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Authors

Zasloff, Michael A.
Rocke, David
Crofford, Leslie J.
et al.

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Treatment of Patients Who Have Fibrodysplasia Ossificans Progressiva With Isotretinoin

Michael A. Zasloff, MD, PhD,**; David M. Rocke, PhD†; Leslie J. Crofford, MD*; Gregory V. Hahn, MD**; and Frederick S. Kaplan, MD***

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

From *The Human Genetics Branch, National Institute of Childhood Diseases, Bethesda, MD; **Division of Molecular Orthopaedics and Metabolic Bone Diseases, Department of Orthopaedic Surgery, The University of Pennsylvania School of Medicine, Philadelphia, PA and †The Graduate School of Management, University of California at Davis, Davis, CA.

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Reprint requests to Frederick S. Kaplan, MD, Division of Metabolic Bone Diseases and Molecular Orthopaedics, Department of Orthopaedic Surgery, The University of Pennsylvania School of Medicine, Silverstein Two, 3400 Spruce Street, Philadelphia, PA 19104.

The phenotype and natural history of fibrodysplasia ossificans progressiva have been well defined.[4,7,9,10,24–26,36,37,40–43] Retinoids are a plausible family of therapeutic agents for fibrodysplasia ossificans progressiva, principally because of their ability to inhibit differentiation of mesenchymal tissue into cartilage

and bone and their ability to alter the response of skeletal precursor cells to growth factors.[20,38,45,49] Specifically, high doses of vitamin A cause limb malformations in the murine embryo by inhibiting the differentiation of limb mesenchyme.[27,32] Vitamin A also inhibits the differentiation of murine limb mesenchymal cells in culture, thus, effectively preventing chondrogenesis.[32] DeSimone and Reddi[13] have shown that retinoic acid and 13-cis-retinoic acid significantly reduced mesenchymal cell proliferation, endothelial cell proliferation, and differentiation of chondrogenic progenitor cells when administered during the proliferative phase of matrix induced endochondral bone formation in the rat. It has been shown recently that the combination of retinoic acid and bone morphogenetic protein (BMP) 4 synergistically induces apoptosis.[20]

The natural retinol vitamin A is stored in the liver over a wide range of intake and is toxic at high doses.[27,39] In contrast, the synthetic vitamin A derivative 13-cis-retinoic acid (isotretinoin, Roche Dermatologics, Nutley, NJ) is not effectively stored by the liver and is, therefore, less toxic than vitamin A for human use.[15,22,31,44] Thirteen-cis-retinoic acid, has been used widely for the treatment of several dermatologic[15,33] and neoplastic[6,28,29,48] disorders, and is the most effective agent for the treatment of cystic acne.[22,31,33,44] Extensive data in humans show that toxicity of chronic administration of this drug is minimal and principally related to effects on the skin and mucous membranes,[13,33] although paradoxical intramembranous hyperostosis has been noted at orthotopic and heterotopic sites.[5,14,16,17,23,34]

On the basis of these preliminary findings, the authors conducted a prospective study to assess the safety and efficacy of 13-cis-retinoic acid in the prevention of new heterotopic lesions in patients who had fibrodysplasia ossificans progressiva.

MATERIALS AND METHODS

An age matched internal control study was designed to determine the effectiveness of isotretinoin in the prevention of new heterotopic lesions in patients who had fibrodysplasia ossificans progressiva. After nearly 1 year of attempted recruitment, it was impossible to assemble an internal age matched and disease severity matched control group. Most patients older than 20 years of age had severe manifestations of fibrodysplasia ossificans progressiva and did not wish to receive isotretinoin. Most patients younger than 20 years of age had more mild manifestations of fibrodysplasia ossificans progressiva and did not wish to receive a placebo. In addition, the extreme paucity of patients who had fibrodysplasia ossificans progressiva made it impractical to assemble an internal age matched and disease severity matched control group. The decision was made, therefore, to use the data from the age controlled and disease severity controlled external control group on fibrodysplasia ossificans progressiva.[7,36] This external control group had been assembled in part to provide a valuable external baseline to evaluate potential new therapies when conditions in this extremely rare disease did not permit the use of a true randomized controlled trial.[36]

Twenty-one patients who had fibrodysplasia ossificans progressiva were recruited sequentially between January 1984 and December 1988, during an initial visit or followup visit to the fibrodysplasia ossificans progressiva clinic at the National Institutes of Health. The study was approved by the Investigational Review Board of the National Institutes of Health. All patients satisfied stringent diagnostic criteria for fibrodysplasia ossificans progressiva, that included congenital malformation of the great toes and progressive heterotopic ossification of soft tissues. Because there was no known effective treatment for fibrodysplasia ossificans progressiva, the authors did not consider intercurrent use of other medications (such as nonsteroidal antiinflammatory medications or bisphosphonates) as criteria for exclusion. Contraindications to the use of isotretinoin during pregnancy were reviewed with all teenaged girls as required, but childbearing was not an issue in the patient population.[30]

A detailed history was obtained and physical examination was performed on each patient at the beginning of the study. Radionuclide bone scans were performed on each patient at the time of entry into the study, at yearly intervals during the study, and at the conclusion of the study. A skeletal survey was performed at the time of entry into

the study, and at the conclusion of the study. Patients were contacted in person, by telephone, or by mail as many as 6 years after termination of the study, and asked to complete a brief questionnaire about the subsequent course of fibrodysplasia ossificans progressiva flareups.

For the purposes of this study, the investigators defined an anatomic region as that area typically represented by any of the following domains on clinical, radiographic, or radionuclide bone scan: the cervical spine, thoracolumbar spine, right shoulder, left shoulder, right elbow, left elbow, right hip, left hip, right knee, left knee, and jaw. The authors considered an anatomic region to be involved with fibrodysplasia ossificans progressiva if there was any clinical, radiographic, or radionuclide evidence of orthotopic or heterotopic ossification anywhere in that region. Conversely, a joint was considered to be uninvolved only if all three modes of evaluation (clinical examination, radiographic evaluation, and radionuclide bone scan) showed no evidence of orthotopic or heterotopic ossification in that region. A complete blood count, plasma transaminase levels, and plasma triglyceride levels were obtained on each patient at entry into the study, at 6–month intervals during the study, and at the conclusion of the study.

Patients who entered the study were treated with a single bedtime oral dose of isotretinoin at a concentration of 1 mg/kg per day. The dose was raised by 1 mg/kg per day for 2-week intervals until a final dose of 5 to 8 mg/kg per day was reached. The medication dosage was adjusted downward if side effects of cheilitis, xerosis, hair loss, dry nasal mucosa, or dry mouth developed in the patient.

Data on regional involvement were collated from the studies in each patient and from the external control study on fibrodysplasia ossificans progressiva.[7,36] A multivariate survival model was fit to the data using software developed specifically for this purpose.[1,11,19,46,47] Assessment of statistical significance was calculated using the robust variance approach.[46]

RESULTS

Twenty-one patients were enrolled in the study during the 5–year period between January 1984 and December 1988 (Table 1). There were 13 males and eight females ranging in age from 3 years to 21 years of age (median age, 14 years). The duration of treatment ranged from 4 months to 10 years (median duration, 3 years). The steady state dose of isotretinoin varied from 0.5 mg/kg per day to 8 mg/kg per day; (median steady state dose, 1.7 mg/kg per day). Seventeen of the 21 patients (81%) completed at least 1 year of therapy with isotretinoin, and 11 of the 21 patients (52%) completed a full 3 years of therapy with isotretinoin. Eight of the 21 patients (38%) elected to continue treatment for longer than 3 years.

Ten (48%) of the 21 patients received intercurrent treatment with an oral nonsteroidal antiinflammatory medication. Eight (38%) of the 21 patients received intercurrent treatment with oral etidronate at doses of between 4 mg/kg per day and 20 mg/kg per day (median dose of etidronate = 10 mg/kg per day.) Fourteen (67%) of the 21 patients received a nonsteroidal antiinflammatory medication or etidronate or both. Seven of the 21 patients (33%) received neither nonsteroidal antiinflammatory medications nor etidronate.

Eleven anatomic regions were assessed in 21 patients for a total of 231 anatomic regions (Table 2). One hundred forty-three anatomic regions were involved with orthotopic or heterotopic bone at the beginning of the study. One hundred forty-four anatomic regions were involved with orthotopic or heterotopic bone at the end of the study. There were 88 uninvolved anatomic regions at the beginning of the study, and 87 uninvolved anatomic regions at the conclusion of the study. Only one anatomic region that was completely uninvolved at the beginning of the study became involved during the course of the study because of an episode of blunt trauma to the left knee (Table 2; Patient 11). Heterotopic ossification developed rapidly in the patient at the site of trauma, and this patient was the only one in the study who sustained heterotopic ossification in a region that had been completely uninvolved at the time that isotretinoin therapy was begun.

TABLE 1. Isotretinoin Dosage Data: Adverse Reactions and Intercurrent Medications

Patient Number	Gender; Age at Entry (years)	Duration of Treatment (years)	Steady State Dose of Isotretinoin (mg kg/day)	Adverse Reactions From Isotretinoin	Intercurrent Medications
1	Male;4	10	0.5	D,T,M	Indomethacin
2	Male;6	5	8.0	D,T	Aspirin
3	Male;12	5	1.7	D,M	Etidronate
4	Male;11	1	0.8		—
5	Male;18	2	1.0	D	—
6	Female;14	0.3	5.0		
7	Male;17	3	1.0	D	Indomethacin and etidronate
8	Male;7	2	4.0	D,T,M	Etidronate
9	Female;16	4	1.5	—	Indomethacin
10	Female;3	3	4.0	T,M	Etidronate
11	Male;6	3	1.6	D,M	Indomethacin and Etidronate
12	Male;3	5	5.0	D	Indomethacin
13	Male;21	0.5	0.8		Etidronate
14	Male;8	0.5	5.0	D,T	Indomethacin
15	Male;21	2	2.7	D,M	
16	Female;19	0.3	1.0	D	
17	Female;15	5	5.0	—	Indomethacin and etidronate
18	Male;16	1	4.5	D,T,M	Indomethacin and etidronate
19	Female;21	5	0.8		Indomethacin
20	Female;16	1.5	1.2	—	
21	Female;5	5	4.0	D	

D = dryness/cheilitis; T = transient elevations in triglycerides; M = metaphyseal bands/growth arrest lines.

Major flareups of heterotopic ossification occurred at 38 of the 143 previously involved regions (27%) in 16 of the 21 patients (76%). Disease flareups during isotretinoin therapy were substantiated by clinical examination, radiographic assessment and radionuclide bone scan evaluation. There did not seem to be any important difference during or after isotretinoin therapy in the frequency of flareups in previously involved regions; however, the data did not allow testing of this hypothesis specifically. None of the patients thought that the isotretinoin was responsible for disease flareups during treatment, nor did there seem to be any increased frequency of immediate posttreatment flareups.

High dose isotretinoin therapy (3–8 mg/kg per day) produced a high incidence of mild adverse reactions. The most common side effects of isotretinoin therapy were dryness of the skin and cheilitis. These side effects occurred in 13 of 21 patients (62%) and required lowering the dose of isotretinoin or discontinuation of therapy. Transient minor elevations in plasma triglyceride levels occurred in six of the 21 patients (29%). Dense metaphyseal bands (growth arrest lines) were seen in seven of the 21 patients (33%) after 1 year of therapy. The metaphyseal bands disappeared after a lowering of the isotretinoin dose to below 2 mg/kg per day. Plasma transaminase levels were not significantly elevated in the patients. One child (Table 1; Patient 21) sustained a traumatic fracture of the left proximal humerus while receiving a steady state dose of isotretinoin of 4 mg/kg per day. The fracture healed uneventfully within 6 weeks after nonoperative treatment. There was no evidence of posttraumatic heterotopic ossifica-

tion. Periosteal hyperostosis was not noted in any of the patients, but might have been difficult to assess.

Among the 11 patients who were able to complete 3 or more years of isotretinoin therapy, steady state doses ranged from 0.5 mg/kg per day to 8 mg/kg per day (median, 1.7 mg/kg per day). In the 11 patients who received medication for 3 years or more, there was no significant difference in the rate of new heterotopic ossification between those who received more than 1.7 mg/kg per day of isotretinoin and those who received less than 1.7 mg/kg per day of isotretinoin. Also, there was no significant difference in the rate of new heterotopic ossification between those 14 patients who received intercurrent treatment with nonsteroidal antiinflammatory medications or etidronate and those seven patients who received only isotretinoin. However, the very small sample sizes mean that differences may have existed that could not be detected with the present data.

The relative risk of heterotopic ossification in a previously uninvolved anatomic region for those treated with isotretinoin was 0.117 corresponding to a reduction in risk of 88% (95% confidence interval: 0.008–0.497; 50% reduction to 99% reduction), compared with a relative risk of 1.00 for those patients in the external control group ($p = 0.0013$).

DISCUSSION

The data suggest that oral isotretinoin therapy may have inhibited heterotopic ossification in completely uninvolved anatomic regions in patients who had fibrodysplasia ossificans

TABLE 2. Involvement of Sites With Heterotopic Ossification in 21 Patients With Fibrodysplasia Ossificans Progressiva

Patient Number	Cervical Spine; Thoracolumbar Spine; Jaw	Shoulder (right; left)	Elbow (right; left)	Hip (right; left)	Knee (right; left)
1	+;⊕;–	+;–	–;–	+;+	–;–
2	⊕;⊕;–	⊕;⊕	–;+	–;–	–;–
3	⊕;⊕;–	+;⊕	+;–	–;–	–;–
4	+;⊕;–	+;–	+;–	+;+	–;⊕
5	+;+;–	+;+	–;–	+;+	–;–
6	+;+;–	+;–	+;–	+;⊕	⊕;⊕
7	+;+;–	+;+	+;+	+;⊕	–;–
8	⊕;⊕;–	⊕;+	–;–	–;+	–;–
9	+;+;–	+;⊕	⊕;⊕	+;⊕	+;–
10	⊕;⊕;–	⊕;⊕	–;–	+;–	–;–
11	+;+;+	+;+	–;–	–;–	–;⊖
12	+;+;–	+;–	+;–	⊕;⊕	+;+
13	+;⊕;+	⊕;⊕	+;+	+;+	+;+
14	+;+;+	+;+	–;–	+;+	–;–
15	+;+;⊕	+;+	–;–	+;+	+;+
16	+;+;–	+;+	+;+	+;+	–;–
17	–;+;+	+;⊕	–;–	–;+	+;+
18	+;+;⊕	+;⊕	–;–	⊕;–	–;–
19	+;+;–	+;+	+;+	⊕;+	+;+
20	+;+;–	⊕;–	+;–	–;+	–;–
	+;+;–	+;+	–;–	–;–	–;–

+ = initial involvement of site; – = initial noninvolvement of site; ⊕ = exacerbation of involvement at a previously involved site; ⊖ = new involvement of previously uninvolved site.

progressiva. The authors have no evidence as to whether isotretinoin changed the risk of heterotopic ossification in anatomic regions that were even minimally involved with orthotopic or heterotopic bone at the time therapy was instituted. Although isotretinoin seemed to have some limited use in the prevention of spontaneous heterotopic ossification in patients who had fibrodysplasia ossificans progressiva, it had no apparent benefit in the prevention of heterotopic ossification after surgery in those patients.[12] Furthermore, it is doubtful that isotretinoin had any effect in the prevention of heterotopic ossification after soft tissue trauma.

Most of the patients who received isotretinoin already had experienced ossification of the cervical spine, thoracolumbar spine, and upper limbs, and there was no benefit of therapy in those regions. If there was a beneficial regional effect of isotretinoin therapy, it was in the lower limbs (especially at the hips and knees), because those anatomic regions were less likely to be affected with orthotopic or heterotopic ossification at a young age when isotretinoin therapy was instituted. Despite the potential benefits of isotretinoin, it was clearly not a panacea for fibrodysplasia ossificans progressiva, because 16 of the 21 patients (76%) had major flareups of previously involved areas develop while administered isotretinoin therapy. Although these flareups were likely attributable to the natural history of the disease, the authors cannot exclude the possibility of a paradoxical stimulation of orthotopic or heterotopic ossification in regions already afflicted with those processes.[5,15,16,17,23,34]

The temporal and spatial progression of lesions in patients who have fibrodysplasia ossificans progressiva follows patterns similar to those seen during normal skeletal embryogenesis.[7,26,42] The molecular basis of this sequential involvement is unknown but may involve the secretion of diffusible morphogens that establish the tissue specific patterns of gene expression.[42] Retinoids profoundly affect morphogenetic gradients and can induce and inhibit gene expression.[18,35,38,45,48,49] Retinoids in combination with BMP 4 synergistically induce apoptosis.[20] It is clear, for example, that the retinoids have different effects on primitive mesenchymal tissue and on differentiated chondroosseous tissue.[13,38,45,49] It is possible that these developmental differences in susceptibility to retinoid exposure could underlie the observed findings of isotretinoin therapy on patterns of orthotopic and heterotopic ossification in patients who have fibrodysplasia ossificans progressiva.

Despite the demonstration of some potential benefits of isotretinoin, there were several major shortcomings of the study. First, there was no comparable internal control group. Such a control group was virtually impossible to assemble considering the rarity of the disease, and the unwillingness of patients to participate in a controlled randomized study. It is doubtful that a randomized study could ever be performed in this group of patients.[3,21]

Second, there were several ways in which the data from this study were not exactly comparable with the data in the external control group.[7,36] In this study, regional anatomic involvement was assessed by clinical, radiographic, and radionuclide bone scan evaluation. In the external control group, regional anatomic involvement was assessed from patient questionnaires and clinical data alone. These differences in the methods of assessment resulted in a different definition of an involved anatomic region. This had two effects. First, because the definition of involvement was more sensitive in this study, the results were biased against the effectiveness of isotretinoin. Thus, a significant difference would have been harder to achieve, but should have been believable if it had occurred. Second, a patient would tend to have fewer anatomic regions at risk for future involvement under the criteria used in this study than under the criteria used in the external control survey; however, this produced no known bias in favor of isotretinoin effectiveness. Despite these limitations, the control population represented the most valid exter-

nal control group that the authors could assemble for assessment of the clinical efficacy of isotretinoin.

Bailar et al,[3] have provided a detailed guideline for interpreting the value of studies without internal controls: "Sometimes questions of clinical interest can be addressed only by investigations without internal controls. Such studies nearly always make use of other types of comparisons (external controls) such as historical controls. These studies have a small but important and unique role in clinical investigation."

Bailar and colleagues described five seminal features that added to the strength and clinical value of such studies: "1. An intent by the investigator expressed before the study that the treatment will affect the outcomes reported. 2. Planning of the analysis before the data are generated. 3. Articulation of a plausible hypothesis before the results are observed. 4. A likelihood that the results would have been of interest even if they had been opposite. 5. Reasonable grounds for generalizing the results from the study subjects to a broader group of patients. In spite of potential pitfalls, carefully selected and reported studies without internal controls can play a substantial part in the acquisition of scientific knowledge."[3] Each of the five criteria for a valid external control group described by Bailar et al were met by this study.

Third, there were major differences in the steady state medication dosages throughout the study because many patients could not tolerate the unpleasant side effects of chronic high dose (5–8 mg/kg per day) isotretinoin therapy. Therefore, the dose of medication was reduced to the highest level tolerable in each patient. Despite the wide range of steady state medication dosages, there seemed to be no important difference in the inhibition of new heterotopic lesions in previously uninvolved regions between patients who received less than the median dose of 1.7 mg per day, and those who received more than that amount of medication. The data therefore suggested that a dose of isotretinoin between 1 and 2 mg/kg per day was sufficient to achieve the observable effects while also minimizing the risk of unpleasant side effects.

Fourth, patients in this study were treated for variable lengths of time. Some were unable to tolerate the side effects of the high dose medication, and stopped the medication early in the course of the protocol. Others who experienced major disease flareups while taking the isotretinoin, became discouraged and stopped the medication. Still others tolerated the isotretinoin, and elected to continue the medication indefinitely. Thus, the study may have inadvertently self selected for patients who responded more favorably to isotretinoin.

If isotretinoin therapy is considered, the authors recommend that the total daily steady state dose not exceed 2 mg/kg per day. Patients must be apprised fully of the potential side effects of treatment. Clinical symptoms, plasma triglyceride, and transaminase levels should be monitored.

To date, no modality (including isotretinoin) used in the prevention or treatment of fibrodysplasia ossificans progressiva has proven to be fully effective in changing the inexorable natural history of the condition.[2] Any enthusiasm that may exist for the use of isotretinoin in the treatment of patients who have fibrodysplasia ossificans progressiva must be tempered even further by the stark realization that the study was flawed by an imperfect control group, and that under the best of circumstances isotretinoin is not a panacea. Nevertheless, the limited benefits derived from isotretinoin therapy have revealed an option for treating some patients who have fibrodysplasia ossificans progressiva. The authors think that the search for a molecular cause for fibrodysplasia ossificans progressiva will lead to much more fruitful therapies.[8,40,42]

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