, Kaplan FS. Limb swelling in patients who have fibrodysplasia ossificans progressiva. *Clin Orthop Relat Res*. 1997;336:247-253. https://doi.org/10.1097/00003086-199703000-00033
39. Verheij VA, Diecidue RJ, Botman E, et al. Palovarotene in fibrodysplasia ossificans progressiva: review and perspective. *Expert Opin Pharmacother*. 2025;26(3):291-299. https://doi.org/10.1080/14656566.2025.2452938
40. Forrest AD, Vuncannon DM, Ellis JE, Grunwald Z, Kaplan FS. Fibrodysplasia ossificans progressiva and pregnancy: a case series and review of the literature. *Case Rep Obstet Gynecol*. 2022;2022:9857766. Published 2022 Sep 16. https://doi.org/10.1155/2022/9857766
41. Kaplan FS, Sponseller PD, Pignolo RJ. Thoracic deformity in fibrodysplasia ossificans progressiva. *JBJS Rev*. 2025;13(5):e25.00042. Published 2025 May 22. https://doi.org/10.2106/JBJS.RVW.25.00042
42. Piram M, Le Merrer M, Bughin V, De Prost Y, Fraitag S, Bodemer C. Scalp nodules as a presenting sign of fibrodysplasia ossificans progressiva: a register-based study. *J Am Acad Dermatol*. 2011;64(1):97-101. https://doi.org/10.1016/j.jaad.2010.04.025
43. Shah PB, Zasloff MA, Drummond D, Kaplan FS. Spinal deformity in patients who have fibrodysplasia ossificans progressiva. *J Bone Joint Surg Am*. 1994;76(10):1442-1450. https://doi.org/10.2106/00004623-199410000-00002
44. Kaplan FS, et al. Early clinical observations on the use of imatinib mesylate in FOP: A report of seven cases. *Bone*. 2018;109:276-280. https://doi.org/10.1016/j.bone.2017.07.019
45. Kaplan FS, et al. Off-on-off-on use of imatinib in three children with fibrodysplasia ossificans progressiva. *Bone*. 2021;150:116016. https://doi.org/10.1016/j.bone.116016

JBMR Plus, 2025, 9, ziaf150
https://doi.org/10.1093/jbmrpl/ziaf150
Guidelines