

Open label trial of tamoxifen in scleroderma

C.K. Thomas-Golbanov,
W.S. Wilke, B.J. Fessler,
G.S. Hoffman

Department of Rheumatologic and Immunologic Diseases, The Cleveland Clinic Foundation, Cleveland, Ohio, USA.

Colleen K. Thomas-Golbanov, MD, Clinical Fellow; William S. Wilke, MD, Senior Staff Rheumatologist; Barri J. Fessler, MD, Senior Staff Rheumatologist; Gary S. Hoffman, MD, Chairman, Department of Rheumatic and Immunologic Diseases.

Please address correspondence to: G.S. Hoffman, MD, Harold C. Schott Chair of Rheumatic and Immunologic Diseases, Cleveland Clinic Foundation, Desk A50, 9500 Euclid Avenue, Cleveland, Ohio 44195, USA.

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ABSTRACT

Background. Previous reports have suggested that treatment with the selective estrogen antagonist tamoxifen may be effective in diminishing primary and secondary Raynaud's vasospasm, including cases occurring in the setting of scleroderma. Tamoxifen treatment has also been associated with improvement of retroperitoneal fibrosis and desmoid tumors, conditions also associated with abnormal fibroblast proliferation. Tamoxifen increases production of the immunosuppressive cytokine TGF β which modulates fibroblast activity. The potential effect of tamoxifen on vascular reactivity and fibrotic lesions raised questions about its utility as a therapeutic agent in scleroderma.

Objective. To determine the utility of tamoxifen therapy in scleroderma.

Methods. Open label preliminary, prospective, proof of concept study of tamoxifen.

Results. Fifteen patients (3 male, 12 female) with scleroderma were enrolled (10 diffuse disease, 5 CREST). Mean age was 55 (34-75) years. Mean duration of scleroderma was 9.3 (1-25) years. Two patients were excluded. For 13 patients, mean duration of treatment was 7 (1.5-32) months. Two of 13 patients treated with tamoxifen experienced transient improvement. They did not appear to have clinical features that identified them as a unique subset. Both patients subsequently relapsed, in one case 12 months, and in the other 24 months after treatment.

Conclusion. Based on these results, we would not recommend tamoxifen for further large scale studies in scleroderma.

Introduction

Treatment options in scleroderma are limited. The many agents that have been utilized in attempts to reverse the fundamental pathological changes of scleroderma have been disappointing (1).

Franco and colleagues had observed the complete disappearance of Raynaud's phenomena in 2 women with breast cancer after radical oophorectomy and treatment with tamoxifen. The authors' subsequent short-term, open

label, crossover trial of 21 patients with Raynaud's phenomenon included 8 patients with scleroderma. Treatment consisted of tamoxifen, 30 to 60 mg daily, for 2 weeks followed by a similar period of treatment with nifedipine, 10 mg daily. Subjective improvement of ischemic symptoms was recorded together with improvement in digital temperature recordings. There was a statistically significant increase in the finger tip basal temperature in the tamoxifen group, compared to the nifedipine group (2). An additional case report of tamoxifen therapy for diffuse scleroderma also described regression of cutaneous lesions (3).

Remarkable regression of desmoid tumours (4-8) and retroperitoneal fibrosis (9-13) following tamoxifen therapy have been reported. These conditions involve abnormal fibroblast proliferation and collagen deposition. Possible mechanisms of tamoxifen action include induction of transforming growth factor beta (TGF- β) (12,14,15) which has been speculated to be inhibitory to abnormal fibroblasts in desmoid tumors and retroperitoneal fibrosis (15). We hypothesized that tamoxifen therapy might be palliative in scleroderma, a female-dominant disease, because of estrogen-antagonistic effects, as well as its estrogen-independent effects on the abnormal fibroblast proliferation, as has been suggested to occur in desmoid tumors and retroperitoneal fibrosis. At the time of this study, it was not recognized that exogenous estrogen, provided over a short time period, may also enhance vasodilation (16-18).

Patients and methods

Fifteen of 21 consecutive, consenting patients with either progressive systemic sclerosis or limited disease such as CREST were treated with tamoxifen 10 mg twice daily. Six patients declined enrollment. Apart from addition of tamoxifen, other existing therapy remained unchanged. The latter included corticosteroids, calcium channel blockers, proton pump inhibitors, ACE inhibitors, coumadin, aspirin, hydroxychloroquine, colchicine, D-penicillamine, methotrexate, cisapride and analgesics. One exception to not changing baseline

medications was estrogen therapy. Hormonal replacement therapy was discontinued in 2 post-menopausal patients prior to enrolling in the trial. This was felt to be necessary in order to avoid possible antagonism to the effects of tamoxifen. Analgesics were allowed to be titrated according to pain severity. For patients receiving coumadin, doses were adjusted based on INR. Tamoxifen was continued for a minimum of 6 weeks before determining a response to therapy.

Formal skin scores were not determined. However, each visit was accompanied by a complete history and evaluation of involved skin. Only clinical changes that were apparent to both the patient and physician were considered as a positive response. Because formal skin scores (20) were not systematically obtained, equivocal skin changes were not considered to be a meaningful therapeutic response. Improvement of skin thickening and decreased digital ischemia (relief of pain, vasospasm and healing of ulcers) were the primary positive end points.

Results

Fifteen patients, 12 females and 3 males, agreed to participate. Mean age was 55 years and mean disease duration was 9.3 years. Two women dropped out in the initial stages of the study after one visit: one was lost to follow-up and another female discontinued tamoxifen after 3 doses because of tremulousness and weakness. The 13 remaining patients, 10 females and 3 males received tamoxifen for 6 weeks to up to 2 years. Mean duration of treatment was 7 months. Clinical profiles of all patients are summarized in Table I.

Only 2 patients (15.4%) demonstrated improvement that appeared to be clinically significant. In one of those patients improvement of Raynaud's vasospasm and skin ulcers was not sustained. In another, improvement had persisted, even 2 years after treatment was discontinued. However, the latter patient has recently relapsed, again demonstrating diffuse features of scleroderma. Further clinical details of the two transient "responder cases" follows.

Case 1

A 46-year-old male machinist had extensive skin thickening of the trunk and extremities, Raynaud's vasospasm and gastrointestinal reflux. He had failed to improve after a 3-month trial of D-penicillamine, which had already been discontinued several months before the tamoxifen trial. Within 3 months after starting tamoxifen, tightness around his face and neck had resolved and fingers were less stiff. There was near complete resolution of skin abnormalities, which was sustained even after tamoxifen was discontinued 2 years later. Worsening of scleroderma recently occurred after a 2-year period of dramatic improvement. In addition, 1 year after discontinuation of tamoxifen, he developed submandibular gland cystic carcinoma. Surgical resection (1 1/2 years follow up) appears to have been curative.

Case 2

A 52-year-old housewife with a 6-year history of debilitating Raynaud's phenomenon, acrocyanosis and digital ulcers, stiff fingers and thickened neck-line skin, felt less pain after one day of tamoxifen therapy. After 4 days of treatment, she could write normally and had less digital pallor. Over the subsequent winter she did not develop digital ulcers, as she had in the past, and she was able to fully flex and extend her fingers 9 months later. Until tamoxifen therapy, she had not been able to make a closed fist with either hand. Tamoxifen was discontinued after 13 months of therapy. However, within the next 8 months she again developed ischemic pain and ulcers. Tamoxifen was reinstated, this time without benefit.

Adverse events

Light headedness and tremulousness in one 49-year-old female and worsening migraines in another 58-year-old female had resulted in discontinuation of therapy. One 34 year-old-female patient died of pulmonary embolism 10 months after discontinuation of tamoxifen. One 57-year-old female died of end stage pulmonary hypertension 6 months after tamoxifen was

withdrawn.

Other clinical events that occurred during tamoxifen therapy were in keeping with the natural history of disease. One patient developed scleroderma renal crisis, and another had progressive digital ischemia that continued to worsen while on tamoxifen.

Discussion

Our study was designed as a pilot open-label assessment of the utility of tamoxifen in scleroderma. It was undertaken because of encouraging preliminary short-term results reported by Franco and colleagues (2). Only 2 of our 13 evaluable patients (15.4%) experienced dramatic improvement. Both patients have since relapsed. Because of the pilot nature of the study, the small numbers of patients enrolled and the absence of controls, it is not possible to determine if improvement in these 2 cases was spontaneous and unrelated to tamoxifen therapy. Eleven patients did not improve. We are unable to determine whether the course of illness in these patients was altered in any fashion by tamoxifen. It was clear that their condition was not perceptibly improved in either their judgement or that of their physicians.

In the treatment of breast cancer, tamoxifen therapy in excess of 20 mg per day did not provide added benefit (20). An analysis of dose-response relationships of tamoxifen in scleroderma were beyond the scope of this small study. It is conceivable that for scleroderma, higher doses may have been necessary to produce more encouraging results. In the short-term (2 week) study of Franco et al, improvement was noted in Raynaud's vasospasm. Higher daily doses of tamoxifen (30-60 mg daily) were employed.

Conclusion

Tamoxifen therapy was associated with improvement of scleroderma in 2 of 13 patients in our study. Improvement persisted for 1 to 2 years. It is not clear whether improvement in these patients may have been treatment related or spontaneous. Eleven of 13 patients did not improve. This single dose open-label study did not produce adequate

Table I.

Pt. no.	Sex/age when tamoxifen started/Ethnicity	Disease duration	Extent of disease: Diffuse/CREST	Duration of tamoxifen therapy	Outcome
1	M/46/Caucasian	3 years	Diffuse	2 years	Marked cutaneous improvement within 3 months, but subsequent relapse
2	F/52/Caucasian	6 years	CREST	2 years	Transient reduction in digital ischemia, then worse
3	F/58/Caucasian	1 year	Diffuse+interstitial lung disease	10 weeks	No cutaneous change, worsening migraine
4	F/57/Caucasian	25 years	CREST+pulmonary hypertension	3 months	No cutaneous change Died of severe pulmonary hypertension
5	M/67/Caucasian	1 year	Diffuse	11 months	No cutaneous change
6	F/51/Caucasian	3 years	Diffuse	6 months	No cutaneous change Renal crisis
7	F/34/African American	5 years	Diffuse	6 weeks	No cutaneous change
8	F/75/Caucasian	24 years	CREST	2 months	No cutaneous change
9	F/69/Arab	10 years	Diffuse+interstitial lung disease	9 months	No cutaneous change
10	M/55/Caucasian	7 years	Diffuse+pulmonary hypertension	2 months	No cutaneous change
11	F/71/Caucasian	4 years	Diffuse+interstitial lung disease	5 months	No cutaneous change
12	F/52/Caucasian	7 years	CREST ...	4 months	No cutaneous change
13	F/34/Caucasian	21 years	Diffuse+interstitial lung disease	2 months	No cutaneous change Died of pulmonary embolism 10 months later
14	F/49/Arab	4 years	CREST	3 doses	Tremulous and weak Stopped treatment
15	F/57/Caucasian	4 years	Diffuse and interstitial lung disease		Lost to follow up

responses for the authors to consider further investigation of tamoxifen therapy for scleroderma.

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