

ORIGINAL ARTICLE

Treatment of keloids using 5-fluorouracil in combination with crystalline triamcinolone acetonide suspension: evaluating therapeutic effects by using non-invasive objective measures

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Abstract

Background Intralesional 5-fluorouracil (5-FU) in combination with triamcinolone acetonide (TAC) has been recommended as a promising alternative for keloids not responding to silicone-based products, cryotherapy or intralesional corticosteroids alone. Although numerous studies support the efficacy of this regime, there is a lack of objective data.

Objectives In this study, we evaluate the therapeutic effect of four courses of intralesional 5-FU in combination with TAC (3 : 1) utilizing 3D analysis (PRIMOS^{®picco}), ultrasound and scar scales such as the Patient and Observer Scar Assessment Scales (POSAS) and the Dermatology Life Quality Index (DLQI).

Methods Twenty-five patients with keloids were treated using 5-FU and TAC every 4 weeks. Objective assessments were performed and the scar scales administered at baseline, as well as during consecutive visits at 1- and 12-month follow-up (FU). Routine laboratory tests were performed at baseline and at 1-month FU.

Results 3D PRIMOS and ultrasound measurements revealed highly significant and stable reductions in height (baseline mean score: 4.0 ± 1.7 mm, 1-month FU mean score: 1.5 ± 0.8 mm, 12-month FU mean score: 1.8 ± 0.9 mm, $P = <0.0001$), volume (baseline mean score: $1,105 \pm 911.5$ mm³, 1-month FU mean score: 416.1 ± 218.1 mm³, 12-month FU mean score: 431.2 ± 253.6 mm³, $P = <0.0001$, respectively) and penetration depth of keloids (relative reduction between baseline and 12-month FU of 74.4%, $P = <0.0001$). The POSAS and DLQI scales confirmed significant objective and subjective improvements in scar appearance in all categories. The life quality associated with keloid appearance improved from a 'moderate effect' to a 'small effect' throughout the course of the study.

Conclusions Results of this study confirm the efficacy and safety of the combination of 5-FU and TAC in keloids. Treatments were well tolerated and demonstrated stable results at 12-month FU.

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Conflicts of interest

The authors declare no conflict of interest.

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Introduction

The extent of scarring following surgery or trauma is difficult to predict and both physicians and patients are highly concerned with minimizing scar appearance and related symptoms. Even small ameliorations in scarring are clinically meaningful. Especially keloids pose a significant challenge for treating physicians. A number of treatment regimens have been developed, such as the application of silicone-based products, cryotherapy or

intralesional corticosteroids. Keloids may affect large parts of the skin surface and lead to severe functional impairment, particularly in genetically prone patients. Successful treatment using conventional means has proven difficult, with low rates of sustained responses and high relapse rates.

The commonly used glucocorticosteroid triamcinolone acetonide has many effects, including an anti-mitotic property inhibiting keratinocytes and fibroblasts and the suppression of tissue inflammation and vasoconstriction, resulting in keloid

[†]Equally contributed to work

Table 1 Patient characteristics

Patient	Age (years)	Skin type	Localization	Number	Existence (years)	Development	Previous therapy	Family history
1	28	IV	Shoulder	5	8	Spontaneous	Cryotherapy, TAC	None
2	30	II	Chest, shoulder	8	11	Spontaneous	Cryotherapy, TAC, laser therapy	None
3	26	II	Chest	4	8	Acne	Cryotherapy, TAC, silicone gel sheeting	Sister
4	38	IV	Chest, back, shoulder	>10	>20	Spontaneous	Cryotherapy, TAC	None
5	22	II	Chest, shoulder	>10	3	Spontaneous	Cryotherapy, TAC	None
6	21	III	Chest, back, shoulder	>10	4.5	Acne	Cryotherapy, TAC	None
7	30	II	Chest	5	6	Injury	Cryotherapy, TAC	None
8	27	II	Chest	1	2	Surgery	Cryotherapy, TAC	None
9	25	III	Back, shoulder	3	9	Spontaneous	Cryotherapy, TAC	Cousin
10	25	II	Shoulder	>10	6	Spontaneous	Cryotherapy, TAC	None
11	19	IV	Shoulder	4	3	Surgery	Cryotherapy, TAC	None
12	22	II	Chest	3	2	Acne	Cryotherapy, TAC	None
13	31	III	Chest, shoulder, thigh	9	17	Spontaneous	Cryotherapy, TAC, pressure therapy, surgery, silicone gel sheeting	None
14	25	II	Arms	2	5	Injury	Cryotherapy, TAC	None
15	37	IV	Chest	2	12	Surgery	Cryotherapy, TAC	Daughter
16	49	II	Chest	1	>20	Surgery	Cryotherapy, TAC, surgery	None
17	21	II	Chest, back, shoulder	>10	4	Acne	Cryotherapy, TAC	None
18	27	IV	Chest, shoulder, arms	6	6	Acne	Cryotherapy, TAC, surgery	Sister
19	22	II	Back, shoulder	>10	7	Acne	Cryotherapy, TAC, silicone gel sheeting, medical needling	None
20	28	II	Chest, shoulder	7	10	Acne	Cryotherapy, TAC	None
21	24	II	Chest, shoulder	>10	8	Acne	Cryotherapy, TAC	None
22	19	II	Back, shoulder	>10	3	Acne	Cryotherapy, TAC	None
23	21	II	Chest, back	>10	5	Acne	Cryotherapy, TAC, laser therapy	Brother, mother
24	48	II	Chest, shoulder	7	>30	Spontaneous	Cryotherapy, TAC	None
25	52	III	Chest	1	10	Spontaneous	Cryotherapy, TAC, silicone gel sheeting	Son

TAC, triamcinolone acetonide.

regression.^{1,2} Whereas, 5-fluorouracil (5-FU) inhibits the proliferation of fibroblasts as a pyrimidine analogue³ and has been successfully used for the treatment of keloids for many years.^{4,5}

Most studies have focused on demonstrating the effects of high-dose 5-FU therapy (40–50 mg/mL), while others have promoted a 'low-dose' therapy using 1.4–3.5 mg/mL of 5-FU.^{6,7} More recently, a growing number of studies have supported the combination of intralesional 5-FU and crystalline triamcinolone acetonide (TAC) in a ratio of either 9 : 1 or 3 : 1. Combinations appear to be superior to monotherapy with TAC.^{8–11}

Based on the relevant literature, combinations of 5-FU and TAC may thus be considered for the treatment of keloids and seem to lack any systemic side effects. However, data on such combinations based on objective measurements are widely

missing. In the majority of studies, follow-up (FU) periods have remained relatively short.

Materials and Methods

Patients and study methodology

Upon ethical approval of the proposed research, 25 patients, six females and 19 males were enrolled in the clinical study. Prospective patients had to be of legal age without any malignant illnesses. Patients enrolled were previously treated with cryotherapy (spray cryotherapy using liquid nitrogen twice for 10 s; cryotherapy was usually performed 15–30 min before the injection of TAC, since success rates appear to be increased based on the larger amount of TAC that can be injected into the scar due

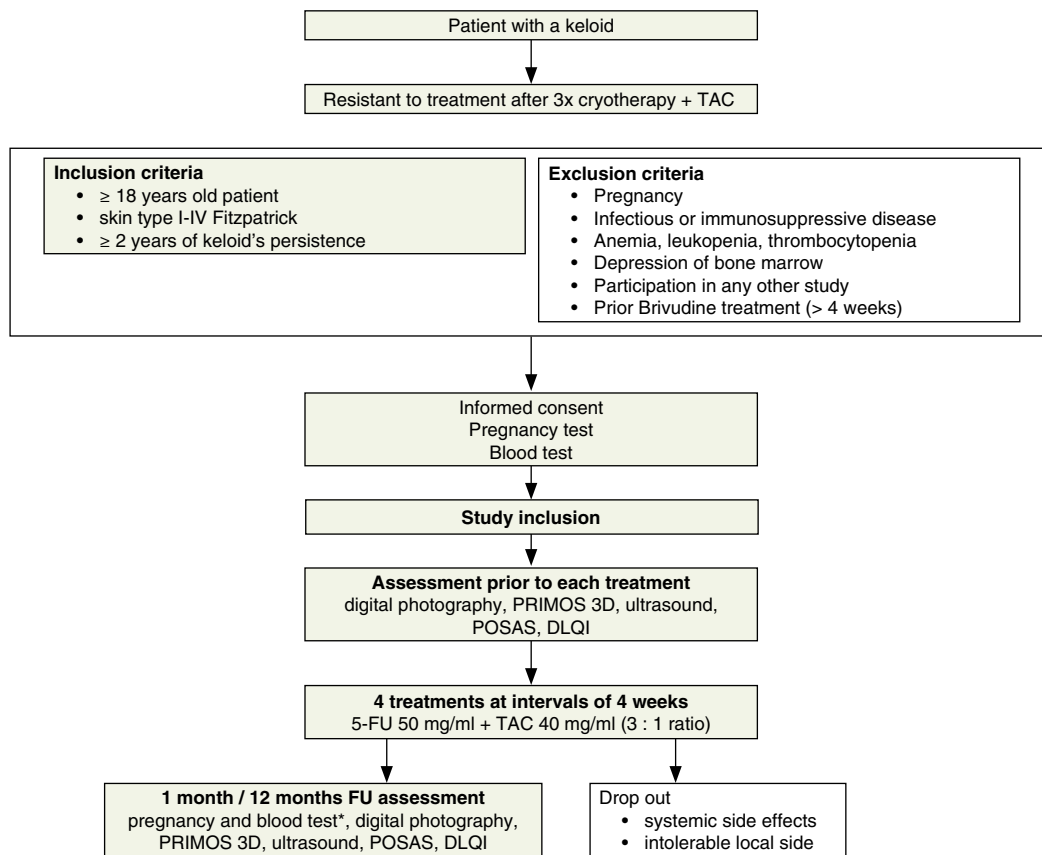


Figure 1 Study algorithm: Every patient with a keloid received four treatments 5-FU/TAC after study inclusion. Data were collected at baseline, prior to each treatment and at one-month and 12-month FU, respectively. (5-FU, 5-Fluorouracil; DLQI, Dermatology Life Quality Index; FU, follow-up; POSAS, Patient and observer scar assessment scale; PRIMOS, phase shift rapid in vivo measurement of skin; TAC, triamcinolone acetonide; *Performed at 1-month FU).

to oedema formation caused by cryotherapy) and TAC every 4 weeks at least three times without significant improvement. In order to ensure the comparability of the results of individual patients, keloids had to have persisted for at least two years. Infectious or immunosuppressive diseases, as well as Brivudine intake up to 4 weeks prior to the study, were considered exclusion criteria. Written informed consent was obtained from each patient.

Routine blood tests with complete blood count, excluding pancytopenia, basic metabolic panel, cholesterol and lipids, thyroid, liver and kidney function and pregnancy tests in females were performed prior to the first treatment session and at 1-month FU.

The mean age of the study cohort was 28.8 ± 9.3 years, with Fitzpatrick skin types ranging from I–IV. Patients showed an average keloid number of 6.3 ± 3.4 per person, with a mean scar age of 8.6 ± 6.7 years. Keloids mostly presented on patients' chests, shoulders and backs and predominantly developed as a

result of acne. In some patients, keloids resulted from surgery or occurred spontaneously without any memorable trauma. In six patients, a positive family history of keloids was recorded (Table 1).

A total of 50 keloids were treated in the patient population. Keloids inflicting a high level of patient distress in terms of pain or aesthetic impairment were chosen. Prior to each treatment, as well as at 1- and 12-month FU, data were collected using digital photography, the three-dimensional Phase shift rapid in vivo measurement of skin (PRIMOS^{®pico}) software, ultrasound and standardized questionnaires (POSAS, DLQI) (Fig. 1).

5-fluorouracil and triamcinolone acetonide

Every patient received four intralesional injections of a combination of 5-FU (50 mg/mL) and a crystalline TAC suspension (40 mg/mL) at a ratio of 3 : 1 until a blanching effect occurred. Injections were administered at monthly intervals. Due to an objection to a negative control by the ethics committee of the

Ludwig Maximilian University, no negative control was allowed. Standardized injection techniques were employed using the same syringe size (5 mL), needle size (27 Gauge), Luer Lock and brands of pharmaceutical drugs. Injection volume depended on the size of each patient's keloids. The average injected suspension volumes per keloid were as follows: visit 1: 1 mL, visit 2: 0.8 mL, visit 3: 0.6 mL and visit 4: 0.4 mL.

Digital photography

Professional photographers documented clinical changes in keloids over the course of the study using a Nikon D5 with an AF-S Micro Nikkor 60 mm lens. Written informed consent was obtained prior to each photograph.

Three-dimensional imaging device: phase shift rapid in vivo measurement of skin (PRIMOS[®]pico)

A total of 50 keloids were objectively measured using PRIMOS[®]pico, a three-dimensional, high-resolution, non-invasive clinical imaging device (Lite Device, GF Messtechnik GmbH, Teltow, Germany). PRIMOS[®]pico has been successfully used to analyse different kinds of pathologic scarring, such as

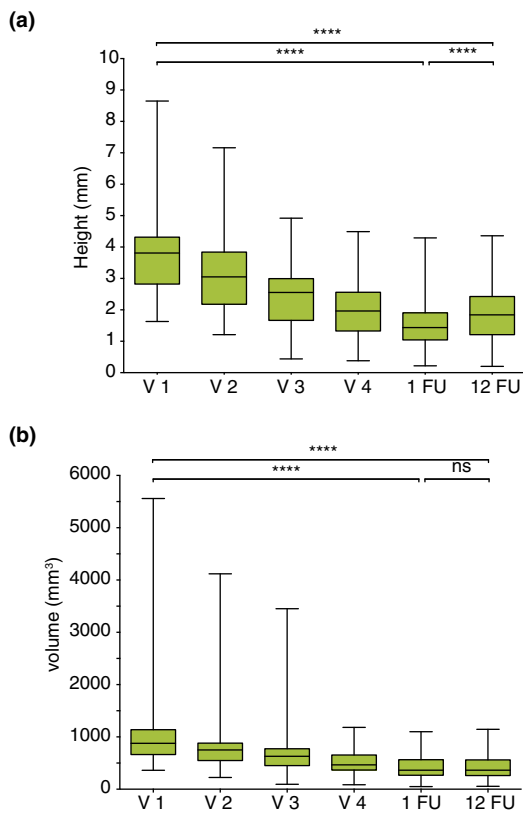


Figure 2 Absolute height (a) and absolute volume of keloids (b) using PRIMOS for objective analysis. ($n = 50$, **** $P = <0.0001$, ns = non-significant, V = visit, FU = follow-up).

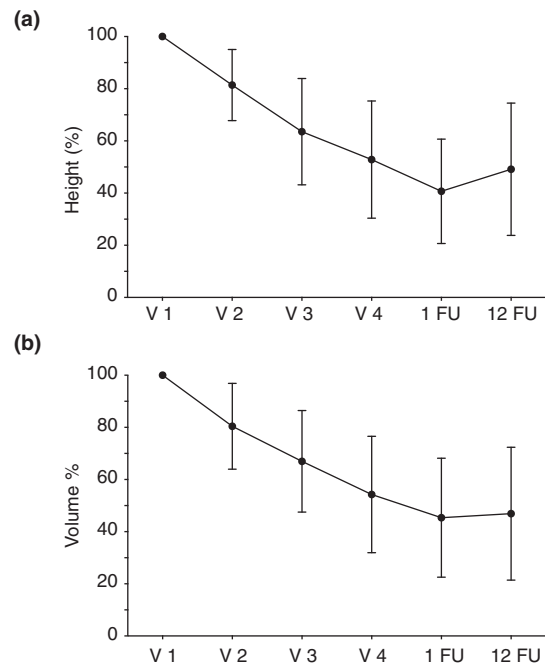


Figure 3 Relative height (a) and relative volume of keloids (b) throughout the study. ($n = 50$, V = visit, FU = follow-up).

hypertrophic burn scars,¹² self-harm scars¹³ and striae distensae albae,¹⁴ and has become a standard for scar imaging.

Ultrasound

A high-resolution B-mode-image sonogram was used for non-invasive analysis of the cutaneous penetration and elevation of keloids. A total of 25 keloids were measured utilizing an 11-MHz transducer (Logiq; P6 Pro; GE Healthcare, Solingen, Germany). One representative keloid was selected per patient.

Assessment scales

To analyse patient quality of life throughout the study, the DLQI was employed. To assess both patients and observers' subjective opinions concerning the severity of scarring, we evaluated the keloids throughout the study using the well-established POSAS.^{15,16}

Data analysis

The GraphPad Prism software (GraphPad software Inc., La Jolla, CA, USA) was used for statistical analysis and visualization of results. P -values of $*P = <0.05$ were considered statistically significant. Data were analysed for Gaussian distribution by the application of D'Agostino and Pearson omnibus normality test. For non-parametric data, the Wilcoxon matched-pairs signed-rank test was used to individually compare changes between baseline and FU visits. The paired t -test was applied to such data without Gaussian distribution.

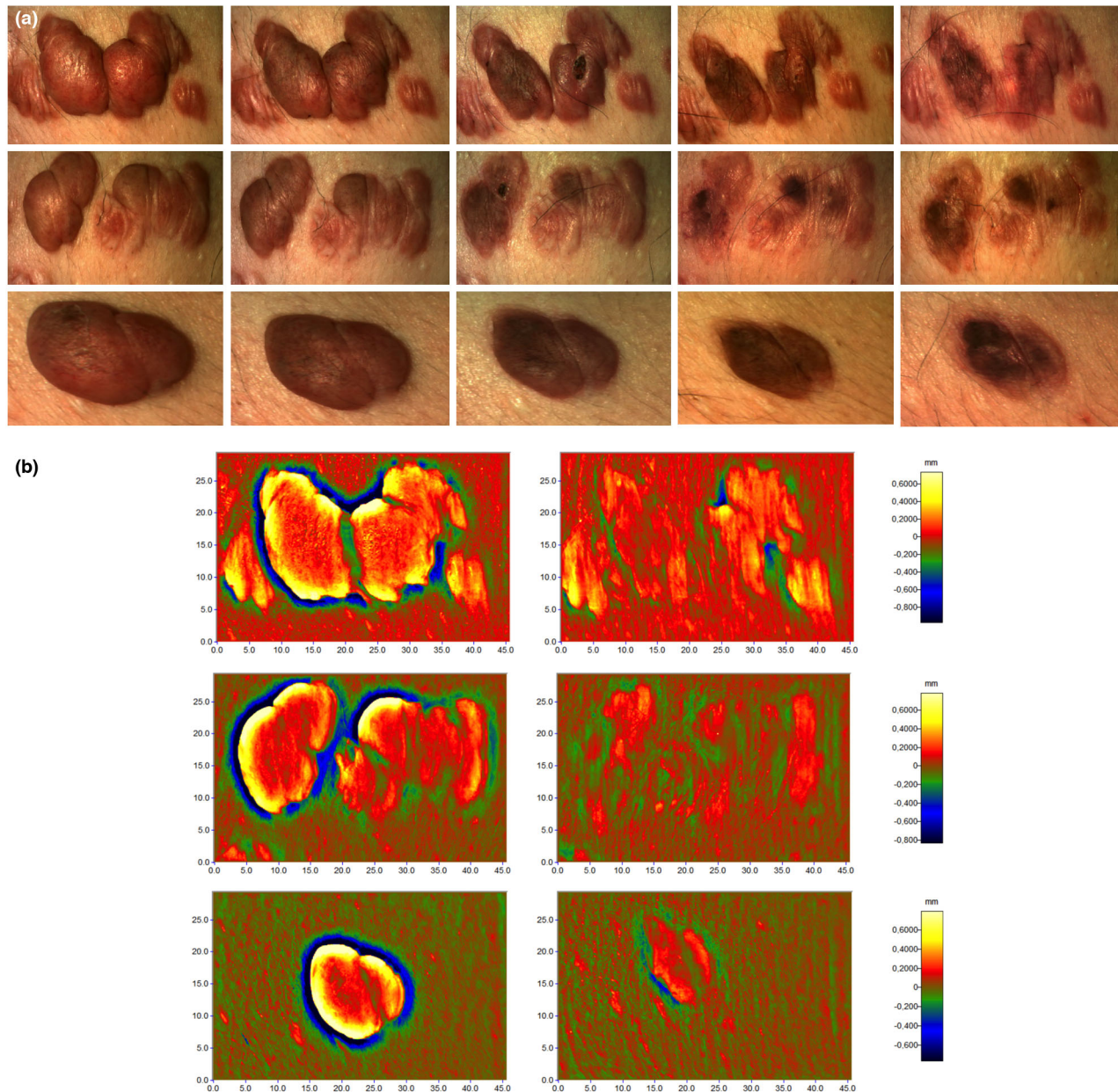


Figure 4 21-year-old male patient suffering from keloids on the chest, back and shoulder persisting for 4.5 years as a consequence to severe acne. PRIMOS data shows baseline, visit 2–4 and 1-month FU, respectively, left to right (a). Baseline (left) and 1-month FU (right) comparison in the colour image filter (b).

Results

PRIMOS[®]pico

Objective evaluation of 50 keloids using PRIMOS[®]pico made it possible to accurately calculate the height (mm) and volume (mm³) of pathologic scars in absolute and relative values.

Throughout the study, both keloid height (Smax) and volume decreased significantly. Keloid height and volume were reduced by 59.3% and 53.1%, respectively, between baseline and 12-month FU. Both values decreased continuously after every treatment session up until 1-month FU, from which point no further progress was observed (Figs 2–4). These results remained stable

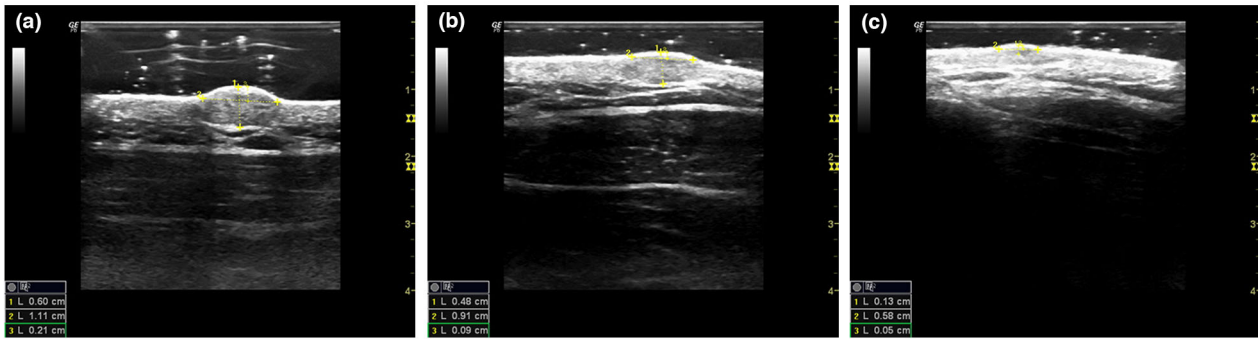


Figure 5 B-mode-ultrasound with measurements of absolute elevation and cutaneous penetration of keloid at baseline (a), at 1-month FU (b) and at 12-month FU (c).

until the 12-month FU for most of the variables measured, with exception of the scar height measured by PRIMOS[®]pico, which revealed a minimal increase between 1- and 12-month FU (1.5 ± 0.8 mm vs. 1.8 ± 0.9 mm, respectively).

Ultrasound

Ultrasound examinations of 25 keloids showed steady decreases in both skin expansion and penetration depth throughout the study. (Fig. 5) Overall, a reduction in skin expansion by 65.2% was observed between the baseline and the 12-month FU measurement. Penetration depth also showed significant improvement, decreasing by 74.4% between baseline and 12-month FU (Fig. 6).

Assessment

Patient and Observer Scar Assessment Scales (POSAS) All parameters in the patient score revealed significant positive changes after treatment. Pruritus and pain were dramatically reduced by 57% and 55%, respectively. Scar thickness and stiffness also showed drastic improvements, scoring 43% and 42% lower at 12-month FU when compared to baseline ($P < 0.0001$ for all measurements). The patients’ overall opinion of the scars improved by 39% throughout the study ($P < 0.0001$) (Fig. 7).

The observer data revealed statistically significant changes in all examined scar parameters. Scar pliability enhanced by 54% throughout the study. Other scar characteristics such as pigmentation, relief and thickness presented with reduced scores by 46%, 45% and 44%, respectively, ($P < 0.0001$ for all measurements). The observer’s overall opinion of the examined scars improved by 52% between the baseline measurements and 12-month FU ($P < 0.0001$) (Fig. 7).

Dermatology Life Quality Index (DLQI) Prior to treatment, keloids had a moderate effect on the quality of life of affected patients (baseline mean score: 8.3 ± 4.8 points). At 1- and 12-

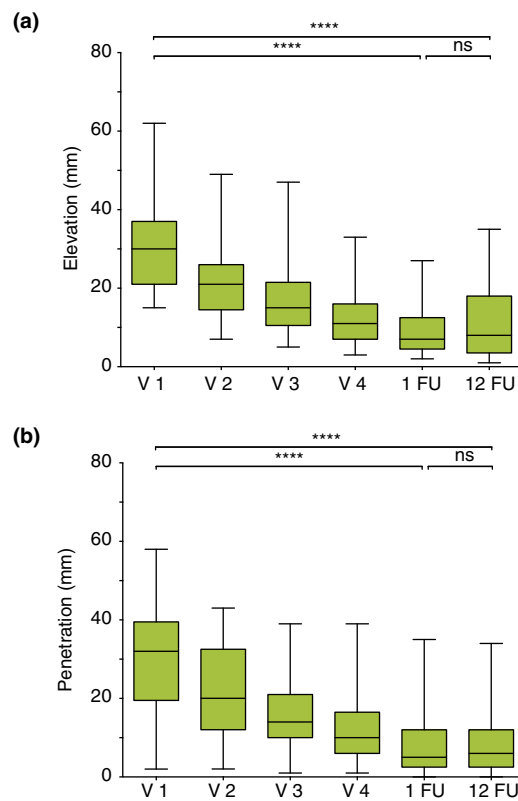


Figure 6 The absolute elevation of keloids (a) as well as the absolute penetration depth of keloids (b) was measured using B-mode ultrasound. ($n = 25$, **** $P = <0.0001$, ns = non-significant, V = visit, FU = follow-up).

month FU, the pathologic scars only had a small effect (1 month FU mean score: 2.6 ± 2.2 points, 12-month FU mean score: 2.6 ± 2.4), thus producing a significant and stable reduction in

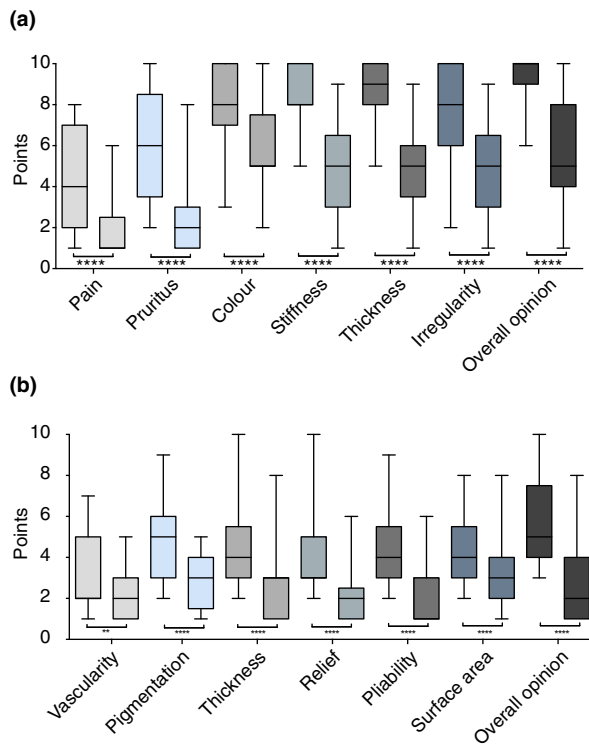


Figure 7 (a) Patient scar assessment scale rating characteristics of keloids comparing baseline to 12 months follow-up. (b) Observer scar assessment scale using characteristics of keloids comparing baseline to 12 months follow-up. ($n = 25$, **** $P < 0.0001$).

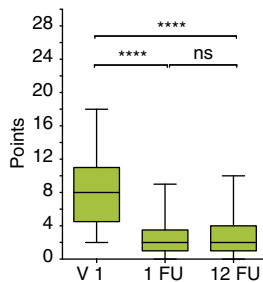


Figure 8 The Dermatology Life Quality Index (DLQI) shows the impact of keloids on patients' quality of life comparing baseline (V1) to 1- and 12-month FU; 0–1 points = no effect on patients' life quality; 2–5 points = small effect; 6–10 points = moderate effect; 11–20 points = very large effect; 21–20 points = extremely large effect. ($n = 25$, **** $P < 0.0001$).

the scar-associated impairment of the patients' quality of life (Fig. 8).

Adverse side effects All 25 patients completed the study. The treatment of keloids with 5-FU and TAC was very well tolerated

Table 2 Adverse side effects resulting from treatments

Adverse side effects	Absolute number ($n = 25$)	Relative number
Hyperpigmentation (resolved with sequelae)	9	36%
Teleangiectasia (resolved with sequelae)	6	24%
Ulceration (resolved without sequelae)	5	20%
Ulceration, hyperpigmentation (hyperpigmentation resolved with sequelae)	3	12%
Systemic side effects	None	0

and regular laboratory tests did not reveal any evidence of systemic side effects.

The most common local side effects were hyperpigmentation ($n = 9$) and telangiectasia of keloids ($n = 6$), lasting over the course of the study. Furthermore, ulcerations were seen in five cases, healing without sequelae. Some patients showed both hyperpigmentation and ulceration ($n = 3$) (Table 2).

All patients were strictly instructed not to scratch the ulcerations and, in case of doubt, to use a light body lotion and to alleviate itching and avoid inducing further keloid formation due to scratching artefacts.

Discussion

Treatment of excessive scarring, in particular keloids, remains difficult. Even though a significant number of patients benefit from conventional therapeutic approaches such as cryotherapy and intralesional corticosteroids,¹⁷ there are still a significant number of keloids that appear not responding to these approaches or that reoccur after initially successful treatments.¹⁸ 5-FU has been utilized for the treatment of keloids for many years.⁴ While TAC only suppresses cell proliferation, 5-FU induces apoptosis and may thus lead to superior and sustained results.¹⁹ Intralesional injections of 5-FU for the treatment of keloids have been relatively well studied and have demonstrated good efficacy in 18 randomized control trials, prospective clinical trials and case series.

5-FU Monotherapy has been shown to deliver good results when treating keloids. Recently, LaRanger and colleagues analysed the efficacy of 5-FU as an adjunct after the excision of severe keloids. After weekly to bi-weekly injections for a total of four sessions beginning 2 weeks after keloid excision, this group documented no recurrence over a follow-up time frame of 2 years.²⁰ Hietanen et al. compared the efficacy of TAC (20 mg/mL) and 5-FU (50 mg/mL) when treating a total of 50 keloids in their randomized trial. During their follow-up, they documented a similar efficacy for both measures but noted a significantly lower rate of side effects for 5-FU treatment.²¹

In particular, the combination of 5-FU and TAC appears more effective than 5-FU or TAC alone.^{8,9,11,22,23}

The ratios of 5-FU and TAC used in different publications vary, although ratios of 1 : 9 or 1 : 3 are most commonly used.

Protocols also show significant variation with regard to the intervals between sessions, ranging from once weekly to every 4 weeks. However, most of these studies rely on rather subjective scales and few objective measurements; in addition, relatively few studies have used long-term FU periods. While all studies show that the combination of TAC and 5-FU has certain benefits, based on discussions among experts in the field of scar management, it becomes apparent that the injection of a 3 : 1 ratio of 5-FU to TAC is becoming the most common procedure (M. Reinholz, A. Gürtler, H. Schwaiger, J. Pötschke, & G.G. Gauglitz, unpublished data). However, two recently published studies have demonstrated the efficacy both using the 1 : 9 ratio comparing the combination of 5-FU/TAC compared with TAC alone or the application of either TAC and 5-FU alone, respectively.^{11,24}

While Srivastava et al. largely relied on the Vancouver Scar Scale, Khalid et al. utilized the POSAS to evaluate their results. Here, we utilized measuring techniques such as PRIMOS[®]pico and ultrasound to objectively prove changes in scar volume, penetration depth and height to validate the efficacy of injecting a 3 : 1 ratio of 5-FU (50 mg/mL) and a crystalline TAC suspension (40 mg/mL) directly into keloid tissue every 4 weeks. The injected volume was limited to 4 mL per injection per patient, this corresponds to a maximum dose of 150 mg 5-FU and 40 mg TAC per injection per patient. Using this approach, the dosage used is below the chemotherapeutic dose of 200–600 mg/m², depending on the indication. Following current guidelines for pathologic scarring,^{1,25} we only included patients who had undergone previous therapeutic approaches which did not exhibit lasting improvements after at least three attempts. In order to ensure the comparability of the results of individual patients, keloids had to have persisted for at least 2 years.

Among our study population of 25 patients, we were able to demonstrate that keloid volume, height and penetration depth significantly decreased after four treatment sessions when comparing baseline and 1-month FU results. These results remained stable until the 12-month FU for most of the variables measured, with exception of the scar height measured by PRIMOS[®]pico, which revealed a minimal increase between 1- and 12-month FU. The latter finding may be the consequence of a small percentage of patients who exhibit signs of minimal recurrence. However, based on their POSAS evaluations, which showed highly significant ameliorations for all variables of interest, all patients and the observer noted significant improvements over the entire study duration. Importantly, all patients demonstrated great improvements in their quality of life as indicated by their DLQI scores. The latter finding may be a compelling motivation for more frequent consideration of this therapy in daily medical practice, as keloids are known to have a significant impact on affected patients' quality of life.²⁶

As with most clinical surveys in the field of scar therapy, our study could not provide certain important information. Most

critically, we were unable to include a control group or a placebo group, as the ethics committee did not permit patients to be left untreated. In addition, a variety of studies have already demonstrated that combinations of TAC and 5-FU may be superior to the respective monotherapies.

In conclusion, the results of this study confirm the efficacy and safety of the use of a combination of 5-FU and TAC in a 3 : 1 ratio in keloids based on objective measurements. Treatments were well tolerated and demonstrated stable results at 12-month FU.

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