

Desmoid Tumors in Familial Adenomatous Polyposis: A Pilot Project Evaluating Efficacy of Treatment With Pirfenidone

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OBJECTIVE: Pirfenidone (Deskar, Marnac Inc., Dallas, TX), 5-methyl-1-phenyl-2-(1H)-pyridone, is a broad-spectrum, noncytotoxic, oral antifibrotic agent that is reported to inhibit or block the action of cytokine growth factors: transforming growth factor β 1, platelet-derived growth factor, epidermal growth factor, and fibroblast growth factor, and to prevent formation of new fibrotic lesions.

METHODS: We enrolled 10 women and four men with extensive familial adenomatous polyposis (FAP)-associated desmoid disease in a 2-yr open-label treatment trial with oral pirfenidone. Imaging of desmoids was conducted at baseline and 6, 12, and 24 months.

RESULTS: No drug toxicity or drug intolerance was encountered. Seven patients dropped out (three because of progressive disease), and seven continued for at least 18 months. Of those that continued, two had partial but significant reduction in the size of all desmoids beginning in the first 6 months of treatment, and two others experienced relief of symptoms without change in desmoid size. Three patients experienced no change in tumor size or symptoms.

CONCLUSION: Pirfenidone is well tolerated by patients with FAP-associated desmoid tumors. Some patients with FAP/desmoid tumors treated with pirfenidone had regression of tumors, some had progression, and some had no response. Patients with rapidly growing tumors did not respond to pirfenidone. A placebo-controlled trial is needed to determine whether there is a subset of patients for whom pirfenidone may result in partial shrinkage of desmoid tumors, because the natural history of desmoid tumors is not predictable or understood. (Am J Gastroenterol 2003;98:1868–1874. © 2003 by Am. Coll. of Gastroenterology)

INTRODUCTION

Desmoid tumors are locally aggressive but histologically benign monoclonal neoplasms composed of proliferating differentiated fibroblastic cells with ill-defined cytoplasmic

borders, delicately staining nucleoli, and rare mitoses. Desmoids that are not related to underlying familial adenomatous polyposis (FAP) are very rare, estimated to occur in two to five persons per million per year (1, 2). However, desmoid tumors occur in at least 10–17% of individuals with FAP, giving a comparative risk of 852 relative to the general population.

Gurbaz *et al.* (3) reported on a series of 825 FAP patients from 161 kindreds. In this group, 30% of kindreds had at least one family member with a desmoid tumor. The female:male ratio was 1.4. Desmoid risk in FAP family members of a desmoid patient was 25% in first-degree relatives compared with 8% in third-degree relatives. Lofti *et al.* (4) reported that 24 of 183 FAP patients had mesenteric fibromatosis (another term for desmoid), with a female:male ratio of 2.5 and with median age of 31 yr in women and 37 yr in men. Twenty-five percent of the fibromatosis group had extraabdominal desmoids, as well as mesenteric lesions.

The diagnosis of a desmoid tumor is often made on clinical grounds, based on history of FAP and history of preceding trauma (*e.g.*, surgical incision); tumors often develop at such trauma sites. CT may be useful in defining the extent of deep tumors, but desmoid CT appearance is heterogeneous with respect to density, definition, and change in size, not only between different patients but also in patients with more than one lesion; thus, measuring tumors is imprecise (5). Magnetic resonance imaging (MRI) is being used increasingly in FAP, but no studies comparing CT with MRI have been reported. Fine needle aspiration of desmoids is often not helpful because of lack of cellularity. Definitive diagnosis, if intraoperative appearance is ambiguous, requires incisional biopsy, which is often avoided because of concern that a surgical incision will incite additional tumor growth. These properties of desmoid tumors have made research on desmoid tumors extremely challenging.

Treatment for desmoids (reviewed below) has not been systematically studied, and no treatment has been consis-

Table 1. Experimental Studies Reporting Antifibrotic Properties of Pirfenidone

Animal Models	Target	Reference
Hamster	Bleomycin-induced pulmonary fibrosis	30–35
Rat	Chemically induced sclerosing peritonitis	36
Hamster	Asbestos-induced lung fibrosis	9
Mice	Cyclophosphamide-induced pulmonary fibrosis	37
Nude mice	Human keloid xenograft	38
Rat	Experimentally induced glomerulosclerosis	39–43
Dog	Idiopathic pulmonary fibrosis	44, 45
Human	Pulmonary fibrosis	46
Human	Sclerosing peritonitis	47
Human	Keloids	48

tently effective; the best treatment for desmoid tumors remains undefined.

Pirfenidone (Deskar), 5-methyl-1-phenyl-2-(1H)-pyridone, is a low molecular weight synthetic, nonpeptide, non-cytotoxic oral antifibrotic agent. It is reported to inhibit the action of cytokine growth factors: transforming growth factor β 1, platelet-derived growth factor, epidermal growth factor, and fibroblast growth factor (6–8). *In vivo* animal fibrosis models and *in vitro* and *in vivo* human fibroblast/other mesenchymal cell culture data suggest pirfenidone may be a useful pharmacologic agent for treatment of a host of disorders resulting from fibrosis (Table 1). These studies have repeatedly demonstrated that pirfenidone (1) inhibits excessive proliferation of human mesenchymal cells and (2) inhibits excessive biosynthesis of collagen matrix by these mesenchymal cells (6–9). Because of the reported properties of pirfenidone, we considered it a good candidate drug for a treatment trial of desmoid tumors in FAP.

MATERIALS AND METHODS

Patients with known FAP-associated desmoid disease were referred to the principal investigator, who conducted a complete history and physical examination and obtained baseline laboratory values (including complete blood cell counts, general chemistry studies, and urinalysis), which were repeated at 6 wk, 12 wk, and every 12 wk throughout the study. Baseline imaging of the desmoid tumors by CT was obtained before starting treatment, and at 6, 12, and 24 months. We enrolled 14 adults with extensive desmoid disease in a 2-yr, open-label treatment trial with oral pirfenidone 800 mg *t.i.d.* (Table 2). We included all adult patients who presented for treatment, who had bi-dimensionally measurable disease, were able to take oral medicine, were willing to stop their current desmoid treatment, and could give informed consent. This included 10 women and four men, with mean ages of 32 (range: 20–49) and 41 (range: 21–61) yr, respectively. Nine subjects had prior treatment with tamoxifen, eight with sulindac, two with

maximal radiation, and one had prior cytotoxic chemotherapy. Imaging of desmoid tumors by CT was conducted at baseline, 6, 12, and 24 months, and the sizes of the desmoid tumor(s) were compared by conducting bi-dimensional measurements of the tumors.

RESULTS

No drug toxicity or drug intolerance was encountered. Seven patients dropped out either because of obvious progressive disease and a desire for more aggressive treatment or because they lost interest in continuing when the first follow-up visit showed no improvement, and one patient simply changed her mind about being in the trial 1 month after beginning. No patient had to discontinue because of drug intolerance or laboratory toxicity. Most patients took their medication with food to prevent nausea, and despite the preexisting GI disorders in most study participants, pirfenidone was tolerated by all.

Seven participants continued for at least 18 months. Of those that continued, two had partial but significant reduction, which began within the first 6 months of treatment, in the size of all desmoids. Figure 1 shows the desmoid tumors of patient 8 before and after treatment. Her largest tumor (Fig. 1A) measured 15×6 cm before treatment and was 7×3 cm (Fig. 1B) after treatment. Her second tumor (Fig. 2A) was 6×6 cm before treatment and not detectable after treatment (Fig. 2B). For patient 13, her largest tumor was 9.0×6.5 cm before treatment (Fig. 3A) and 7.4×3 cm after treatment (Fig. 3B), whereas her second tumor was 8.0×7.0 cm before (Fig. 4A) and 8.1×2.0 cm after treatment (Fig. 4B).

Two other patients experienced significant relief of symptoms without any appreciable size reduction in their tumors, including a 61-yr-old man with a large gluteal/posterior thigh and calf desmoid. Before treatment, he was not able to sit for more than an hour because of pain and numbness in his leg. Within days of starting pirfenidone, he reported relief of pain and return of feeling in his affected leg, such that he could drive for hours without stopping and could return to playing golf. He also thought his desmoid felt softer in consistency, though we could not confirm this by objective measures. This symptom relief persisted for the entire 2 yr of his treatment. A second patient with no apparent size change in her mesenteric desmoid had nearly weekly partial bowel obstructions before treatment, manifesting as abdominal pain and vomiting, requiring narcotics and a liquid diet. Approximately 5 months after starting pirfenidone, she stopped having these attacks, and this lasted for approximately 1 yr, at which time she began to have unrelated problems with her urinary stent (infections and fevers) and consequently was quite ill, though not with her original desmoid symptoms. Three patients had no change in tumor size or symptoms. However, one of these with no apparent radiographic desmoid size change spontaneously passed her ureteral stent and did not require re-

Table 2. Summary of Patient Demographics and Treatment Outcomes

Patient	Age at enrollment (yr)	M/F	Age at colectomy (yr)	Age at First Desmoid (yr)	Location of Desmoid(s)	Prior Desmoid Treatment	Months Taking Pirfenidone	APC Gene Abnormality	Pirfenidone Response
1	26	F	23	24	Intraabdominal, pelvic	Tam, sul	3		Tumor growth rapid and steady. Proceeded to cytotoxic chemotherapy
2	31	F	26		Intraabdominal	Tam, sul	3		No change. Proceeded to chemotherapy
3	20	F	Not yet	15	Abdominal wall and breast	Surg	1		Dropped out of trial before evaluation
4	30	F	22	25	Intraabdominal	Surg, tam, sul, maximal radiation	6		Some tumors grew; some shrunk; some no change
5	61	M	40	45	Gluteal, posterior thigh	Tam	24		No change in size; symptoms markedly improved
6	29	F	27	27	Intraabdominal	Sul	18	Truncation seg 3, codon 1450	No change by CT; ureteral stent no longer needed
7	21	M	18	18	Intraabdominal	None	18		No change
8	32	F	28	29	Pelvic	Surg, tam, tor, sul	24	Truncation seg 2, codon 1064	All tumors smaller (see Fig. 1)
9	49	M	NA*	44	Neck and shoulder	Maximal radiation	6	Truncation codon 1526, Alu I insertion	Discontinued trial for more aggressive therapy
10	43	F	32	38	Multiple extra-abdominal	Multiple surg	6	Truncation codon 1532	One tumor grew, one shrunk, others unchanged
11	34	M	32	33	Lower abdominal wall	Sul	3	Truncation seg 3, codon 1575	Proceeded to cytotoxic therapy
12	24	F	19	20	Intraabdominal	Sul	24		No change
13	49	F	42	42	Intraabdominal and abdominal wall	Sul, tam, surg	24	Truncation seg 3, codon 1472	Both masses progressively smaller (see Fig. 2)
14	40	F	27	27	Intraabdominal	Tam, tor, surg, methotrexate + vinblastine; doxorubicin + other	24	Truncation seg 1, codon 267	Symptomatic improvement but tumors same; see text

M = male; F = female; Tam = tamoxifen; Sul = sulindac; Tor = toremifene; Surg = surgical excision, partial or complete attempted.

* Familial desmoid disease, family reported by Halling et al (1999).

stenting. Demographics of all 14 enrollees and their responses to pirfenidone treatment are detailed in Table 2.

Genotyping was performed on all study participants. Results are listed in Table 2 and seem fairly typical of adenomatous polyposis coli (APC) mutations in polyposis in general. Of note, the patients with the size change in tumors did not have similar locations of their mutations.

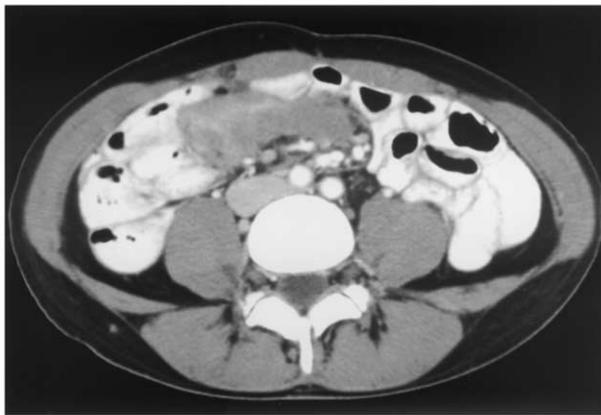
DISCUSSION

In recent years, scientists have begun to study the molecular biology of desmoid tumors both in FAP and in non-FAP patients, but much remains poorly understood. FAP is caused by mutations in the APC tumor suppressor gene on chromosome 5q21. Desmoids in FAP have been shown to have both somatic and germline APC mutations in FAP,

consistent with APC being involved with the pathogenesis of desmoids (10, 11), and mutation analysis indicates some genotype-phenotype correlations, with 3' APC mutations being strongly associated with development of desmoids (12, 13). Desmoids contain elevated β -catenin protein levels (14). Unlike most preneoplastic and neoplastic lesions, desmoids have no detectable telomerase activity (15). Hoos *et al.* (16) reported on 24 desmoid tumors that were analyzed for immunohistochemical expression of Ki-67, Bcl-2, retinoblastoma gene product, and p53: Desmoid tumors had a normal phenotype for all these markers. Mills *et al.* (17) used immunohistochemistry to demonstrate localized increased expression of cytokines in aggressive fibromatosis, including epidermal growth factor, transforming growth factor β , tumor necrosis factor α , vascular endothelial growth factor, and interleukin-1- β but no increase in plate-



A

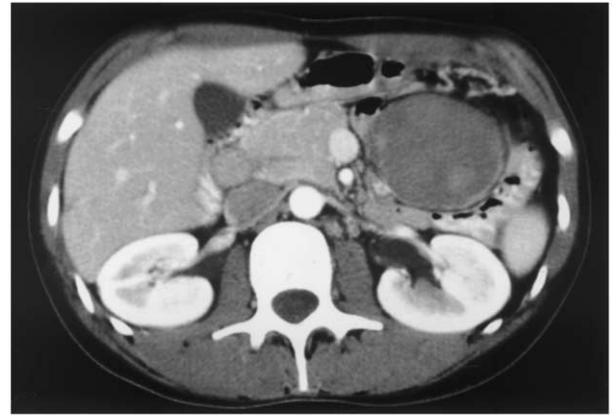


B

Figure 1. Patient 8 with tumor before (A) and after (B) treatment. We selected the CT level showing maximal tumor size, which for this tumor appeared to be at a different level than the pretreatment level.

let-derived growth factor. Of 24 desmoid tumors studied by Serpell *et al.* (18), all were estrogen- and progesterone-receptor negative. Most were proliferating cell nuclear antigen positive. Dubus *et al.* (19) reported that immunohistochemical staining with anti-TrkC antibody was positive in a desmoid tumor, but a Tel-TrkC fusion transcript was not present, as is often seen in congenital fibrosarcomas. These studies are beginning to shed light on the biology of desmoid tumors and may help define categories of medications most likely to be effective in treatment of desmoid tumors.

Wide local excisions, if feasible, may offer the best chance for cure of desmoids, but recurrence is common (approximately 40%) even after apparently complete resection (20). Rodriguez-Bigas *et al.* (21) reported on 21 patients with surgical procedures related to desmoid tumors. Major morbidity after palliative or curative surgery was 47%. They concluded that “unresectability and recurrence are more common than cure” and that “palliative and curative resections have a high morbidity.” Because long-term survival is possible with unresected desmoids, authors in this field often recommend operative management only to address



A



B

Figure 2. Patient 8 with second tumor before (A) and after (B) treatment.

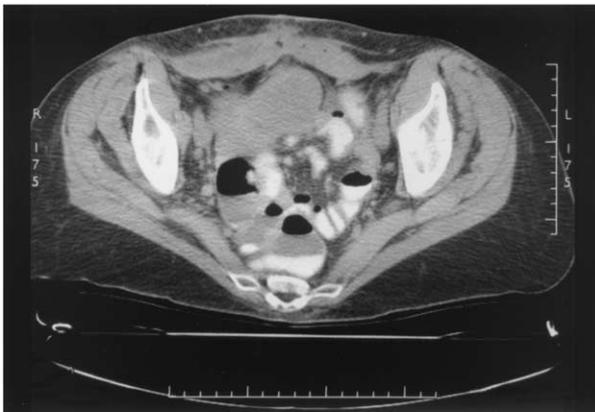
functional problems caused by desmoids (21, 22). Recently, Chatzipetrou *et al.* (23) reported the outcome of intestinal transplantation for FAP-associated mesenteric desmoid tumors in nine patients, seven of whom were alive at 11–53 months after transplantation.

Literature on radiation therapy in desmoids was reviewed in 1996 by Anthony *et al.* (24). Forty-six patients, reported in four articles, were identified. The largest group reported a 77% local control rate with adjuvant radiation therapy. No control group with operation alone was used. Reported complications associated with use of radiation therapy include soft tissue fibrosis with limited joint mobility, soft tissue necrosis, skin ulcerations, bowel obstruction, and intestinal fistulas. Looking again at the literature, Nuytens *et al.* (25) compared patients with surgery alone, surgery with radiotherapy, and radiotherapy alone, and concluded that the best local tumor control was achieved by radiotherapy alone or a combination of radiotherapy with surgery, even in cases with free surgical margins.

A variety of pharmacologic agents have been used to treat desmoids in FAP: cytotoxic agents, cyclic adenosine monophosphate modulators (theophylline, chlorothiazide, ascorbic acid, testolactone), cyclooxygenase inhibitors (especial-



A



B

Figure 3. Patient 13 with first tumor before (A) and after (B) treatment.



A



B

Figure 4. Patient 13 with second tumor before (A) and after (B) treatment.

ly sulindac), interferon α , and antihormonal agents (tamoxifen, toremifene) (26, 27). Each has had reported successes in uncontrolled studies. Overall, it appears that noncytotoxic therapy is generally ineffective in progressive desmoid disease, whereas some response to cytotoxic chemotherapy has been seen in the majority of cases with progressive disease (28, 29).

We took a candidate drug approach in selecting pirfenidone (because an animal model of desmoid tumor was not developed until after the study began), based on pirfenidone's reported *in vitro* antifibrotic properties and on results of treatment in laboratory animals with a variety of fibrosing disorders, which showed promising results. We gained some knowledge from this small trial. First, the agent used, pirfenidone, seems to be well tolerated, even in individuals with preexisting altered GI function and anatomy. In addition, no drug-related biochemical toxicity was encountered.

Second, we were readily able to enroll our maximum number of eligible patients and had to turn away an even greater number of additional patients, indicating the level of interest and need for research in this area. Thus, despite the rarity of FAP-associated desmoid tumors in the general

population, we believe a larger multicenter clinical trial would be feasible.

Third, interpretation of any future clinical trials of treatment of desmoid tumors will be greatly enhanced by having an untreated/placebo control group. Although we had two patients with significant tumor shrinkage and two more with marked reduction in clinical symptoms, we are not able to conclude that these effects are attributable to pirfenidone and not just the natural history of desmoid tumors. We knew of this potential study limitation at the outset; however, it seemed important to determine whether there were sufficient numbers of patients interested in clinical trials of desmoid tumors to conduct a study, and it seemed reasonable to determine whether there were *any* potential responders at all in a phase II trial of pirfenidone before trying to conduct a large, placebo-controlled trial. We are sufficiently encouraged by having two people with tumor shrinkage and two more with symptom relief in this small study to begin planning a larger controlled trial of pirfenidone in the treatment of FAP-associated desmoid tumors.

Our experience with pirfenidone needs to be compared with what might have been expected in a patient population

such as this if left untreated. How often do desmoid tumors regress spontaneously? The answer is not known. Among clinicians caring for patients with desmoid tumors, there are anecdotal reports of tumor regression related in time to virtually all of the treatments listed above and of spontaneous regression as well. Unfortunately the frequency of tumor regression among patients with desmoid tumors has never been determined. We reviewed the Mayo Clinic medical records of 75 patients who were seen for FAP-associated desmoid tumors at Mayo Clinic Rochester between 1975 and 1999. In this clinic-based population, we identified only one patient who had an apparent spontaneous regression of a desmoid tumor, and that was in an FAP patient with an intraabdominal tumor (unpublished observations). Although this was a retrospective review, and not all patients had serial scans, it is our impression that regression of desmoid tumors is not a common event, and to observe two of seven patients on pirfenidone having regression of large tumors within 1 yr is intriguing.

We were surprised by the improvement in clinical symptoms experienced by two of the patients, as described above. Although we cannot rule out possible placebo effects, improvement in the male patient occurred so soon after treatment initiation that we postulate that alteration of cytokines by pirfenidone, rather than tumor size, may have mediated a decrease in his symptoms. With the female patient, her improvement happened after several months of treatment, and it may be possible that she had some change in tumor size that was not radiographically evident. Future studies with pirfenidone need to prospectively look at quality of life.

In conclusion, pirfenidone is well tolerated by patients with FAP-associated desmoid tumors. Some patients with FAP/desmoid tumors treated with pirfenidone had regression of tumors, some had progression, and some had no response. Patients with rapidly growing tumors did not respond to pirfenidone. Two patients had symptom relief without tumor shrinkage, suggesting a potential quality-of-life effect unrelated to tumor size alone. A placebo-controlled trial is necessary to determine whether there is a subset of patients for whom pirfenidone may result in partial shrinkage of desmoid tumors, given that the natural history of desmoid tumors is not predictable or understood.

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REFERENCES

1. Reitamo JJ, Pekka H, Nykri E. The desmoid tumor I. Incidence, sex, age, and anatomic distribution in the Finnish population. *Am J Clin Pathol* 1982;77:665-73.
2. Dahn I, Jonsson N, Lundh G. Desmoid tumors. A series of 33 cases. *Acta Chir Scand* 1963;126:305-14.
3. Gurbaz AK, Giardiello FM, Petersen GM, et al. Desmoid tumours in familial adenomatous polyposis. *Gut* 1994;35:377-81.
4. Lofti AM, Dozois RR, Gordon H, et al. Mesenteric fibromatosis complicating familial adenomatous polyposis: Predisposing factors and results of treatment. *Int J Colorectal Dis* 1989;4:30-6.
5. Brooks AP, Reznick RH, Nugent K, et al. CT appearances of desmoid tumors in familial adenomatous polyposis. Further observations. *Clin Radiol* 1994;49:601-7.
6. Marnac, Inc. In vivo research programs with experimental models of fibrotic disorders. Dallas, TX: Basic Research Files of Marnac, Inc., 1994:75225.
7. Lee BS, Margolin SB, Nowak RA. Pirfenidone: A novel pharmacological agent that inhibits leiomyoma cell proliferation and collagen production. *J Clin Endocrinol Metab* 1998; 83:219-23.
8. Lefkowitz SS, Margolin SB. Pirfenidone inhibits tumor necrosis factor and subsequent endotoxin shock. Abstract presented at the Fourth International Symposium on Clinical Immunology; June 19-22, 1997; Amsterdam, The Netherlands.
9. Margolin SB, Lefkowitz SS. Pirfenidone: A novel pharmacologic agent for prevention and resolution (removal) of lung fibrosis. *FASEB J* 1994;8:A382 (abstract).
10. Miyaki M, Konishi F, Kikuchi-Yanoshita R, et al. Coexistence of somatic and germ-line mutations of the APC gene in desmoid tumors from patients with familial adenomatous polyposis. *Cancer Res* 1993;53:5079-82.
11. Giarola M, Wells D, Mondini P, et al. Mutations of adenomatous polyposis coli (APC) gene are uncommon in sporadic desmoid tumours. *Br J Cancer* 1998;78:582-7.
12. Caspari R, Olschwang S, Friedl W, et al. Familial adenomatous polyposis: Desmoid tumors and lack of ophthalmic lesions (CPRPE) associated with APC mutations beyond codon 1444. *Hum Mol Genet* 1995;4:337-40.
13. Halling KC, Lazzarola CR, Honchel R, et al. Hereditary desmoid disease in a family with a germline Alu I repeat mutation of the APC gene. *Hum Hered* 1999;49:97-102.
14. Li C, Bapat B, Alman BA. Adenomatous polyposis coli gene mutation alters proliferation through its beta-catenin-regulatory function in aggressive fibromatosis (desmoid tumor). *Am J Pathol* 1998;153:709-14.
15. Scates DK, Clark SK, Phillips RK, et al. Lack of telomerase in desmoids occurring sporadically and in association with familial adenomatous polyposis. *Br J Surg* 1998;85:965-9.
16. Hoos A, Lewis JJ, Antonescu CR, et al. Characterization of molecular abnormalities in human fibroblastic neoplasms: A model for genotype-phenotype association in soft tissue tumors. *Cancer Res* 2001;61:3171-5.
17. Mills BG, Frausto A, Brien E. Cytokines associated with the pathophysiology of aggressive fibromatosis. *J Orthop Res* 2000;18:655-62.
18. Serpell JW, Tang HS, Donovan M. Factors predicting local recurrence of desmoid tumors including proliferating cell nuclear antigen. *Aust N Z J Surg* 1999;69:782-9.
19. Dubus P, Coindre JM, Groppi A, et al. The detection of Tel-Trk chimeric transcripts is more specific than TrkC immunoreactivity for diagnosis of congenital fibrosarcoma. *J Pathol* 2001;193:88-94.
20. Easter DW, Halasz NA. Recent trends in the management of desmoid tumors. Summary of 19 cases and review of the literature. *Ann Surg* 1989;204:765-9.
21. Rodriguez-Bigas M, Mahoney MC, Karakousis CP, et al. Desmoid tumors in patients with familial adenomatous polyposis. *Cancer* 1994;74:1270-4.
22. Jones IT, Fazio VW, Weakley FL. Desmoid tumors in familial polyposis coli. *Ann Surg* 1986;204:94-7.

23. Chatzipetrou MA, Tzakis AG, Pinna AD, et al. Intestinal transplantation for the treatment of desmoid tumors associated with familial adenomatous polyposis. *Surgery* 2001;129:277-81.
24. Anthony T, Rodriguez-Bigas M, Weber TK, et al. Desmoid tumors. *J Am Coll Surg* 1996;182:369-77.
25. Nuyttens JJ, Rust PF, Thomas CR Jr, et al. Surgery versus radiation therapy for patients with aggressive fibromatosis or desmoid tumors: A comparative review of 22 articles. *Cancer* 2000;88:1517-23.
26. Hardell L, Breivald M, Hennerdal S, et al. Shrinkage of desmoid tumor with interferon alfa treatment: A case report. *Cytokines Cell Mol Ther* 2000;6:155-6.
27. Samuels BL. Management of recurrent desmoid tumor after surgery and radiation: Role of cytotoxic and non-cytotoxic therapies. *Surg Oncol* 1999;8:191-6.
28. Soravia C, Bert T, McLeod RS, et al. Desmoid disease in patients with familial adenomatous polyposis. *Dis Col Rectum* 2000;43:363-9.
29. Poritz LS, Blackstein M, Berk T, et al. Extended follow-up of patients treated with cytotoxic chemotherapy for intra-abdominal desmoid tumors. *Dis Col Rectum* 2001;44:1268-73.
30. Iyer SN, Gurujeyalakshmi G, Giri SN. The mechanism for the antifibrotic action of pirfenidone in the bleomycin-hamster model for lung fibrosis. *FASEB J* 1995;9:A169 (abstract).
31. Iyer SN, Wild JS, Schiedt MJ. Dietary intake of pirfenidone ameliorates bleomycin-induced lung fibrosis in hamsters. *J Lab Clin Med* 1995;125:779-85.
32. Gurujeyalakshmi G, Hollinger MA, Giri SN. Modulation of platelet derived growth factor A and B mRNA abundances by pirfenidone in the bleomycin hamster model of lung fibrosis. *Am J Respir Crit Care Med* 1997;155(4 pt 2):A313 (abstract).
33. Iyer SN, Gurujeyalakshmi G, Giri SN. Down regulation of procollagen and TGF-beta gene expression by pirfenidone in the bleomycin-hamster model of lung fibrosis. *Am J Respir Crit Care Med* 1997;155(4 pt 2):A741 (abstract).
34. Mansoor JK, Schelegle ES, Giri SN. Pirfenidone attenuates bleomycin-induced changes in pulmonary mechanics in hamsters. *Am J Respir Crit Care Med* 1997;155(4 pt 2):A322 (abstract).
35. Iyer SN, Hyde DM, Giri SN. Anti-inflammatory effect of pirfenidone in the bleomycin-hamster model of lung inflammation. *Inflammation* 2000;24:477-91.
36. Suga H, Teraoka S, Ota K, et al. Preventive effect of pirfenidone against experimental sclerosing peritonitis in rats. *Exp Toxicol Pathol* 1995;47:287-91.
37. Kehrer JP, Margolin SB. Pirfenidone diminished cyclophosphamide-induced lung fibrosis in mice. *Toxicol Lett* 1997;90:125-32.
38. Shetlar MR, Shetlar CL. Effect of antifibrosis drug on the survival of keloid transplants in athymic mice. *FASEB J* 1995;9:A967 (abstract).
39. Shimizu T, Fukagawa M, Kuroda T, et al. Pirfenidone ameliorates the progression of renal failure by preventing collagen accumulation in 5/6 nephrectomized rats. *Nephrology* 1997;3:S375 (abstract).
40. Shimizu F. Pirfenidone prevents the progression of irreversible glomerular sclerotic lesions. *J Am Soc Nephrol* 1996;7:1765 (abstract).
41. Tsuruta Y, Maeda K, Obayashi S, et al. Preventative effect of pirfenidone on Thy-1 nephritis in rats. *Nephrology* 1997;3:S235 (abstract).
42. Fukagawa M, Yamauchi S, Shimizu T, et al. Therapeutic use of pirfenidone (PFD) on the established and progressive renal lesions in 5/6 nephrectomized rats. *Nephrology* 1997;3:S123 (abstract).
43. Shimizu T, Fukagawa M, Kuroda T, et al. Pirfenidone prevents collagen accumulation in the remnant kidney in rats with partial nephrectomy. *Kidney Int Suppl* 1997;63:S239-43.
44. Margolin S, Margolin B, Margolin D. Removal of interstitial pulmonary fibrosis (asbestos-induced) by oral chemotherapy with pirfenidone. *Fed Proc* 1982;41:1550.
45. AMR Biological Research. Therapeutic method for inhibition and dissolution of lung interstitial hyperplasia (fibrosis) accompanying advancing age in the dog with pirfenidone (120-1435A-107). AMR Biological Research, a subsidiary of Princeton Nassau International, Princeton, NJ: 1978.
46. Raghu G, Johnson WC, Lockhart D, et al. Treatment of idiopathic pulmonary fibrosis with a new antifibrotic agent, pirfenidone: Results of a prospective, open-label Phase II study. *Am J Respir Crit Care Med* 1999;159(4 Pt 1):1061-9.
47. Teroaka S. Therapeutic effect of newly developed antifibrotic agent, pirfenidone combined with home parenteral nutrition on sclerosing encapsulated peritonitis. Presented at the 33rd European Dialysis Transplant Association meeting. 1996; Amsterdam, The Netherlands.
48. Investigational study of clinical indications for pirfenidone ointment. report from Japan on Human Topical Dermal Trials. Department of Medicine, Maruko Central Hospital, Maruko, Nagano Prefecture, Japan: 1993.