Ineffective Treatment of Keloids with Interferon Alpha-2b

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Background: Keloids are exuberant, disfiguring scars that result from an abnormal healing process. Current established treatment strategies include surgical resection, triamcinolone steroid injection, pressure therapy, silicone therapy, and radiotherapy. None of these therapies, either alone or in combination, offers consistent recurrence-free rates above 70 to 80 percent. The antiproliferative, antifibrotic cytokine, interferon alpha-2b, may be useful in keloid management because of its ability to interfere with collagen synthesis and fibroblast proliferation.

Methods: To determine the efficacy of interferon alpha-2b in keloid management, the authors prospectively evaluated the effects of interferon alpha-2b as postexcisional adjuvant therapy for keloids. Thirty-nine keloids in 34 patients were photographed, measured, and surgically excised. The wound bed was injected twice with either interferon alpha-2b (treatment group; $n = 13$ keloids) or triamcinolone (control group; $n = 26$ keloids) at surgery and 1 week later. The patients were followed up in the plastic surgery clinic.

Results: The trial protocol was terminated at midtrial surveillance. Among the 13 keloids that were treated with postoperative intralesional interferon alpha-2b, seven recurred (54 percent recurrence rate). In contrast, in the 26 keloids that received triamcinolone (control group), only four recurred (15 percent recurrence rate). Recurrence in either group did not correlate with location of the keloid or race.

Conclusion: Interferon does not appear to be effective in the clinical management of keloids. (*Plast. Reconstr. Surg.* 117: 247, 2006.)

Keloids are the result of an abnormal scarring process predominately seen in darker skinned patient populations. Keloid management has no single ideal treatment protocol, and multiple therapeutic regimens can be offered to the patient. We present the use of intralesional interferon alpha-2b with surgical excision in this study. Current established treatment strategies include surgical resection, steroid injection, pressure therapy, silicone therapy, and radiotherapy. Surgical resection alone has consistently resulted in poor outcomes in keloid treatment, with recurrence rates reported between 40 and 100 percent.[1–6] Steroid injections, radiotherapy, and pressure therapy used for monotherapy for keloids similarly result in treatment failures.[7–14] Combinations of the above modalities with surgical excision have been attempted, with some success in decreasing recurrence rates to below 40 percent[3,11,15–21]; surgical resection followed by intralesional steroid injection has yielded cure rates of 58 to 93 percent in multiple studies.[8,10,22,23] Silicone gel and tape have been efficacious as adjuvant therapy following excision in several controlled clinical trials.[12,24–27] 5-Fluorouracil, an antimetabolite, and retinoids, vitamin A derivatives, have been used locally as monotherapy or postexcisional adjuvant therapy with some efficacy in clinical trials.[28–31] However, there is still no single effective treatment protocol for keloid management.

The lack of effective therapy and the suspected role of growth factors in keloid pathogenesis have led to novel treatment strategies such as interferons that modulate growth factor composition. Interferons are cytokines that exhibit antiproliferative, antifibrotic, and antiviral effects in multiple cell types.[32] Interferons are used in keloid management because of their ability to interfere with collagen synthesis and fibroblast proliferation, and thereby produce an antifibrotic effect that has been speculated to be me-

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diated through transforming growth factor-β1 modulation.[33–36] In addition, interferon alpha-2b can increase collagenase levels and inhibit secretion of collagenase inhibitors such as metalloproteinases.[33–36]

Although preliminary findings of interferon therapy for keloids appeared promising, further studies at different institutions yielded equivocal results.[37–42]

PATIENTS AND METHODS

To investigate the efficacy of interferon in keloid management, we conducted a prospective, controlled clinical trial of interferon alpha-2b as postexcisional adjuvant therapy for keloids. Patients with keloids at the plastic surgery clinic at Georgetown University Medical Center volunteered to enter the study with informed consent and institutional review board approval. Ineligible patients included pregnant or lactating women; children younger than 18 years; patients taking theophylline or zidovudine; or patients with serious cardiac, liver, or diabetes disease. Initially, 25 patients per treatment group, 50 patients in all, were to be included in the study. The sample number allowed a power of 90 percent to investigate the efficacy of interferon adjuvant therapy versus conventional therapy (postexcisional triamcinolone) with a binary outcome.

Keloids were measured and photographed at presentation and then underwent complete surgical excision with local anesthesia under sterile conditions in the operating room. The wounds were closed with a minimal amount of buried, interrupted Monocryl (Ethicon, Inc., Somerville, N.J.) sutures, leaving the surface tension free. After complete surgical resection of the keloid, patients were randomized to immediately receive either interferon alpha-2b or triamcinolone injected intradermally through the incision. Triamcinolone acetate (40 mg/ml, Kenalog; Bristol-Myers Squibb Co., Princeton, N.J.) was injected at 10 mg per linear centimeter intraoperatively, followed by a repeated injection 1 week later. Interferon α-2b (10 million units/ml, Intron A; Schering Corp., Kenilworth, N.J.) was injected at 1 million units per linear centimeter (maximum, 5 million units) intraoperatively, followed by a repeated injection 1 week later.

Patients were followed up in the plastic surgery clinic at 1 week, 1 month, 6 months, and 1 year. The main outcome was keloid recurrence, which was defined as any exuberant scar that extended 5 mm beyond the surgical incision.

Prospective patients were informed about the randomized format of this trial and the experimental status of interferon alpha-2b for keloid therapy. Nonetheless, after enrollment and randomization, and before treatment, many patients from the treatment arm decided to discontinue the trial for one of two reasons. Because insurance preauthorization was required before surgery (and the first interferon alpha-2b treatment), and because this study was not funded, insurance carriers frequently refused to cover the cost of interferon alpha-2b and patients in turn often refused to pay out of pocket for the interferon alpha-2b (over $100 per treatment). Second, although patients were informed of the side effects of interferon alpha-2b before enrollment in the trial and randomization, several of the patients who were randomized to the interferon alpha-2b group decided to drop out of the trial when they were informed (for the second time) of the potential side effects of interferon alpha-2b immediately before treatment. Patients who discontinued the trial after randomization, but before treatment, were excluded from the trial. For this reason, the number of patients who completed the control (triamcinolone) and treatment (interferon alpha-2b) arms of the study are not equal. The final number of keloids included in the final analysis, representing patients who enrolled in and completed the study, was 13 keloids in the treatment (interferon alpha-2b) arm and 26 patients in the control (triamcinolone) arm.

Statistical analysis of the collated data was conducted by testing the difference between recurrence rates in the two groups. Treatment and control groups were treated as independent normally distributed samples of binomial trials, and a test statistic was calculated based on the difference of their sample parameters and evaluated using the chi-square test.

RESULTS

Thirty-nine keloids were resected from 34 patients; ages ranged from 18 to 62 years, with an average age of 30.1 years. Their ethnicity varied, with 21 African American, 13 Caucasian, four Hispanic, and one Asian. The keloid location also varied, with 10 on the ear, eight on the face/scalp, seven on the chest, six on an extremity, four on the abdomen, and four on the neck. Of the 39 treated keloids, 11 recurred within 2 years of follow-up (overall 28 percent recurrence). Among the 13 keloids that were treated with postoperative intralesional interferon alpha-2b, seven recurred (54 percent recurrence rate) (Fig. 1). In contrast,

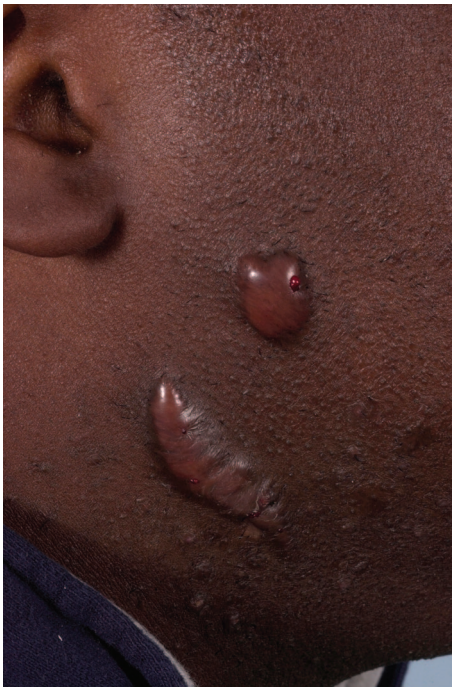

Fig. 1. Keloid recurrence after surgical resection followed by intralesional interferon alpha-2b.

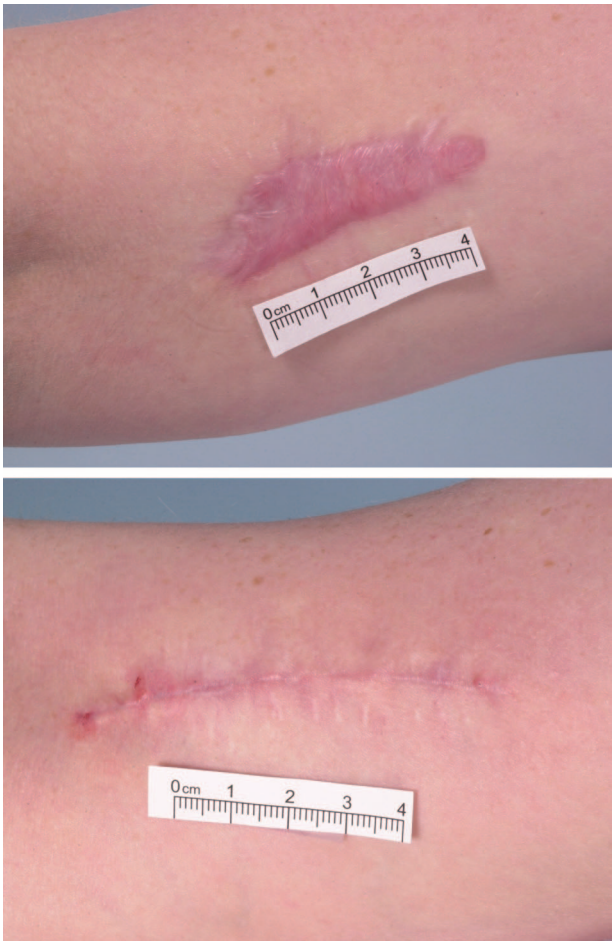

Fig. 2. Successful keloid management in a control subject, (*above*) before and (*below*) after surgical resection followed by intralesional triamcinolone.

in the control group that received postoperative intralesional triamcinolone (Fig. 2), only four keloids recurred among 26 treated (15 percent recurrence rate). This clinical trial was prematurely halted because midtrial recurrence rates in the treatment arm (postexcisional interferon alpha-2b) significantly exceeded those of the control group (postexcisional triamcinolone) ($p < 0.05$ using the chi-square test).

The average time to recurrence for patients who failed postexcisional interferon alpha-2b therapy was 10 months; in contrast, the average time to recurrence for patients who failed postexcisional triamcinolone therapy was 4 months. African Americans tended to have more keloid recurrences with intralesional interferon alpha-2b (Table 1), and keloids of the ear tended to recur more with intralesional interferon alpha-2b (Table 2) than with triamcinolone. In the triamcinolone group, there were two patients with multiple keloids where one keloid recurred and another on a second location did not recur. Two of the 11 patients treated with intralesional IFN α-2b experienced flu-like symptoms, a known side effect.

DISCUSSION

Considerable speculation has surrounded interferon treatment for keloids over the past 15 years. This clinical trial is the first controlled study that definitively demonstrates lack of efficacy for interferon alpha-2b as postexcisional adjuvant treatment for keloids.

Berman and Duncan first introduced interferon to keloid management in 1989 because of the collagen reducing effects in vitro.[33,43–46] In vitro studies suggested that interferon raised collagenase activity and inhibited collagen and glycosaminoglycan synthesis. After two intralesional injections of interferon alpha-2b in Berman and Duncan's case report, the keloid surface area decreased by 41 percent initially, supporting the hypothesized mechanism of action.[33] However, the patient's keloid resumed growth and was refractory to further interferon treatment.

After this initial case report, intralesional interferon alpha-2b and interferon gamma have been tested in a number of clinical trials for keloid management. Larrabee achieved a modest size re-

Table 1. Recurrence of Keloid following Postoperative Adjuvant Therapy by Race of Patient*

	Caucasian	African American	Hispanic	Asian	Total
Interferon alpha-2b	1/3	5/8	0/1	1/1	7/13
Triamcinolone	1/10	2/13	1/3	0/0	4/26
Total	2/13	7/21	1/4	1/1	11/39

*Numbers refer to keloids treated (some patients had more than one keloid).

duction and softening in seven keloids with corresponding histologic changes after weekly intralesional interferon gamma.[38] Granstein et al. found significant early decreases but long-term recurrences in six of the eight keloids treated with interferon gamma alone in a double-blinded clinical trial.[37] Broker et al. also demonstrated short-term improvement in three of seven keloids treated with weekly interferon gamma.[41]

Placebo-controlled trials at different institutions using interferon alpha-2b failed to demonstrate efficacy in keloid management.[39,40,42] Al-Khawajah, whose placebo-controlled trial did not show any benefit from intralesional interferon alpha-2b alone, suggested that interferon alpha-2b may need to be used in conjunction with surgical excision for efficacy.[42] Furthermore, Conejo-Mir et al. presented an uncontrolled series of 30 patients treated with carbon dioxide laser excision of keloids followed by intralesional interferon alpha-2b, with a 66 percent cure rate on long-term follow-up.[47]

Our trial was designed to evaluate the effectiveness of interferon therapy in light of the above studies. Because earlier studies suggested that any effectiveness of interferon would be seen following keloid resection, we used intralesional interferon alpha-2b as postexcisional adjuvant treatment. However, the findings from our clinical trial suggest that interferon alpha-2b used as postexcisional adjuvant therapy, similar to interferon alpha-2b used as sole treatment, is inferior to conventional therapy using postoperative intralesional triamcinolone.

Interferon has shown clear efficacy in the experimental treatment of several fibrotic conditions by means of modulation of transforming growth factor-β1, including scleroderma, systemic fibrosis, pulmonary fibrosis, and Dupuytren's disease. In contrast, although keloid formation mimics fibrotic growth, the lack of effectiveness of interferon in keloid progression suggests that other mechanisms may be dominant in keloid pathogenesis.

Another disadvantage of adjunct interferon therapy over triamcinolone for keloids is that intralesional interferon produces adverse systemic effects. Triamcinolone can cause thinning or hypopigmentation of the scar and telangiectasia at the injection site, and both triamcinolone and interferon will cause temporary pain at the injection site. However, dose-dependent flu-like symptoms including pyrexia, myalgia, fatigue, and headache follow interferon treatment.[23,33,37,38] These adverse effects are consistent with phase I interferon trials in the early 1980s on patients with metastatic cancer, that reported similar flu-like symptoms along with reversible granulocytopenia, increased serum triglycerides, and increased hepatic transaminases following various routes of administration.[48,49]

CONCLUSIONS

The findings of this study failed to demonstrate a benefit of interferon alpha-2b over conventional triamcinolone as a postexcisional adjuvant therapy in the management of established keloids. The findings from this trial, along with the cumulative conclusions from earlier studies and the adverse side effects, suggest that further clinical investigation of interferon for therapy of keloids might not be warranted. Aggressive research directed at understanding the molecular basis and pathogenesis of keloids is the most promising ap-

Table 2. Recurrence of Keloid following Postoperative Adjuvant Therapy by Location

	Ear	Face/Scalp	Chest	Extremity	Abdomen	Neck	Total
Interferon alpha-2b	2/4	1/2	2/4	1/1	0/1	1/1	7/13
Triamcinolone	0/6	2/6	1/3	0/5	1/3	0/3	4/26
Total	2/10	3/8	3/7	1/6	1/4	1/4	11/39

proach to the development of effective treatments.

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