to assemble a back-up team: an anesthesiologist and a surgeon experienced in emergency airway management. Sharing the anesthesia plan with the patient and the family is useful to diffuse apprehension and foster cooperation on the day of surgery.

The special care and the skills required by the anesthesiologist to treat an FOP patient may not be available at peripheral locations or community hospitals. In these situations, the referring physician, the patient, and the family should seek referral to a major medical center with practitioners who are skilled in the care of FOP patients.

Intraoperative management:

Positioning. The operating room table should be adjusted according to patient's needs. Extra padding will help minimize soft tissue trauma during the surgical procedure.

Monitoring. Routine monitoring is required for most surgical procedures (ECG, non-invasive blood pressure, pulse oximeter, end-tidal CO_2, and temperature). Significant co-morbidities, lengthy surgical procedures, or a compromised cardio-respiratory system may require the addition of additional monitors. In patients whose upper limbs are ankylosed in adduction and flexion, the application of a blood pressure cuff may be difficult or impossible. The cuff may be applied on the lower extremity. A thin layer of padding under the cuff may reduce the impact of the frequent inflations of the cuff on the extremity.

Intravenous access. Careful venipunctures are not a problem. An indwelling intravenous catheter may rarely lead to the formation of an ossified tract at the site of insertion. Therefore, the smallest intravenous catheter appropriate for the procedure is selected for insertion.

General anesthesia and sedation: The administration of general anesthesia and the maintenance of a patent airway are particularly challenging matters in patients who have FOP, and should be planned with exacting care. Guidelines for general anesthesia have been reported (Nussbaum et al., 2005).

Physicians and patients may be tempted to use sedation techniques and perform minor surgical procedures at an office-based or out-patient facility. The risks of catastrophic airway emergencies far outweigh the potential benefits of this option. Procedures should be performed only at facilities equipped with the skills and support systems necessary for a safe outcome. For patients with advanced disease, it is recommended that even minor procedures (colonoscopies, dental procedures) be performed at a major medical center under general anesthesia with a secured airway by endotracheal intubation.

Patients who can open the mouth: In patients who are able to open the mouth, it is imperative to avoid over-stretching the TMJ during direct laryngoscopy. Careful positioning of the patient and the head, maintenance of a sniffing position and the use of a Glidescope (GlideScope® Video laryngoscopes (GVL®) with minimal mouth opening is one approach of securing the airway. In cases where adequate mouth opening is questionable, an awake fiberoptic naso-tracheal intubation is recommended.

Patients who cannot open the mouth. In patients who present with fusion of the cervical vertebrae, limited mouth opening, or ankylosis of the TMJ, oral access for endotracheal intubation is not possible. For these patients, an awake fiberoptic naso-tracheal intubation under light sedation is recommended. This should be performed by well-trained anesthesia teams who are familiar and experienced with this type of procedure (Nussbaum et al., 2005; Tumolo et al., 2006). The team should consist of two experienced anesthesiologists. A back-up surgeon (usually an otorhinolaryngologist) experienced in performing trachcostomies should be present with an immediately available tracheotomy tray. Nasal fiberoptic endotracheal intubation is performed with attention to administration of vasoconstrictors to the nose and

the use of lubricated nasopharyngeal tubes starting with a small one and increasing the diameter up to 32-34 Fr.

Postoperative pain management and regional anesthesia:

Most patients with FOP present with advanced ossifications at the thoraco-lumbar area precluding access to spinal or epidural analgesia.

Postoperative pain management is accomplished with intravenous medications. Patients using patient controlled analgesia (PCA) devices should receive supplemental oxygen with careful monitoring of oxygenation at all times. Oral medications are prescribed to patients who can open the mouth.

All questions regarding general anesthesia should be directed to Dr. Zvi Grunwald (please see section X. for contact information).

L. Orthodontics & FOP

Most people seek orthodontic care for aesthetic and functional reasons. For the FOP population, self image is as important as in the general population. Orthodontic therapy can be safely performed on patients with FOP who have normal or nearly normal oral opening (Luchetti et al., 1996).

Patients who have FOP often develop mandibular hypoplasia with a maxillary overbite and, therefore, orthodontic therapy may be considered. However, many patients find that the overbite provides a means of access for eating as well as for oral and dental hygiene. Posterior and anterior dental crossbites can have an effect on the TMJs and should be corrected. For children with functional TMJs and with anterior open bites that are less than 15 mms, orthodontics is not recommended as the overbite will facilitate nutrition and subsequent dental care if the TMJ does eventually ankylose.

When orthodontic care is considered, brief appointment times should be used to lessen stress on the TMJs. The use of nonextraction therapy is also recommended. To prevent the need for extractions in FOP patients, it may be advisable to align the anterior segments for aesthetics, leaving posterior dental crowding untreated. Crowded posterior teeth may be a better alternative than the risks of flare-up and TMJ ankylosis that can accompany an extraction (Levy et al., 1999).

M. Hearing Impairment in FOP

Hearing impairment is a common feature of FOP and occurs in approximately 50 percent of patients. The onset is usually in childhood and may be slowly progressive. Hearing loss is usually conductive in nature and may be due to middle ear ossification, but in some patients, the hearing impairment is neurologic in nature. Children with FOP should generally have audiology evaluations every other year; more often, if necessary. Hearing aids are often helpful and can diminish developmental problems due to hearing loss (Levy et al., 1999).

N. Kidney Stones & FOP

Clinical observations prompted a worldwide survey of patient-members of the International Fibrodysplasia Ossificans Progressiva Association (IFOPA) on the disease burden of kidney stones. The survey examined risk factors for the development of kidney stones in FOP patients, and provided a basis for prevention of stones in this already devastating disease (Reviewed in Glaser et al., 2005).

Although geographical variation exists, patients with FOP have approximately a two-fold higher prevalence of kidney stones than the general population. Immobilization coupled with increased bone turnover is a significant risk factor in the development of kidney stones in this population. There has been no comprehensive study of stone composition in FOP patients.

A low fiber diet was the only dietary factor in this study to significantly increase the risk of developing kidney stones in this population, although deficient water intake and excess animal protein intake were associated with the condition. FOP patients with a history of urinary tract infections are at increased risk for developing kidney stones. Extracorporeal shock wave lithotripsy, uteroscopic stone removal, percutaneous nephrolithotomy, and laser lithotripsy have all been used as treatment modalities, but there are no long-term data to evaluate the safety or efficacy of one treatment over another.

Ideally, we would like to make recommendations to prevent kidney stones. This becomes increasingly important as FOP patients become progressively more immobilized. Patients should drink sufficient water to keep the urine volume above three liters daily. Patients should substitute whole wheat bread for white bread and eat natural fiber cereals. Patients should also limit their intake of Vitamin C and oxalate-rich foods, and refrain from adding salt to their food. Patients should not restrict dairy products; however, they should be careful not to overindulge either (reviewed in Glaser et al., 2005).

O. Rehabilitation Issues in FOP

As heterotopic bone accumulates in FOP, range of motion is progressively lost, leading to near complete immobility. Present and future rehabilitation approaches should be focused on enhancing activities of daily living. Occupational therapy and vocational education consultations may be extremely useful. Passive range of motion must be avoided, as it will likely lead to disease exacerbations. Despite the widespread heterotopic ossification and progressive disability, most patients lead productive and fulfilling lives (Levy et al., 1999; Levy et al., 2005).

Many of the limitations exacerbated by disease progression can be ameliorated with thoughtful rehabilitation.

Occupational Therapy Issues: Dressing may be enabled with pull-over shirts and blouses, elastic waistbands, Velcro closures, sock donners (devices where the sock is placed over a cuff attached to a cord), elastic shoe laces, and long handled shoe horns and reachers. Raised toilet seats, custom-angled commodes, bedside urinals (shaped for men or women), and bidets all enable toileting. Widened doorways and grab bars increase bathroom safety and accessibility. Long-handled sponges, combs, or modified reachers, electric toothbrushes, water pics, and suction devices help insure cleanliness and personal hygiene.

Strategically placed stools and elevated platforms, long-handled eating utensils and straws, help at the dinner table. Meal preparation may facilitated by electrical can and jar openers, cutting boards with spikes

to hold food while it is prepared or cut, and rotating shelves (lazy Susans). For individuals with limited ability to masticate, food may be ground-up or pureed.

Depending on the stage of disease progression, canes, walkers, crutches, and/or custom shoes may be necessary for mobility. For more severe limitations, power wheelchairs may be necessary. Considerations for power wheelchairs include customized seating, power seat elevation and depression, anterior and posterior tilt and recline function. Lap trays with mounts for laptop computers allow participation in work and school.

Vocational and Educational Issues: Because even minor trauma can trigger disabling heterotopic ossification, it is sensible to encourage intellectual pursuits and computer skills. Public school systems in the United States must provide each disabled child with an individualized educational plan, and an education in the least restrictive environment. Children are entitled to occupational, physical and speech therapy as well as classroom aides if indicated. Each state is required to offer some sort of vocational rehabilitation to help people with disabilities enter or remain in the work force.

Transportation and Home Modification: Vans can be customized to accept an FOP power chair. Ramps and lifts can be installed, roofs can be raised, floors can be lowered, new controls and motors can be installed to allow the van to "kneel", lowering ground clearance to ease ascent into a van.

Home modifications include elimination or minimization of indoor steps, installation of grab bars, widened hallways, accessible bathrooms and kitchens. Environmental control units operate appliances, doors, televisions and telephones remotely. To facilitate sleep, there are tilt table beds that rotate from vertical to horizontal, specialized mattresses and overlays to redistribute pressure to provide comfort and protect skin integrity.

Sexuality and reproduction: Physical acts of sexual intimacy require tact and thoughtfulness. Pillows and bolsters may be necessary to support the unusual and inflexible postures. Genetic counseling and discussion of contraception are warranted for the sexually active or those who are considering such activity.

Aquatic therapy allows individuals to perform active range of motion, cardiopulmonary, and resistive exercise in a safe, low impact environment. Warm water can facilitate pain relief and. Modified lifts, elevators or ramps may be necessary for pool entry and exit.

Iontophoresis involves the introduction of topically applied physiologically active ions (acetic acid, steroids) through the epidermis using continuous direct current. Anecdotal reports suggest that acetic acid iontophoresis may help restore some lost temporomandibular joint range of motion in FOP.

P. Pregnancy Issues in FOP

The decision to have a child is one of the most important and serious life decisions an individual or couple can make. Because FOP is an inherited disease, anyone (man or woman) with FOP will have similar concerns about passing the FOP mutation to his/her child. If a parent has FOP, the chance that the child will have FOP is fifty percent. Women, specifically, have additional matters to consider. In addition to the usual risks that any woman might encounter during pregnancy, a woman with FOP has additional concerns that must be carefully considered. Pregnancy in a patient with FOP is perilous, and poses substantial life-threatening risks to both the mother and child (Davidson et al., 1985; Thornton et al., 1987).

Specific risks to the mother include, but are not limited to:

1. Risk of FOP flare-ups during pregnancy. To protect the fetus, the use of palliative medications that are often used to treat flare-ups may have to be limited.

2. Risk of breathing difficulties during the latter part of pregnancy. FOP causes severe limitation of expansion of the chest wall due to developmental anomalies in the costovertebral joints. Breathing problems can also arise due to bone formation in the chest muscles. As the fetus grows in the

womb, it presses upward on the diaphragm. This upward pressure on the diaphragm further limits the space for the mother's lungs to expand resulting in increased difficulty breathing. Breathing may be rendered even more difficult if the mother has already formed heterotopic bone in the abdominal wall that restricts outward growth of the fetus. As a result, the growing baby will further press upwards on the mother's diaphragm, restricting breathing even further.

3. Risk of childbirth complications. Caesarian section is necessary for a mother with FOP due to the pelvic deformity, joint fusions, and decreased plasticity of the birth canal that will not safely accommodate a normal vaginal delivery. It would not be safe or even possible to have normal childbirth due to the physical limitations and mobility restrictions of FOP.

4. Risk of the general anesthesia for Caesarian delivery. Caesarian delivery is a surgical procedure requiring anesthesia. Due to FOP, regional anesthetics are technically unfeasible, dangerous, and can not be used. General anesthesia is required. In addition to the dramatic increased risks to the mother, general anesthetics pose substantial risks to the fetus/newborn baby (see below).

5. Risk of phlebitis and pulmonary embolism. These potentially life-threatening complications can arise due to the severe immobility of FOP. The added constraints of pregnancy, such as extended bedrest mandated by a high-risk pregnancy along with the lower limb edema that invariably occurs in the last trimester of pregnancy further increase the risk of these life-threatening complications.

Specific risks to the child include, but are not limited to:

1. Risk that the child may have FOP. If a parent has FOP, the chance that the child will have FOP is fifty percent.

2. Risk of prematurity. The mother may not be able to carry to full-term due to breathing difficulties. As a result, there is a severe risk of premature delivery. Numerous lifelong consequences are often associated with premature birth.

3. Risk of severe fetal distress. The risk of severe fetal distress, a condition in which the fetus is at risk of dying or suffering severe brain injury, is primarily due to hypoxia (diminished oxygen to the fetus). This complication may result from maternal breathing difficulties or other unrecognized problems later in pregnancy (see above).

4. Risk of cerebral palsy. There is a high risk of cerebral palsy due to oxygen deprivation to the fetus, especially if fetal distress occurs during the latter part of pregnancy or during delivery.

5. Risk of complications from general anesthesia. There is a high risk of complications to the newborn resulting from general anesthesia during Caesarian section (see above). General anesthesia is required, as the more preferable local or regional anesthesia are technically impossible when the mother has FOP. At delivery, there should be a team skilled in resuscitation of high risk infants.

Additional complications to consider are: Who will care for the mother during the complications and added stress of pregnancy? Who will care for the child if the mother is disabled from FOP? What is the role of the father, siblings, and grandparents in the care of the newborn child?

Although it is possible for a woman with FOP to carry a child to term, and at least four known instances have been reported in the medical literature, there are substantial life-threatening risks to both the mother

and child. Pregnancy in FOP should never be undertaken without serious consideration and family planning. Unwanted pregnancies should be assiduously avoided. Independent genetic counseling is available, if desired.

Should a pregnancy occur, guidance and care at a high-risk pregnancy center are imperative. At least two lives are at stake: that of the mother and that of the child. In addition, the lives of many others will be impacted by a pregnancy in a mother with FOP – specifically, those of other family members who, by necessity, are involved in the consequences of any such occurrence.

In summary, pregnancy in FOP poses major life-threatening risks to both mother and child as well as life-altering consequences to the entire family that must be carefully considered and balanced.

IV. CURRENT TREATMENT CONSIDERATIONS

At the present time, there are no established preventions or treatments for FOP. The disorder's rarity, variable severity, and fluctuating clinical course pose substantial uncertainties when evaluating experimental therapies. To date, there have been no double-blinded randomized placebo-controlled clinical trials to assess the relative efficacy of any potential therapy.

REPORT FROM THE INTERNATIONAL FOP CLINICAL CONSORTIUM: A GUIDE FOR CLINICIANS

An international panel of physicians has reviewed and updated current treatment considerations in FOP (Tables 1). The panel reviewed many current and potential treatment options for this disorder. The unpredictable nature of FOP has made controlled trials extremely difficult to perform, but all agreed that the obstacles were surmountable.

In evaluating each potential treatment, the group focused on the known mechanism of action of the treatment as it relates to the proposed pathogenesis of FOP. Consideration for use of each medication was made based on balancing the clinical uncertainty of each agent when used to treat FOP against the compassionate need to adequately and safely control the disabling symptoms of the disease, especially during flare-ups. Each pharmacologic agent was classified into one of three categories based on experimental or anecdotal experience with the drug as well as knowledge of each drug's safety profile.

Class I: Medications that have been widely used to control symptoms of the acute flare-up in FOP (swelling and pain), with anecdotal reports of favorable clinical results and generally minimal side effects. *Examples:* Short-term use of high-dose corticosteroids, and use of non-steroidal anti-inflammatory drugs (NSAIDs) including the new anti-inflammatory and anti-angiogenic cox-2 inhibitors.

Class II: Medications that have theoretical application to FOP, are approved for the treatment of other disorders, and have limited and well-described effects. *Examples:* Leukotriene inhibitors, mast cell stabilizers, and aminobisphosphonates (Pamidronate; Zoledronate).

Class III: Investigational new drugs
Examples: Signal transduction inhibitors and monoclonal antibodies targeting ACVR1 (presently under development).

PHYSICIANS TREATING PATIENTS WHO HAVE FOP SHOULD KEEP IN MIND THAT NONE OF THESE MEDICATIONS (OR ANY OTHER MEDICATIONS TO DATE) HAVE BEEN PROVEN TO ALTER THE NATURAL HISTORY OF FOP.

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. The decision to use or withhold a particular medication must ultimately rest with an individual patient and his or her physician.

Class I Medications: For acute flare-ups, the immediate use of prednisone at a dose of 2 mg/kg/day can be considered as a single daily dose for a maximum of four days. For maximal beneficial effect, the prednisone should be started within 24 hours of the onset of a flare-up, which corresponds to the earliest phase of acute and intense lymphocytic infiltration into skeletal muscle. If the flare-up is more than two 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-day course with a subsequent 10-day taper can be considered. 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, may accelerate heterotopic ossification, 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 the prednisone is discontinued (or if a flare-up existing for more than 48 hours is being considered for treatment), treatment may be considered with a non-steroidal anti-inflammatory agent. A cyclooxygenase-2 (cox-2) inhibitor can be used instead of a traditional NSAID (Table 1). Compassionate off-label use of cox-2 inhibitors has been reported anecdotally in children with FOP, as young as two years of age. As with all non-steroidal anti-inflammatory medications, gastrointestinal precautions should prevail. If long-term use of the cox-2 inhibitors 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 added at the physicians' discretion. The leukotriene inhibitor montelukast (Singulair) can be considered at a dose of 5 mg or 10 mg per oral daily (depending upon age; see Table 1) in order to help abrogate the inflammatory symptoms of an FOP flare-up. The combined use of montelukast and a non-steroidal anti-inflammatory agent or a cox-2 inhibitor can be considered as a long-term treatment, following the discontinuation of a single 4-day steroid burst.

Sodium cromolyn is a generally well-tolerated mast cell inhibitor. However, oral absorption is poor, and its potential effectiveness in FOP is unknown.

The clinical rationale and early anecdotal experience with cyclical intravenous administration of the aminobisphosphonates is described in detail in the body of this report.

Class III Medications are under development and are not yet available.

V. CLASSES OF MEDICATIONS (TABLE 1)

CLASS I MEDICATIONS

GENERIC	TRADE	CLASS	PROPOSED MECHANISM OF ACTION AS IT RELATES TO FOP	DOSING	MAJOR SIDE EFFECTS
Prednisone	**Prednisone**	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. *Do not use for flare-ups involving chest or back (see text).*	2 mg/kg once daily by oral administration (PO) x 4 days maximum. Max dose: 150 mg/day. If flare-up recurs immediately, may repeat 4 day course with longer taper. May also use longer treatment with taper for flare-ups in the submandibular region, especially those that affect breathing or swallowing. Should be started within 24 hours of the onset of a flare-up for maximal effectiveness. With the exception of life-threatening sub-mandibular flare-ups, do not use if the flare-up is more than two days old. (Medication should be taken with food). FOR PATIENTS IN INDIGENOUS REGIONS, ANTI-PARASITIC PRECAUTIONS MAY BE NECESSARY Alternatively, high dose intravenous corticosteroid (Prednisolone) therapy may be considered, but must be performed during an inpatient hospitalization to monitor for potentially dangerous side-effects of hypertension. The standard protocol for IV corticosteroid therapy is as follows: Day 1: 20-30 mg/kg of prednisolone IV Day 2: No medication Day 3: 20-30 mg/kg of Prednisolone IV Day 4: No medication Day 5: 20-30 mg/kg of Prednisolone IV. **Total daily dose not to exceed 1000 mg.**	- avascular necrosis of hip - diabetes-cataracts - osteoporosis - chronic dependency - immune suppression - adrenal suppression - growth retardation - acne - peptic ulcers - hypertension - glaucoma - weight gain - skin bruising - sleep and mood disturbance
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 inflammatory prostaglandins	Peds: 4-10 mg/kg PO every 6 hrs, as needed. Adult: 200-800 mg PO every 6 hrs, as needed. (Medication should be taken with food).	- gastrointestinal bleeding - impaired renal function

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 inflammatory prostaglandins	Peds: 2-4 mg/kg/day PO; or 150-200 mg/day (whichever is less); divided tid Adult: 50 mg PO tid or Indocin – SR (sustained release) at a dose of 75 mg. PO bid (Medication must be taken with food).	- gastrointestinal bleeding - impaired renal function
Piroxicam	**Feldene**	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 inflammatory prostaglandins	Adult: 20 mg PO once daily (medication should be taken with food)	- gastrointestinal bleeding - impaired renal function
Celecoxib	**Celebrex**	Cyclo-oxygenase-2 inhibitor (highly selective)	Anti-inflammatory and potent anti-angiogenic; symptomatic relief during a flare-up; Potential use in prevention by inhibiting inflammatory prostaglandins	Peds and Adults: 100-200 mg po bid for maintenance, at discretion of M.D. -For acute & chronic flare-ups, not to exceed maximum anti-angiogenic dose of 250 mgs/M^2 po bid or 6 mg/kg po bid (whichever is lower; rounded-up or rounded-down to the closest multiple of 100 mg) and not to exceed a maximum total daily dose of 600 mgs. for more than 16 months. Medication should be taken with a fatty snack for maximum absorption. Although used compassionately in children, not yet approved for pediatric use. -Patients should be monitored for adequate hepatic and renal function. -Use with caution in FOP patients with a history cardiovascular disease or in older FOP patients who are severely immobilized or completely non-ambulatory. - MUST NOT BE TAKEN BY PATIENTS WHO ARE ALLERGIC TO SULFONAMIDES OR BY PATIENTS WITH ASPIRIN-SENSITIVE ASTHMA.	- gastrointestinal bleeding - impaired renal function -concern about cardiovascular and cerebrovascular risks -NOT TO BE TAKEN BY PATIENTS WITH KNOWN ALLERGIES TO SULFONAMIDES OR BY PATIENTS WITH ASPIRIN-SENSITIVE ASTHMA
Nabumetone	**Relafen**	Non-steroidal anti-inflammatory Medication (mainly Cox-2 inhibitor but also non-specific activity)	Anti-inflammatory and anti-angiogenic; symptomatic relief during a flare-up; Potential use in prevention by inhibiting inflammatory prostaglandins	-Adults: 1000 mg PO once or twice daily. May be useful for individuals who have allergy to sulfonamides and thus cannot use Celebrex	-gastrointestinal bleeding -impaired renal function

CLASS II MEDICATIONS

GENERIC	TRADE	CLASS	PROPOSED MECHANISM AS IT RELATES TO FOP	DOSING	MAJOR SIDE EFFECTS
Montelukast	Singulair	Leukotriene receptor antagonist	Blocks inflammatory mediators; complementary action to cyclooxygenase inhibitors.	Peds (2-5 yo): 4 mg PO at bedtime 6-14 yo: 5 mg PO at bedtime Adults: 10 mg PO at bedtime	Generally well-tolerated. Rarely angioedema, headache, flu-like syndrome, fatigue, abdominal pain; possible association with behavior/mood changes, suicidal thinking and behavior, and suicide. Patients should be monitored for changes in behavior and mood.
Cromolyn	Gastrocrom	Mast cell stabilizer	Reduces mast cell degranulation, but poorly absorbed from GI tract. May be more effective if used chronically.	Peds (0-2 yo): 20 mg/kg/d PO div qid. (2-12 yo): 100 mg PO qid Adult: 200 mg PO qid	Generally extremely well-tolerated. Rarely throat irritation, dry throat, cough, bitter taste.
Pamidronate	Aredia	Amino-bisphosphonate	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.	Peds (2-3 yo): 0.75 mg/kg/day by slow IV infusion for three days. For children older than 3 yo and for adolescents and adults: 1.0 mg/kg/day for three days. Medication should be infused slowly each day over 4-5 hours. **Note**: 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-day cycle of treatment should be repealed no more than 4 times annually. For dilution instructions, see text. Patients should have the following blood tests checked prior to Pamidronate treatment: serum calcium, phosphate albumin, alkaline phosphatase, BUN, creatinine, CBC. All patients should receive adequate supplemental dietary calcium and vitamin D daily during and indefinitely following Pamidronate treatment. Photographs and clinical measurements of the flare-up should be obtained prior to treatment and daily thereafter for 14 days. Plain radiographs of the affected area should be obtained prior to treatment and 6 weeks thereafter to document the formation of any heterotopic ossification.	Generally well-tolerated. There are no known interactions with other medications. An acute phase reaction characterized by fever, malaise, and myalgia occurs commonly during IV infusion of Pamidronate and may persist for 18-24 hours. Pre-treatment with acetaminophen may lessen symptoms. In case of fever or other symptoms of acute phase reaction, give standard acetaminophen treatment. Pamidronate should not be used in patients who are hypocalcemic as tetany may result. Daily oral calcium and vitamin D supplementation should be provided to all patients who receive Pamidronate (not just on days of infusion, but daily on a continual basis for at least two weeks). Frequent high-dose use of aminobisphosphonates in children can lead to osteopetrosis. See cautions in text for osteonecrosis of jaw.
Zoledronate	Zometa	Amino-bisphosphonate	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.	Adult (18 y.o and older): 4 mg, by slow IV infusion over 30 minutes. Not for use in children. Patients should have the following blood tests checked prior to Zoledronate treatment: serum calcium, phosphate albumin, alkaline phosphatase, BUN, creatinine, CBC. All patients should receive adequate supplemental dietary calcium and vitamin D daily during and indefinitely following Pamidronate treatment. Photographs and clinical measurements of the flare-up should be obtained prior to treatment and daily thereafter for 14 days. Plain radiographs of the affected area should be obtained prior to treatment and 6 weeks thereafter to document the formation of any heterotopic ossification.	Generally well-tolerated. There are no known interactions with other medications. An acute phase reaction characterized by fever, malaise, and myalgia occurs commonly during IV infusion of Pamidronate and may persist for 18-24 hours. Pre-treatment with acetaminophen may lessen symptoms. In case of fever or other symptoms of acute phase reaction, give standard acetaminophen treatment. Pamidronate should not be used in patients who are hypocalcemic as tetany may result. Daily oral calcium and vitamin D supplementation should be provided to all patients who receive Pamidronate (not just on days of infusion, but daily on a continual basis for at least two weeks). Frequent high-dose use of aminobisphosphonates in children can lead to osteopetrosis. See cautions in text for osteonecrosis of jaw.

CLASS III MEDICATIONS

GENERIC	TRADE	CLASS	PROPOSED MECHANISM OF ACTION AS IT RELATES TO FOP	DOSING	MAJOR SIDE EFFECTS
ACVR1/ALK2 Signal Transduction Inhibitor	Dorsomorphin Derivatives	Signal Transduction Inhibitor	Blocks ACVR1/ALK2 signal transduction	Not applicable at present time; under development	Not yet determined
Monoclonal Antibody Against ACVR1/ALK2	mAb-FOP	Receptor Antibody	Blocks Receptor at Cell Surface	Not applicable at present time; under development	Not yet determined

VI. SUMMARY OF KEY PRACTICE POINTS

This very brief guide will summarize the current symptomatic management of FOP (Kaplan et al., 2008).

Activities: Avoid soft tissue injuries, contact sports, overstretching of soft tissues, and muscle fatigue. Avoid biopsies, surgical removal of heterotopic bone and all non-emergent surgical procedures.

Anesthesia: If general anesthesia is required, perform awake intubation by nasotracheal fiber-optic technique. Highly-skilled FOP-aware anesthesiologists should be present for all elective intubations.

Falls: Locked upper limbs may accentuate head and neck trauma from falls. Epidural hematomas are common (surgical emergency). Use protective headgear in children who have upper limb involvement. All head and neck injuries must be evaluated immediately on an emergent basis.

Flare-up: (Back/chest): Use non-steroidal anti-inflammatory medications or cox-2 inhibitors with GI precautions. Use analgesics and/or muscle relaxants, as needed.

Flare-up: (Limbs/throat): Prednisone – 2 mgs/kg once daily (per oral) for four days; begin within first 24 hours of flare-up. Keep medication on-hand for emergencies. Use analgesias and/or muscle relaxants, as needed, with GI precautions.

Flare-ups (Protection): Most flare-ups result from over-use and soft tissue injuries. Prednisone - 2 mgs/kg, (per oral) once daily for three days to prevent flare-up after severe soft-tissue injury. Do not use after minor bumps or bruises.

Hearing: Conductive hearing impairment is common. Perform periodic audiology evaluations. Hearing aids may improve conductive hearing loss.

Immunizations: Avoid all intramuscular immunizations. Subcutaneous immunizations are acceptable when FOP is quiescent. Avoid immunizations during flare-ups.

Influenza: Administer influenza vaccines subcutaneously, but never during flare-ups. Avoid live attenuated flu vaccine as it may cause flu-like symptoms and exacerbate FOP. Household contacts of FOP patients should be immunized annually. Cough suppression may alleviate undo stress on chest musculature.

IV's: Superficial IV access and venipuncture is acceptable. Traumatic IV's and arterial punctures may cause heterotopic ossification.

Limb swelling: Lymphedema and transient neuropathy may occur with flare-ups of limbs. Elevate legs while sleeping and recumbent. Use support stockings. Take one baby aspirin daily with food. Rule-out deep vein phlebitis with Doppler ultrasound.

Occupational therapy (OT): Perform periodic OT evaluations as activities of daily living change.

Physiotherapy: Avoid passive range of motion. Warm water hydrotherapy may be helpful.

Pulmonary function. Perform baseline pulmonary function tests (PFTs) and echocardiogram. Repeat periodically. Supplemental oxygen should not be used in an unmonitored setting.

School: Use school aides to protect and assist children. Request medical letter and preschool evaluation.

Surgery: Avoid surgery, except in emergencies.

Teeth: Avoid mandibular blocks, over-stretching of the jaw, and muscle fatigue.

VII. CONCLUSIONS

In the book "Dark Remedy: The Impact of Thalidomide and Its Revival as a Vital Medicine," there is a poignant discussion about the utility of double-blind randomized placebo-controlled studies as the "gold standard" for medication assessment. The authors write that our job as disciplined scientists is "to find the right questions to ask, the right tests to perform, and then to eliminate from interpretation of the data any expectations, assumptions, biases, or hopes that we may have in order to see the significance of the results with objective clarity. That clarity can make the difference between finding a cure for an incurable disease and raising false hopes for millions." (Stephens & Brynner, 2001). There is little doubt that the testing of drugs for FOP, either for prevention or treatment, will require the same stringent principles and strategy.

A physician treating a patient with FOP must never withhold an available medication or treatment that may be truly helpful, but those medications must also be tested with scientific clarity to determine if they are, in fact, truly helpful or just simply the products of wishful thinking. As the Roman dramatist Terence warned more than two thousand years ago, "One easily believes what one earnestly hopes for." In the absence of clear evidence-based research from controlled clinical trials, it is difficult to advocate a particular therapy with enthusiasm. Although it is appealing to attempt to swim across multiple therapeutic currents to safety, the waters of FOP are deep and dangerous. The carefully designed and well-controlled clinical trial may ultimately be the safest bridge across these troubled waters of FOP. Such an approach will require the patience and fortitude of the entire FOP community. In the meanwhile, the physician caring for a patient with FOP must constantly review evolving scientific information and chart the safest, and most responsible course for the patient until the enduring bridges are built and their safety and efficacy verified.

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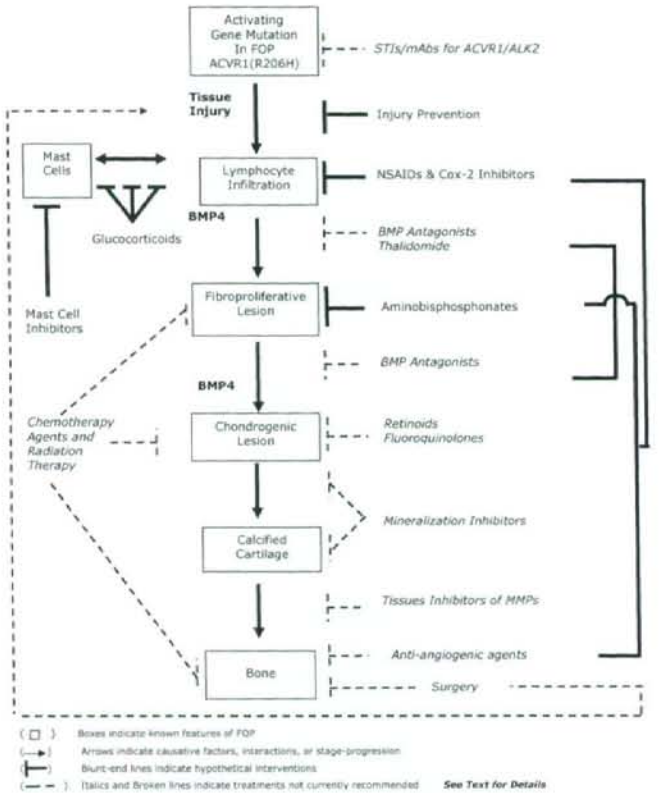
FIGURE 1: SYMPTOMATIC TREATMENT SCHEMA IN FIBRODYSPLASIA OSSIFICANS PROGRESSIVA



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III. SPECIAL MEDICAL CONSIDERATIONS

A. Introduction

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VI. SUMMARY OF KEY PRACTICE POINTS

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VII. CONCLUSIONS

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X. THE INTERNATIONAL CLINICAL CONSORTIUM ON FIBRODYSPLASIA OSSIFICANS PROGRESSIVA

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