表1　admission FVC and survival in a hospice

low	97	30
31	112	47
51	152	34
81	198	23
pos	196	51
mi	259	6

(Del Bene ML, et al：2003より改変)

る．入力機器にもさまざまなものがあり，少しでも随意的に動かせる部位があればピックアップできるので障害に応じて使い分けていく．さらに脳波や脳血流より入力するものなども商品化されている．人工呼吸器を装着して5年以上たつとごく一部の症例（20%以下）は現在使用可能なさまざまな方法を駆使してもまったくコミュニケーションのとれないトータルロックドインとなってしまうが[1]多くの症例は10年以上たってもコミュニケーションが可能であり，社会活動が可能である．

4．呼吸筋障害

呼吸筋障害に対しては，呼吸リハビリがある程度有効であるが，進行期にはかえって呼吸筋疲労をきたすので，注意が必要である．呼吸機能検査は2，3ヵ月ごとに繰り返し，%VCが50%以下になった段階では人工呼吸器についての方針をたてるべきである．コロンビア大学が報告した余命についてのデータを提示する（**表1**）が，多くの症例では進行期には呼吸機能検査が不正確となるため，病初期からマスク式でも計測し，データをとっておくと比較できる．最近当院では鼻をする圧を測定するSniff Nasal Inspiratory Pressure（SNIP）という方法を試みているが，より末期まで計測することができ，予後予測に役立つ[2]．%VCがうまく測定できないときにはPCO_2値を参考にする．PCO_2が45 Torr以上になったら人工呼吸器の方針につき確認を開始し，50 Torr以上になったら感染症や誤嚥などで急に呼吸状態が悪化したときのために少なくともNPPVについての方針を固める．

日中の疲労感やPCO_2の上昇傾向が現れたら夜間のみNPPVを導入する．NPPVの導入にあたっては指導も含め入院で試みたほうがよいが，体制を整えれば外来でも導入できる．最初から抵抗なく使用できる人は少ないことを十分に伝えて，数分ずつから除々に慣らしていく．痰の喀出が困難な例ではカフマシーンを併用すると導入できる場合もある．

NPPVは多くの場合は排痰の援助にはなりにくく，換気効率の悪さによりNPPVだけでは長期間の延命はできない．IPPVを選択する気持ちにはなれないが，まだもう少し時間が欲しいという症例には適応になると考える．当院では最近では8割以上の症例で一時的にせよNPPVを導入している．

IPPVの選択については，長期入院施設の確保が困難な現状では在宅人工呼吸療法を原則としてお話をするが，どうしても在宅生活が望めない場合には入院先を紹介する．現実的にはQOLがある程度保てる長期入院先の確保は難渋することが多い．

ALSの緩和ケアについて

ALSの苦悩は診断時からあり，疾患の受容，進行や死への恐怖に対する精神的サポート，四肢麻痺にともなうさまざまな痛みへの対処など，緩和ケアを継続して行う．通常は十分な繰り返すインフォームド・コンセント，傾聴，消炎鎮痛薬の投与，抗不安薬，酸素投与などで対応できるが，なかには呼吸苦や疼痛の対処に難渋する場合がある．このような場合はモルヒネなどを用いて終末期に苦しませないという保証をすることが大切である．適量のオピオイドやモルヒネ（厳密にはALSに対する保険適応はない）は意識障害をきたさずに苦痛を取り除くという意味で利点がある[3]．

当院では以前よりチーム医療を実践し終末期の意思決定ができている場合には書類として携帯してもらっているが[4-6]，平成19年5月に厚生労働省より『終末期医療の決定プロセスに関するガイドライン』[7]が発表され，医療行為の中止も含め係わっているチームで検討することが謳われている．しかし，人工呼吸管理のALSを終末期というのかはチームで判断すべきとされ，ガイドラインにどの程度の法的免責力があるのかも不明であり，慎重な対応が求められる．そのほか，倫理的知識，社会福祉的知識なども必要となるが他稿を参考にされたい[8]．

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87 侵襲的人工呼吸療法を選択しない方の緩和ケア

緩和ケアとは

「緩和ケア」ときくと通常がんにおける終末期ケアを思い起こす方が多いと思う。本来緩和ケアとは「治癒を目的とした治療に反応しなくなった疾患をもつ患者に対して行われる積極的で全体的な医学的ケア。痛みや苦しみ、その他の症状、および心理的、社会的、スピリチュアルな問題の解決が最も重要な課題である。

緩和ケアの目標は、患者と家族にできる限り良好なQOLを実現させることにある。そのため緩和ケアは終末期だけでなく、もっと早い病気の患者に対しても病変の治療と並行して実施すべき多くの利点を持っている。」(厚生労働省・日本医師会　平成17年がん緩和ケアに関するマニュアルより抜粋)と解されている。そして緩和ケアの実践にあたっては次のようなことがあげられている。

(1) 生きることを尊重し、誰にも例外なく訪れる「死にゆく過程」にも敬意を払う
(2) 死を早めることも、死を遅らせることも意図しない
(3) 痛みのマネジメントと同時に、痛み以外の諸症状のマネジメントを行う
(4) 精神面でのケアやスピリチュアルな面のケアも行う
(5) 死が訪れるとしたら、その時まで積極的に生きていけるように患者を支援する
(6) 患者が病気に苦しんでいる間も、患者と死別した後も家族の苦難への対処を支援する

このように考えてくると、ALS診療においてのすべてのケアが緩和ケアであると言い換えられることに気付く。なぜならばALSにおいては病初期から症状だけでなく、告知や疾患受容など苦悩があり、経過でみられるあらゆる肉体的精神的苦痛に対応していくことが必要であるからである。その中で終末期緩和ケアはALS緩和ケアの一部でしかないが、われわれ日本の神経内科医はその点においてはすこし、しり込みがあったように思う。

日本と欧米のモルヒネの使用状況

神経内科領域ではがんを扱うことは少ないので、通常我々はモルヒネ等の麻薬（オピオイド）を使いなれていない。また、痛みが強い患者さんに対してモルヒネを使用するという可能性は考えても、呼吸抑制が副作用として考えられるモルヒネを、呼吸が弱くなっているがために、苦しんでいる終末期のALSの患者さんに使用するということに、非常に違和感を覚えたのは私だけではないと思う。

一方、日本は人工呼吸器を選択するALSの患者さんが世界一多い国ではあるが、いまだ約8割の方が、人工呼吸器を選択することなく、亡くなっていかれる。その方々すべてがモルヒネが必要な状態となるわけではない。ただし、約50%の方が呼吸筋麻痺から来る呼吸苦を訴えるといわれており(O´Brien T 1992, Oliver D 1993, Saunders C 1981)、一方米国のホスピスの現況ではモルヒネを用いることによって81%の患者で呼吸苦を取り除くことができると報告されている(O´Brien T 1992)。

アメリカ神経学会の提唱しているALSの終末期ケアでもモルヒネの使用が推奨されている（The ALS Practice Parameters Task Force Neurology 1999）が、欧米では終末期をホスピス施設または在宅ホスピスで迎える方がほとんどなので、がんの方に対してと同様に使用されやすい環境にある。衆知のように日本では神経難病はホスピスの対象疾患として認められておらず、多くの患者さんは通院中の病院（おそらくは神経内科）で最後を迎えられている。

そもそも日本のがんにおけるモルヒネの使用においても1日当たりのモルヒネ消費量は、カナダの10分の1、アメリカの7分の1と、極端に少ない状況にある。ましてや、がん以外の疾患に対しての使用はもっと少ないと思われる。日本におけるALSに対

表1　モルヒネの種類

		製品例	剤型	非経口投与	量の調節	半減期(hr)	投与回数	塩酸モルヒネ換算
短時間型	塩酸モルヒネ	塩酸モルヒネ末	散剤	◎	◎		6回	1
		塩酸モルヒネ錠	錠剤	△	△	1.9±0.5	6回	1
		塩酸モルヒネ注	注射	◎	◎		持続	1
		オプソ液	液剤	◎	◎		6回	1
		アンペック坐薬	坐剤	○	○	4.2(10mg)	4回	1
長時間型	硫酸モルヒネ	MSコンチン	徐放	×	×	4.91±1.9(20mg)	2回	1
		カディアンカプセル	カプセル	○	○	9.2	1回	1
		カディアンスティック	散剤	○	○	9.2	1回	1
		モルペス細粒	散剤	◎	◎		2回	1
	フェンタニール	デュロテップパッチ	貼付剤	◎	△	34.6	3日に1回	約20-50
	塩酸オキシコドン	オキシコンチン	錠剤	×	×	5.7±1.1(20mg)	2回	1.5

するモルヒネ使用についてのデータはないが、それほど多くないと考えられる。これは保険適応になっていないことも大きく影響しているが、使い慣れていないということも理由として挙げられる。

当院でも全例ではないが、進行期に長いこと呼吸苦を訴え、NIPPVや鎮静投与、抗不安薬、抗うつ薬等、従来用いていた方法を用いても、なかなか緩和できない症例を経験していた。苦渋の選択で人工呼吸器を選択しないと決められた患者さんが終末期になってまで苦しい思いをするのをなんとかできないかと思っていた。海外からは、がん疼痛に用いるよりも少量で副作用なく呼吸苦をとれる、中には年余にわたって投与する患者もいると報告されており、試みてみる価値があると考えた。

しかし、欧米とは使用できるモルヒネの種類や量も異なることも考えられ、どのような場合に本当に有効であるのか、がんの場合の使用方法とどのように異なるのか、呼吸抑制などの副作用のでかたはどうなのかなど、多くの点で、検証する必要があると考えた。

北里大学におけるALS終末期におけるモルヒネの使用

モルヒネの選択とプロトコールの作成

使用にあたり、まずどのような種類のモルヒネを用いるべきかを検討した。モルヒネにも多くの種類があり、表1のように短時間型の塩酸モルヒネ、長時間型の硫酸モルヒネ、フェンタニルなどがあり、投与形態としても錠剤、散剤、液剤、貼付剤、注射薬などがある。これまでの報告から呼吸苦にはがん

コツ　モルヒネの選択

ALSにモルヒネを使用する場合、多くの症例ではがん比べて非常に少量ですむ。投与経路として、経口投与が困難な症例が多いので、経管投与できる薬剤が望ましい。PEGの場合はある程度太い径の場合が多いが、それでも薬剤によっては詰まることがあり、経鼻経管では特に詰まりやすい。そのため、できるだけ粒子の細かい薬剤を使用することが必要となる。

塩酸モルヒネの場合は散剤も粒子が細かく使用しやすいが、水剤のオプソも用いやすい。長時間型を用いたい場合、現在日本で市販されている硫酸モルヒネのうち粒子が細かいものを選択して用いているが、カディアンでも20Frのチューブが詰まったことがあり、現在はモルペスを用いている。パシーフも粒子が細かいときいているが、脱カプセルで用いることになるため、まだ使用経験はない。また、オキシコンチンは徐では よく用いられるが、徐放剤は錠剤しかなかったので、ALSでは用いにくく使用経験がなかった（現在は散剤がでました）。

貼付剤は使用しやすいが、1枚が塩酸モルヒネ換算で50～60mgと大量となってしまい、量の調節が困難なため用いていない。どうしても貼付剤を用いなければならないときには皮膚にオプサイトなどの皮膚保護剤をはり、皮膚に密着させる貼付剤の範囲を調節することにより容量コントロールすることができる。しかし、大変高価な薬であり、無駄が多い。細かく切り離せる添付剤が発売予定ということなので、将来的には使用しやすくなるかもしれない。

表2　導入法（プロトコール）

①有効1回量の決定
塩酸モルヒネ散 2.5mgを頓服で使用．10mg/回まで増量可。2時間以上あけて反復投与可

↓

②初時間作用型オピオイドの1日必要量の決定
有効1回量×1日の頓服投与回数

↓

③10mg/日を越える場合，長時間作用型オピオイドに変更
硫酸モルヒネ(モルペス®)10mg～

↓

④症状が出たらレスキュードーズとして短時間作用型モルヒネ製剤を追加
（内服：1日基本量の1/6～1/10，持続注射：1/24）
追加分を翌日の基本量に上乗せする。

↓

⑤必要に応じて塩酸モルヒネ持続注射（静注・皮下注）に変更
（その場合，投与量は1日経口投与量の1/2とする。）

の疼痛と異なった作用機序があり，がんで用いられているオピオイドが必ずしも呼吸苦に有効とは限らないことがわかった。

肺がんの経験等より，呼吸苦には塩酸モルヒネ，硫酸モルヒネが用いられており，当院でもそれらの薬剤を用いることにした。また，多くの症例では終末期には経口摂取が困難になっていることが多く，経管栄養でも使用しやすい形態を選択する必要があったため，散剤，液剤，などから選択した。注射薬は継続的な効果を得るためには持続皮下注射などを用いるようになるため，在宅で生活する患者の抵抗感も考え，経口薬の投与を選択した。

以上の検討の結果，表2のように投与のプロトコールを作成した。

適応患者の選択基準の設定

前述のようにすべての患者でモルヒネが必要となるわけではない。最初にモルヒネを使用する対象としたのは以下のような症例である。

(1) 十分なインフォームドコンセントのもと，熟慮の上，侵襲的人工呼吸療法を選択しないという決定を行ったALS症例
(2) 呼吸障害がある程度進行した状態であり，終末期で入院され，呼吸苦の訴えが強い
(3) 抗不安薬，抗うつ薬，向精神薬や少量のO₂吸入やNPPVでは改善されない呼吸困難
(4) 特にオピオイドの使用が問題となるような腎機能障害等の合併症がない
(5) 副作用などの十分なインフォームドコンセントを行い，本人および家族が十分に納得した上でオピオイドによる緩和治療を希望する場合

実際の使用例の経験

平成17年1月から平成18年4月に北里大学東病院神経内科に入院した進行期（終末期）ALS患者16例中，上記適応基準に該当した症例は6例（37.5%，男性3例，女性3例）いらした。上記プロトコールにそってモルヒネを使用したが，表3のごとく，意識レベルを低下させることなく，呼吸苦が改善し，中には動脈血液ガスでも改善がみられた症例もあった。また，副作用も下剤で対応できる便秘程度であり，今回用いた量では呼吸抑制などの心配された副作用はきたさなかった。

以上の経験より，従来のALS終末期における呼吸苦緩和方法では意識レベルを低下させやすいのに比して，少量のモルヒネ投与は意識レベルの低下や呼吸状態を悪化させず呼吸苦や不安が緩和できるところが最大のメリットであった。十分にコミュニケーションがとれる状態で苦痛が緩和するため，退院して在宅生活が可能となったり，家族との有意義な時間を確保できた。

ALSの呼吸苦とモルヒネの作用

ALSにおいてはさまざまな理由で呼吸苦をきたす。通常は酸素が足りない状態になると息苦しさとして自覚するが，たとえ動脈血ガスにて異常がなくとも，つまり酸素が足りない状態や，二酸化炭素がふえてしまっている状態までいってなくとも呼吸が苦しいと感じることがある。これには様々な理由があり，痰ががらんだり，のみ込みが上手くできない状態になっているときなど，唾液がたまこんで，うまく咳き込めないために，苦しいと感じたり，呼吸の機能としての換気は十分にできていたとしても，深く息を吸えないということが呼吸苦として感じたりする。血液ガスデータでなく，呼吸の状態をよく観察するべきである。

モルヒネの呼吸困難改善のメカニズムとしては，呼吸中枢の感受性を低下させることによって苦しさを感じにくくする作用や，呼吸数減少による酸素消費量の減少，鎮咳作用，中枢性の鎮静作用などがあげられている。ALSにおいてもこれらの作用がお互いに影響しあって，結果的に楽になると考えられる。

表3　6症例のまとめ

①使用オピオイド	塩酸モルヒネまたは硫酸モルヒネ
②剤型	散剤または粒カプセルによる経鼠
③投与方法	経PEG
④有効一回量	2～5mg（平均3.6mg）
⑤有効一日量	8mg～90mg（平均34.6mg）
⑥平均投与期間	平均41.8日，1例は4ヶ月以上継続治療中
⑦NPPV導入	全例
⑧血中CO2濃度	1例軽減，3例横ばい，2例軽増
⑨意識レベル	覚気（+）だが1ほぼ清明，2例は多幸的
⑩呼吸苦の軽減	全例で軽減
⑪副作用	軽度の便秘，1は嘔のみ

ALSにおけるモルヒネの使用と保険適応

ALSにおけるモルヒネの使用は海外では標準的な使用方法となっているが，日本においてはALSの呼吸苦に対するモルヒネの使用は保険適応にはなっておらず，ALSでモルヒネの保険適応を考えるとすると疼痛に対して塩酸モルヒネが適応になるだけである。塩酸モルヒネは短時間しか有効でないため，持続的効果を期待するとなると持続皮下注射または持続静脈注射で使用することになる。

今回使用したような長時間型の経口（もしくは経管）モルヒネは，がんの疼痛に対してのみ保険適応となっており，がん以外の苦痛の緩和には厳密には保険は適応にならない。使用する際には必要理由などを詳細に記して保険請求するが，保険で認められない場合もありうる。

現在，自費請求と保険請求を同時に行うことはできないため，他の医療費を保険請求するとなると，保険適応とならないモルヒネの使用については病院負担となってしまう。経済的理由のみならず，保険適応外使用における副作用発生時の責任の問題などもあり病院によっては保険適応外の使用を認めないところもある。

モルヒネの使用と患者の明示の意思

前述のように，モルヒネは必ずしも全例に必要というわけではないので，どのような症例に対して使用するのか，よく検討する必要がある。苦しみを感じる感受性は人によって異なり，状況によっても異なる。薬物療法以前に試みるべき他の方法がないのかも注意深く検討する必要がある。また，日本においてまだ一般的治療となっていない現状では，保険適応の問題や副作用がありうることなど，モルヒネを使用することによるデメリットもよく説明し，理解納得を得た上で，患者自ら使用したいという明示の意思があってはじめて開始すべきと考える。

ALSの場合，呼吸苦の究極の緩和は侵襲的人工呼吸器の装着であるが，たとえ，当初は装着を断念していても，気持ちが変わる場合もありうる。侵襲的人工呼吸器装着にたいする十分な検討がないままに安易にモルヒネ使用にいたることも問題であるし，たとえ，いったん緩和ケアとしてモルヒネの使用を始めたとしても，いつでも装着すると変更してもよいのだということを医療側も，患者側も理解して治療を進めるべきである。

最終末期のモルヒネの使用

これまでの経験では，使用時期は呼吸苦を感じた早期から使用しても少量で増量することなく長期間使用できており，あまり使用することに躊躇する必要はないと考える。しかし，死の数日前からはこれまでの使用量では呼吸苦を緩和しきれなくなり，増量を余儀なくされることがある。これはあくまで呼吸苦を緩和するために行う増量であり，決して安易に死を早めるために行われる医療行為ではない。

がんにおける終末期緩和ケアの考え方と共通のものであり，緩和ケアにおいては死を早めることも，遅くすることも意図して行われるものではない。その時々で必要十分な苦痛の緩和を行うべきで，モルヒネを使用もしくは増量することを躊躇すべきではない。

実際に使用してみて，モルヒネを用いた緩和ケアはより良い終末期を迎える一策であると感じている。安易に使用すべきではないが，同時に躊躇すべきでもない。

患者のQOL向上に役立つか，役立たないのかという観点から判断すべきであろう。ひとりひとりの人間が最後まで，できるだけ苦痛なく生き抜くために必要な治療であるならば，がんと同様にALSの緩和ケアとしても保険適応にすべきである。

（荻野　美恵子）

THE MEDICAL MANAGEMENT OF FIBRODYSPLASIA OSSIFICANS PROGRESSIVA: CURRENT TREATMENT CONSIDERATIONS

The International Clinical Consortium
on
Fibrodysplasia Ossificans Progressiva[1]

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[1]See Section **X** (pages 71-85) for Complete Author Listing.

ABSTRACT

Fibrodysplasia ossificans progressiva (FOP) is a rare and disabling genetic condition characterized by congenital malformations of the great toes and progressive heterotopic ossification (HO) in specific anatomic patterns. FOP is the most catastrophic disorder of HO in humans. Flare-ups are episodic; immobility is cumulative.

Recently, a recurrent mutation in activin receptor IA/activin-like kinase-2 (ACVR1/ALK2), a bone morphogenetic protein (BMP) type I receptor, was discovered in all sporadic and familial cases of classic FOP. The discovery of the FOP gene establishes a critical milestone in understanding FOP, reveals a highly conserved therapeutic target in the BMP signaling pathway, and propels approaches for developing novel inhibitors of ACVR1/ALK2-mediated BMP signaling. While effective therapies for FOP will likely be based on interventions that block overactive ACVR1/ALK2 signaling, present management is focused on early diagnosis, assiduous avoidance of iatrogenic harm, symptomatic amelioration of painful flare-ups, and optimization of residual function.

Here, we briefly review the clinical and basic science background of FOP, the scientific basis for the use of various medications, special medical considerations, and guidelines for the symptomatic relief of FOP based upon currently available medications and therapies. This report is not intended to present a specific approach for managing the symptoms of FOP, but rather is intended to present a view, statement, or opinion of the authors which may be helpful to others who face similar challenges.

Further advances in therapeutics await the elucidation of disease mechanisms at the molecular and cellular level, the refinement of genetically-based animal models for drug testing, and the commencement of rigorous clinical trials to assess novel and emerging treatment and prevention strategies.

I. THE CLINICAL AND BASIC SCIENCE BACKGROUND OF FOP

A. Introduction

Here, we provide a brief summary of the clinical and basic science background of FOP in order to place the treatment guidelines that follow into a clinical and scientific context (Kaplan et al., 2005). Detailed references are provided for each subsection in REFERENCES (Section IX). Comprehensive clinical reviews of FOP are available (McKusick, 1972; Connor & Evans, 1982; Smith, 1998; Kaplan et al., 2002; Kaplan et al., 2005; Kaplan et al., 2006).

B. Classic Clinical Features of FOP

Two clinical features define classic FOP: malformations of the great toes and progressive heterotopic ossification. Individuals with FOP appear normal at birth except for characteristic malformations of the great toes which are present in all classically affected individuals. During the first decade of life, most children with FOP develop episodic, painful inflammatory soft tissue swellings (or flare-ups). While some flare-ups regress spontaneously, most transform soft connective tissues including aponeuroses, fascia, ligaments, tendons, and skeletal muscles into mature bone. Ribbons, sheets, and plates of heterotopic bone replace skeletal muscles and connective tissues through a process of endochondral ossification that leads to an armament-like encasement of bone and permanent immobility. Minor trauma such as intramuscular immunizations, mandibular blocks for dental work, muscle fatigue, blunt muscle trauma from bumps, bruises, falls, or influenza-like viral illnesses can trigger painful new flare-ups of FOP leading to progressive heterotopic ossification (Reviewed in Kaplan et al., 2006). Attempts to surgically remove heterotopic bone risks provoking explosive and painful new bone growth.

Heterotopic ossification in FOP progresses in characteristic anatomic and temporal patterns that mimic the patterns of normal embryonic skeletal formation. Heterotopic ossification typically is first seen in the dorsal, axial, cranial, and proximal regions of the body and later seen in the ventral, appendicular, caudal, and distal regions (Cohen et al., 1993). Several skeletal muscles including the diaphragm, tongue, and extra-ocular muscles are spared from FOP. Cardiac muscle and smooth muscle are spared from heterotopic ossification.

Bone formation in FOP is episodic, but disability is cumulative (Rocke et al., 1994). Most patients with FOP are confined to a wheelchair by the third decade of life, and require lifelong assistance in performing activities of daily living. Severe weight loss may result following ankylosis of the jaw. Pneumonia or right-sided heart failure may complicate rigid fixation of the chest wall. The severe disability of FOP results in low reproductive fitness, and fewer than ten multigenerational families are known worldwide. The median age of survival is approximately 41 years, and death often results from complications of thoracic insufficiency syndrome (Kaplan & Glaser, 2005).

C. Other Skeletal Anomalies in FOP

While malformation of the great toes is characteristic of FOP, other developmental anomalies are frequently observed particularly in the thumbs and cervical spine. Stiffness of the neck is an early finding in most patients and can precede the appearance of heterotopic ossification at that site. Characteristic

anomalies of the cervical spine include large posterior elements, tall narrow vertebral bodies, and fusion of the facet joints between C2 and C7. Although the cervical spine often becomes ankylosed early in life, any minimal residual movement may eventually result in painful arthritic symptoms (Schaffer et al., 2005).

Other skeletal anomalies associated with FOP include short malformed thumbs, clinodactyly, short broad femoral necks, and proximal medial tibial osteochondromas (Deirmengian et al., 2008).

D. Radiographic Features of FOP

Radiographic and bone scan findings suggest normal modeling and remodeling of the heterotopic skeleton (Kaplan et al., 1994). Bone scans are abnormal before HO can be detected by conventional radiographs. Computed tomography and magnetic resonance imaging of early lesions have been described. While these evaluation methods are generally superfluous from a diagnostic standpoint, they can provide a useful and three-dimensional perspective of the disease process (Reinig et al., 1986). The definitive diagnosis of FOP can be made by simple clinical evaluation that associates rapidly appearing soft tissue lesions with malformations of the great toes (Mahboubi et al., 2001; Kaplan et al., 2005).

E. Histopathology of FOP Lesions

The histopathology of FOP lesions has been well described (Kaplan et al., 1993; Gannon et al., 1998; Hegyi et al., 2003; Pignolo et al., 2005). Early FOP lesions contain an intense mononuclear and perivascular infiltration of monocytes, macrophages, mast cells, B-cells and T-cells. The precise role of these cells in the evolution of FOP flare-ups is unknown although focal inflammation from any cause is a known trigger of disease activity. Subsequent migration of mononuclear inflammatory cells into affected muscle precedes widespread death of skeletal muscle, a process that precedes the formation of an heterotopic endochondral anlagen, and may be mistaken for lymphoma.

Following a rapid and destructive inflammatory stage, there is an intense fibroproliferative reaction associated with robust angiogenesis and neovascularity. Early fibroproliferative lesions are histologically indistinguishable from aggressive juvenile fibromatosis. As lesions mature, fibroproliferative tissue undergoes an avascular condensation into cartilage followed by a revascularization stage with osteogenesis in a characteristic process of endochondral ossification. The resultant new ossicle of heterotopic bone appears histologically normal with mature lamellar bone and often contains marrow elements.

Mast cells have been identified at every histological stage of FOP lesions, and are found in much greater abundance compared with normal skeletal muscle and nonlesional FOP muscle. In fact, during the intense fibroproliferative stage of the lesion, mast cells are found at a density much higher than in any other inflammatory myopathy (Gannon et al., 2001).

All stages of histological development are present in an active FOP lesion, indicating that different regions within the lesion mature at different rates. Although heterotopic bone formation in FOP is similar in some respects to bone formation in embryonic skeletal development and postnatal fracture healing, an important difference is the lack of inflammation in primary skeletal formation.

F. Laboratory Findings in FOP

Routine biochemical evaluations of bone mineral metabolism are usually normal, although the serum alkaline phosphatase activity and the erythrocyte sedimentation rate may be increased, especially during disease flare-ups (Lutwak, 1964). Urinary basic fibroblast growth factor levels may be elevated during disease flare-ups coinciding with the pre-osseous angiogenic phase of early fibroproliferative lesions (Kaplan et al., 1998).

G. The Immune System & FOP

Mounting evidence from all levels of investigation suggests involvement of the inflammatory component of the immune system in FOP. The presence of macrophages, lymphocytes and mast cells in early FOP lesions, macrophage and lymphocyte-associated death of skeletal muscle, flare-ups following viral infections, the intermittent timing of flare-ups, and the beneficial response of early flare-ups to corticosteroids support involvement of the innate immune system in the pathogenesis of FOP lesions (Lanchoney et al., 1995; Kaplan et al., 2005; Kaplan et al., 2007). For further detailed discussion of this important topic, see Section II. H. Bone Marrow Transplantation.

H. Misdiagnosis of FOP

FOP is commonly misdiagnosed as aggressive juvenile fibromatosis, lymphedema, or soft tissue sarcoma. Clinicians often fail to associate the rapidly developing soft tissue swellings that appear on the head, neck, and upper back with the malformed great toes. The misdiagnosis of FOP approaches 90 per cent of affected individuals worldwide (Kitterman et al., 2005). The correct diagnosis of FOP can be made clinically even before radiographic evidence of heterotopic ossification is seen if soft tissues lesions are associated with symmetrical malformations of the great toes. Children often undergo unnecessary and harmful diagnostic biopsies that exacerbate the progression of the condition (Zaghloul et al., 2008). This can be particularly dangerous at any anatomic site, but especially so in the neck, back, or jaw where asymmetric HO can lead to rapidly progressive spinal deformity, exacerbation of thoracic insufficiency syndrome, or rapid ankylosis of the temporomandibular joints. The high rate of misdiagnosis of FOP may be due, at least in part, to the inadequate descriptions of FOP in most textbooks of medicine, pediatrics, oncology and podiatry.

I. Epidemiologic, Genetic & Environmental Factors in FOP

FOP is rare with a worldwide prevalence of approximately one in two million individuals. There is no ethnic, racial, gender, or geographic predisposition (Shore et al., 2005). Most cases arise as a result of a spontaneous new mutation. A paternal age effect has been reported (Rogers & Chase, 1979). When observed, genetic transmission is autosomal dominant and can be inherited from either mothers or fathers (Kaplan et al., 1993). Maternal mosaicism may exist (Janoff et al., 1996). Fewer than ten small multigenerational families are known worldwide (Shore et al., 2005). Phenotypic heterogeneity is observed (Janoff et al., 1995; Virdi et al., 1999).

Both genetic and environmental factors affect the phenotype of FOP. A study of three pairs of monozygotic twins with FOP found that within each pair, congenital toe malformations were identical. However, postnatal heterotopic ossification varied greatly depending on life history and environmental exposure to viral illnesses and to soft tissue trauma. Genetic determinants strongly influence disease

phenotype during prenatal development while environmental factors strongly influence postnatal progression of heterotopic ossification (Hebela et al., 2005).

J. FOP & the BMP Signaling Pathway

The classic and consistent FOP phenotype of great toe malformations and progressive heterotopic endochondral ossification suggested that the primary molecular pathology might involve the bone morphogenetic protein (BMP) signaling pathway (Kaplan et al., 1990). A number of seminal discoveries provided evidence of profound dysregulation of the BMP signaling pathway in cells from FOP patients (Shafritz et al., 1996; Roush, 1996; Gannon et al., 1997; Ahn et al., 2003; Glaser et al., 2003; Hegyi et al., 2003; Serrano de la Peña et al., 2005; Fiori et al., 2006; Shore et al., 2006; Fukada et al., 2007; Kaplan et al., 2007; O'Connell et al., 2007; Shen et al., 2007; Billings et al., 2008).

K. The FOP Gene

In order to identify the chromosomal locus for the FOP gene, a conservative genome-wide linkage analysis was conducted using a subset of five families with the most stringent and unambiguous features of FOP. This approach identified linkage of FOP to chromosome 2q23-24. The gene encoding activin receptor type IA/activin-like kinase 2 (ACVR1/ALK2), a BMP type I receptor, was identified in the linkage interval. DNA sequencing of the ACVR1/ALK2 gene determined that a recurrent heterozygous missense mutation in the glycine-serine (GS) activation domain (c.617G>A;R206H) occurs in all sporadic or familial classically affected individuals (Shore et al., 2006; Couzin, 2006; Kaplan, 2006; Kaplan et al., 2007). Recently, additional mutations have been identified in the GS-domain and kinase domain of ACVR1 in individuals with atypical forms of FOP (Furuya et al., 2008; Kaplan et al., 2008). Noggin mutations have been reported but are erroneous (Xu M., et al., 2000).

L. Protein Modeling of the FOP Mutation

Protein homology modeling of the mutated receptor predicts destabilization of the glycine-serine (GS) activation domain, consistent with an overactive BMP signaling pathway as the underlying cause of the ectopic chondrogenesis, osteogenesis, and joint fusions seen in FOP (Shore et al., 2006; Groppe et al. 2007). The identified mutation is consistent with previous findings of an overactive BMP signaling pathway in FOP cells and provides a rational basis for understanding both the postnatal heterotopic ossification and the congenital skeletal malformations that are ignominious signatures of this devastating disease. Models of protein structure are being developed to understand both inter-and intramolecular interactions of the mutant receptor (Groppe et al., 2007).

The GS domain of all BMP type I receptors is a critical site for binding and activation of pathway-specific Smad signaling proteins and is a binding site of FKBP12, an inhibitory protein that prevents uninhibited low-level constitutive activation of the BMP type I receptor in the absence of ligand (Wang et al., 1996; Chen et al., 1997). FKBP12 also recruits a Smad – Smurf ubiquitin ligase complex that regulates the concentration of the receptor at the membrane (Yamaguchi et al., 2006). Leaky activation of BMP signaling and accumulation of BMP type I receptors at the cell membrane in FOP cells, supports aberrant association with FKBP12 in FOP (reviewed in Kaplan et al., 2007). One possibility is that FKBP12 interactions with the GS domain may be altered, leading to promiscuous ACVR1/ALK2 activity (Kaplan et al., 2007). Preliminary data strongly support this hypothesis (Shen et al., 2007). Exactly how the R206H mutation in ACVR1/ALK2 specifically perturbs BMP signaling in FOP is presently unknown but

could involve dysregulation of BMP receptor oligomerization, internalization, degradation and/or intensity and duration of downstream signaling. This is presently the subject of intense investigation.

M. Genetic Testing & FOP

Definitive genetic testing of FOP is now available prior to the appearance of heterotopic ossification. Clinical suspicion of FOP early in life on the basis of malformed great toes can lead to early clinical diagnosis, confirmatory diagnostic genetic testing (if appropriate), and the avoidance of harmful diagnostic and treatment procedures. Clinicians should be aware of the early diagnostic features of FOP which are congenital malformation of the great toes and episodic soft tissue swelling even before the appearance of heterotopic ossification. This awareness should prompt genetic consultation and testing (if appropriate) and the institution of assiduous precautions to prevent iatrogenic harm (Kaplan et al., 2008). At the present time, genetic testing is available on a clinical and research basis at several laboratories. Please contact the corresponding author for more information.

N. Animal Models of FOP

Animal models of FOP will be important in deciphering the pathophysiology of FOP and in testing possible therapies. Laboratory-generated animal models with some features of FOP have provided the opportunity to better understand the biology of BMP-associated heterotopic ossification and to study the effectiveness and safety of currently available and emerging therapies (Olmsted et al., 1998; Glaser et al., 2003; Kan et al., 2004; Kaplan et al., 2005; Fukada et al., 2006). Development of a knock-in mouse model carrying the classic FOP disease-causing mutation in ACVR1/ALK2 will be critical in establishing specificity of treatment for FOP as well as investigating many previously unexplored aspects of the condition. Such a genetically engineered knock-in mouse is presently being developed.

O. Challenges of Therapeutic Assessment in FOP

Flare-ups of FOP are sporadic and unpredictable, and there is great individual variability in the rate of disease progression. 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 characteristic anatomic patterning has been described. The rarity of FOP 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 (Rosenstirn, 1918):

> *"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 as they did when they were written nearly a century ago. Presently, there is no proven effective prevention or treatment for FOP. With the discovery of the FOP gene and emerging understanding of the pathology and molecular genetics of FOP, new pharmacologic strategies will emerge to definitively treat FOP (Kaplan et al., 2007; Kaplan et al., 2008; Yu et al., 2008). Presently, 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 (Hellman & Hellman, 1991; Passaman; 1991; Miller & Rosenstein, 2003; Auerbach et al., 2007). Although such studies would be 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.

In the next section of this report, we will review the major classes of medications that have been used (and that are being used) to manage symptoms in patients who have FOP, and we will provide a perspective on indications and contraindications for the use of such medications until more specific disease-modifying medication and therapies are available.

II. THE PATHOLOGIC AND PATHOPHYSIOLOGIC-BASED TREATMENT 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.

A. Introduction

The ultimate treatment of FOP will likely be based on integrated knowledge of the cellular and molecular pathophysiology of the condition. An abbreviated outline of our current knowledge is presented in Figure 1. Several recent reviews of treatment in FOP provide general background references (Glaser & Kaplan, 2005; Kaplan et al., 2008), but interested clinicians are guided to this text for the most recent review of symptomatic treatments.

B. Corticosteroids

The rational use of corticosteroids early in the course of an FOP flare-up is based primarily on its potent anti-inflammatory effects (Rhen & Cidlowski, 2005). Widespread favorable anecdotal reports from the FOP community suggest that a brief 4-day course of high-dose corticosteroids, begun within the first 24 hours of a flare-up, may help reduce the intense inflammation 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
- The jaw
- The submandibular area

Corticosteroids should not generally be used for the symptomatic treatment of flare-ups involving the back, neck, or trunk due to the long duration and recurring nature of these flare-ups, and the difficulty in assessing the true onset of such flare-ups. On rare occasions, a brief course of corticosteroids may be used to break the cycle of recurrent flare-ups often seen in early childhood. However, the utility of this approach is not widely accepted, as flare-ups tend to recur rapidly following cessation of corticosteroid therapy.

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 corticosteroids is dependent upon body weight. A typical dose of prednisone is 2 mg/kg/day, administered as a single daily dose for no more than 4 days (Table 1).

Alternatively, high dose intravenous corticosteroid pulse therapy may be considered, but must be performed with an inpatient hospitalization to monitor for potentially dangerous side-effects of hypertension (Table 1). When prednisone is discontinued, a non-steroidal anti-inflammatory medication or cox-2 inhibitor (in conjunction with a leukotriene inhibitor) may be used symptomatically for the duration of the flare-up (Table 1). Corticosteroids should not be used for the long-term chronic treatment of FOP as chronic dependence and other steroid-associated side-effects will likely result.

Corticosteroids are an important component in the management of a submandibular flare-up of FOP. 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 (Janoff et al., 1996).

While patients are encouraged to contact their physician at the earliest sign of a flare-up, many find it comforting to have a supply of prednisone on hand at home in case of an emergency. This "pill in the pocket" approach has been feasible and safe with a monitored reduction in emergency room and hospital visits.

C. Mast Cell Inhibitors

Among the most typical features of FOP flare-ups are the intense muscle edema, fibroproliferation, and angiogenesis characteristic of early pre-osseous 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 and their mediators 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 not terminally differentiated 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 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 (Kaplan, 2002).

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 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 microscopically unless

special stains are used to detect them. Mast cells are stimulated by a myriad of external and internal stimuli 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 (Kaplan, 2002).

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 (Gannon et al., 2001).

The findings of this 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 (Gannon et al., 2001).

The following hypothesis was developed based on observations and experimental data in the mast cell study:

> Tissue injury in patients with FOP leads to macrophage, mast cell, and lymphocyte migration into normally appearing skeletal muscle. 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. Eventually, transforming growth factor beta, released by mast cells and connective tissue progenitor cells limits the lymphocytic recruitment and migration and thus the size and extent of the expanding lesion, while endogenous overactivity of ACVR1/ALK2 in the core of the fibroproliferative lesion drives the 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 model that is 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.

Mast cells, macrophages, 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 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 (Simmons, 2004). The optimal use of these

medications and their potential efficacy in FOP is presently unknown. However, general guidelines for their use are provided in Table 1.

D. Cyclo-oxygenase 2 inhibitors & NSAIDs

Selective cyclo-oxygenase-2 (cox-2) inhibitors and non-steroidal anti-inflammatory medications have important implications for the management of FOP symptoms.

The body produces two types of prostaglandins: "physiological" prostaglandins and "inflammatory" prostaglandins. Physiological prostaglandins are normally produced in many of the body's tissues and serve to 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 tissue injury and repair. Traditional non-steroidal anti-inflammatory drugs such as aspirin, ibuprofen and indomethacin inhibit the formation of both the physiological and inflammatory prostaglandins. The selective cyclo-oxygenase-2 (cox-2) inhibitors primarily inhibit the inflammatory prostaglandins and leave most, but not all, of the physiological prostaglandins relatively intact (Katori & Majima, 2000; Van Ryn & Pairet, 2000).

Inflammatory prostaglandins are potent co-stimulatory molecules along with BMPs in the induction of heterotopic bone. Studies in the orthopaedic literature have shown that lowering inflammatory prostaglandin levels in experimental animals dramatically raises the threshold for heterotopic ossification, thus, making it more difficult for heterotopic bone to form. Animals pretreated with inhibitors of prostaglandin synthesis fail to form heterotopic bone following intramuscular injections of BMP-containing demineralized bone matrix (DiCesare et al., 1991). In contrast, animals treated with prostaglandin inhibitors co-incident with or following an injection of demineralized bone matrix still form heterotopic bone.

These data suggest, that in order for inhibitors of prostaglandin synthesis to be truly effective in preventing heterotopic ossification, the medication must be "in the system" (in other words circulating in the blood at therapeutic levels) before a bone-induction signal occurs. In addition to their potent anti-inflammatory properties, non-steroidal anti-inflammatory drugs (NSAIDs) and cox-2 inhibitors have potent anti-angiogenic properties especially at high dosages, a feature that makes them even more desirable for consideration in FOP.

An important paper published in 2002 showed convincingly that animals genetically engineered to lack both copies of the gene encoding the cox-2 enzyme (cox-2 knockouts) failed to generate new bone formation at a fracture site, thus demonstrating the importance of the cox-2 enzyme in inflammatory bone formation (Zhang et al., 2002). While pharmacologic doses of cox-2 inhibitors (medications that block the activity of the cox-2 enzyme) given to normal animals had a similar effect, the inhibition of bone formation in both sets of animals (cox-2 knockouts and animals treated with cox-2 inhibitors) could be overcome with massive amounts of recombinant BMP, indicating that cox-2 activity occurs upstream of BMP signaling and that overactivity of the BMP pathway (as is seen in FOP) could plausibly overcome a cox-2 blockade (Zhang et al., 2002). Similar results were reported in a separate study published in 2002 (Simon et al., 2002).

Inflammatory prostaglandin levels are dramatically elevated in the urine of patients who have FOP, especially during times of a disease flare-up (Levitz et al., 1992). Inflammatory prostaglandins directly stimulate the induction of angiogenic peptides which can further promote the osteogenic process (Weinreb et al., 1997; Jones et al., 1999). These observations suggest the following hypothesis:

> Lowering baseline levels of inflammatory prostaglandins in patients with FOP may raise the threshold for heterotopic ossification even in the presence of promiscuously active ACVR1/ALK2.

Compared to the parent class of NSAIDs, the selective cox-2 inhibitors offer the possibility of a lower gastrointestinal risk profile, although much controversy still exists. Also, the half-life of most of the new cox-2 inhibitors is conducive to a once or twice daily dosage regimen, a factor which may help promote patient compliance (Deeks et al., 2002).

Substantial concerns have been raised about the safety of the cox-2 inhibitors, including rofecoxib (Vioxx), celecoxib (Celebrex), and valdecoxib (Bextra) in patients at high risk of cardiovascular and cerebrovascular disease (White et al., 2002; White et al., 2003; Couzin, 2004; Grosser et al., 2006). Although the cox-2 enzyme is necessary for the synthesis of inflammatory prostaglandins, it also controls the synthesis of prostacyclin, a prostaglandin that is essential for the health and potency of blood vessels, especially in the heart and brain.

On September 30, 2004, Merck & Co. announced voluntary worldwide withdrawal of rofecoxib (Vioxx), based on three-year data from a prospective randomized double-blind placebo-controlled clinical trial to assess the safety and efficacy of high-dose rofecoxib in preventing recurrence of colorectal polyps in patients with a history of colorectal adenomas (Merck & Co., 2004). In the study, there was an increased relative risk for confirmed cardiovascular and cerebrovascular events including heart attack and stroke, beginning after 18 months of treatment in patients taking rofecoxib compared to those taking placebo. The sudden withdrawal of Vioxx by Merck & Co. caused much confusion and concern throughout the FOP community especially for those taking the medication to reduce painful symptoms of FOP.

The voluntary worldwide withdrawal of rofecoxib by Merck & Co. in late September 2004 came less than three weeks after the US Food and Drug Administration (USFDA) approved rofecoxib for use in children with rheumatoid arthritis, and only three weeks after Merck & Co. agreed to fund a USFDA-approved and a University of Pennsylvania Investigational Review Board approved double-blind randomized placebo controlled study to assess the efficacy of rofecoxib in preventing flare-ups in patients who have FOP. That study, of course, will not take place.

Similar concerns have been raised about all cox-2 inhibitors including celecoxib and valdecoxib. Editorials published in The New England Journal of Medicine, carefully outlined the data, the controversies, and the possible alternatives for patients and physicians (Fitzgerald, 2004; Topol, 2004). Before the recent studies showing increased cardiovascular risk for rofecoxib and celecoxib were confirmed, the scientific evidence of decreased gastrointestinal events from the cox-2 inhibitors (compared to NSAIDs) in several trials clearly outweighed the evidence of cardiovascular risk. While the absolute gastrointestinal benefit of cox-2 inhibitors over traditional non-steroidal anti-inflammatory medications remains in question, selective cox-2 inhibitors remain a rational choice for patients at low cardiovascular risk who have had serious gastrointestinal events or in patients who are at high risk of serious gastrointestinal events, such as those with FOP who may need to use glucocorticoids (prednisone) intermittently and/or intercurrently for the treatment of acute flare-ups.

At the present time, the cox-2 inhibitor celecoxib (Celebrex) is available, although questions have been raised about its safety as well, especially in patients at high risk of cardiovascular complications. Presently, safety and pharmacokinetic data are available for celecoxib in the pediatric population (Stempak et al., 2002). While this medication is being used anecdotally and compassionately in patients with juvenile rheumatoid arthritis, the only published study on the use of celecoxib in children is in the

field of pediatric oncology. The investigators studied the metabolism of celecoxib as part of an ongoing clinical trial evaluating the use of high dose celecoxib in conjunction with other chemotherapeutic agents for anti-angiogenic treatment in children with recurrent solid tumors. Because children differ from adults with respect to drug metabolism, one objective of the study was to determine the single-dose and steady-state pharmacokinetics as well as the safety of anti-angiogenic doses of celecoxib in pediatric patients with solid tumors. The medication was studied in 11 pediatric patients between the ages of six and 16 years of age. Children with various recurrent solid tumors (and one with refractory leukemia) were studied. The observations confirmed the overall safety of the high-dose anti-angiogenic celecoxib (Celebrex) regimen in children and showed a faster clearance and shorter half-life of celecoxib in the pediatric population when compared with adults. This indicated that higher doses and/or more frequent administration may be necessary in the pediatric population compared to the high-dose anti-angiogenic regimen used in adults. Recent data strongly suggest that high-fat foods such as peanut butter taken with the medication may increase plasma concentrations of the celecoxib without increasing the dose of the medication (Stempak et al., 2002).

Celecoxib was extremely well-tolerated by the children in the oncology study despite the fact that they were receiving doses that were significantly higher than those used in adults for the treatment of rheumatoid arthritis or osteoarthritis. The children tolerated drug administration for extended periods of time (as long as 16 months in some cases) without the occurrence of any adverse events. No patient had to be removed from the study for celecoxib-associated toxicity. The authors concluded that celecoxib was well-tolerated by children and appeared to be safe for long-term administration, although the size of the study was small.

Cox-2 inhibitors are still available by prescription. They are currently being tested in children with rheumatoid arthritis, and are being used by pediatric specialists for the treatment of solid tumors and severe inflammatory conditions such as FOP where few other treatment options exist. Studies on the NSAIDs and selective cox-2 inhibitors integrate important findings from the FOP laboratory on prostaglandin production, mast cell recruitment, and angiogenic factor release with the pathologic findings of severe inflammatory pre-osseous lesions of FOP. 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.

Finally, with all of the existing controversy still swirling around the selective cox-2 inhibitors, the standard NSAIDs, which inhibit both cox-1 and cox-2 non-selectively, are still available and remain an important option to consider as maintenance medications in children and adults with FOP (Table 1). As with the chronic use of all NSAIDs, the risks of serious gastrointestinal side-effects, especially gastrointestinal bleeding, are possible, and special precautions may be warranted in susceptible individuals.

E. Aminobisphosphonates

Bisphosphonates are a potent class of medications that have profound effects on bone remodeling and exert their primary effect by decreasing the life span of osteoclasts. Bisphosphonates are thus widely used in the treatment of numerous bone diseases where bone resorption exceeds bone formation -- disorders such as osteoporosis, osteogenesis imperfecta, Paget's disease, fibrous dysplasia, and bone cancer (Orcel & Beaudreuil, 2002).

The first clinically used bisphosphonate, Etidronate, when administered at high doses, also potently inhibits mineralization of newly formed cartilage and bone protein and had been proposed as a possible

treatment for FOP and other disorders of heterotopic ossification as far back as 35 years ago. Etidronate has been studied in FOP 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 impairs ossification of the entire skeletal system, not just the heterotopic bone of the "second skeleton." Its utility is therefore limited.

The effects of intravenously administered Etidronate and oral corticosteroids were evaluated (Brantus & Meunier, 1998). Thirty-one FOP flare-ups were observed in seven patients during a mean follow-up of 6 years. In 29 flare-ups, the authors observed a rapid diminution of local inflammation, swelling, and pain during the first 7 days of treatment. However, despite Etidronate treatment, ten new ossifications were observed, causing severe deterioration of joint mobility in all affected patients. In 21 flare-ups, no new ectopic ossification appeared. The radiologic pattern of pre-existing ossifications did not change during the treatment. The results suggest the possibility that administration of intravenous Etidronate and oral corticosteroids may be helpful, but more control data on the spontaneous resolution of early flare-ups are needed. 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 routinely for the treatment of FOP.

While its effectiveness in FOP is uncertain, Etidronate has enjoyed limited use in the treatment of more focal disorders of heterotopic ossification such as those that arise following soft tissue trauma or injuries to the central nervous system. Unlike Etidronate, the newer aminobisphosphonates have no appreciable affect on inhibiting mineralization at doses which are hundreds to thousands of times more potent than Etidronate in inhibiting bone resorption. This property is the basis for the clinical success of aminobisphosphonates in a wide range of bone diseases characterized by excessive bone resorption (Brumsen et al., 1997; Body, 2001; Green, 2002; Still et al., 2003; Black et al., 2007).

So, why would the newer aminobisphosphonates, which act primarily to inhibit bone resorption, even be considered for use in FOP, a condition in which resorption of the heterotopic skeleton would be highly desirable? Not infrequently, an unintended or unexpected use for an old medication is discovered serendipitously in the course of clinical practice.

Ironically, several credible and anecdotal reports (to FSK) from physicians and FOP patients worldwide highlighted the response of FOP flare-ups to Pamidronate, one of the newer aminobisphosphonates. One of these reports came from Dr. Mordechai Weiss, M.D., Chief of The Endocrine Institute of Assaf Harofeh Medical Center in Zerifin, Israel and his FOP patient, Dr. Orly Doron-Goldstein, a molecular biologist at The Weizmann Institute of Science in Rehovot, Israel. Dr. Weiss carefully documented his clinical observations on the use of Pamidronate in FOP flare-ups. But, why would Pamidronate even be considered for the treatment of FOP flare-ups? Ironically, in all three cases reported to us, the medication had been used with the mistaken belief that Pamidronate was more potent than Etidronate in inhibiting mineralization. It is not. None of the newer bisphosphonates including Pamidronate have any effect on inhibiting mineralization. Nevertheless, all three patients and their physicians independently reported substantially decreased swelling, redness, and pain following intravenous Pamidronate administration during a new flare-up. In one patient, the Pamidronate was administered alone, while in the other two patients, it was administered along with an oral steroid (such as Prednisone) for several days during the early phases of a new FOP flare-up.

All of us in the FOP community know that such anecdotal observations could be purely coincidental - that is, that the flare-ups might have receded spontaneously without treatment and that the Pamidronate might have had nothing to do whatsoever with the reported improvement, especially since oral glucocorticoids were used intercurrently in two of the three FOP patients. Also, one cannot discount a potent placebo

effect in any uncontrolled observation. Nevertheless, we also know that such observations of potential improvement in an FOP flare-up cannot be ignored. It is entirely possible to stumble on something worthwhile even for the wrong reason!

As word of this Pamidronate-associated response (with or without steroids) spread rapidly throughout the FOP community, more than a dozen patients (in consultation with us and their local physicians), have used Pamidronate empirically (either alone or with steroids) for the treatment of acute flare-ups, especially those involving major joints. In 10 of the 13 patients (77%), there was reported improvement in the symptoms and signs of an FOP flare-up. In three of the 13 patients (23%), there was no reported improvement in the symptoms or signs of the flare-up by either the physician or the patient. Interestingly, there seemed to be no protective effect whatsoever on the occurrence of subsequent flare-ups in any of the patients treated with either a single dose or a brief course of intravenous Pamidronate. Therefore, whatever improvement there may have been was transient and affected only the lesion present at the time of the flare-up. While these patient reports are not scientifically valid, they constitute an important set of anecdotal observations that compel further stringent scientific inquiry in controlled laboratory and clinical studies.

The treatment protocols varied slightly between the patients (depending on age, body weight, and site of involvement) but in general were similar. The most commonly used protocol is summarized in Section V/Classes of Medications/Table 1. In all patients, serum calcium was monitored prior to treatment to assure that it was in the normal range, as hypocalcemia is a contraindication to the use of intravenous Pamidronate or any of the aminobisphosphonates (Rosen & Brown, 2003). All patients had adequate daily oral calcium and vitamin D supplementation during and following treatment. A serum calcium, phosphate, albumin, alkaline phosphatase, BUN, creatinine and complete blood count (CBC) should also be obtained at baseline. If Pamidronate is used to treat an FOP patient, we recommend that plain radiographs of the affected area should be obtained prior to treatment and six weeks thereafter to document the formation of any heterotopic ossification.

Treatment schedules were based upon published guidelines for children and adolescents with osteogenesis imperfecta as that group constitutes the largest known group of children and adolescents in whom intravenous Pamidronate has been used (Rauch et al., 2002; Falk et al., 2003; Rauch et al., 2003; DiMeglio & Peacock 2006). Patients between two and three years of age received Pamidronate at a dose of 0.75 mg/kg/day for three consecutive days by slow intravenous infusion over 4-5 hours each day. Patients over the age of three years received Pamidronate at a dose of 1.0 mg/kg/day for three days by slow intravenous infusion over 4-5 hours each day, with a maximal dose of 60 mgs/daily. On the first day of the first cycle of treatment, the patient receives half the dose. Lower total doses of Pamidronate (½ listed dose on days 2 and 3) and substantially longer durations of infusions (8-10 hours) have been reported anecdotally and have been well-tolerated. The three-day cycle of treatment should be repeated only during flare-ups and no more than 4 times annually. Pamidronate should be administered as early following the appearance of the flare-up as possible and preferably within the first 48 hours. Pamidronate should be diluted in normal saline according to the following table (Guidelines courtesy of F.H. Glorieux: Shriner's Hospital for Children, Montreal):

mg of Pamidronate	ml of Normal Saline	ml/hour
0-5	50	15
5.1-10	100	30
10.1-15	150	45
15.1-25	250	75
25.1-50	500	150
50.1-60	600	180

The maximal concentration of Pamidronate should be 0.1 mg/ml. The IV tubing should be flushed at the end of the infusion to ensure full dose delivery.

Oral corticosteroids (prednisone) can be added to the treatment regimen according to the guidelines listed (Table 1). In general, oral corticosteroids are administered concurrently for 4-5 days for the treatment of flare-ups involving major peripheral joints, the jaw, or the submandibular region. Corticosteroids are generally not used in conjunction with Pamidronate for flare-ups involving the neck, back, or chest as the timing of the onset of flare-ups in those areas is generally more difficult to determine and the reported success of prednisone for flare-ups in those regions has been more equivocal than for flare-ups in the major peripheral joints. The combined use of prednisone and Pamidronate for flare-ups in the trunk and back has therefore not been systemically assessed.

For treatment of acute flare-ups involving major peripheral joints, consider a 4-day course of oral prednisone. If swelling recurs following the discontinuation of prednisone, a second 4-day course of high dose prednisone may be given with a slow taper of the prednisone over the following 10 days, in conjunction with a 3-day cycle of IV Pamidronate.

Side-effects of intravenous Pamidronate infusions in FOP patients included flu-like symptoms of fever, chills, and muscle aches. These symptoms can often be lessened by pre-treatment with acetaminophen. One patient developed tetany (uncontrolled muscle contractions due to a low vitamin D level in the blood prior to ameliorative therapy), and one patient developed peripheral phlebitis (inflammation of the vein) at the intravenous infusion site, which required inpatient intravenous antibiotic treatment. A recently published case report documents the development of iatrogenic osteopetrosis in a child treated with 60 mgs. of intravenous Pamidronate every three weeks for two years. The child did not have FOP and the cumulative doses reported far exceeded any published recommendations for the use of Pamidronate in skeletal diseases (Whyte et al., 2003; Marini, 2003).

One important cautionary note about the bisphosphonates is necessary. Osteonecrosis of the jaw (ONJ) has been increasingly suspected to be a complication of bisphosphonate therapy, especially recurrent intravenous administration of the more potent aminobisphosphonates, such as Pamidronate and Zoledronate (Bilezikian, 2006; Khosla et al., 2007). ONJ, a rare dental condition, is diagnosed when an area of exposed jaw bone shows no sign of healing eight weeks after an invasive dental procedure, such as a tooth extraction. The gum that would normally cover the bone becomes atrophic, and the underlying jawbone is exposed. Some ONJ patients experience discomfort in the affected part of the mouth. Antibiotics have been effective for some patients, but generally there is no effective treatment and, like FOP, surgical manipulation of the affected site may exacerbate the underlying condition and should

usually be undertaken only by practitioners familiar with ONJ. Clinicians and patients should be aware of this potential complication and a patient's dentist should be made aware of any history of using bisphosphonate medications. Should people taking bisphosphonates for FOP be concerned? Perhaps, but bisphosphonates are used to treat millions of people, and only an exceedingly small number of patients have developed ONJ. However, a small risk is present, and a few precautions are recommended: a dental exam, if possible, before Pamidronate treatment should be considered. Pamidronate should be avoided, if possible within 8 weeks of major dental surgery.

Insight and support for the use of Pamidronate in FOP was provided recently by a study in children and adolescents with OI. Treatment with cyclical intravenous Pamidronate infusions (3-4 cycles annually) has led to substantial improvements in the clinical management of children and adolescents with OI, with generalized increases in bone density and dramatically fewer resultant fractures throughout the skeleton. Despite its well-known beneficial effects on skeletal remodeling and bone strength, the effects of Pamidronate on the new endochondral skeletogenesis of the type that would occur at a fracture site, have not been well characterized.

In an extensive study, Dr. Francis Glorieux and colleagues at the Shriner's Hospital for Children and McGill University in Montreal showed that incomplete fracture healing in patients with OI was more than twice as frequent when Pamidronate therapy had been started before the fracture occurred. Furthermore, delayed osteotomy healing was almost four times more frequent when Pamidronate had been started before surgery. The study demonstrated the cyclical intravenous Pamidronate therapy was associated with a significant delay in osteotomy healing in children and adolescents with OI. Although the study was conducted for entirely different reasons and in a different patient population than FOP, the study provides support for the hypothesis that Pamidronate can increase bone density and decrease fracture incidence in the normotopic skeleton through its effect on bone remodeling, while simultaneously inhibiting endochondral skeletogenesis at orthotopic sites (Munns et al., 2004). It remains to be seen in FOP and in appropriate animal models of BMP-induced heterotopic ossification, whether cyclical infusions of Pamidronate or the more potent aminobisphosphonate zoledronic acid (Zoledronate) can impair endochondral skeletogenesis at heterotopic sites.

In 2005, Schuetz and colleagues reported generally beneficial anecdotal effects of high-dose aminobisphosphonates in preventing recurrence of heterotopic ossification in high-risk patients with established heterotopic ossification who were undergoing surgery to excise heterotopic bone. One of the five patients reported had FOP. The authors note that the conclusions are preliminary (Schuetz et al., 2005).

Apart from their postulated and observed effect on endochondral skeletogenesis, the use of the aminobisphosphonates could be considered in any FOP patient who is treated intermittently with high dose glucocorticoids for new FOP flare-ups. The aminobisphosphonates generally have an excellent safety and efficacy profile in protecting the normotopic skeleton from the profound osteopenic effects of intermittent high-dose glucocorticoids in the type of regimen that is frequently used to manage acute flare-ups of FOP (Nogginuera et al., 2003; Sambrook et al., 2003; Staa & Cooper, 2003).

An important question that observations from routine clinical care of FOP patients raises is: What might be the physiologic basis for any potential beneficial effect of aminobisphosphonates in the treatment of FOP flare-ups? As a consequence of their potent inhibition of bone resorption, the aminobisphosphonates effectively inhibit the release of growth factors and morphogens (such as BMPs) which are stored in the extracellular bone matrix of the skeleton. The action of the bisphosphonates on the suppression of bone resorption is exceedingly long, longer than for any other class of medications, and on the order of months to years. Therefore, if aminobisphosphonates inhibited FOP lesions by decreasing the release of BMPs

sequestered in the skeleton, one would expect a more pronounced effect on the prevention of subsequent flare-ups than was seen in the patients treated. Clearly, if the aminobisphosphonates are truly beneficial in the treatment of FOP flare-ups, there must be a mechanism of action that is very brief and substantially different from that of osteoclast inhibition from which the medication derives its beneficial effects in the normotopic skeleton.

All bisphosphonates have an affinity for sites of normal and pathological mineralization. The latter effect plausibly explains the avid uptake of bisphosphonates at sites of severe skeletal muscle injury where calcium is released from the mitochondria and sarcoplasmic reticulum of dying muscle cells. This seminal property of all bisphosphonates to home to areas of normal and pathological mineralization suggests a plausible mechanism of bisphosphonate sequestration at sites of early FOP lesions where muscle cells are dying. If bisphosphonates are sequestered at sites of early FOP flare-ups as suggested by radionuclide bone scans, the bisphosphonates would be biologically available to a wide variety of endocytic target cells (monocytes, macrophages, fibroproliferative cells, and angiogenic cells) that compose the early stages of an FOP lesion. Once internalized by a target cell (not yet determined for FOP lesional cells), Pamidronate will disrupt the mevalonate pathway by specifically inhibiting the activity of the farnesyl diphosphate synthase enzyme within the cell. As a result of this enzymatic inhibition, the target cell is rendered incapable of post-translational prenylation of small GTPases such as Ras, Raf, and Rac which are essential for cellular activity. Consequently, target cells are rendered functionally inactive and undergo apoptotic cell death. (Pechersturfer et al., 2000; Dunford et al., 2001).

While the potential mechanism of action of the aminobisphosphonates on early FOP lesions or BMP-induced FOP-like lesions remains speculative, several recent papers provide some additional clues. These papers, published in the peer-reviewed cancer literature, document the potent antiangiogenic effects of Pamidronate and zoledronic acid *in vitro* and *in vivo*. Also, Pamidronate administered intravenously was shown to dramatically decrease serum vascular endothelial growth factor (VEGF) levels and basic fibroblast growth factor (bFGF) levels in cancer patients with bone metastasis. Both VEGF and basic FGF are potent tumor–associated angiogenesis factors (Fournier et al., 2002; Santini et al., 2002; Wood et al., 2002).

Angiogenesis is one of the most prominent histopathologic features of pre-osseous FOP lesions, and thus a potential target for therapy (as discussed previously). Also, basic fibroblast growth factor (bFGF) is an extremely potent *in vivo* stimulator of angiogenesis and has been implicated in the growth of solid tumors as well as FOP lesions. Urinary bFGF levels are markedly elevated in FOP patients especially during acute flare-ups (see Section I. F). Furthermore, bFGF is highly expressed in lesional cells of FOP biopsy specimens. These data strongly suggest that bFGF may be a biochemical marker for disease activity and provide a biochemical basis for considering anti-angiogenic therapy and anti-bFGF therapy at early stages of the disease process. The goal of anti-angiogenic therapy in FOP (regardless of the medication used) 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.

The powerful anti-angiogenic effect of some aminobisphosphonates has been demonstrated in mice and may explain the beneficial adjuvant effects of these medications in the treatment of various cancers. The short circulatory half-life of aminobisphosphonates could explain why these medications could benefit active flare-ups when administered early but are unable to prevent future flare-ups.

Intravenous aminobisphosphonates have also been shown to modulate macrophages and various lymphocyte subpopulations in the circulation and may be responsible for its dose-related side-effects of causing flu-like symptoms. We cannot yet rule-out the possibility that Pamidronate may affect early lymphocytic and monocytic infiltration into skeletal muscle seen in both BMP4-induced FOP-like lesions

and in FOP lesions themselves. It is also likely that the aminobisphosphonates directly inhibit the metabolic activity of monocytes and macrophages that play such key roles in the response of the innate immune system to soft tissue injury (Perchersturfer et al., 2000; Dunford et al., 2001).

Other possible mechanisms by which the aminobisphosphonates might affect FOP lesions include a direct inhibition on the proliferation of a rapidly dividing population of cells. Such an effect was noted in studies investigating the effects of aminobisphosphonates on cancer cells *in vitro*. (Tassone et al., 2000; Green, 2003). It is possible that Pamidronate and Zoledronate may affect one or more cell types in an early FOP lesion. Another study showed recently (Idris et al., 2008) that aminobisphosphonates cause osteoblast apoptosis and inhibit bone nodule formation *in vitro*, thus suggesting that aminobisphosphonates may have a direct effect on inhibiting osteoblastic ability, especially in early bone nodules, as in FOP.

Finally, one must consider the stark possibility that there may be no positive effects whatsoever of the aminobisphosphonates on FOP lesions and that the reports to date are the results of observational bias and/or coincidence. Only rigorous controlled investigations *in vitro* and *in vivo*, as well as placebo–controlled clinical trials will be able to definitively decipher these possibilities and provide a solid rational basis for determining whether or not one or more of the aminobisphosphonates may have a beneficial role in the treatment of FOP.

Will Pamidronate and the newer generation of aminobisphosphonates be a goldmine for FOP therapy or will it simply be fool's gold? Only time and rigorous experimental approaches will provide clear answers to that question. While BMP receptor antagonists and BMP pathway signal transduction inhibitors may eventually be definitive in the treatment and prevention of FOP, we hope that the use of more immediately available medications such as glucocorticoids, leukotriene inhibitors, mast cell inhibitors, cox-2 inhibitors, and perhaps the aminobisphosphonates will allow us to buy time for FOP patients. As Jeri Licht, the mother of Daniel Licht stated so eloquently and passionately in the **BBC** documentary, ***The Skeleton Key***, "They need to slow down the progression of this condition and slow down or stop the formation of the bone once the flare-up starts. Then they'll have the time, and we'll have the luxury to have them look for a cure for the condition completely."

F. Acute & Chronic Pain Management in FOP

There are many causes of acute and chronic pain in FOP, and each individual must be carefully evaluated before effective treatment can be planned and implemented (Kaplan et al., 2008). Many FOP flare-ups, especially those around the hips and knees, are extremely painful and may require a brief course of well-monitored narcotic analgesia in addition to the use of non-steroidal anti-inflammatory medications, cox-2 inhibitors, and/or oral or IV glucocorticoids. Other types of transient pain syndromes may be caused by neuropathies resulting from acute flare-ups, transient bursitis, inflammation of osteochondromas, arthritis and muscle fatigue, to mention only a few. Most individuals with FOP are pain-free between flare-ups and require little or no chronic analgesia. A small percentage of patients with advanced FOP suffer from generalized chronic pain of diffuse musculoskeletal origin and may require more specialized pain management programs directed by pain management specialists. Attempts should be made to minimize chronic discomfort, and maximize physical and cognitive function. In most cases, narcotic agents should be avoided to minimize the risk of dependency on these agents. While some may require chronic narcotic analgesics late in the course of their disease process, attempts should be made to monitor this carefully to avoid constipation and respiratory suppression. For those with more chronic pain management issues, a consultation with a pain management specialist may be helpful.

G. Muscle Relaxants

The concept of using muscle relaxants during acute flare-ups has enjoyed recent popularity among clinicians treating FOP patients (Glaser & Kaplan, 2005). Early FOP flare-ups are associated with intense mast cell, macrophage, and lymphocytic infiltration into skeletal muscle and are often accompanied by intense inflammatory changes within regions of locally damaged or necrotic skeletal muscle. Areas of relatively healthy skeletal muscle bordering the lesion are thus subject to metabolic changes that would lead to muscle spasm and fiber shortening. The judicious short-term use of muscle relaxants such as cyclobenzaprine (Flexeril), metaxalone (Skelaxin), or liorisal (Baclofen) may help to decrease muscle spasm and maintain more functional activity even in the setting of an evolving FOP lesion. This is especially true for painful flare-ups involving the major muscle groups of the back and limbs. The chronic use of muscle relaxants between episodes of flare-ups has not been as widely reported to us by colleagues treating patients with FOP. As with all such medications, careful attention to dosing schedules is important, as certain muscle relaxants (such as liorisal) need to be tapered slowly to avoid side-effects.

H. Chemotherapy Agents & 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. As a result, many children with FOP are misdiagnosed as having a wide range of benign or malignant conditions. It is not surprising, therefore, that many children with FOP have been treated with unnecessary chemotherapy, dangerous surgical excisions, and damaging 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 has been no convincing anecdotal evidence that either radiation therapy or any of the standard chemotherapy agents such as actinomycin, colchicine, vincristine, vinblastine, cyclosphosphamide, doxorubicin, ifosfamide, adriamycin, or any others were helpful for patients with FOP. In fact, many of these medications caused harmful long-term side-effects. The use of these approaches is, therefore, contraindicated in the treatment of FOP (Glaser & Kaplan, 2005; Kaplan et al., 2008). There is, however, one case report in the literature that documents apparently successful treatment of FOP with surgical excision of heterotopic bone, indomethacin, and irradiation. Follow-up was brief (Benetos et al., 2006). At the present time, this approach cannot be endorsed.

I. Bone Marrow Transplantation

A recently published study documented the role of hematopoietic stem cells in FOP. Bone marrow derived stem cells have been implicated in the ectopic bone formation of FOP (reviewed in Kaplan et al., 2007). The replacement of these stem cells by bone marrow transplantation has been suggested as a possible cure for FOP. However, the definitive contribution of bone marrow derived stem cells to the formation of heterotopic bone has remained obscure. Careful clinical observations were made of an FOP patient who underwent bone marrow transplantation twenty-five years earlier for the treatment of intercurrent aplastic anemia. We found that replacement of the FOP patient's bone marrow with normal donor bone marrow cured his fatal bone marrow condition but was not sufficient to prevent further heterotopic ossification and progression of his FOP. However, acute immunoablation and chronic immunosuppression quenched the activity of his FOP.

In complementary transplantation studies in mice, we found that blood cells derived from the bone marrow contributed to the early inflammatory and to the late marrow repopulating stages of BMP4-induced bone formation, but were not present in the fibroproliferative, chondrogenic or osteogenic stages of the FOP-like lesions (Kaplan et al., 2007).

Taken together, these findings demonstrated that bone marrow transplantation did not cure FOP in this patient, most likely because the blood-making stem cells from the bone marrow were not the source of cells that formed the FOP lesions. However, even normal bone marrow-derived cells were capable of stimulating heterotopic ossification in a genetically susceptible individual (Kaplan et al., 2007).

These findings are of immense research interest and vital clinical importance, and they exemplify powerfully how much can be learned by careful observation in an individual patient. They also illustrate the importance of the immune system in triggering FOP flare-ups. At present, however, the general use of potent immunosuppressive medications is not advocated in the routine management of FOP, and would likely be extremely dangerous and possibly life-threatening if it were applied broadly to the FOP community. At the present time, (and until further studies are performed in appropriate animal models), this international consortium recommends against the use of chronic immunosuppressive medications in the management of FOP.

J. Miscellaneous Agents

The chronic use of calcium binders, mineralization inhibitors, antiangiogenic agents, fluoroquinolone antibiotics, retinoids, and warfarin have been reported with either unsatisfactory or equivocal results. At the present time, the use of these medications or approaches can not be endorsed (Moore et al., 1986; Wieder, 1992; Zasloff et al., 1998). TNF-alpha inhibitors might theoretically provide some benefit (Olsen & Stein, 2004). Recently, there have been some anecdotal reports on the use of TNF-alpha inhibitors, but data are scant and no published series are available. While there has been one case report of successful surgical excision of heterotopic bone in a patient with FOP, such an approach is not recommended, as the literature is littered with casualties following similar adventures (Benetos et al., 2006).

K. Targeting ACVR1/ALK2: Definitive Targets for Therapy

"With so much being discovered about how the BMPs act, it might be possible to develop drugs that would block some part of the BMP pathway and therefore prevent the progression of what is a horrible, nightmare disease."

- Brigid Hogan (Roush, 1996)

The ultimate goal of FOP research is the development of treatments that will prevent, halt, or even reverse the progression of the condition. The prevention and treatment of heterotopic ossification in FOP, as in any of the more common forms of heterotopic ossification, will ultimately be based on at least one of four approaches: disrupting the inductive signaling pathways, suppressing the inflammatory triggers, altering the relevant osteoprogenitor cells in the target tissues, and/or modifying the tissue environment so that it is less conducive to heterotopic osteogenesis.

The identification of the recurrent heterozygous missense point mutation that causes FOP in all classically affected individuals provides a specific pharmaceutical target and a rational point of intervention in a critical signaling pathway. The discovery of the FOP gene identifies ACVR1/ALK2 as a susceptible

pharmaceutical target for the treatment of FOP. Plausible therapeutic strategies to inhibiting BMP signaling in FOP include inhibitory RNA technology, monoclonal antibodies directed against ACVR1/ALK2, and orally available small molecule selective signal transduction inhibitors (STIs) of ACVR1/ALK2 (Shore et al., 2006; Kaplan, 2006; Fukada et al., 2007; Kaplan et al., 2007; Shen et al., 2007; Kaplan et al., 2008; Yu et al., 2008).

Recently, Dorsomorphin has been identified as a powerful orally-available signal transduction inhibitor of BMP signaling (Yu et al., 2008). Dorsomorphin and its derivatives are powerful inhibitors of BMP type I receptors in FOP cells (Fukada et al., 2007), and preliminary data suggest that this category of STIs may play a powerful role in inhibiting heterotopic ossification in animal models of promiscuous ACVR1/ALK2 activity (Cuny et al., 2008; and Personal Communication). Further extensive testing in animal models of true FOP will be necessary to more completely evaluate potential efficacy and safety.

It is still too early to determine which one of these approaches or combinations of approaches will be most effective, and all are being studied intensively in the laboratory. Much of the present worldwide collaborative research effort in FOP is focused on this area of research, and detailed accounts of the work and progress can be found in the Seventeenth Annual Report of the FOP Collaborative Research Project (Kaplan, Pignolo et al., 2008), as well as in recent reviews.

III. SPECIAL MEDICAL CONSIDERATIONS

A. Introduction

Individuals who have FOP can also develop common problems (gall bladder disease, appendicitis, colds, earaches, etc.) as with anyone in the general population. Generally, the safest way to diagnose and treat these problems in a patient with FOP is to ask the question: "How would I evaluate this patient if he or she did not have FOP?" Following that, the "FOP filter" can be applied to ask: "Given the nature of the possible intercurrent medical problem, and the relative risks that particular problem presents in relation to FOP, are there any diagnostic or treatment procedures that should or should not be undertaken (or perhaps alternative diagnostic procedures might be more appropriate)?" Using that approach, diagnostic dilemmas can often be resolved and appropriate care delivered. When questions remain, experts on FOP should be consulted (Kaplan et al., 2008; see Section X. The International Clinical Consortium on FOP).

In addition to common medical problems that individuals with FOP might have, there are a number of special medical considerations for FOP patients that are worthy of very special attention. They are presented below.

B. Injury Prevention in FOP

Prevention of soft-tissue injury and muscle damage remain a hallmark of FOP management. Intramuscular injections must be avoided. Routine childhood diphtheria-tetanus-pertussis immunizations administered by intramuscular injection pose a substantial risk of permanent heterotopic ossification at the site of injection, as do arterial punctures whereas measles-mumps-rubella immunizations administered by subcutaneous injection and routine venipuncture pose no significant risk (Lanchoney et al., 1995). Biopsies of FOP lesions are never indicated and may cause additional heterotopic ossification.

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 that will lead to heterotopic ossification, and local anesthetic drugs are extremely toxic to skeletal muscle (Luchetti et al., 1996).

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 of FOP, which result in heterotopic ossification and joint ankylosis. Mobility restriction from joint ankylosis severely impairs balancing mechanisms, and causes instability, resulting in more falls (Glaser et al., 1998).

Falls in the FOP population are more likely to result in 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 and to anatomic abnormalities of the cervical spine in individuals with FOP. FOP patients are much more likely to be admitted to a hospital following a fall and have a permanent change in physical function because of the fall. In a group of 135 FOP patients, 67 percent of the reported falls resulted in a flare-up of the FOP. Use of a helmet by young patients may help reduce the frequency of severe head injuries that can result from falls.

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. 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.

When a fall occurs, prompt medical attention should be sought, especially when a head or neck injury is suspected. Any head or neck 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. An FOP patient should be examined carefully by a healthcare professional if a head or neck injury is suspected.

C. Spinal Deformity in FOP

Spinal deformities are common in individuals who have FOP. A study in 40 FOP patients showed that 65 percent had radiographic evidence of scoliosis. The initial clinical abnormality was a rapidly developing scoliosis associated with a spontaneously occurring lesion in the paravertebral soft tissues. Once established, these deformities lead to rapid, permanent loss of mobility and to progressive spinal deformity with growth (Shah et al., 1994).

The formation of a unilateral osseous bridge along the spine prior to skeletal maturity limits growth on the ipsilateral side of the spine while growth continues uninhibited on the contralateral side. If an osseous bridge occurs bilaterally and the two bridges are relatively symmetrical, or if an osseous bridge forms after skeletal maturity, scoliosis will not result.

Severe scoliosis in FOP can lead to pelvic obliquity, similar to that seen in scoliosis resulting from other causes, and the obliquity can impair the balance of the trunk as well as standing and/or sitting balance.

Anecdotal experience in five patients suggests that traditional operative approaches to scoliosis in FOP patients can seriously exacerbate the disease. Furthermore, three patients in the series who had operative correction of the scoliosis continued to have progression of the spinal curve even after a spinal arthrodesis. In two of these patients, the arthrodesis was performed posteriorly and not anteriorly. Thus, continued anterior growth of the spine exacerbated rotational deformity. Indications for correction of spinal deformity associated with more usual types of scoliosis do not pertain to patients with FOP. With the limited knowledge available, the risks of severe complications (most notably, the exacerbation of heterotopic ossification at sites remote from the operative field) that are associated with correction of spinal deformity in FOP may outweigh the benefits.

A recent study of three patients with rapidly evolving chin-on-chest deformities suggests that a more aggressive surgical approach may be necessary to prevent and/or correct such rapidly progressive deformities in patients who have FOP (Moore et al., 2008).

D. Cardiopulmonary Function in FOP

Patients with FOP develop thoracic insufficiency syndrome (TIS) that can lead to life-threatening complications. Features contributing to TIS in patients with FOP include:

- Costovertebral malformations with orthotopic ankylosis of the costovertebral joints
- Ossification of intercostal muscles, paravertebral muscles and aponeuroses
- Progressive spinal deformity including kyphoscoliosis or thoracic lordosis

Pneumonia and right-sided heart failure are the major life-threatening hazards that result from TIS in patients with FOP. Prophylactic measures to maximize pulmonary function, minimize respiratory compromise, and prevent influenza and pneumonia are helpful in decreasing the morbidity and mortality from TIS in patients with FOP (Kussmaul et al., 1998; Kaplan & Glaser, 2005).

Individuals with FOP develop progressive limitations in chest expansion, resulting in restrictive lung disease, with reduced vital capacity but no obstruction to air flow. Those with advanced disease have extremely limited chest expansion and rely on the diaphragm for inspiration (Kussmaul et al., 1998). The low inspiratory capacity results in low expiratory flow rates, in many cases. Consequently, individuals with FOP are subject to atelectasis, retained secretions, and pneumonia.

The respiratory problems seen in patients with FOP are similar to those seen in patients with respiratory muscle weakness such as cervical spinal cord injury, or other skeletal abnormalities such as kyphoscoliosis. Strategies similar to those used in these other populations to maximize respiratory muscle functional and clear secretions may be beneficial in those with FOP.

Inspiratory and expiratory muscle training should be routinely practiced. A variety of incentive spirometers are available to encourage deep breathing. Inspiratory muscle training devices permit progressive resistance exercise training of the diaphragm.

Careful attention should be directed toward the prevention and therapy of intercurrent chest infections. Such measures should include prophylactic pneumococcal pneumonia and influenza vaccinations (given subcutaneously), chest physiotherapy, and prompt antibiotic treatment of early chest infection. Upper abdominal surgery should be avoided if possible, as it interferes with diaphragmatic respiration. Sleep studies to assess sleep apnea may be helpful, and positive pressure assisted breathing devices such as BiPAP® (Bi-level positive airway pressure) masks without the use of supplemental oxygen may also be helpful.

Patients with FOP who have advanced TIS and who use unmonitored oxygen have a high risk of sudden death. Sudden correction of oxygen tension in the presence of chronic carbon dioxide retention suppresses respiratory drive. Patients who have FOP and severe TIS should not use supplemental oxygen in an unmonitored setting (Kaplan & Glaser, 2005).

There is also much that can be done in prevention. Individuals with FOP are often born with congenital malformations of the costovertebral joints that cause some degree of chest restriction even before the appearance of heterotopic bone, although these restrictions may not lead to any clinical problems early in life. However, because of these restrictions, individuals with FOP are more likely to rely, even early in life, on diaphragmatic breathing. It is recommended that individuals with FOP be evaluated by a pulmonologist by the end of the first decade of life in order to perform baseline pulmonary function tests and echocardiograms. The results of these tests may further help guide preventative care for the cardiopulmonary system.

During hospitalizations or in more advanced disease, individuals with FOP may have more trouble clearing secretions. This can lead to atelectasis, pneumonia and respiratory failure requiring intubation. Secretion clearance is enhanced by adequate hydration, guaifenesin, and use of bronchodilators and mucolytics, as needed. Several devices are available to loosen secretions from relatively simple handheld devices that cause vibration of the airway walls during exhalation, to garments that vibrate the chest wall to high technology specialty beds that turn and oscillate. Care must be taken when using such devices in patients with a weak cough, as they may unable to expectorate the secretions once loosened. Use of mechanical insufflation-exsufflation can non-invasively extract retained secretions from individuals with ineffective cough. The device can dramatically increase peak cough expiratory flow in individuals with impaired expiratory muscle function. Combining a method to loosen secretions with in-exsufflation to remove them may prevent respiratory failure and the need for mechanical ventilation.

Various activities can help maximize the strength of the diaphragm and perhaps decrease the risk of intercurrent pulmonary problems. In addition to the intermittent use of incentive spirometry, other activities such as deep breathing, swimming/hydrotherapy, and singing, may help improve long-term pulmonary function.

E. Influenza & FOP

Flare-ups of FOP are most commonly triggered by soft tissue injury. After observing severe flare-ups of FOP in two half-sisters with culture-confirmed influenza B infections, we hypothesized that influenza-like viral illnesses can also trigger flare-ups of FOP. To address this hypothesis, we designed a questionnaire to assess whether patients with FOP experienced influenza symptoms during an influenza season, and whether these symptoms were correlated with flare-ups of the condition. The questionnaire was sent to patients with FOP worldwide. Of the 264 patients surveyed, 123 (47%) responded. The survey revealed that the risk of a disease flare-up of FOP during an influenza-like viral illness was elevated by at least a factor of three and possibly much more (Scarlett et al., 2004). Thus, patients with FOP have a substantial additional risk of flare-ups from influenza-like viral illnesses. Such flare-ups affect the chest wall and imperil the already precarious respiratory status. Patients with FOP should prompt seek medical attention of influenza-like syndromes (Scarlett et al., 2004).

The survey data strongly supported the hypothesis that influenza-like viral illnesses were associated with disease flare-ups in patients who have FOP. Influenza-like viral illnesses in FOP patients may be a source of previously unrecognized muscle injury leading to heterotopic ossification and permanent loss of mobility. These findings have important implications for understanding and preventing environmental triggers of disease activity in this population of patients genetically susceptible to progressive heterotopic ossification.

Influenza is a dangerous disease even for healthy individuals, and it is even more dangerous for those who have FOP. The United States Center for Disease Control and Prevention in Atlanta estimates 20,000 deaths and 114,000 hospitalizations annually due to complications of influenza. Common complications include severe life-threatening pneumonia as well as severe muscle damage that leads to kidney failure, requiring dialysis. The greatest risk of complications from flu occurs in infants, the elderly and those who are disabled. Patients who have FOP are particularly susceptible to complications from the flu. This is due to the severe restrictive disease of the chest wall that occurs at an early age and leads to a lifelong increased risk of developing life-threatening complications of respiratory infections.

Patients with FOP should consider receiving influenza immunizations annually. Additionally, unaffected household members of patients with FOP should consider annual immunizations to decrease the risk of spreading the flu to highly susceptible FOP patients.

It is generally recommended that patients who have FOP avoid intramuscular immunizations. A published report which examined different routes of administration of the flu vaccine (in non-FOP patients) suggested that the flu shot can be given subcutaneously and induces similar levels of antibodies against the flu compared to the intramuscular immunization (Halperin et al., 1979).

Shortage of flu vaccine in the United States during the 2004-2005 season prompted several important studies to determine if the flu vaccine was effective at a fraction of its normal strength when administered intradermally (in the skin). Intradermal administration of the influenza vaccine facilitates exposure of influenza-antigens to dendritic cells in the skin that can stimulate the lymph nodes to mount a protective antibody response. As compared with intramuscular immunizations, intradermal immunizations were hypothesized to induce similar antibody responses with a smaller quantity of vaccine (Belshe et al., 2004; Cooper et al., 2004; Kenney et al., 2004; La Montagne & Fauci, 2004; Pearson, 2004).

One study showed that an intradermal injection of a reduced dose of influenza vaccine (as compared with an intramuscular injection of full-dose influenza vaccine), resulted in similarly vigorous antibody responses among persons 18-60 years of age. In two other studies, intradermal administration of one-fifth or one-tenth of the standard intramuscular dose of influenza vaccine elicited an immune response that was similar or better than that elicited by the full dose intramuscular injection. Intradermal administration could therefore be used to expand the recipient population for influenza vaccine, but further studies are needed before the strategy can be recommended for routine use. Nevertheless, the intradermal route of administration, which was explored and studied in an attempt to expand the availability of the vaccine, can cautiously be applied to the FOP patient population who cannot otherwise receive intramuscular injections. The intradermal route of administration bypasses the need to give an intramuscular immunization, and may be as effective. The studies do not prove conclusively that the weaker dose of the vaccine given intradermally prevents active influenza during the flu season as effectively as a normal dose nor do they show what is the best dose for high-risk groups such as young children, the elderly, or those who have FOP. Nevertheless, the published studies offer a possible alternative that could be used compassionately in high-risk populations including FOP patients.

The decision to have a flu shot (as well the route of administration) is a personal decision that must be made by each patient who has FOP in consultation with his/her physician.

The flu vaccine should never be given to someone who is allergic to eggs (since the flu vaccine is developed and cultured in eggs). The flu vaccine should never be given to anyone who has had a previous severe adverse reaction to the influenza vaccine. Most importantly, the flu vaccine should never be given to an FOP patient during the time of an active flare-up. Neuraminidase inhibitors could be considered if influenza develops (Moscona, 2005), but there has been little experience with them in the FOP community.

An intranasal influenza vaccine was approved by the US Food & Drug Administration (FDA) and is now available for administration, where not otherwise contraindicated, in individuals from 5 to 49 years of age (Belshe et al., 2007). This would circumvent the need for a flu shot of any type and might be an attractive option in some patients who have FOP. The intranasal influenza vaccine is much more expensive than the traditional flu shot, but is readily available. This method of immunization is quite new and uses a live attenuated flu virus. There is also much less experience with the intranasal influenza vaccine in the FOP community. One young child who received the intranasal flu vaccine developed a severe flare-up of FOP two days after receiving the vaccine. This might have been coincidental or might have been due to the live virus vaccine. It is impossible to say. However, several other children with FOP have received the intranasal flu vaccine without any adverse effects. Interestingly, among young children, the intranasal flu vaccine had significantly better efficacy than the inactivated vaccine (Belshe et al., 2007).

Whatever decision is made for a particular individual, it should be made following careful consideration of the FOP patient's past medical history and consultation with his/her local physician. Many patients have strong views about immunizations and there are no easy answers here. It is important to remember, however, that influenza can be an extremely severe and life-threatening disease even in healthy individuals, and even more so in patients who have FOP. Thus, while there are risks of immunization, there are also substantial and life-threatening risks of influenza infection. Many patients incorrectly attribute symptoms of a cold to "influenza." It is an important to remember that influenza is a completely different illness than a bad cold, and flu can be a severe life-threatening infection to anyone, especially to young children, to the elderly, and to the disabled.

The old adage about an ounce of prevention is still true. Common sense old-fashioned methods to decrease the risk of an influenza infection need to be heeded. Those include avoidance of crowds, keeping well rested, and well-hydrated, and washing ones hands frequently as well as avoiding touching one's hands to the face, and rubbing the eyes. Avoidance of influenza is a multi-faceted process and includes annual immunizations, as well as common sense methods of prevention.

F. Limb Swelling & FOP

Limb swelling is a common problem in patients who have FOP, yet little is known about this complication of the condition. In a published study, detailed medical records were reviewed on a large group of FOP patients who had a documented history of FOP to determine the prevalence and natural history of limb swelling (Moriatis et al., 1997). Acute swelling of the limbs occurred in association with flare-ups of the condition in nearly all cases. Acute swelling in the upper limbs was focal and nodular in contrast to acute swelling in the lower limbs, which was more diffuse. The intense angiogenesis and edema seen on histopathologic evaluation of preosseous FOP lesions may play a role in the pathogenesis of the limb swelling. In addition, proximal lesions in the limb may cause a mechanical blockage of distal limb lymphatic drainage thus causing or exacerbating the swelling.

The acute and often severe limb swelling seen with acute flare-ups of FOP is understandable on the basis of the intense inflammation, angiogenesis and capillary leakage demonstrable in the early FOP lesions. Limb swelling associated with an acute FOP flare-up may grow to extraordinary and alarming size and lead to extravascular compression of nerves and tissue lymphatics. The appearance of such massive acute swelling in the lower limbs can provoke serious considerations of a deep vein thrombosis. Massive tissue edema may last for 9-12 weeks after the onset of acute swelling. As fibrocartilaginous tissue matures into chondroosseous tissue and finally into bone, swelling diminishes. During the following six months, swelling may regress slowly or may persist as chronic limb swelling. As skeletal muscle in the lower limbs is replaced by heterotopic bone, the normal pumping action of the muscle is lost, further exacerbating lymphatic stasis and dependent edema. Progressive ankylosis of the joints continues inexorably and loss of mobility ensues, further increasing venous and lymphatic stasis and dependent edema (Moriatis et al., 1997).

Some patients who have advanced FOP involving the lower limbs have venous stasis and/or lymphedema. Definitive studies to exclude deep vein thrombosis may be difficult to obtain and interpret due to severe existing deformity and joint ankylosis from previous flare-ups. A decision to anticoagulate a patient should not be made without substantial evidence of deep vein thrombosis. The differential diagnosis of acute upper limb swelling is not nearly as difficult as is the differential diagnosis of acute lower limb swelling in patients who have FOP. Differences in the regional appearance of the FOP lesions cannot be explained at the present time, but may be due to mechanical factors affecting aponeuroses and fascial planes (Moriatis et al., 1997).

Limb swelling is often difficult to treat effectively in patients who have FOP. Non-steroidal anti-inflammatory medications and glucocorticoids generally have not been effective. Support stockings are poorly tolerated by most patients, and elevation of the affected limbs is often impossible because of ankylosis of the major joints, especially later in the disease process. Where tolerated, support stockings may be helpful. The use of pneumatic compression devices has not been evaluated. Additionally, many have reported anecdotal beneficial effects following treatments at lymphedema clinics.

G. Pressure Sores in FOP

Skin breakdown and pressure sores are common and troublesome problems in individuals who have FOP. Skin breakdown can occur from increased pressure over normotopic or heterotopic bone. Pressure sores can develop suddenly, progress rapidly, and be difficult to treat (Kantanie, 2008). Preventive measures include:

- Frequent changes in position.
- Use of a pressure-reducing mattress or bed.
- Daily skin inspections.
- Adequate nutrition.

If a pressure sore is detected at an early stage when the skin is erythematous but there is no open sore, it will be much easier to treat. Pressure sores involving open wounds require considerably more care. Follow these suggestions as soon as a problem is identified (Thomas, 2001; Reddy et al., 2006; Mayo Clinic, 2008):

- Change positions frequently and use special cushions designed to relieve pressure.
- Keep the area clean to prevent infection. A stage I wound (no open skin) can be gently washed with water and mild soap. Anything more serious should be washed with saline (salt) solution, which can be obtained from a pharmacy. Avoid using antiseptics such as hydrogen peroxide or iodine which can damage the skin and delay healing.
- Use a special dressing/bandage that protects wounds and helps promote healing. Name brands include Tegaderm and Duoderm. These dressings help keep the wound moist (to promote cell growth) while keeping the surrounding tissue dry.
- If necessary, damaged tissue can be removed. A wound needs to be free of dead and/or infected tissue to heal properly. There are several ways that this can be done safely, even in FOP.
- Whirlpool baths can be helpful because they help keep the skin clean and naturally remove dead tissue.

H. Fractures & FOP

In FOP, fractures can occur in both normotopic and heterotopic bone. Fractures of heterotopic bone occur commonly and heal rapidly. Elevation, rest, splinting, and local application of ice are often helpful in controlling pain and swelling, and may be supplemented by narcotic analgesia, as needed. Fractures of normotopic bone need to be carefully evaluated, as in any patient. Closed reduction and splinting is sufficient for most fractures. Open reduction or internal fixation is almost never warranted and can lead to rapid onset of heterotopic ossification. Healing may be delayed in osteoporotic bone. Nonunion has not been reported in FOP (Einhorn & Kaplan, 1994).

I. Preventive Oral Healthcare in FOP

Individuals with FOP have developmental anomalies of the temporomandibular joints (TMJs) (Connor & Evans, 1982; Renton et al., 1982). Spontaneous or post-traumatic ankylosis of the TMJs is common and leads to severe disability with resultant difficulties in eating and poor oral hygiene. Great care must be taken not to provoke flare-ups of the TMJ (Luchetti et al., 1996).

Preventive oral and dental health care measures are essential in patients with FOP, especially during childhood years (Young et al., 2007). Periodontic and preventative oral care is crucial to prevent long-term dental and oral complications in FOP patients. Fluoridation of water is suggested for all patients who have FOP. The use of high dose fluoride toothpaste is recommended along with use of fluoride gels and rinses to help prevent the need for restorative dental care. Chlorhexidine rinses are encouraged to prevent gingivitis and tooth decay. Frequent flossing and brushing are necessary in patients with FOP as in anyone, but may be difficult due to limited jaw opening as FOP progresses. FOP patients who still have mouth opening can be treated with normal dental instruments as in unaffected individuals, but great care must be exercised to prevent overstretching of the TMJs during dental procedures. In patients who have ankylosed TMJs, professional instrumentation and special toothbrushes may be helpful, but are often limited to use on the buccal surfaces. Antimicrobial and fluoride rinses may be the only method to reach the lingual and palatal surfaces (Nussbaum et al., 2005).

J. Dental Anesthesia in FOP

FOP patients have limited options for dental anesthesia. Mandibular blocks are forbidden as they will lead to ossification of the pterygoid muscles and rapid ankylosis of the TMJ (Luchetti et al., 1996). Infiltration anesthesia is difficult in the mandibular posterior molar areas of permanent teeth. Successful anesthesia in mandibular primary teeth can be achieved by infiltration through the dental pulp.

Interligamentary infiltration may be helpful, if performed carefully. However, in some patients, this type of local anesthesia may not be possible. General anesthesia may be needed for dental care in FOP patients (Nussbaum et al., 1996; Nussbaum et al., 2005).

K. General Anesthesia in FOP

Preoperative preparation:

Preparation for a surgical procedure in an FOP patient should follow the same guidelines and recommendations as for all un-affected individuals. The American Society for Anesthesiologists has posted recommendations and guidelines: **Patient Education Web Site for the American Society of Anesthesiologists (ASA)** on the following web site: http://www.asahq.org/patienteducation.htm. The reader will find answers to questions related to preoperative preparation, pain management, and awareness during surgery.

A preoperative visit and meeting with the anesthesiologist prior to the date of surgery is crucial for conducting a safe and smooth general anesthesia course. The anesthesiologist should become familiar with FOP, learn about the extent of the disease affecting the individual patient, and carefully plan the perioperative anesthesia care. In the case of a patient presenting with advanced disease, significant ankylosis of multiple joints, and/or limited mobility and co-morbidities, the anesthesiologist should plan