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THE MEDICAL MANAGEMENT OF FIBRODYSPLASIA OSSIFICANS PROGRESSIVA: CURRENT TREATMENT CONSIDERATIONS

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ABSTRACT

The ultimate goal of research on fibrodysplasia ossificans progressiva (FOP) is the development of treatments that will prevent, halt, or even reverse the progression of the condition. In order to achieve that goal, it is imperative to determine the molecular and genetic cause of the disease, and to integrate those molecular and genetic insights into the developmental, metabolic and physiologic pathways through which the putative damaged gene causes progressive and disabling heterotopic ossification.

Despite great strides during the past decade in understanding the molecular pathology and pathophysiology of FOP, few tangible advances have yet been realized in the treatment of FOP or in the prevention of its disabling complications. At the present time, there are no therapies with scientifically-proven benefits for the prevention or treatment of FOP. The present lack of effective therapy for FOP arises primarily from the lack of definitive knowledge about the primary genetic damage that causes FOP and that orchestrates the complex developmental changes of the condition both pre-and postnatally. Additionally, the erratic natural history of the disease, the inability to obtain diagnostic biopsies at defined stages in the evolution of the disease, the lack of a genetically relevant animal model for drug testing, the lack of multi-generational families to study natural disease variability, and the lack of randomized double-blinded placebo-controlled studies further confound the efforts to establish a basis for rationale therapy in this complex disorder with genetic, developmental, post-traumatic, and autoimmune features.

Despite these daunting obstacles, the therapeutic horizon is infinitely brighter than it was a decade ago. Through the efforts of a collaborative international FOP research team dedicated to the eventual cure of FOP, major and fundamental advances have been made in understanding the molecular basis of the condition, and in understanding the detailed genetic, cellular, molecular, physiologic, and developmental changes that lead to the panoply of clinical changes that characterize FOP, and underlie the suffering of those who have it.

Profound insights in lymphocyte and mast cell biology, angiogenesis, apoptosis, BMP molecular cell biology, osteogenic induction, and endochondral bone formation, have lead to the development of

treatment strategies that are at various stages of pre-clinical development, some of which will soon emerge into the arena of clinical testing. Identification of the gene that causes FOP will propel the development of a relevant genetic animal model that, when available, will dramatically accelerate the pace of drug testing and provide insight into the potential relevance of treatments such as bone marrow transplantation and definitive gene therapy with BMP antagonists.

In the meanwhile, work continues in parallel on both the basic science and treatment fronts to advance the therapy of FOP. Despite the lack of definitive treatments at the present time, there have been numerous anecdotal reports of limited symptomatic benefit with various medications based on the results of uncontrolled studies. Further insight into some of these already available medications will await the design of randomized double-blinded placebo-controlled clinical studies, the most accepted method of obtaining truly useful information on the safety and efficacy of potential treatments.

In this article, we will review the scientific basis for considering various treatment and prevention options based upon the known pathology and molecular pathophysiology of FOP, while at all times keeping in mind that there are presently no proven preventions or treatments for the condition. Nevertheless, this document will attempt to present rationale guidelines for the use of medications in the symptomatic treatment of FOP based upon the current state of knowledge. This report is not intended to present the only approach for FOP, but rather is intended to represent a view, statement, or opinion of the authors which may be helpful to others who face similar situations.

Further advances in therapeutics await the unequivocal identification of the FOP gene, the development of relevant genetically-based animal models for drug testing, and the inception of urgently needed, well-designed, randomized, double-blinded, placebo-controlled studies to assess the various treatment and prevention options in a rigorous scientific manner. At the present time, we have focused our urgent attention in each of these areas.

INTRODUCTION

Fibrodysplasia ossificans progressiva (FOP) is a rare autosomal dominant disorder of connective tissue characterized by congenital malformation of the great toes and by progressive post-natal heterotopic ossification of soft tissue.[8,31,32,43,58,59] Heterotopic ossification usually appears within the first decade of life following spontaneous or trauma-induced flare-ups.[7,8,20,31,32,50,58,59] These flare-ups are often misdiagnosed as tumors and characterized by large painful swellings in soft connective tissues including tendons, ligaments, fascia and skeletal muscle.[17,43] Pre-osseous swellings, especially those involving the trunk, occasionally regress spontaneously.[31,58] Most often, however, the swellings progress through an endochondral pathway to form mature heterotopic bone.[28,29] Progressive episodes of heterotopic ossification lead to ankylosis of all major joints of the axial and appendicular skeleton, rendering movement impossible.[50,55] Most patients are confined to a wheelchair by their early twenties and require lifelong assistance in performing activities of daily living.[7,50] Severe restrictive disease of the chest wall places patients at increased risk of associated cardiopulmonary problems.[34,55] Surgical trauma associated with the resection of heterotopic bone, and intramuscular injections for immunizations or dental work lead to new episodes of heterotopic ossification.[35,39,55] Conductive hearing impairment is a common and poorly-understood associated feature of the condition.[37]

Flare-ups of FOP are sporadic and unpredictable, and there is great interpersonal and intrapersonal variability in the rate of disease progression.[8,23,25,50,52,62] Several large studies on the natural history of FOP have confirmed that it is impossible to predict the occurrence, duration or severity of an FOP flare-up, although a characteristic anatomic progression has been described.[7,8,59] The rarity of the disease and the unpredictable nature of the condition make it extremely difficult to assess any therapeutic intervention, a fact recognized as early as 1918 by Julius Rosenstirn:[52]

> "*The disease was attacked with all sorts of remedies and alternatives for faulty metabolism; every one of them with more or less marked success observed solely by its original author but pronounced a complete failure by every other follower. In many cases, the symptoms of the disease disappear often spontaneously, so the therapeutic effect (of any treatment) should not be unreservedly endorsed.*"

These words ring true today in 2001 as they did when they were written nearly a century ago. At the present time, there is no proven effective prevention or treatment for FOP. With better understanding of the pathology of FOP, new pharmacologic strategies are emerging to treat FOP. Thus, physicians are faced with an increasing number of potential medical interventions. Unfortunately, clinical experience using these medications for FOP is mostly anecdotal.

The gold standard for all medication studies is a double-blinded randomized placebo-controlled study.[21,47] Although such studies would be extremely difficult to conduct in the FOP community considering the few patients afflicted with the disorder, the erratic natural history of the disease, and the extreme interpersonal and intrapersonal variability of FOP, such a design still remains the best approach for obtaining unambiguous answers to our most perplexing dilemma - the proper assessment of true therapeutic utility. Future studies urgently need to consider this approach although, like any approach, it too has its pitfalls. FOP's extreme rarity, variable severity, and fluctuating clinical course, pose daunting uncertainties when evaluating experimental therapies.

Another major factor that has impaired exploration of effective therapy for FOP has been the lack of a genetically-based animal model for the condition. Although heterotopic ossification can be induced in an animal by the injection, surgical implantation, or genetic overproduction of bone morphogenetic proteins, or proto-oncogenes, there are no naturally occurring animal models of heterotopic ossification that accurately reproduce the clinical features of FOP.[46] Although we continue to search for such models and are working assiduously to produce them artificially, the fastest route to success in this difficult area may

be to identify the genetic damage responsible for FOP and then attempt to reproduce that exact genetic damage in an animal model.

The purpose of this report is to review the major classes of medications that have been used (and are being considered) in the treatment and management of patients who have FOP, and to provide a perspective on indications and contraindications for the use of such medications until more rigorous controlled studies can be instituted, hopefully in the very near future.

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 within an individual patient and his or her physician.

THE PATHOPHYSIOLOGY OF FOP

A wealth of emerging knowledge on the molecular genetics, pathology, and pathophysiology of FOP has provided potential targets for therapeutic intervention (Figure 1).

Lymphoblastoid cell lines derived from patients with FOP overexpress bone morphogenetic protein 4 (BMP4) and underexpress potent BMP antagonists (such as noggin and gremlin) in response to a BMP stimulus.[27,54] BMP4 attracts mononuclear cells, induces angiogenesis, stimulates fibroproliferation (from putative mesenchymal stem cells) and apoptosis, and provokes endochondral bone induction which results in the formation of mature ossicles of heterotopic bone that replace skeletal muscle and other connective tissues.[reviewed in 54,57,58]

Biopsies from patients with early FOP lesions, obtained prior to the definitive diagnosis of FOP, have demonstrated an intense peri-vascular B-cell and T-cell lymphocytic infiltrate which subsequently migrates into affected skeletal muscle.[18] Massive death of skeletal muscle fibers is noted in early biopsy specimens.[18] Intermediate stage lesions are microscopically indistinguishable from aggressive juvenile fibromatosis and exhibit an intense fibroproliferative reaction with profound neovascularity and angiogenesis.[17,28] The fibroproliferative cells express robust amounts of BMP4 and smooth muscle proteins but the exact origin of these cells remains uncertain.[17] An abundance of tissue mast cells has been identified at every stage of the disease process.[19] Mast cells can induce cell-mediated processes including fibroproliferation, edema and angiogenesis, and can potentiate severe soft-tissue swelling.

While the stages of bone formation in FOP closely resemble those in embryonic skeletal induction and post-natal fracture-healing, there are some important differences. The inflammatory infiltrate in early FOP lesions is predominantly lymphocytic, while the inflammatory infiltrate in early fracture healing is predominantly neutrophilic and monocytic. As a further contrast, there is no inflammation associated with embryonic skeletal induction.

While the developmental progression of an FOP lesion follows the general pattern of lymphocytic infiltration, skeletal muscle death, fibroproliferation, angiogenesis, chondrogenesis and osteogenesis, all stages of the developmental process are present in the FOP lesion within days of its induction, providing evidence that different portions of the FOP lesion mature at different rates.[18] For example, the outer portion of an FOP lesion appears to mature at a much more rapid rate than the internal portion.[28,31] In reality, all stages of an FOP lesion are present very soon after its induction, and any attempt to successfully inhibit the maturation process will likely entail the inhibition of multiple stages in the developmental process. Thus, the earlier a lesion can be inhibited, the greater likelihood there may be in preventing heterotopic bone formation. In theory, the best approach would successfully prevent the induction of heterotopic ossification. As June Osborn from the University of Michigan stated in a

different context about the benefits of prevention, "If prevention is done absolutely right, absolutely nothing happens."[51]

THE PATHOPHYSIOLOGIC-BASED TREATMENT OF FOP

The optimal treatment of FOP will likely be based upon integrated knowledge of the cellular and molecular pathophysiology of the condition. An abbreviated outline of our current knowledge is presented in Figure 1.

Gene Correction

FOP is a genetic disease, and the ultimate treatment will likely involve a gene correction or gene bypass approach in the cells and tissues involved in the disease process.[8,9,10,31,58] The single most important piece of knowledge currently missing in the FOP puzzle is the identity of the FOP gene.[8,15,27,66] Such knowledge will immediately provide insight into the most promising therapeutic approaches for FOP, and will propel development of the most genetically relevant animal models for rapid testing of potential therapies. Much of the present laboratory effort in FOP is focused on this area of research, and detailed accounts of the work and progress can be found in the Tenth Annual Report of the FOP Collaborative Research Project.[27]

Bone Marrow (Stem Cell) Transplantation

Recent advances in basic and clinical research suggest that stem cells may lie at the heart of a cure for FOP.[1,16,17,22,54] Hematopoietic cells have been found in biopsies of lesions, and stem cells have been recently found to give rise to multiple mesenchymal tissues, including muscle and bone.[2,3,18,19,22,40,44,48,63] Given these new insights, it is rational to ask whether we should treat patients with FOP by replacement of their hematopoietic stem cell pool, via bone marrow, peripheral blood or umbilical cord blood stem cell transplantation. To answer this question, it is necessary to consider how stem cell transplantation might cure FOP, how it might fail, and the clinical risks that patients would necessarily undergo to obtain the chance for cure via current stem cell transplantation techniques.[13]

How Might Stem Cell Transplantation Successfully Treat or Cure Fibrodysplasia Ossificans Progressiva?

In light of the data indicating that Epstein-Barr Virus transformed lymphoblastoid cell lines from patients with FOP express abnormally high levels of mRNA and protein for bone morphogenetic protein 4, it is hypothetically possible that an abnormal hematopoietic cell, most likely a lymphocyte, could trigger the pathophysiology of FOP.[54] Although there is no evidence that the white blood cells themselves secrete bone matrix proteins, cells such as fibroblasts, myoblasts, pericytes, or other mesenchymal cells could lay down the bony exoskeleton in response to abnormal osteoinductive signals from white blood cells.[2,3,5,48]

If FOP is triggered by abnormal osteogenic proteins produced by white blood cells, then complete replacement of the hematopoietic (blood-producing) compartment by stem cell transplantation would permanently eliminate the pathogenic FOP cells. Although the genetic abnormality would still be present in the patient, the cells capable of expressing the abnormality would be removed. Moreover, even if a small percentage of abnormal hematopoietic cells remained immediately after the transplant, they would be eliminated over several months by the new immune system arising from the transplanted cells. Thus, FOP would be essentially cured by the stem cell transplantation procedure.

Even if abnormal blood cells do not trigger bone induction in patients with FOP, stem cell transplantation could still cure the disease. We now know that cells found in the stem cell compartment within the bone marrow and blood are capable of giving rise to endothelial cells, perivascular cells, muscle cells, cartilage cells, and even nerve cells.[2,48,63] Moreover, transplanted stem cells from the bone marrow have recently been shown to contribute cardiac muscle cells to repairing myocardial infarcts, and to partially correcting neurological defects following cerebral ischemia.[48] Therefore, it is conceivable that stem cell transplantation procedures could lead to amelioration or cure of FOP even if the pathogenic cell were of muscle, endothelial or other connective tissue origin. Over months to years, turnover of patient tissues by new cells derived from the transplanted stem cells would gradually reduce the burden of diseased connective tissue.

Why Might Stem Cell Transplantation Fail to Successfully Treat or Cure Fibrodysplasia Ossificans Progressiva?

At this time, although studies show that stem cells can generate soft tissue cells from many lineages, this appears to be a very low-efficiency process. In vitro, fewer than one bone marrow cell in five million has the potential to generate mesenchymal (connective tissue) cells, and the number of cells produced from each mesenchymal stem cell is finite. Following current stem cell transplantation protocols, only very small numbers, probably less than 0.1 per cent of total mesenchymal cells of any lineage, can be found to be donor-derived even months to years following stem cell transplantation. Therefore, without new advances in stem cell transplantation techniques, this process is not likely to be efficient enough to replace most of the abnormally responding myoblasts, fibroblasts, endothelial cells, pericytes, or other connective tissue cells.[40,48,63]

Allogeneic bone marrow transplantation, most often replaces all of the hematopoietic cells, so this should cure the disease. However, turnover is not instantaneous. Immediately following traditional allogeneic transplantation, there is a tremendous inflammatory response to the chemotherapy and/or radiotherapy, which could cause the remaining abnormal hematopoietic cells to activate and trigger promiscuous and catastrophic heterotopic ossification. Even over the following six to twelve months, residual host lymphocytes could trigger heterotopic bone. While the frequency and severity of such episodes would in theory decline over time, the patient might die of complications before a cure could be effective.

Whatever the cellular genesis of FOP, to cure the disease by stem cell transplantation requires that the patients survive the extremely dangerous stem cell transplantation itself. Allogeneic transplantation is accompanied by a prolonged period of immunodeficiency in which the patients are at heightened risk for viral, bacterial and fungal infections. Patients with FOP have severe restrictive chest wall disease with a dramatically increased risk of pulmonary compromise and pneumonia, even during childhood.[34] In addition, the engrafting immune system often recognizes the patient's tissues as foreign and attempts to reject them, so-called "graft-versus-host disease." Overall, the mortality of allogeneic bone marrow

transplantation as currently performed, in any scenario, is always greater than 10-15 per cent, and can be 50 per cent or greater in some settings.

Without knowing the exact cellular and molecular cause of FOP, we could still be missing the true therapeutic target of the underlying pathophysiologic process.[31] We could perform a non-toxic, successful allogeneic stem cell transplantation for a patient, and still not cure the disease. This creates a serious dilemma.

Stem cell transplantation is theoretically a very attractive approach to cure FOP, but it could be dangerous, without any guarantee of cure, or even benefit. To compound the problem, if a patient failed to be cured, or died during a transplant, we might not even know why the treatment had failed. Without an abnormal gene or cell to follow, the clinician and patient would be entering a dangerous trial, like trying to fly an airplane blindfolded without navigational equipment. Given that most patients with FOP are not in a truly life-threatening clinical condition, and that severely affected patients would be at the highest risk for transplant morbidity and mortality, stem cell transplantation at present would be extremely risky.

What Would Favor the Therapeutic Index in the Direction of Stem Cell Transplantation for Fibrodysplasia Ossificans Progressiva?

Fundamentally, the therapeutic index for bone marrow stem cell transplantation in patients with FOP must be improved by decreasing the risk of the transplant procedure and/or improving the likelihood of success. Several approaches to decreasing the risk of the transplant procedures include:

- Non-myeloablative stem cell transplantation, which may decrease transplant morbidity by decreasing inflammation and encouraging gradual, progressive chimerism.[38,44]
- Artificial thymic organoids, which might be used to prevent post-transplant immunodeficiency and graft-versus-host disease.[49]
- Novel pharmaceuticals to prevent graft-versus-host disease, such as anti-granzyme and anti-Fas reagents, and anti-dendritic cell antibodies.[6,14,41,56]

Increasing the likelihood of therapeutic efficacy, on the other hand, requires the identification of the cellular trigger of FOP and, of course, the genetic defect itself. This will allow pre-clinical investigations, perhaps in a xenogeneic stem cell transplantation model where stem-cell enriched peripheral blood cells from patients with FOP are transplanted into Non-obese Diabetic/Severe Combined Immmunodeficiency Mice, so that treatment modeling for FOP can be investigated before the first clinical transplant is performed in humans. Thus, much research remains to be done before stem cell transplantation can be considered in the treatment of FOP.

Injury Prevention

Prevention of soft-tissue injury and muscle damage, as well as prevention of falls remain a hallmark of FOP management. Intramuscular injections must be assiduously avoided.[8,35] The one exception to this rule may be flu shots in older patients who have already experienced joint ankylosis, but who have substantial risk of cardiopulmonary complications from influenza infection.[64] Routine childhood diphtheria-tetanus-pertussis immunizations administered by intramuscular injection cause a substantial risk of permanent heterotopic ossification at the site of injection, whereas measles-mumps-rubella immunizations administered by subcutaneous injection and routine venipuncture pose no significant risk.[35]

Permanent ankylosis of the jaw may be precipitated by minimal soft tissue trauma during routine dental care. Assiduous precautions are necessary in administering dental care to anyone who has FOP. Overstretching of the jaw and intramuscular injections of local anesthetic must be avoided. Mandibular blocks cause muscle trauma, and local anesthetic drugs are extremely toxic to skeletal muscle.[39,45]

Falls suffered by FOP patients can lead to severe injuries and flare-ups. Patients with FOP have a self-perpetuating fall cycle. Minor soft tissue trauma often leads to severe exacerbations, which result in heterotopic ossification and joint ankylosis. Mobility restriction from joint ankylosis severely impairs balancing mechanisms, and causes instability, resulting in more falls (Figure 2).[20]

Falls in the FOP population may cause severe head injuries, loss of consciousness, concussions, and neck and back injuries, compared to people who do not have FOP due to the inability to use the upper limbs to absorb the impact of a fall. FOP patients are much more likely to be admitted to a hospital following a fall and have a permanent change in function because of the fall. In a group of 135 FOP patients, 67% of the reported falls resulted in a flare-up of the FOP. Use of a helmet in young patients may help reduce the frequency of severe head injuries that can result from falls.[20]

Measures to prevent falls should be directed at modification of activity, improvement in household safety, use of ambulatory devices (such as a cane, if possible), and use of protective headgear. Redirection of activity to less physically interactive play may also be helpful. Complete avoidance of high-risk circumstances may reduce falls, but also may compromise a patient's functional level and independence, and may be unacceptable to many. Adjustments to the living environment to reduce the number of falls within the home may include installing supportive hand-railings on stairs, securing loose carpeting, removing objects from walkways, and eliminating uneven flooring including doorframe thresholds.[20]

Prevention of falls due to imbalance begins with stabilization of gait. The use of a cane or stabilizing device may improve balance for many patients. For more mobile individuals, the use of a rolling cane or a walker will assist in stabilization. Augmentation of the patient's protective functions should be performed to minimize injury when a fall does occur.[20]

When a fall occurs, prompt medical attention should be sought, especially when a head injury is suspected. Any head injury should be considered serious until proven otherwise. A few common signs and symptoms of severe head injury include increasing headache, dizziness, drowsiness, obtundation, weakness, confusion, or loss of consciousness. These symptoms often do not appear until hours after an injury. A patient should be examined carefully by a healthcare professional if a head injury is suspected.[20]

Corticosteroids

The rational use of corticosteroids early in the course of an FOP flare-up is based primarily upon its potent suppressive effect on lymphocytes, cells which are seen in the earliest FOP lesions.[18,31,32,58] Widespread anecdotal reports within the FOP community suggest that a brief 4 day course of high-dose corticosteriods begun within the first 24 hours of a flare-up may help reduce the intense lymphocytic infiltration and tissue edema seen in the early stages of the disease. The use of corticosteroids should be restricted to the extremely early symptomatic treatment of flare-ups that affect major joints. Corticosteroids should not be used for the symptomatic treatment of flare-ups involving the back of the neck or trunk due to the long duration and recurring nature of these flare-ups, and the difficulty in assessing the true onset of a flare-up.

Corticosteroids seem most effective if used within the first 24-hours of a new flare-up that affects the movement of a major joint. The dose of corticosteroid is dependent upon body weight, and a typical dose of prednisone would be 2 mg/kg/day administered as a single daily dose for no more than 4 days. When prednisone is discontinued, a non-steroidal anti-inflammatory drug or cox-2 inhibitor in conjunction with a leukotriene inhibitor may be used symptomatically for the duration of the flare-up. Corticosteroids should not be used for the long-term chronic treatment of FOP as chronic dependence and other steroid-associated side-effects will result. Preliminary data from the laboratory also suggest that chronic use of corticosteroids may actually potentiate the expression of BMP4 in lymphocytes.

Corticosteroids are an important component in the management of a submandibular flare-up of FOP.[24] Submandibular swelling in patients who have FOP can be a medical emergency and requires intensive precautionary measures to avoid catastrophic clinical deterioration. These measures include early identification of the submandibular flare-up, avoidance of lesional manipulation, airway monitoring, aspiration precautions, nutritional support due to the difficulty in swallowing, and the use of corticosteroids. The potentially dangerous nature of flare-ups in the submandibular region may dictate a slightly longer use of corticosteroids with an appropriate taper for the duration of the flare-up or until the acute swelling subsides.[24]

Mast Cell Inhibitors

Among the most puzzling features of FOP are the intense muscle edema, fibroproliferation, and angiogenesis (new blood vessel formation) characteristic of early pre-osseous (pre-bony) FOP lesions, and the rapid spread of the lesions into adjacent tissue. As most patients and families know all too well, a lesion may appear within hours and can reach an alarming size literally overnight. The sudden appearance and rapid spread of an FOP lesion suggests involvement of an armada of inflammatory mediators along with an abnormal connective tissue wound response, and points to a potential role for inflammatory mast cells in the extension of the disease process.

Mast cells are indigenous cells in the body's connective tissues and arise from the bone marrow. They circulate through the blood as committed, but undifferentiated cells, and migrate into numerous tissues including skeletal muscle where they mature and reside as harmless bystanders until provoked by a traumatic or inflammatory stimulus. Mast cells are found in close proximity to blood vessels and nerves. In normal skeletal muscle, mast cells are found very sparsely distributed in the connective tissues between the muscle bundles. Mast cells contain granules of very potent stored chemicals that induce edema, fibroproliferation and angiogenesis when the granules are released into the surrounding tissue. For many years, the role of mast cells was unknown, but it now appears that they play an important role in tissue repair and wound healing.

When mast cell recruitment and activation goes awry, the process can lead to severe inflammatory reactions. This has long been recognized with mast cell activation in the skin and lungs, resulting in many of the symptoms of hives and asthma, respectively. However, very little is known about mast cells in the deeper tissues of the body such as the skeletal muscles. Mast cells are not easily visible under the microscope unless special stains are used to detect them. Mast cells are stimulated by a myriad of different external and internal stimula such as internal immune responses and external tissue injury.

Mast cells contain granules whose sequestered contents include histamine, heparin, angiogenic proteins, and matrix degrading enzymes that allow injured tissue to repair itself. Potent angiogenic proteins released by mast cells include basic fibroblast growth factor, vascular endothelial growth factor, and

transforming growth factor beta. Mast cells also release a litany of inflammation-causing molecules including tumor necrosis factor alpha, prostaglandins, and leukotrienes. Upon release from the mast cells, these substances influence a vast array of biological processes including inflammation, immune function, angiogenesis, fibrous tissue formation, extracellular tissue remodeling, and tissue repair. Mast cells are also hijacked by invading tumors. Mast cells accumulate at the leading edge of invading tumors where they are conscripted for angiogenesis and local tumor invasion, but mast cells are not found in the core of the invading tumors.

The intense inflammatory muscle edema, fibroproliferation, and angiogenesis characteristic of early pre-osseous FOP lesions and the rapid spread of these lesions along muscle planes into adjacent tissue suggested a potential role for mast cells in the FOP process. As little is known about the resident mast cells in skeletal muscle, a comprehensive analysis was undertaken of mast cell distribution in normal skeletal muscle, in uninvolved FOP muscle, in FOP lesions, in inflammatory and genetic muscle diseases, and in experimentally-induced animal models of heterotopic ossification.[19]

The findings of the study were startling and unexpected. Mobilization and activation of inflammatory mast cells was found at all stages of FOP lesional development. These data documented an important role for mast cells in the pathology of FOP lesions.[19]

The following hypothesis was developed based on observations and experimental data in the mast cell study: Tissue injury in patients with FOP leads to lymphocyte migration into normally appearing skeletal muscle.[18] Some of these lymphocytes overproduce BMP4 and appear to lead to mast cell mobilization, a finding which is supported strongly by the FOP pathology and by experimental models of heterotopic ossification using recombinant BMP.[19] Mediators released by mast cells stimulate a cycle of inflammatory edema, fibrosis, and angiogenesis which is potentiated at the leading edge of an advancing FOP lesion. Reactive fibroblasts within the muscle tissue produce proteins which lead to further proliferation of mast cells and a self-sustaining escalation of the disease process known as a flare-up.[17] Eventually, transforming growth factor beta, released by mast cells and other lesional cells, limits the

lymphocytic recruitment and migration and thus the size and extent of the expanding lesion, while endogenous overexpression of BMP4 in the fibroproliferative core drives the fibroproliferative lesion towards ossification through an endochondral pathway.

The observation of mast cell mobilization in FOP lesions provides a novel and previously unrecognized opportunity to evaluate anti-mast cell therapies in limiting the spread of FOP lesions. Data from a unique model of BMP implantation into an animal genetically reduced in mast cells suggest that completely blocking mast cell function is not presently possible. However, reduction of mast cell activity may play an important role in limiting the inflammatory component of the process and thus the local extent of the lesional swelling.[19,27]

Mast cells, lymphocytes, and their associated inflammatory-mediators may also be reduced with the use of mast cell stabilizers, long-acting non-sedating antihistamines, leukotriene inhibitors, non-steroidal anti-inflammatory medications, and the new cox-2 inhibitors. Mast cell membrane stabilizers may reduce the release of angiogenic and chemotactic factors, while anti-histamines and leukotriene inhibitors may reduce the downstream effects of released mediators. The optimal use of these medications and their potential efficacy in FOP is presently unknown.

Cyclo-oxygenase 2 inhibitors

During the past year, an important new category of drugs has emerged with previously unexpected and important implications for the treatment of FOP. These are the cyclo-oxygenase-2(cox-2) inhibitors, medications that specifically target pro-inflammatory prostaglandins.[33,61]

The body essentially produces two types of prostaglandins: “physiological” prostaglandins and “inflammatory” prostaglandins. Physiological prostaglandins are normally produced in many of the body’s tissues and protect organs such as the stomach from metabolic injury. Inflammatory prostaglandins are produced in response to injury, and play a major role in the inflammatory response to injury. Traditional non-steroidal anti-inflammatory drugs such as aspirin, ibuprofen and indomethacin

inhibit the formation of both the physiological and inflammatory prostaglandins. The new cyclo-oxygenase 2 (cox-2) inhibitors primarily inhibit the inflammatory prostaglandins and leave the physiological prostaglandins relatively intact.[33,61]

Inflammatory prostaglandins are potent co-stimulatory molecules along with BMPs in the induction of heterotopic bone.[11,65] Studies in the orthopaedic literature have shown that lowering prostaglandin levels in experimental animals dramatically raises the threshold for heterotopic ossification, thus, making it more difficult for bone to form.[65] Animals pretreated with prostaglandin inhibitors failed to form heterotopic bone following intramuscular injections of BMP-containing demineralized bone matrix. In contrast, animals treated with prostaglandin inhibitors at the same time, as or following a demineralized bone matrix injection still formed heterotopic bone.[11] These data suggest that in order for prostaglandin inhibitors to be truly effective in preventing heterotopic ossification, the medication must be "in the system" (in other words circulating in the blood at the therapeutic levels) before a bone-induction signal occurred. In addition to their potent anti-inflammatory properties, a recent study unexpectedly demonstrated that the new cox-2 inhibitors have potent anti-angiogenic properties as well as anti-inflammatory properties, a feature that makes them even more desirable for consideration in FOP.[26]

Inflammatory prostaglandin levels are dramatically elevated in the urine of patients who have FOP, especially during times of a disease flare-up.[36] Inflammatory prostaglandins directly stimulate the induction of angiogenic peptides which can further promote the osteogenic process. These observations suggest the following hypothesis: lowering baseline prostaglandin levels in patients with FOP may raise the threshold for heterotopic ossification even in the presence of substantial endogenous levels of BMP4. This hypothesis is amenable to clinical testing and will be the focus of a placebo-controlled study to assess the safety and efficacy of cox-2 inhibitors in the prevention of FOP flare-ups. While the potential benefit of the new cox-2 inhibitors in preventing heterotopic ossification is no greater than the parent class of non-steroidal anti-inflammatory medications, the new cox-2 inhibitors offer the possibility of a lower gastrointestinal risk profile than the parent compounds. In addition, the half-life of some of the new cox-2 inhibitors is conducive to a once-daily dosage regimen, a factor which helps promote patient

compliance.[33,61]

While the cox-2 inhibitors are generally safe, their action must be carefully monitored, especially in those who are taking the medications for long periods of time, as rare but life-threatening side-effects and kidney-damaging effects can occur. As with any condition, the relative risks and benefits of potential therapies must be weighed against the potential risks of the underlying condition being treated.[33,61]

Cox-2 inhibitors are available by prescription. They are currently being tested in children with rheumatoid arthritis, and are being used sporadically by pediatric specialists for the treatment of severe inflammatory conditions where few other treatment options exist. In the next year, we will design a placebo-controlled study of the cox-2 inhibitors in preventing flare-ups in patients with FOP. It will be the best way to determine whether this new class of medications may be truly beneficial in preventing flare-ups in FOP.

The work on the cox-2 inhibitors integrates important findings from the laboratory on prostaglandin production, mast cell recruitment, and angiogenic factor release with the pathologic findings of severe inflammatory pre-osseous lesions of FOP.[18,19,30,36]

BMP Antagonists

> *"With so much being discovered about how the BMPs act, it might be possible to develop drugs that would block some part of the BMP4 pathway-and therefore prevent the progression of what is a horrible, nightmare disease."*[53]
>
> - Brigid Hogan

Noggin gene therapy continues to be the most promising longterm treatment for FOP based upon our present knowledge of the condition.[27] The importance of noggin to the FOP story became apparent after the discovery of BMP4 overexpression in FOP, and noggin was brought to the forefront of development for FOP treatment. Noggin is involved in controlling the amount of skeleton and bone that is formed by

regulating the concentrations of BMP4 available in the body's tissue. For this reason, noggin offers promise for controlling the rampant bone growth of FOP.[27]

BMP4 is produced by skeletal muscle and its expression can be upregulated at sites of soft tissue injury. Under normal circumstances, BMP4 dramatically upregulates the expression of BMP antagonists such as noggin and gremlin which diffuse more rapidly than TGF-∃ family members.[27] FOP cells show a markedly attenuated response to BMP4 stimulation. A blunted BMP antagonist response following soft tissue trauma would permit the rapid expansion of a BMP4 signal conducive to progressive bone formation. The growth of highly vascular pre-osseous fibroproliferative tissue seen locally in response to BMP overexpression would be magnified in the setting of a blunted BMP antagonist response and could explain the explosive bone induction seen during an FOP flare-up. These findings from FOP illustrate the importance of a critical balance between an inductive signal like BMP4 and its secreted antagonists in the formation of an ectopic organ system and suggest the potential for developing BMP antagonist-based strategies in the therapy of FOP.[27]

Although the genes for noggin and BMP4 do not appear to be damaged in FOP, the results of pre-clinical studies prove conclusively that noggin can effectively inhibit BMP-induced heterotopic bone formation.[12,58]

The development of noggin vectors for experimental testing in animal models of heterotopic ossification was reported recently.[12] Before gene therapy with noggin can become a clinical reality, methods must be developed for safely regulating noggin gene expression in the body. Work has focused on the development of a novel delivery system. Data from ongoing animal experiments during this past year continue to be encouraging. Vectors have been created to drive noggin expression from constitutive and inducible promoters and are being studied in animal models.[12,27] If pre-clinical animal efficacy and safety data are satisfactory (in a BMP4 bone-induction model), we will continue to develop this therapy for human clinical trials.

Successful gene therapy in FOP, as with any genetic disease, will require the coordinated and collaborative work of geneticists, virologists, immunologists, cell biologists, and clinicians. Geneticists will be necessary to identify the genetic contributions to FOP. Virologists will generate safe and efficient viral vectors for introducing the extra copies of the noggin gene into the human body. Molecular biologists will help to design vectors capable of cell and tissue specific expression of the noggin gene carried by the transducing vectors. Immunologists will work out ways to prevent unwanted immunological consequences of the viral delivery vehicles and their noggin cargo. Cell biologists will devise ways to facilitate gene transfer to various tissues and will take the lead in identifying muscle or blood stem cells through which the vector can be introduced. Clinicians will carry out clinical trials on patients with FOP with the best vectors that the scientists can supply. To achieve successful gene therapy, nearly all branches of biology will have to contribute to this endeavor.

Anti-angiogenic Agents

Development and growth of the human embryo as well as growth and regression of tumors are dependent on the control of new blood vessel formation (angiogenesis). Angiogenesis is also an absolute requirement for the formation and development of the skeleton, for the successful healing of fractures, and for the formation of heterotopic bone. The early stages of skeletal embryogenesis correspond to the highly vascularized pre-osseous fibroproliferative lesions seen in FOP.[28,30] Angiogenesis, a prominent histopathologic feature of pre-osseous FOP lesions, thus becomes a potential target for therapy.[17,18,28,30]

Basic fibroblast growth factor (bFGF), a heparin-binding endothelial cell growth factor, is an extremely potent in-vivo stimulator of angiogenesis, and has been implicated in the growth of solid tumors. bFGF has been investigated in FOP patients to determine if it is implicated in the pre-osseous lesions. Urinary bFGF levels are markedly elevated in patients who have FOP, especially during acute flare-ups of the disease process. In contrast, elevations of urinary bFGF were not detected during times of disease quiescence. These data suggested that urinary bFGF may be a biochemical marker for disease flare-ups in FOP patients and provides a biochemical basis for considering anti-angiogenic therapy at early stages of the disease process.[30]

The goal of anti-angiogenic therapy in FOP is to inhibit new blood vessel formation in order to slow down or inhibit the subsequent production of new bone formation once a new lesion has appeared. Angiogenesis may potentially be minimized with anti-angiogenic agents such as thalidomide, squalamine, cycloxygenase-2 (cox-2) inhibitors, and vascular growth factor traps. At present, several of these agents are in pre-clinical development or early phase I clinical studies.[27]

Squalamine, a new anti-angiogenic agent, with potential interest for FOP, was discovered in 1992 in the FOP laboratory by Dr. Michael Zasloff. Dr. Zasloff isolated squalamine from the body tissues of the dogfish shark, and discovered its anti-angiogenic properties by accident. Squalamine is a naturally occurring cholesterol-like molecule that inhibits the proliferation of endothelial cells (blood vessel cells) and exhibits potent-anti-angiogenic activity in laboratory animals and humans. During the past year, the cellular mechanism of action of squalamine has been elucidated. Squalamine modifies the response of endothelial cells to proteins that organize their shape and structure.[27]

Squalamine is currently produced synthetically under sterile conditions and does not have to be obtained from sharks. In pre-clinical studies, squalamine has been shown to inhibit angiogenesis and the subsequent growth of solid tumors. By directly blocking the angiogenic process, squalamine has the potential to slow the progression of the FOP lesions in muscle.

A phase I clinical trial of squalamine in FOP will be targeted to a small group of adult FOP patients who are having severe pre-osseous flare-ups. The initial study will be designed to evaluate the safety and efficacy of intravenous squalamine on the inhibition of angiogenesis, and will enroll no more than 10 adult patients with FOP. Data from the phase I Safety and Efficacy Trial will be used to design a larger controlled phase II Study. The study will require full approval by the FDA, the Institutional Review Board of The University of Pennsylvania, The Clinical Research Center of the Hospital of the University of Pennsylvania, The Radiation Safety Board and The Clinical Studies Monitoring Unit of The University of Pennsylvania School of Medicine.

The regulatory and safety issues involved in testing new drugs in humans are enormous and complex. Further information on the commencement of this Phase I clinical trial will be forthcoming in later editions of the ***FOP Connection***, and online immediately when it is fully approved.

Thalidomide

Thalidomide (a-N-phthalimidoglutarimide) was initially used in Europe as a sedative in the 1950's. Initially, there were no acute toxicity issues and no fatalities from even large overdoses. However, in 1961 the teratogenic effects of thalidomide were reported following its use as an antiemetic in pregnant women. An association between limb defects in babies and maternal thalidomide use was described. Thirty years later, investigators demonstrated that thalidomide potently inhibited angiogenesis in a rabbit corneal model, and postulated that the limb defects seen with thalidomide exposure were due, in part, to an inhibition of blood vessel growth in the developing fetal limb bud. Despite thalidomide's potent teratogenicity in pregnant women, it remains a relatively safe medication in non-pregnant humans. While its exact mechanism of action remains unknown, it clearly possesses important properties as an anti-angiogenic agent, a tumor necrosis factor regulator, and as an immunomodulator.[60]

Considering that angiogenesis is a prominent feature of the pre-osseous fibroproliferative lesions in patients with FOP, utilizing an anti-angiogenic agent during acute flare-ups seemed logical in preventing progression of the lesion towards heterotopic ossification. The objective of the Phase I-II Thalidomide trial was to determine the potential efficacy and to evaluate the acute and chronic toxicity of thalidomide in patients with FOP flare-ups.[27]

Starting in August of 1998, patients with FOP were enrolled in the open-label Phase I thalidomide trial (Dr. Deanna Mitchell; Principal Investigator). Patients began an escalating dose of thalidomide (initially starting at 1 mg/kg/day) with the onset of symptoms of an acute flare-up. Doses were escalated every 15 days to a maximum of 10 mg/kg/day if the flare-up persisted and if thalidomide was tolerated without excessive sedation or peripheral neuropathy. Thalidomide was utilized for a maximum of 60 days for each flare-up. Patients were monitored for efficacy and toxicity by keeping records of flare-up location, size and duration, and by a monthly physical examination by their investigator. Laboratory assessment

including a complete blood count and serum chemistries were monitored every three months. Female patients who had reached menarche were informed fully of the severe birth defects that could be caused by thalidomide, and utilized either total abstinence or two standard methods of birth control. Investigators completed a neuropathy symptom questionnaire along with the monthly exam to monitor for side-effects of peripheral neuropathy.[27]

As of January 2001, 15 patients had enrolled in the thalidomide study. All 15 patients tolerated each dose escalation of thalidomide without significant toxicity. Mild sedation was the most commonly observed side-effect, and was not limiting to any patient's usual life activities. There was no evidence of significant peripheral neuropathy in the first 15 patients. One patient reported transient numbness and tingling in his fingers and toes, however, this did not persist despite ongoing treatment with thalidomide.

Flare-ups of FOP continued to occur in patients on thalidomide. The intensity and duration of flare-ups, as perceived by the patients and/or their parents, were subjectively improved with thalidomide treatment in 14 of 15 patients. As of January 2001, seven patients have had their second annual nuclear medicine bone scan reviewed by the study radiologist. Six of the seven patients showed no new site of heterotopic bone formation compared to the original bone scan. A second patient, treated with thalidomide and a pulse of prednisone, suffered a clinically significant flare-up involving her hip. Her nuclear medicine bone scan at one year on study demonstrated no abnormal uptake in her hip and she had no loss of motion in her hip. A third patient who had a flare-up of the hip was treated with thalidomide and prednisone, and showed uptake on her bone scan and loss of mobility at her hip.

The Phase I/II thalidomide trial in patients with fibrodysplasia ossificans progressiva (FOP) is presently being evaluated. The data are preliminary and subject to additions and clarification. Consideration is being given for a Phase III double-blinded placebo-controlled trial using thalidomide for the treatment of FOP flare-ups.

Retinoids

Retinoids are a plausible family of therapeutic agents for fibrodysplasia ossificans progressiva due to their ability to inhibit differentiation of connective tissue into cartilage and bone. A prospective Phase I/II study was conducted to assess the safety and efficacy of isotretinoin (13-cis-retinoic acid) in the prevention of heterotopic ossification in 21 patients.[67] Eleven anatomic regions were assessed in each patient by clinical examination, radiographs, and bone scans. An anatomic region was considered to be involved if there was clinical, radiographic, or radionuclide evidence of orthotopic or heterotopic ossification anywhere in the region. There were 143 involved anatomic regions and 88 uninvolved anatomic regions at the beginning of the study. Only one of the 88 anatomic regions that was completely uninvolved at the beginning of the study became involved during isotretinoin therapy. However, 16 of the 21 patients (76%) experienced major flare-ups in 38 of 143 (27%) previously involved anatomic regions while isotretinoin therapy was being administered. Isotretinoin at steady state doses of 1 to 2 mg/kg per day decreased the incidence of heterotopic ossification at uninvolved anatomic regions compared with an external control group, as long as the medication was started before the appearance of any orthotopic or heterotopic ossification in that anatomic region. The data did not allow the determination of whether isotretinoin was effective or detrimental in preventing disease flare-ups in regions that had even minimal orthotopic or heterotopic ossification at the time the therapy began. Common side effects of the medication were headaches, dry skin and mouth, gastrointestinal distress, and anemia. Extreme caution should be exercised when using this medication in FOP patients.[67]

A phase III double-blinded randomized placebo-controlled clinical trial was attempted with isotretinoin but was not possible due to lack of patient interest in this approach.[67]

Mineralization Inhibitors

Ethane-1-hydroxy-1-diphosphonate (etidronate) has been studied because of its inhibitory effect on bone mineralization and its potential to impair ossification at high dosages. Unfortunately, at high doses, it also causes osteomalacia (soft bones) and can impair ossification of the entire skeletal system, not just the heterotopic bone of the "second skeleton." Its utility is therefore extremely limited.

In the only published series, the effects of intravenously administered etidronate and oral corticosteroids were evaluated.[4] Thirty-one fibrodysplasia ossificans progressiva attacks were observed in seven patients during the mean follow-up of 6 years. In 29 attacks, the authors observed a rapid diminution of local inflammation, swelling, and pain during the first 7 days of treatment. However, despite the ethane-1-hydroxy-1-diphosphonate treatment, 10 new ossifications were observed, causing severe deterioration of joint mobility in all affected patients. In 21 attacks, no new ectopic ossification appeared. The radiologic pattern of pre-existing ossifications did not change during the treatment. The results suggest the possibility that intravenous administration of ethane-1-hydroxy-1-diphosphonate and oral corticosteroids may be helpful, but more control data on the spontaneous resolution of early flare-ups are needed.[4] While high-dose etidronate has proven effects on inhibiting mineralization, the newer bisphosphonates do not possess this activity. At the present time, we do not use etidronate regularly for the treatment of FOP, and there is no obvious rational basis for the use of the newer bisphosphonates.

Chemotherapy Agents and Radiation Therapy

The definitive diagnosis of FOP is often delayed due to the rarity of the condition and the failure to associate the tumor-like soft tissue swellings with the congenital malformations of the great toes.[17,28] As a result, many children with FOP are originally misdiagnosed as having aggressive fibromatosis, fibrosarcoma, soft tissue chondrosarcoma, soft tissue osteosarcoma, or lymphoma.[17] It is not surprising, therefore, that many children with FOP have been treated with various extensive regimens of chemotherapy and radiotherapy before the definitive diagnosis of FOP has been made. It would be important to note retrospectively if radiation therapy or any of the chemotherapy agents had been helpful in altering the natural history of the condition. There was, however, no convincing anecdotal evidence that either radiation therapy or any of the standard chemotherapy agents such as tamoxifen, colchicine, vincristine, vinblastine, cytoxan, methotrexate, adriamycin, or any others were helpful for patients with FOP. In fact, many of these medications caused harmful longterm side-effects. The use of these approaches is, therefore, contraindicated in the treatment of FOP.

Miscellaneous Agents

The progression of the fibroproliferative FOP lesion to cartilage, calcified cartilage and bone may potentially be slowed with the use of fluoroquinolone antibiotics and tissue inhibitors of matrix metaloproteases.[19] However, the fluoroquinolones are toxic to growth plate and joint cartilage at high doses and there are presently no adequate animal models in which to test their relative safety and potential efficacy in FOP. The chronic use of calcium binders, mineralization inhibitors, and warfarin have been reported with either unsatisfactory or unequivocal results.[42] At the present time, the use of these medications or approaches is not indicated.

SPECIFIC 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 AN FOP CLINICAL WORKSHOP - A GUIDE FOR CLINICIANS

At the Third International Symposium on FOP (Philadelphia, PA; November 2-5, 2000), an international panel of physicians participated in a clinical workshop to review current treatment considerations in FOP (Tables 1 and 2). The panel reviewed many current and potential treatment options for this disorder. The unpredictable nature of FOP has made controlled trials 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 few side effects.
Examples: Leukotriene inhibitors and mast cell stabilizers
Sodium cromolyn is a generally well-tolerated mast cell inhibitor. However, oral absorption is poor, and its potential effectiveness is unknown in FOP.

Class III: Investigational new drugs
Examples: Thalidomide, squalamine, VEGF trap, noggin

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.

CURRENT TREATMENT CONSIDERATIONS

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 within 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 correspond 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, it is unlikely that a repeat dose will be helpful. Prednisone should 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 longterm use and can have longterm harmful effects. The use of prednisone is meant only to suppress or abort the early lymphocytic infiltration into skeletal muscle, 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 and a leukotriene inhibitor (Class II medication). For patients older than 16 years of age, a cyclooxygenase-2 (cox-2) inhibitor can be used instead of a traditional NSAID. The dose of the medication should be titrated to the clinical response. 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, assiduous gastrointestinal precautions should prevail. If longterm use of the cox-2 inhibitors is considered, serum liver and kidney function tests should be monitored.

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 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 (maximum) 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.

Class III Medications are under development and should not be used except in an approved clinical study. Anti-angiogenic agents (thalidomide and squalamine) are in the clinical trial or the pre-clinical trial review stage respectively. Potential use of vascular endothelial growth factor traps are being considered. The BMP antagonist (Noggin) is under intense investigation in pre-clinical development.

CONCLUSIONS

In the recently published 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.[60] 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." There is little doubt that the testing of drugs for FOP, either for prevention or treatment, will require the same stringent principles and strategy.[21,47]

A physician treating a patient with FOP must never withhold an available medication 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. 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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REFERENCES

1. Bhatia M, Bonnet D, Wu D, Murdoch B, Wrana J, Gallacher L, Dick JE: Bone morphogenetic proteins regulate the developmental program of human hematopoietic stem cells. **J Exp Med** 189:1139-1147, 1999
2. Bianco P, Robey PG: Marrow stromal stem cells. **J Clin Invest** 105:1663-1668, 2000
3. Bosch P, Musgrave DS, Lee JY, Cummins J, Shuler T, Ghivizanni TC, Evans T, Robbins TD, Huard J: Osteoprogenitor cells within skeletal muscle. **J Orthop Res** 18:933-944, 2000
4. Brantus JF, Meunier PJ: Effects of intravenous etidronate and oral corticosteroids in fibrodysplasia ossificans progressiva**. Clin Orthop Rel Res** 346: 117-120, 1998
5. Brighton CT, Lorich DG, Kupcha R, Reilly TM, Jones AR, Woodbury RA 2nd: The pericytes as a possible osteoblast progenitor cell**. Clin Orthop Rel Res** 275: 287-299, 1992
6. Bruno AP, Lautier D, d'Orgeix AT, Laurent G, Quillet-Mary A: Acute myeloblastic leukemic cells acquire cellular cytotoxicity under genotoxic stress: implications of granzyme B and perforin. **Blood** 96: 1914-1920, 2000
7. Cohen RB, Hahn GV, Tabas J, Peeper J, Levitz CL, Sando A, Sando N, Zasloff M, Kaplan FS: The natural history of heterotopic ossification In patients who have fibrodysplasia ossificans progressiva. **J Bone Joint Surg** 75-A:215-219, 1993
8. Connor JM, Evans, DA: Fibrodysplasia ossificans progressiva (FOP) : the clinical features and natural history of 34 patients. **J Bone Joint Surg Br** 64:76-83, 1982
9. Connor JM: Fibrodysplasia ossificans progressiva - lessons from rare maladies. **N Engl J Med** 335: 591-593, 1996
10. Delatycki M, Rogers JG: The genetics of fibrodysplasia ossificans progressiva. **Clin Orthop Rel Res** 346: 1518, 1998.
11. DiCesare PE, Nimni ME, Pen L, Yazdi M, Cheung DT: Effects of Indomethacin on demineralized bone-induced heterotopic ossification in the rat**. J Orthop Res** 9:855-861, 1991
12. Economides AN, Liu X, Gannon FH, Shore EM, Kaplan FS, Kimble R, Stahl N: Therapeutic potential of the BMP antagonist noggin. **Proceedings of The Third International Symposium on Fibrodysplasia Ossificans Progressiva**; November 2-5, 2000, University of Pennsylvania School of Medicine

13. Emerson SG, Kaplan FS: Marrow stem cell transplantation - fibrodysplasia ossificans progressiva. **Clin Orthop Rel Res** (in press), 2001
14. Faustman DL, Steinman RM, Gebel HM, Hauptfeld V, Davie JM, Lacy PE: Prevention of rejection of murine islet allografts by pretreatment with anti-dendritic cell antibody. **Proc Natl Acad Sci USA** 81: 3864-3868, 1984
15. Feldman G, Li M, Martin S, Urbanek M, Urtizberea JA, Fardeau M, Le Merrer M, Connor JM, Triffitt J, Smith R, Muenke M, Kaplan FS, Shore EM: Fibrodysplasia ossificans progressiva (FOP), a heritable disorder of severe heterotopic ossification, maps to human chromosome 4q 27-31**. Am J Hum Genet** 66:128-135, 2000
16. Friedenstein AY, Lalykina KS: Lymphoid cell populations are competent systems for induced osteogenesis. **Calc Tiss Res** 4 (supplement) 105-106, 1970
17. Gannon FH, Kaplan FS, Olmsted E, Finkel G, Zasloff MA, Shore EM: Bone morphogenetic protein 2/4 in early fibromatous lesions of fibrodysplasia ossificans progressiva**. Hum Pathol** 28:339-343, 1997
18. Gannon FH, Valentine BA, Shore EM, Zasloff MA, Kaplan FS: Acute lymphocytic infiltration in an extremely early lesion of fibrodysplasia ossificans progressiva**. Clin Orthop Rel Res** 346: 19-25, 1998
19. Gannon FH, Glaser D, Caron R, Thompson LDR, Shore EM, Kaplan FS: Mast cell involvement in fibrodysplasia ossificans progressiva (FOP). **Human Pathology**, in press, 2001
20. Glaser DL, Rocke DM, Kaplan FS: Catastrophic falls in patients who have fibrodysplasia ossificans progressiva. **Clin Orthop Rel Res** 346:110-116, 1998
21. Hellman S, Hellman DS: Of mice but not men: problems of the randomized clinical trial. **New Engl J Med** 324: 1585-1589, 1991
22. Horwitz EM, Prockop DJ, Fitzpatrick LA, Koo WW, Gordon PL, Neel M, Sussman M, Orchard P, Marx JC, Pyeritz RE, Brenner MK: Transplantability and therapeutic effects of bone marrow-derived mesenchymal cells in children with osteogenesis imperfecta. **Nature Med** 5: 309-313, 1999
23. Janoff HB, Tabas JA, Shore EM, Muenke M, Dalinka MK, Schlesinger S, Zasloff MA, Kaplan FS: Mild expression of fibrodysplasia ossificans progressiva. **J Rheumatol** 22:976-978, 1995

24. Janoff HB, Zasloff MA, Kaplan FS: Submandibular swelling in patients with fibrodysplasia ossificans progressiva. **Otolaryngol Head Neck Surg** 114:599-604, 1996
25. Janoff HB, Muenke M, Johnson LO, Rosenberg A, Shore EM, Okereke E, Zasloff M, Kaplan FS: Fibrodysplasia ossificans progressiva in two half-sisters: evidence for maternal mosaicism. **Am J Med Genetics** 61:320-324, 1996
26. Jones, MK, Wang H, Peskar BM, Levin E, Itani RM Sarfeh IJ, Tarnawski AS: Inhibition of angiogenesis by nonsteroidal anti-inflammatory drugs: insight into mechanisms and implications for cancer growth and ulcer healing. **Nature Med** 5: 1418-1423, 1999
27. Kaplan FS, Shore EM: The tenth annual report of the fibrodysplasia ossificans progressiva (FOP) collaborative research project. **FOP Connection** 14(2):16-31, 2001
28. Kaplan FS, Tabas J, Gannon FH, Finkel G, Hahn GV, Zasloff MA: The histopathology of fibrodysplasia ossificans progressiva: an endochondral process. **J Bone Joint Surg** 75-A:220-230, 1993
29. Kaplan FS, Strear CM, Zasloff MA: Radiographic and scintigraphic features of modeling and remodeling in the heterotopic skeleton of patients who have fibrodysplasia ossificans progressiva. **Clin Orthop Rel Res** 304: 238-247, 1994
30. Kaplan FS, Sawyer J, Connors S, Keough K, Shore E, Gannon F, Glaser D, Rocke D, Zasloff M, Folkman J: Urinary basic fibroblast growth factor: a biochemical marker for preosseous fibroproliferative lesions in patients with FOP. **Clin Orthop Rel Res** 346:59-65, 1998
31. Kaplan FS, Delatycki M, Gannon FH, Rogers JG, Smith R, Shore EM: Fibrodysplasia ossificans progressiva. In Emery EH (ed). **Neuromuscular Disorders: Clinical and Molecular Genetics**. Chichester, John Wiley & Sons Ltd. 289-321, 1998
32. Kaplan FS, Shore EM, Whyte, MP: Fibrodysplasia ossificans progressiva. pp. 435-437. In Favus MJ (ed). **Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism** - Fourth Edition. The American Society for Bone and Mineral Research, Lippincott-Raven, Philadelphia, 1999
33. Katori M, Majima M: Cyclooxygenase-2: its rich diversity of roles and possible application of its selective inhibitors. **Inflammation Res** 49: 367-392, 2000

34. Kussmaul WG, Esmail AN, Sagar Y, Ross J, Gregory S, Kaplan FS: Pulmonary and cardiac function in advanced fibrodysplasia ossificans progressiva. **Clin Orthop Rel Res** 346: 104-109, 1998
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 Pediatrics** 126:762-764, 1995
36. Levitz CL, Cohen RB, Zasloff MA, Kaplan FS: The role of prostaglandins in bone formation. Abstracts from The First International Symposium on Fibrodysplasia Ossificans Progressiva, September 25-26, 1991, Philadelphia, Pennsylvania. **Calcif Tissue Int** 50:385-388, 1992
37. Levy CE, Lash AT, Janoff HB, Kaplan FS: Conductive hearing loss in individuals with fibrodysplasia ossificans progressive. **Am J Audiol** 8: 29-33, 1999
38. Little M-T, Storb R: The future of allogeneic hematopoietic stem cell transplantation: minimizing pain, maximizing gain. **J Clin Invest** 105:1679-1681, 2000
39. Luchetti W, Cohen RB, Hahn GV, Rocke DM, Helpin M, Zasloff M, Kaplan FS: Severe restriction in jaw movement after route injection of local anesthetic in patients who have fibrodysplasia ossificans progressiva. **Oral Surg Oral Med Oral Pathol Oral Radiol Endod** 81:21-25, 1996
40. McKay R: Stem cells - hype and hope. **Nature** 406: 361-364, 2000
41. Micheau O, Solary E, Hammann A, Dimanche-Boitrel ME: Fas ligand-independent, FADD-mediated activation of the Fas death pathway by anticancer drugs. **J Biol Chem** 274: 7987-7992, 1999
42. Moore, SE, Jump A, Smiley JD: Effect of warfarin sodium therapy on excretion of 4-carboxy-L-glutamic acid in scleroderma, dermatomyositis, and myositis ossificans progressiva. **Arthritis Rheum** 29:344-351, 1986
43. Moriatis JM, Gannon FH, Shore EM, Bilker W, Zasloff MA, Kaplan FS: Limb swelling in patients who have fibrodysplasia ossificans progressiva (FOP). **Clin Orthop Rel Res** 336: 247-253, 1997
44. Nilsson SK, Dooner MS, Weier HU, Frenkel B, Lian JB, Stein GS, Queensberry PJ: Cells capable of bone production engraft from whole bone marrow transplants in nonablated mice. **J Exp Med** 189: 729-734, 1999

45. Nussbaum BL, O'Hara, I, Kaplan FS: Fibrodysplasia ossificans progressiva (FOP) : report of a case with guidelines for pediatric dental and anesthetic management. **ASDC J Dent Child** 63: 448-450, 1996

46. Olmsted EA, Gannon FH, Wang Z-Q, Grigoriadis AE, Wagner EF, Zasloff MA, Shore EM, Kaplan FS: Embryonic overexpression of the c-fos proto-oncogene: a murine stem cell chimera applicable to the study of fibrodysplasia ossificans progressiva in humans. **Clin Orthop Rel Res** 346:81-94, 1998

47. Passamani E. Clinical trials - are they ethical? **New Engl J Med** 324: 1589-1591, 1991

48. Pittenger MF, Mackay AM, Beck SC, Jaiswal RK, Douglas R, Mosca JD, Moorman MA, Simonetti DW, Craig S, Marshak DR: Multilineage potential of adult human mesenchymal stem cells. **Science** 284: 143-147, 1999

49. Poznansky MC, Evans RH, Foxall RB, Olszak IT, Piascik AH, Hartman KE, Brander C, Meyer TH, PyKett MJ, Chabner KT, Kalams SA, Rosenzweig M, Scadden DT: Efficient generation of human T cells from a tissue-engineered thymic organoid. **Nat Biotechnol** 18: 729-734, 2000

50. Rocke DM, Zasloff M, Peeper J, Cohen RB, Kaplan FS: Age and joint-specific risk of initial heterotopic ossification in patients who have fibrodysplasia ossificans progressiva. **Clin Orthop Rel Res** 301:243-248, 1994

51. Rogers DE, Osborn JE: Another approach to the AIDS epidemic. **N Engl J Med** 324: 1498-1500, 1991

52. Rosenstirn J: A contribution to the study of myositis ossificans progressiva. **Ann Surg** 68:485-520, 591-637, 1918.

53. Roush W: Protein builds second skeleton. **Science** 273:1170, 1996

54. Shafritz AB, Shore EM, Gannon FH, Zasloff MA, Taub R, Muenke M, Kaplan FS: Overexpression of an osteogenic morphogen in fibrodysplasia ossificans progressiva (FOP). **N Engl J Med** 335: 555-561, 1996

55. Shah PB, Zasloff MA, Drummond D, Kaplan FS: Spinal deformity in patients who have fibrodysplasia ossificans progressiva. **J Bone Joint Surg** 76-A:1442-1450, 1994

56. Shlomchik WD, Couzens MS, Tang CB, McNiff J, Robert ME, Liu J, Shlomchik MJ, Emerson SG: Prevention of graft versus host disease by inactivation of host antigen-presenting cells. **Science** 285: 412-415, 1999

57. Shore EM, Xu M-q, Shah PB, Janoff HB, Hahn GV, Deardorff MA, Sovinsky L, Spinner NB, Zasloff MA, Wozney MA, Kaplan FS: The human bone morphogenetic protein (BMP-4) gene: molecular structure and transcriptional regulation. **Calcif Tissue Int** 63: 221-229, 1998

58. Shore EM, Rogers JG, Smith R, Gannon FH, Delatycki M, Urtizberea JA, Triffitt J, Le Merrer M, Kaplan FS: Fibrodysplasia ossificans progressiva (Chapter 12: pp 211-236). In Econs MJ**. The Genetics of Osteoporosis and Metabolic Bone Disease.** Humana Press. Totowa, N.J., 2000

59. Smith R: Fibrodysplasia (myositis) ossificans progressiva. **Clin Orthop Rel Res** 346, 7-14, 1998

60. Stephens T, Brynner R: **Dark Remedy**: The Impact of Thalidomide And Its Revival as a Vital Medicine. Perseus Books, 208 pages, 2001

61. Van Ryn J, Pairet M: Clinical experience with cyclooxygenase-2 inhibitors**. Inflammation Res**. 48:247-254, 2000

62. Virdi AS, Shore EM, Oreffo RO, Li M, Connor JM, Smith R, Kaplan FS, Triffitt, JT: Phenotypic and molecular heterogeneity in fibrodysplasia ossificans progressiva. **Calcified Tissue Int** 65: 250-255, 1999

63. Vogel G: Stem cells: new excitement, persistent questions. **Science** 290: 1672-1674, 2000

64. Wagman RB, Kantanie SL, Kaplan FS: Should people with FOP have flu shots? In, Kantanie SL, Kaplan FS. (eds): **What is FOP? A Guidebook for Families.** Second edition. International FOP Association; Winter Springs, Florida, 1997

65. Weinreb, M, Suponitsky I, Keila S: Systemic administration of an anabolic dose of PGE2 in young rats increases the osteogenic capacity of bone marrow. **Bone** 20:521-526, 1997

66. Xu M-Q, Feldman G, Le Merrer M, Shugart YY, Glaser DL, Urtizberea JA, Fardeau M, Connor JM, Triffitt J, Smith R, Shore EM, Kaplan FS: Linkage exclusion and mutational analysis of the noggin gene in patients with fibrodysplasia ossificans progressiva. **Clin Genet** 58: 291-298, 2000

67. Zasloff MA, Rocke DM, Crofford LJ, Hahn GV, Kaplan FS: Treatment of patients who have fibrodysplasia ossificans progressiva with isotretinoin. **Clin Orthop Rel Res** 346:121-129, 1998

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, and not as a specific set of recommendations. 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 within an individual patient and his or her physician.

TABLE 1

CLASSES OF MEDICATIONS: FOP CLINICAL WORKSHOP					
CLASS I MEDICATIONS					
GENERIC	**TRADE**	**CLASS**	**PROPOSED MECHANISM OF ACTION AS IT RELATES TO FOP**	**DOSING**	**MAJOR SIDE EFFECTS**
Prednisone	**Prednisone**	Corticosteroid	Decreases lymphocyte recruitment and tissue infiltration; potent anti-inflammatory drug. Decreases inflammation, swelling and edema especially when involving throat and major joints. Do not use for flare-ups involving trunk. Should be started within 24 hours of the start 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.	2 mg/kg/d x 4 days maximum. Max dose: 60 mg qd May use longer duration with a taper for flare-ups in the submandibular region, especially those that affect breathing or swallowing	-- avascular necrosis -- cataracts-cataracts -- osteoporosis -- chronic dependency -- myopathy and somnolence -- adrenal suppression -- growth retardation
Ibuprofen	**Advil Motrin**	Non-steroidal anti-inflammatory medication (non-specific)	Anti-inflammatory and anti-angiogenic; symptomatic relief during a flare-up; Potential use in prevention by inhibiting prostaglandins	Peds: 4-10 mg/kg PO every 6 hrs as needed Adult: 200-800 mg PO every 6 hrs as needed	~ gastrointestinal bleeding -- impaired renal function
Indomethacin	**Indocin**	Non-steroidal anti-inflammatory medication (non-specific)	Anti-inflammatory and anti-angiogenic; symptomatic relief during a flare-up; Potential use in prevention by inhibiting prostaglandins.	Peds: 2-3 mg/kg/d div tid. Adult: taper dose	-- gastrointestinal bleeding ~ impaired renal function
Celecoxib	**Celebrex**	Cyclooxygenase-2 inhibitor (highly selective)	Anti-inflammatory and potent anti-angiogenic; symptomatic relief during a flare-up; Potential use in prevention by inhibiting prostaglandins	Peds: not approved Adult 100-200 mg PO bid (contraindicated in patients with allergy to sulfa drugs)	-- gastrointestinal bleeding (less than ibuprofen and indomethacin) ~ impaired renal function
Rofecoxib	**Vioxx**	Cyclooxygenase-2 inhibitor (highly selective)	Anti-inflammatory and potent anti-angiogenic; symptomatic relief during a flare-up. Potential use in prevention by inhibiting prostaglandins	Peds: not approved Adult: 12.5-25 mg PO qd, 50 mg qd x 5 days for relief of acute pain	-- gastrointestinal bleeding (less than ibuprofen and indomethacin) -- impaired renal function
CLASS II MEDICATIONS					
Montelukast	**Singulair**	Leukotriene inhibitor	Blocks inflammatory mediators, complementary action to cyclooxygenase inhibitors, potential use in prevention by inhibiting inflammatory leukotrienes	Peds: (2-5 yo) 4 mg qhs (6-14 yo) 5 mg qhs Adults: 10 mg qhs	Generally considered well-tolerated. Rarely urticaria, headache, flu-like syndrome, fatigue, abdominal pain
Cromolyn	**Gastrocrom**	Mast cell stabilizer	Reduces mast cell degranulation but poorly absorbed from GI tract.	Peds: (1-2 yo) 20 mg/kg/d div qid; (2-12 yo) 100 mg qid Adult: 200 mg qid	Generally considered well-tolerated. Rarely throat irritation, dry throat, cough, bitter taste.
CLASS III MEDICATIONS					
Thalidomide	**Thalidomide**		Anti-angiogenesis, immune modulator		
Squalamine	**None**		Anti-angiogenesis		
Noggin	**None**		Blocks action of BMP4		
VEGF-Trap	**None**		Blocks action of VEGF		

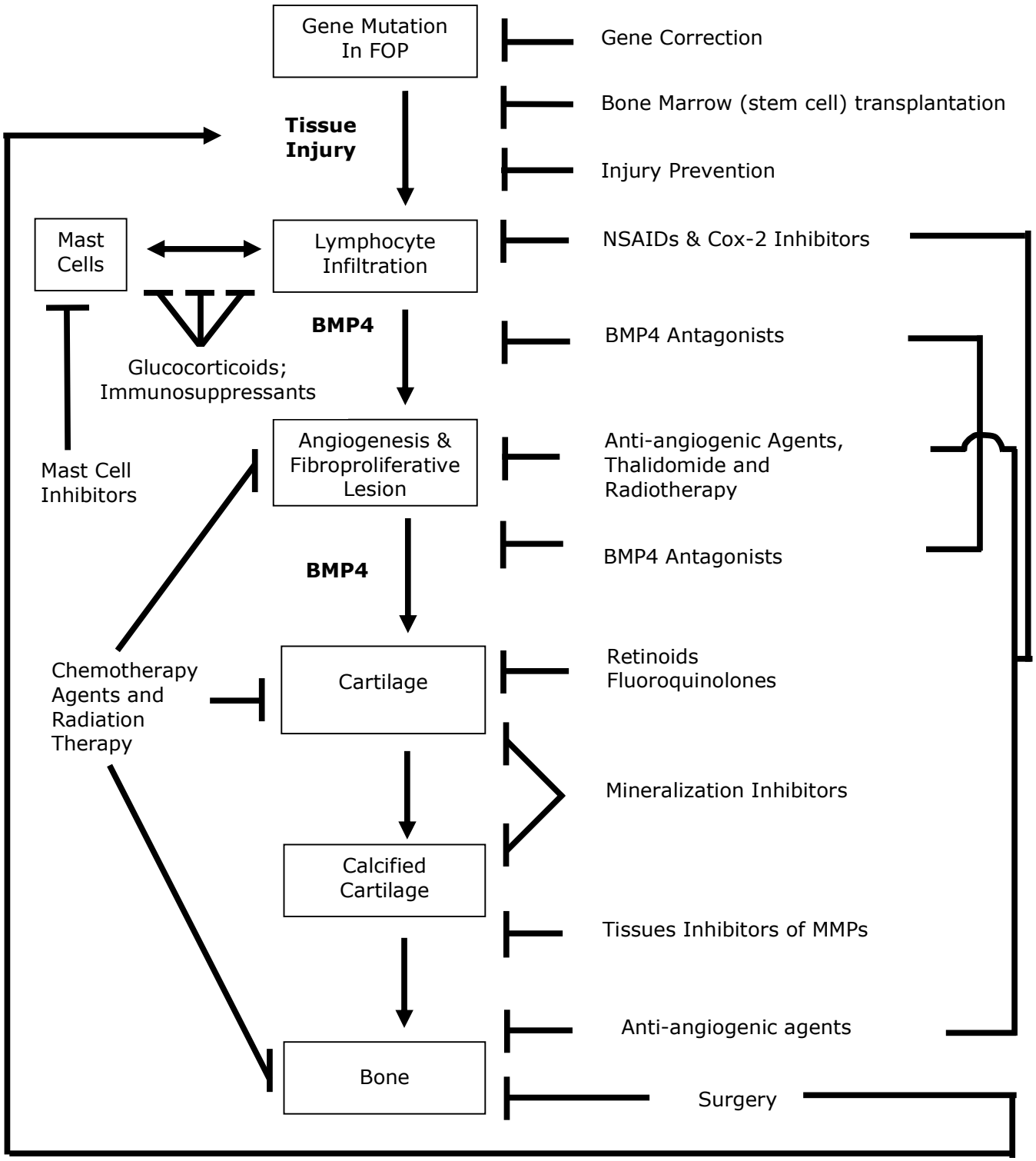
TABLE 2

COMMONLY ARISING CLINICAL SITUATIONS IN PATIENTS WITH FOP: FOP CLINICAL WORKSHOP CONSIDERATIONS	
SITUATION	**TREATMENT CONSIDERATIONS**
Head trauma (usually following falls)	~ Patient must be evaluated immediately by a physician ~ (see: Glaser DL, Rocke DM, Kaplan FS. Catastrophic falls in patients who have fibrodysplasia ossificans progressiva. **Clin Orthop Rel Res** 346:110-116, 1996)
Severe soft tissue trauma threatening use of a limb (for example, following a severe fall)	~ Apply ice intermittently, as tolerated, to injured area for 24 hours ~Consider brief course of prednisone at a dose of 2 mg/kg/day in single daily dose for 4 days only, beginning immediately after the trauma. After 4 doses of prednisone, stop. Do not repeat. If flare-up subsequently occurs, treat symptomatically as indicated below.
Flare-up (acute or ongoing) involving trunk (chest, back) or back of neck	~ Do not use steroids (prednisone) ~ Consider symptomatic treatment with a non-steroidal anti-inflammatory medication or cox-2 inhibitor and leukotriene inhibitor (montelukast) to decrease inflammation until acute or ongoing flare-ups subside
Flare-up involving (limiting movement of) a major joint of the limbs or involving movement of the jaw	~ Consider brief course of prednisone at a dose of 2 mg/kg/day in a single daily dose for 4 days only; then stop. If flare-up recurs immediately, do not repeat prednisone dose. For maximal effectiveness, prednisone should be taken within 24 hours of the start of a flare-up. ~ If the flare-up has been present for more than 24 hours, do not use prednisone. Instead consider symptomatic treatment with a non-steroidal anti-inflammatory medication or cox-2 inhibitor and leukotriene inhibitor (montelukast) to decrease inflammation and swelling until flare-up subsides.
Flare-up involving submandibular area (underneath jaw)	~ Strict avoidance of lesional manipulation or repeated palpation ~ Airway monitoring ~ Aspiration precautions ~ Nutritional support ~ Consider using prednisone for a longer term with a taper (3-4 weeks or until flare-up subsides) to decrease soft tissue swelling to this vulnerable area if airway appears threatened, or if swallowing is extremely difficult. This is one of the only situations in which a more prolonged use of corticosteroids is justified. ~ (see: Janoff HB, Zasloff MA, Kaplan FS. Submandibular swelling in patients with fibrodysplasia ossificans progressiva **Otolaryngol Head Neck Surg** 114: 599-604, 1966.
Chronic maintenance between flare-ups; possible prevention of flare-ups	~ Injury prevention ~ Presently there are no proven medical preventions for FOP flare-ups. ~ Double-blinded placebo-controlled prevention protocols with cox-2 inhibitors are being considered (see cyclo-oxygenase 2 inhibitors section of this report).

COMMONLY ARISING CLINICAL SITUATIONS IN PATIENTS WITH FOP: FOP CLINICAL WORKSHOP CONSIDERATIONS	
SITUATION	**TREATMENT CONSIDERATIONS**
General Notes for Dental Care	~ Preventive dental care is imperative for patients with FOP. Children should receive regular topical fluoride treatments. Radiographic exams (to intercept caries for early treatment) are necessary. For FOP patients with jaw fusion, fluoride rinses are helpful for prevention at any age. Chlorhexidine gluconate rinses can control gingival inflammation. Fluoride varnishes combined with chlorhexidine may be able to control incipient caries. ~ Caries must be treated in the earliest stages, if possible. For surface lesions, treatment without the use of local anesthetics would be helpful. Pain control is necessary in all patients. If the carious lesion requires an anesthetic or the tooth requires an extraction, the following must be considered: no overstretching of the jaw muscles, and no mandibular block anesthesia. Infiltration anesthesia, and intraligamentary anesthesia have been reported as successful solutions. ~ Orthodontics may be performed with caution for FOP patients. Extractions should be avoided if possible. It would be better to have some posterior crowding than to extract teeth. ~ Have your dentist or child's dentist contact Dr. Helpin or Dr. Nussbaum with any questions, especially for complex dental problems requiring more extensive treatment. ~ (See: Luchetti W, Cohen RB, Hahn GV, Rocke DM, Helpin M, Zasloff M, Kaplan FS. 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** 81:21-25,1996; and, Nussbaum BL, O'Hara I, Kaplan FS. Fibrodysplasia ossificans progressiva : Report of a case with guidelines for pediatric dental and anesthetic management. **ASDC J Dent Child 63**: 448-450, 1996.
Immunizations and flu-shots	~ (See: "Can injections cause problems?" and "Should people with FOP have flu shots?" in Section VII: (Care and Treatment) **"What Is FOP: A Guidebook for Families."** The Guidebook is available on the web at: www.ifopa.org). ~ (also see: 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 Pediatrics** 126:762-764, 1995). ~ Updated recommendations on flu shots will be made following tabulation and analysis of the recent IFOPA Flu survey.
Routine hearing evaluation	~ Suggest routine evaluation in all children with FOP . (see: Levy CE, Lash AT, Janoff HB, Kaplan FS. Conductive hearing loss in individuals with fibrodysplasia ossificans progressiva. **Am J Audiol** 8: 29-33, 1999).

FIGURE 1

HYPOTHETICAL TREATMENT SCHEMA IN FIBRODYSPLASIA OSSIFICANS PROGRESSIVA



(□) Boxes indicate known features of FOP
(→) Arrows indicate causative factors, interactions, or stage-progression
(⊣) Blunt-end lines indicate hypothetical interventions ***See Text for Details***

FIGURE 2

Self-perpetuating fall cycle in patients who have fibrodysplasia ossificans progressiva. Minor soft tissue trauma can lead to severe exacerbations of fibrodysplasia ossificans progressive with resultant heterotopic ossification and joint ankylosis. Mobility restriction from joint ankylosis severely impairs balancing mechanisms, causing instability, resulting in subsequent falls.