Evolving Management of Fibrodysplasia Ossificans Progressiva

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Current Strategies for Fibrodysplasia Ossificans Progressiva (FOP) Management

At present, there are no approved treatments for FOP that can reverse the condition or prevent heterotopic ossification, the abnormal growth of bone in soft tissues and muscles.[1] Current goals of FOP management are supportive and focus on prevention and management of disease flare-ups, delay of heterotopic ossification, and improvement of the quality of life for people with FOP. Gentle physical activities—especially activities that promote respiratory health, like singing or hydrotherapy—are encouraged for all people with FOP. However, activities with a risk of physical contact or injury must be avoided. Likewise, people affected by FOP should avoid activities that promote overstretching of soft tissues. There is a temptation to engage in physical therapy to regain lost joint range of motion through stretching or passive range-of-motion exercises. Unfortunately, these practices may cause new tissue injury, resulting in further heterotopic ossification, and are thus discouraged. Iatrogenic injuries—specifically the trauma associated with a biopsy, the surgical removal of heterotopic bone, and all nonemergent surgical procedures—are also to be avoided, because these procedures can initiate the precipitous, painful growth of new bone.

The International Clinical Council on FOP, a body of clinicians with expertise in the management of FOP, issued updated guidelines in March of 2019 for the medical management of FOP; an addendum was published in June of 2019.[1] These guidelines address a range of therapeutic issues in FOP, including prevention and management of localized flare-ups and pain, rehabilitative care, administration of immunizations, use of anesthesia, and pathophysiologic-based treatments for FOP.

Assessing FOP Severity

In an effort to quantify disease severity and disability in FOP, Kaplan et al developed the Cumulative Analogue Joint Involvement Scale, or CAJIS.[2] This scale is a simple, rapidly administered clinical assessment of the range of movement of 12 joints (shoulders, elbows, wrists, hips, knees, and ankles) and 3 body regions (cervical spine, thoracolumbar spine, and jaw) in FOP. Individual joint assessments are graded on a scale of 0 (<10% deficit), 1 (10%-90% deficit), or 2 (>90% deficit or functionally ankylosed). The possible total score ranges from 0 to 30, with high scores indicating greater impairment and disability. Kaplan et al showed that greater total and regional CAJIS scores correlate with older age and provide an overall snapshot of general debility.[2,3] Higher upper extremity CAJIS scores correlate with a reduced capacity to perform activities of daily living, and higher lower extremity CAJIS scores correlate with impaired ambulation. Regional scores of upper and lower extremities on the CAJIS thereby serve as indicators of self-care and mobility, respectively.

Prevention of Injury and Flare-ups

Flare-ups are best managed by their prevention through measures that reduce the risk of physical trauma and injury.[1] Some flare-ups in FOP may spontaneously regress, but most lead to the transformation of connective tissue into mature heterotopic bone. Even minor iatrogenic trauma, such as that occurring from unskilled venipuncture, intramuscular (IM) injections, or anesthetic blocks for dental work, can produce flare-ups. Likewise, viral illness, overexertion, and blunt trauma from bumps and falls can precipitate flare-ups and heterotopic ossification. More invasive trauma, such as surgical attempts to remove heterotopic bone, is followed by dramatic and painful new bone growth.[4]

Management directed at the prevention of falls and the associated injury is important, while simultaneous care must be taken to not further compromise the function and independence of people living with FOP.[1,5] Measures to reduce the risk of falls include modification of activities to minimize physical contact. Home

ACVR1	Activin A receptor type 1
ALK2	Activin receptor-like kinase 2
CAJIS	Cumulative Analogue Joint Involvement Scale
COX2	Cyclo-oxygenase 2
DPT	Diphtheria–pertussis–tetanus
FOP	Fibrodysplasia ossificans progressiva
IM	Intramuscular
IV	Intravenous
NSAID	Non-steroidal anti-inflammatory drug
TMJ	Temporomandibular joint

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improvements to prevent falls include installing protective hand railings in hallways and on stairs, improving uneven flooring, securing carpeting and rugs, and removing impeding objects and furniture from main household pathways. The gait of people with FOP may be stabilized and balance may be improved by the use of a cane or walker. To minimize injury when a fall does occur, protective headgear can reduce the risk of severe head injury. When falls do happen, medical attention should be sought promptly, and any head injury should be considered serious until proved otherwise.

Rehabilitative Care

Although physical therapy with passive range-of-movement exercise should be avoided in FOP, warm-water aquatic therapy allows individuals with FOP to perform active range-of-motion, cardiopulmonary, and resistance exercises in a low-impact environment.[1,6] Warm water can also ease FOP-associated pain. Occupational therapists are essential members of the care team for people with FOP, as they can recommend and implement valuable accommodations to aid essential activities of daily living, such as dressing, toileting, bathing and grooming, meal preparation and eating, mobility and transportation, education or work, sleep, and sexual activity. Dressing may be enabled by clothing and footwear that is easy to put on, fasten, and take off. Bathroom needs are addressed by commode adjustments, widened doorways, and grab bars. Utensils and devices with modified handles are often useful for daily grooming, routine dental care, food preparation, and eating. In addition to the use of a cane or walker, customized orthotics and shoes can aid and preserve independent mobility.[7] For people with severely limited ambulation, power wheelchairs may be customized for individual seating needs via personalized height, tilt, seating, and reclining functions. Mounts for laptops and other devices on power wheelchairs enable essential participation in school, work, and creative leisure activities. Safe sex in FOP is facilitated by thoughtful discussions and physical accommodations, such as pillows and bolsters. Given the autosomal-dominant nature of FOP, genetic counseling is warranted in sexually active individuals with FOP, and contraceptive measures and reproductive options should be discussed. Psychologists, social workers, and other mental health professionals, vocational and school counselors, creative arts therapists, and recreational therapists are valuable team members who can help affected individuals and family members adjust to the limitations and inconveniences imposed by FOP and help pave the way to achieving present and future goals.

Preventive Healthcare

Immunizations are essential for people with FOP because they are at the same risk of infectious diseases as the general population.[1] In FOP, immunizations by subcutaneous administration are recommended for all vaccines that can be administered by that route, and IM immunizations should be avoided, as they can precipitate flare-ups. Specifically, the routine IM administration of the childhood diphtheria–tetanus–pertussis (DPT) vaccine poses a substantial risk of permanent heterotopic ossification. Lanchoney et al reported that IM DPT vaccination caused flare-ups and subsequent heterotopic ossification in 27% of children with FOP.[8] In some cases, permanent loss of joint motion was sustained. It also has been observed that the subcutaneous injection of DPT-type vaccines may cause flare-ups, heterotopic ossification, and loss of joint mobility in FOP. Therefore, it is recommended no DPT-type vaccines should be administered to individuals with FOP. Intranasal influenza immunization with live or attenuated viruses should also be avoided for the same reason. Notably, there have been no reported cases of FOP flare-ups after the subcutaneous administration of the measles–mumps–rubella) or measles–mumps–rubella–varicella vaccines, despite the fact that they contain attenuated viruses. No immunizations should be given during flare-ups, and immunizations should be avoided for 6-8 weeks after flare-ups resolve.

People with FOP can tolerate peripheral venipuncture and the placement of peripheral intravenous (IV) lines, provided that they are performed by skilled practitioners.[1] It is critical that the procedures be performed as gently as possible and with minimal trauma. Tourniquet time during these procedures should be brief. In cases of IV access, the smallest appropriate catheter should be used to avoid the formation of heterotopic ossification along the IV tract and at the site of catheter insertion. Unless critical for medical management, the placement of a central line or peripherally inserted central catheter and arterial punctures must be avoided because they may trigger heterotopic ossification.

Preventive oral healthcare is essential in FOP, especially during childhood.[1] Dental care in FOP, however, is challenging, owing to the fact that developmental anomalies and spontaneous or post-traumatic ankylosis of the temporomandibular joint (TMJ) are common in FOP.[9-11] Recommendations to maintain oral health and prevent dental caries and periodontal disease include the fluoridation of water and the use of high-dose fluoride toothpaste, gels, and rinses. The use of fluoride sealants on primary and permanent teeth is recommended to avert the development of dental caries. Brushing and flossing are critical but may be difficult because of limited jaw opening due to TMJ dysfunction. Accommodations include ultrasonic tooth brushes with small heads, water picks, and floss wands. When normal mouth opening is possible, people with FOP can be treated with routine dental instruments; however, care must be taken to avoid overstretching of the TMJ. When TMJ function is limited, antimicrobial and fluoride rinses may be the only option to reach the palate and buccal mucosa. Anecdotal reports suggest that iontophoresis, the dermal application of physiologically active ions by continuous direct current, may help restore some lost TMJ range of motion in FOP.[11]

Nonsurgical treatment of dental caries is recommended, when possible, and minor procedures can be performed in the dental office by using interligamentary anesthesia or lasers. Mandibular blocks are expressly prohibited in FOP,

however. In cases of office procedures, an assessment of mouth opening should be performed, and a mouth prop can be judiciously used, provided that the mouth is opened no more than 3-4 mm less than its maximal opening. Saliva testing is recommended in adolescents and adults with FOP to determine volume, flow, and pH; deficiencies can be remedied with saliva substitutes, pastes, or xylitol-containing gum and rinses. Generally, any measure that reduces the risk of poor oral health should be applied in FOP management. The International Clinical Council on FOP has provided specific age-based recommendations for the maintenance of oral health and dental treatment. Detailed guidelines for maintaining the oral health of people for FOP also have been published by Nussbaum et al.[12]

General Anesthesia in FOP

General anesthesia is particularly dangerous and has even been implicated as a cause of death in people with FOP.[13] Detailed guidelines exist for its administration.[1,10,12] In most cases of general anesthesia in FOP, the procedure is performed for the purposes of dental care. Many routine anesthetic procedures, such as IM injections, peripheral nerve blocks, and the placement of spinal or epidural catheters, are to be avoided in FOP because they can cause heterotopic ossification. Even the missed placement of an IV catheter can result in heterotopic ossification along the IV tract and at the point of insertion. Airway management is one of the most demanding challenges when administering general anesthesia to people with FOP because of limited mouth opening and restricted neck movement due to TMJ immobility and cervical spine fusion, respectively. Both impairments make visualization of the airway and standard intubation very difficult. Likewise, mechanical ventilation in FOP can be compromised because of restricted chest-wall movement and thoracic insufficiency. In these cases, there may be a need for high inspiratory pressures. Sedation, pulmonary reserve, and oxygen saturation must be diligently monitored in anesthetized people with FOP. Light sedation helps patients control their own secretions.

A 10-year retrospective review (2001-2011) from the Departments of Anesthesiology and Dentistry at Thomas Jefferson University Hospital and the University of Pennsylvania in Philadelphia evaluated data from 30 people with FOP who had undergone general anesthesia for 42 dental rehabilitative procedures.[14] These patients ranged in age from 5 to 36 years; more than one-half were of pediatric age. In most of these procedures (35/42 [83%]), general anesthesia was achieved by means of awake fiberoptic intubation, which is the preferred modality for airway management in people with FOP. Awake fiberoptic intubation avoids overstretching of the jaw that can result from direct laryngoscopy. However, the process does require some cooperation from the patient, who is typically under light IV sedation. Therefore, awake fiberoptic intubation is generally not used in the pediatric population. In this study, general anesthesia was induced in 4 pediatric patients by means of spontaneous ventilation, which was then followed by fiberoptic intubation. In most cases, intubation was achieved through the nasotracheal route. In all cases, extubation was performed successfully in the operating room.

The success of general anesthesia in FOP depends on sound foreknowledge of the patient, an initial interdisciplinary plan, careful preoperative positioning, and a backup plan in cases of failed intubation.[14] In addition to the anesthesiologist, anesthetic management in FOP typically involves a dental or oral surgeon, a primary care physician (including a pediatrician), and any number of specialists (including a cardiologist). Otolaryngologists on standby are useful when intubation is especially difficult. Most people with FOP undergoing surgery receive intraoperative and postoperative glucocorticoids. When age-appropriate, input from the patient is helpful in preoperative positioning and the administration of inhaled anesthesia.

Pharmacotherapy for FOP

The medical prevention and treatment of flare-ups is generally addressed through the use of corticosteroids and nonsteroidal anti-inflammatory drugs (NSAIDs).[11] Other medications that have a theoretical mechanistic-based application to the management of flare-ups include leukotriene inhibitors, mast-cell stabilizers, bisphosphonates, and a tyrosine-kinase inhibitor (**Table I**).

Steroids

In cases of severe soft-tissue injury, the prophylactic use of daily oral prednisone, 1-2 mg/kg, for 3-4 days may be considered. Oral prednisone also is used prophylactically before any dental and surgical procedures in people with FOP. In cases of active flare-ups, corticosteroids are used because of their powerful anti-inflammatory effects. Multiple consistent anecdotal reports indicate that a 4-day course of high-dose corticosteroids, begun early during a flare-up, helps to reduce the soft-tissue swelling and associated inflammation that defines the early stage of heterotopic ossification. However, successful results with corticosteroids are not uniform. In a study of corticosteroid treatment in several hundred people with FOP flare-ups, a little more than one-half reported an occasional improvement in symptoms, and approximately one-third reported universal improvement.[15] Only 12% reported complete resolution of a flare-up with corticosteroid therapy, and 43% experienced rebound symptoms within a week after treatment was completed. In cases of active flare-ups, corticosteroid use is restricted to the early (within 24 hours) treatment of flare-ups affecting the major joints, jaw, and submandibular area.[11] Alternatively, high-dose glucocorticoids (eg, IV methylprednisolone, IV prednisolone) may be considered in these cases (**Table I**). Early treatment of flare-ups is facilitated when people with FOP already have prednisone on hand (ie, a "pill in pocket" approach). Because flare-ups of the jaw and submandible are potentially dangerous, a slightly longer course of corticosteroids may be appropriate in these cases. Corticosteroids are generally not recommended for neck or

Table I. Medications for the treatment of FOP flare-ups (Adapted from the International Clinical Council on FOP and Consultants, 2019[1])

Drugs	Dosing	Major side effects
Class I medications: widely used for FOP flare-ups or chronic arthropathy with generally minimal side effects		
Corticosteroids		
Oral prednisone	Within 24 h: 2 mg/kg qd × 4 days; maximum daily dosage, 100 mg May repeat 4-d course with longer taper May use longer treatment with taper for flare-ups in submandibular region	• Avascular necrosis of hip • Diabetes • Cataracts • Osteoporosis • Cushing disease • Chronic dependency • Immune suppression • Adrenal suppression • Growth retardation • Acne • Peptic ulcers • Hypertension • Glaucoma • Weight gain • Skin bruising • Sleep and mood disturbance
IV methylprednisolone	7-15 mg/kg qd × 3 d	
IV prednisolone	20-30 mg/kg qd × 3 d, either consecutive or alternate	
Oral NSAIDs (nonspecific COX-1 and COX-2 inhibitors)		
Ibuprofen	Children: 4-10 mg/kg q 6 h, as needed Adults: 200-800 mg q 6 h, as needed	• Gastrointestinal bleeding • Impaired renal function
Indomethacin	Children: 2-4 mg/kg/d or 150-200 mg/d, whichever is less, divided tid Adults: 50 mg tid; sustained-released, 75 mg bid	• Cardiovascular and cerebrovascular risks
Celecoxib* (COX-2 inhibitor)	For acute and chronic flare-ups: ≤250 mg/m^2 bid or 6 mg/kg bid, whichever is lower (rounded to the closest multiple of 100 mg); not to exceed 600 mg/d for more than 16 months For maintenance in children and adults: 100-200 mg bid, at discretion of prescriber	• Gastrointestinal bleeding • Impaired renal function • Cardiovascular and cerebrovascular risks • Not to be taken by patients with known allergies to sulfonamides or by patients with aspirin-sensitive asthma
Class II medications: theoretically applicable to various aspects of FOP, are approved for other disorders and have limited and well-described effects; use considered with caution and at a physician's discretion		
Montelukast (oral leukotriene-receptor antagonist)	2-5 y of age: 4 mg qhs 6-14 y of age: 5 mg qhs Adults: 10 mg qhs	• Possible behavior/mood changes, suicidal thinking and behavior • Rare: angioedema, headache, flu-like syndrome, fatigue, abdominal pain
Cromolyn (oral mast-cell stabilizer)	0-2 y of age: 20 mg/kg/d, divided qid 2-12 y of age: 100 mg qid Adults: 200 mg qid	• Rare: throat irritation, dry throat, cough, bitter taste
Bisphosphonates		
IV pamidronate	Children 2-3 y of age: 0.75 mg/kg/d by slow infusion × 3 d Children >3 y of age, adolescents, and adults: 1.0 mg/kg/d × 3 d Half-dose given on first cycle of treatment In case of fever, give standard acetaminophen therapy 3-d cycle of treatment should be repeated no more than 4 times annually	• Contraindicated in renal dysfunction, hypocalcemia • Short-term acute phase reaction characterized by fever, malaise, and myalgia • Osteopetrosis and possibly low-energy femoral fractures in children • Osteonecrosis of jaw
IV zoledronate*	Adults: 5 mg by slow infusion over 30 min	
Imatinib (selective oral tyrosine-kinase inhibitor that induces mast-cell apoptosis)	Children and adolescents: 340 mg/m^2/d qd; maximum daily dosage, 600 mg Adults: 400 mg qd; may be increased to 600 mg qd (800 mg qd has been used) Dose adjustments for renal and hepatic impairments, hematologic toxicity, and nonhematologic toxicities	Data anecdotal with very limited case reports

qd, daily; *qhs*, nightly, before bedtime; *qid*, 4 times per day; *tid*, 3 times per day.
*Not approved for pediatric use.

trunk flare-ups because of their typically vague onset, lengthy duration, and recurrent nature. Corticosteroids should not be used long-term owing to the risk of adrenal suppression and other steroid-associated side-effects such as osteoporosis and iatrogenic Cushing disease.

Nonsteroidal Anti-Inflammatory Drugs

Oral or topical NSAIDs, cyclo-oxygenase-2 (COX-2) inhibitors, mast-cell stabilizers, leukotriene inhibitors, and IV bisphosphonates all have been reported to reduce the pain and other symptoms of FOP.[1,16,17] When corticosteroids are discontinued, an NSAID or a COX-2 inhibitor (in conjunction with a leukotriene inhibitor) may be used for continued symptomatic relief of a flare-up. NSAIDs or COX-2 inhibitors may also provide symptomatic relief of flare-ups and chronic arthropathy, when corticosteroids are not indicated. These drugs inhibit inflammatory prostaglandins, which are known to stimulate the induction of both normal and heterotopic bone. However, there is no evidence that these medications prevent flare-ups. All NSAIDs increase the risk of gastrointestinal bleeding, myocardial infarction, and stroke. Selective COX-2 inhibitors are more likely to cause cardiovascular events, whereas less selective NSAIDs are more likely to cause gastrointestinalbleeds.[18] Topical NSAIDs avert the risk of systemic side effects and may be considered as alternatives to oral medication. In addition to the use of other inflammatory or mast-cell mediators (**Table I**), pain-management measures in FOP include muscle relaxants and the application of local ice packs. Opioids, however, are generally avoided in the management of FOP because of their multiple risks including respiratory suppression, particularly in people with more advanced disease.

Bisphosphonates

The newer bisphosphonates pamidronate and zoledronate have been used empirically in the management of FOP flare-ups, particularly when flare-ups do not respond to corticosteroids.[11] Anecdotal reports suggest rapid improvement in three-quarters of cases. The mechanism of action of bisphosphonates in FOP is unclear, but the compounds are known to have profound effects on bone remodeling, macrophage activity, and angiogenesis. Of note, the inhibition of osteoclasts by bisphosphonates does not appear to have an effect on heterotopic ossification in genetic animal models of FOP.[19] During the past 15 years, many people within FOP have used the bisphosphonate pamidronate empirically for the symptomatic relief of flare-ups that are prolonged or fail to respond to corticosteroids.[11] Bisphosphonates also protect against the osteopenic effects of the long-term, intermittent use of high-dose corticosteroids. People receiving bisphosphonates should undergo the following blood tests before receiving treatment: serum calcium, phosphate, albumin, alkaline phosphatase, 25-hydroxyvitamin D, blood urea nitrogen, creatinine, and complete blood count. Daily dietary calcium and vitamin D supplements are also mandatory during and after treatment for an indefinite period of time. Photographs and clinical measurements of flare-ups before treatment and daily thereafter for 14 days help to document baseline clinical status and any treatment response. Plain radiographs of the affected area(s) also should be obtained before treatment and for 6 weeks thereafter to document possible heterotopic ossification. Zoledronate should not be used in children. Important rare, but serious, complications of bisphosphonate treatment include low-energy femoral fractures and osteonecrosis of the jaw.

Emerging Targeted Therapies

The discovery of mutations in the activin A receptor type-1/activin receptor-like kinase 2 (*ACVRI/ALK2*) gene as the cause of FOP provides a rational and potentially disease-modifying target for therapy.[1,16] There are several plausible therapeutic approaches that might be used to inhibit the errant bone morphogenetic protein signaling that is caused by the mutated *ACVRI/ALK2* gene in FOP: inhibitory RNA technology, monoclonal antibodies directed at ligands of the aberrant ACVR1/ALK2 receptor, and small-molecule inhibitors of the ACVR1/ALK2 receptor. A number of such compounds are in development (**Table II**).[1,20]

A selective retinoic acid receptor γ agonist, palovarotene, was assessed in a mouse model of heterotopic ossification on the premise that retinoid signaling is a strong inhibitor of an activated bone morphogenic protein pathway.[21,22] The compound, along with other retinoic acid receptor γ agonists, was observed to inhibit heterotopic ossification in treated mice. Pooled data from two phase 2 interventional studies and one natural history study were used to evaluate whether palovarotene could reduce heterotopic ossification, as measured by computed tomography, after an FOP flare-up.[23] Palovarotene regimens were prescribed for flare-ups or as a continuous ("chronic") daily dosage plus a flare-up dosage (**Table III**).[22] In all treatment groups, heterotopic

Table II. Investigational agents in development for FOP.[1,20]

Compounds	Proposed mechanism of action in FOP	Phase of development
Palovarotene	Small-molecule RARγ agonist; inhibits BMP signaling	3
Garetosmab (REN2477)	Monoclonal antibody that binds ACVR1/ALK2 receptor ligand (activin A)	2
Rapamycin	Immunosuppressant	2
Saracatinib	Kinase inhibitor of ACVR1 receptor	2
BLU-782	Kinase inhibitor of ACVR1 receptor	1
INCB000928	Kinase inhibitor of ACVR1 receptor	1

BMP, bone morphogenic protein; *RAR*γ, retinoic acid receptor γ.

Table III. Changes in heterotopic ossification at 12 weeks during palovarotene therapy[22]

Treatment groups	No. flare-ups	Treatment regimen	Heterotopic ossification volume (mm^3) at 12 wk	Reduction (%) in heterotopic ossification volume at 12 wk	*P* value*
Placebo/untreated (n = 41)	49	–	11 014	–	–
Palovarotene flare-up (n = 27)	48	10 mg/d × 2 wk 5 mg/d × 4 wk	2731	75.2	.05
Palovarotene flare-up (n = 12)	18	20 mg/d × 2 wk 10 mg/d × 8+ wk	3045	72.3	.02
Palovarotene "chronic"/flare-up (n = 23)	33	5 mg/d ("chronic") 20 mg/d × 2 weeks 10 mg/d × 8+ weeks	3018	72.6	.16

*Versus placebo/untreated patients.

ossification was considerably reduced at 12 weeks when compared with placebo-treated or untreated patients. The heterotopic ossification difference from baseline was statistically significantly different in the group receiving a flare-up regimen of 20 mg daily for 2 weeks and then 10 mg daily for 8 or more weeks. The proportion of flare-ups with baseline edema that formed new heterotopic ossification was substantially lower in the group receiving daily palovarotene along with a flare-up regimen. Adverse events associated with palovarotene were primarily mucocutaneous and dose-related.

On the basis of these data, a global, multicenter, open-label phase 3 trial of palovarotene (MOVE) was initiated in children (≥4 years of age) and adults with the classic FOP mutation.[21,24] The primary efficacy outcome of this study is to measure the annualized change in new heterotopic ossification volume (via low-dose whole-body computed tomography) with a daily maintenance regimen of palovarotene 5 mg daily for 24 months and a flare-up regimen of palovarotene 20 mg daily for 4 weeks followed by 10 mg daily for 8 weeks. The comparator group consists of untreated people with FOP from a natural history study. In December 2019, trials of palovarotene were placed on partial clinical hold due to reports of early growth plate closure in pediatric patients receiving palovarotene. Currently dosing of palovarotene in the MOVE trial has been reinitiated in patients over the age of 14, while a phase 2 pediatric trial has been terminated.[25]

Garetosmab (REGN2477) is a fully human monoclonal antibody that binds to activin A, a stimulating ligand of the genetically altered ACVR1 receptor in FOP.[26,27] Like palovarotene, garetosmab has been shown to prevent the development and progression of heterotopic ossification in mouse models of FOP. A global, multicenter, placebo-controlled phase 2 study of garetosmab (LUMINA-1) is currently underway in adults with classic FOP.[28] Primary end points include safety, tolerability, and changes in heterotopic ossification from baseline. In January 2020, the trial sponsor released initial favorable results of the study, including an approximate 90% reduction in the formation of new heterotopic bone with garetosmab. The majority of adverse events associated with garetosmab were mild to moderate in severity. However, more patients treated with garetosmab than placebo experienced epistaxis and skin events including loss of eyebrows, acne, and skin infections, and two patients developed serious abscesses requiring hospitalization.[29] In October 2020, the trial was put on clinical hold due to fatal serious adverse events in the garetosmab arm of the trial. Investigators are currently evaluating the risk/benefit profile of garetosmab to better understand how to proceed.[30]

Other agents in early-phase investigation include rapamycin, a well-known immunosuppressant drug used in transplantation, and several kinase inhibitors that block activity of the ACVR1 receptor (Table II).

Conclusions

At present, care for people with FOP is currently supportive and rehabilitative, designed to avert trauma, treat inflammatory flare-ups, and prevent heterotopic ossification. Anti-inflammatory medications with longtime experiential support in FOP management include corticosteroids and NSAIDs. Bisphosphonates also have been used to great extent in FOP on the basis of repeated anecdotal success. Particular management challenges in FOP include diligent attention to dental and oral healthcare and the careful administration of general anesthesia, typically to provide dental care. Thoughtful customized rehabilitative methods, including specific occupational-therapy recommendations and mobility and transportation accommodations, are essential to maintaining self-care and independence in people with FOP. Because of the specific identified pathogenic variant in classic FOP, several targeted therapies hold great promise for disease modification in the near future. ■

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References

1. The International Clinical Council on FOP (ICC) and Consultants [homepage on the Internet]. 2019 [last updated June 2020]. The Medical Management of Fibrodysplasia Ossificans Progressiva: Current Treatment Considerations. Accessed September 2, 2020. https://d3n8a8pro7vhmx.cloudfront.net/ifopa/pages/212/attachments/original/1559059247/FOP_TREATMENT_GUIDELINES_June_2019.pdf
2. Kaplan FS, Al Mukaddam M, Pignolo RJ. A cumulative analogue joint involvement scale (CAJIS) for fibrodysplasia ossificans progressiva (FOP). Bone 2017;101:123-8.
3. Pignolo RJ, Baujat G, Brown MA, De Cunto C, Di Rocco M, Hsiao ED, et al. Natural history of fibrodysplasia ossificans progressiva: cross-sectional analysis of annotated baseline phenotypes. Orphanet J Rare Dis 2019;14:98.
4. Kaplan FS, Glaser DL, Shore EM, Deirmengian GK, Gupta R, Delai P, et al. The phenotype of fibrodysplasia ossificans progressiva. Clin Rev Bone Miner Metab 2005;3:183-8.
5. Glaser DL, Rocke DM, Kaplan FS. Catastrophic falls in patients who have fibrodysplasia ossificans progressiva. Clin Orthop Relat Res 1998;346:110-6.
6. Levy CE, Berner TF, Bendixen R. Rehabilitation for individuals with fibrodysplasia ossificans progressiva. Clinic Rev Bone Miner Metab 2005;3:251-6.
7. Levy C, Berner TF, Sandhu PS, McCarty B, Denniston NL. Mobility challenges and solutions for fibrodysplasia ossificans progressiva. Arch Phys Med Rehabil 1999;80:1349-53.
8. 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;126:762-4.
9. Connor JM, Evans DA. Extra-articular ankylosis in fibrodysplasia ossificans progressiva. Br J Oral Surg 1982;20:117-21.
10. Renton P, Parkin SF, Stamp TC. Abnormal temporomandibular joints in fibrodysplasia ossificans progressiva. Br J Oral Surg 1982;230:31-8.
11. Carvalho DR, Farage L, Martins BJ, Speck-Martins CE. Craniofacial findings in fibrodysplasia ossificans progressiva: computerized tomography evaluation. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2011;111:499-502.
12. Nussbaum BL, Grunwald Z, Kaplan FS. Oral and dental healthcare and anesthesia for persons with fibrodysplasia ossificans progressiva. Clin Rev Bone Miner Metab 2005;3:239-42.
13. 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;92:686-91.
14. 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;118:298-301.
15. Pignolo RJ, Bedford-Gay C, Liljesthröm M, Durbin-Johnson BP, Shore EM, Rocke DM, et al. The natural history of flare-ups in fibrodysplasia ossificans progressiva (FOP): a comprehensive global assessment. J Bone Miner Res 2016;31:650-6.
16. Kaplan FS, Le Merrer M, Glaser DL, Pignolo RJ, Goldsby RE, Kitterman JA, et al. Fibrodysplasia ossificans progressiva. Best Pract Res Clin Rheumatol 2008;22:191-205.
17. Pignolo RJ, Shore EM, Kaplan FS. Fibrodysplasia ossificans progressiva: diagnosis, management, and therapeutic horizons. Ped Endocrinol Rev 2013;10:437-48.
18. Davis A, Robson J. The dangers of NSAIDs: look both ways. Br J Gen Pract 2016;66:172-3.
19. Kawao N, Yano M, Tamura Y, Okumoto K, Okada K, Kaji H. Role of osteoclasts in heterotopic ossification enhanced by fibrodysplasia ossificans progressiva-related activin-like kinase 2 mutation in mice. J Bone Miner Metab 2016;34:517-25.
20. International Fibrodysplasia Ossificans Progressiva Association [homepage on the Internet]. 2020. Ongoing clinical trials in FOP. Accessed September 9, 2020. https://www.ifopa.org/ongoing_clinical_trials_in_fop
21. International Fibrodysplasia Ossificans Progressiva Association [homepage on the Internet]. 2020. Palovarotene. Accessed September 9, 2020. https://www.ifopa.org/palovarotene
22. Shimono K, Tung WE, Macolino C, Chi AH, Didizian JH, Mundy C, et al. Potent inhibition of heterotopic ossification by nuclear retinoic acid receptor-γ agonists. Nat Med 2011;17:454-60.
23. Kaplan F, Hsiao EC, Baujat G, Keen R, De Cunto C, Di Rocco M, et al. Palovarotene inhibits the development of new heterotopic ossification in fibrodysplasia ossificans progressiva (FOP). Bone Abstracts 2019;7:Abstract OC27.
24. ClinicalTrials.gov [homepage on the Internet]. 2017 [last updated August 28, 2020]. An efficacy and safety study of palovarotene for the treatment of FOP (MOVE). Accessed September 9, 2020. https://www.clinicaltrials.gov/ct2/show/NCT03312634
25. Ipsen [homepage on the Internet]. 2020. Ipsen provides update on palovarotene clinical programs. Accessed December 1, 2020. https://www.ipsen.com/press-releases/ipsen-provides-update-on-palovarotene-clinical-programs/
26. International Fibrodysplasia Ossificans Progressiva Association [homepage on the Internet]. 2020. REGN2477 (garetosmab). Accessed September 10, 2020. https://www.ifopa.org/regn2477
27. Vanhoutte F, Liang S, Ruddy M, Zhao A, Drewery T, Wang Y, et al. Pharmacokinetics and pharmacodynamics of garetosmab (anti-activin a): results from a first-in-human phase 1 study. J Clin Pharmacol 2020;60:1424-31.
28. ClinicalTrials.gov [homepage on the Internet]. 2017 [last updated September 17, 2020]. A study to examine the safety, tolerability and effects on abnormal bone formation of REGN2477 in patients with fibrodysplasia ossificans progressiva (LUMINA-1). Accessed October 16, 2020. https://clinicaltrials.gov/ct2/show/NCT03188666
29. Regeneron [homepage on the Internet]. 2020. Regeneron announces encouraging garetosmab phase 2 results in patients with ultra-rare debilitating bone disease. Accessed September 10, 2020. https://investor.regeneron.com/news-releases/news-release-details/regeneron-announces-encouraging-garetosmab-phase-2-results
30. Regeneron [homepage on the Internet]. 2020. Regeneron provides update on the garetosmab phase 2 LUMINA-1 trial in fibrodysplasia ossificans progressive (FOP). Accessed December 1, 2020. https://investor.regeneron.com/static-files/1a038387-67e6-4446-91fa-813b0225235e