

Clinical trial

# Clinical and histological results in the treatment of atrophic and hypertrophic scars using a combined method of radiofrequency, ultrasound and transepidermal drug delivery

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## Abstract

Scars are problematic for thousands of patients. Scarring is a natural part of the healing process after an injury. However, the appearance of a scar and its treatment depend on multiple factors and on the experience of the therapist and the options available. Despite a plethora of rapidly evolving treatment options and technical advances, the management of atrophic and hypertrophic scars remains difficult. Innovative technologies provide an attractive alternative to conventional methods in the treatment of scars. The purpose of this trial was to determine the clinical and histological results of a method of treatment that combines radiofrequency, ultrasound and transepidermal drug delivery. This was a prospective study conducted in 14 patients with scars of different sizes, types and characteristics. All patients underwent six treatment sessions with the Legato device. Atrophic scars were treated with retinoic acid and hypertrophic scars with triamcinolone. Photographs and biopsies were taken before treatment and at 6 months after the last treatment session. The scars improved significantly ( $P < 0.0001$ ). The mean attenuation in the severity of scars was 67% (range: 50–75%), where 100% indicates complete disappearance of the scar. Clinical and histological images of scar tissue in six patients in whom attenuation in the range of 55–75% was achieved are shown. Biopsies show regenerative changes in the scar tissue, in both the epidermis and dermis. The method makes it possible to treat extensive, heterogeneous scars on different sites with good results that are similar and predictable.

## Introduction

Scars are problematic for the many patients who consult with the intention of having them removed. Many treatments and methods of improving scars have been developed, such as cryoslush (with carbon dioxide [CO<sub>2</sub>] snow), liquid nitrogen cryopeeling, surgical scar revision, electrosurgical planing, chemical peeling, filler substance implantation, dermabrasion and laser treatments, among others. These treatments are disadvantaged by being either too mild and ineffective, or too aggressive and complicated.<sup>1</sup>

Recent studies have shown that some radiofrequency (RF)-based technologies, applied in isolation, significantly improve acne scarring,<sup>1–4</sup> with results similar to those of CO<sub>2</sub> fractional lasers and with fewer side effects.<sup>4</sup> A new method for attenuating atrophic and hypertrophic scars and stretch marks has also been reported. This combines high-power fractional ablative unipolar RF and ultrasound for the transepidermal delivery of drugs and bioactive compounds through microchannels.<sup>5–8</sup> Preliminary

studies of this method have been limited to investigations into its clinical efficacy and safety, and histological results that verify possible changes to the scar tissue are not available. Preliminary published results are of considerable interest and show minimal complications and adverse effects.<sup>5–8</sup>

The objective of this study is to determine the level of clinical improvement and histological changes to scars treated with retinoic acid (atrophic scars) or triamcinolone (hypertrophic scars) immediately after epidermal microablation using RF. The aforementioned drugs were used because they have already been applied, with good results, in this procedure.<sup>5,6</sup>

## Materials and methods

A heterogeneous group of 14 patients (five men and nine women), with skin of phototypes II–IV, was selected. Patients presented one or more scars of different etiologies, characteristics, sizes and sites. Only patients who had already undergone previous treatment in attempts to remove the scars,

and patients suffering from physical or psychiatric diseases that might interfere with the evaluation of the results or with adherence to the study were excluded. All patients accepted the conditions for participation in the trial and signed the corresponding informed consent. The trial was approved by the ethics committee of the Fundación Antoni de Gimbernat (Cambrils, Tarragona, Spain).

The causes of scarring included burns in four patients, postoperative scarring in four patients, and trauma of different types, including self-inflicted wounds, in six patients. The characteristics of the patients and the scars are shown in Table 1.

All patients underwent six treatment sessions delivered at intervals of 3 weeks. The interventions were performed by the same physician, who did not take part in the evaluation of the results. Photographs and biopsies of the scars were taken before the first treatment session and at 6 months after the last treatment session.

#### Description of the device and the treatment procedure

The Legato device (Alma Lasers Ltd, Caesarea, Israel) was used. The device comprises a new bimodal system that uses fractional ablative micro-plasma unipolar RF and acoustic pressure ultrasound technologies to introduce drugs and bioactive compounds into the dermis.<sup>7,9</sup> It includes a new high-power unipolar RF technology (iPixel™ RF), with technical and application characteristics that differ from those used to date.<sup>5–8,10</sup> The device uses the iPixel™ RF to cause thermal damage and fractional ablation through microchannels. Each microchannel is, on average, 80–120 μm in diameter and has a depth of 100–150 μm, depending on the RF power settings.

After topical application of the drug to be introduced into the microchannel, the ultrasound generated by the Impact™ module facilitates penetration into the dermis. The mode of operation is based on mechanical (acoustic) pressure and torque by propagation of ultrasound waves via the sonotrode to the distal tip and the creation of a hammer-like effect, which removes intracellular fluid from within the microchannels and forces the treatment substance through the dermo–epidermal junction.<sup>7</sup>

Both the RF and ultrasound (Impact™) handpieces are connected to a console that also houses the software that controls the operation of both modules. The RF handpiece has a removable single-use wheel tip which comprises multiple needle-like electrodes through which a unipolar RF is emitted, creating high-density micro-plasma discharge to cause microscopic perforations on the skin. During the procedure, the wheel is rolled over the skin, governed by the action of the handpiece trigger. When the rolling wheel is applied firmly to the skin surface, an electrical discharge occurs, passing to the interior of the skin so that most of the thermal effects take place in the dermis.<sup>7</sup>

The electrical RF current passes through the dermis in search of the opposite electrode, according to the principles of RF mechanisms of action. When the passage of the electric current is interrupted, the RF energy is absorbed, producing heating effects as a result of absorption. However, when the RF wheel tip is rolled without pressure on the skin, with minimal contact between the needles and the epidermis, microscopic plasma sparks are generated. These plasma sparks cause subtle peeling of the superficial keratin layer covering the epidermis. Further, the micro-plasma effect is intended to create microchannels in the epidermis as a consequence of

Patient	Sex	Age, years	Origin of scar	Age of scar, years	Location	Type	%Ev1	%Ev2	Mean
1 <sup>a</sup>	F	38	Burn	4	Leg	Atrophic	60%	80%	70%
2	F	54	Trauma	2	Leg	Atrophic	70%	70%	70%
3	M	27	Burn	1	Face	Hypertrophic	60%	70%	65%
4 <sup>a</sup>	M	24	Trauma	8	Arm	Atrophic	70%	70%	70%
5	F	44	Trauma	3	Neckline	Hypertrophic	50%	50%	50%
6 <sup>a</sup>	F	36	Burn	5	Neck	Atrophic	70%	80%	75%
7	M	29	Trauma	1	Thorax	Atrophic	60%	60%	60%
8	F	3	Burn	1	Neck	Hypertrophic	80%	70%	75%
9 <sup>a</sup>	F	52	Surgery	3	Abdomen	Hypertrophic	50%	60%	55%
10	F	42	Trauma	1	Face	Atrophic	70%	80%	75%
11 <sup>a</sup>	M	39	Surgery	4	Thorax	Hypertrophic	60%	80%	70%
12 <sup>a</sup>	M	57	Surgery	7	Thorax	Hypertrophic	70%	80%	75%
13	F	56	Surgery	12	Abdomen	Atrophic	50%	70%	60%
14	F	66	Trauma	1	Face	Atrophic	80%	70%	75%

**Table 1** Characteristics of patients and scars

<sup>a</sup>Patients shown in Figs 1–6

F, female; M, male; %Ev1, percentage of attenuation observed by evaluator 1; %Ev2, percentage of attenuation observed by evaluator 2; mean, mean percentage of attenuation of both evaluators

contact with the RF needle-like electrodes that discharge a high amount of electrical energy.<sup>7</sup>

In the case of atrophic scar tissue, treatment with RF is initiated by rolling the wheel tip in four criss-cross passes in which the tissue is firmly pressed, followed by another four criss-cross passes without pressure, to create microchannels in the epidermis. The aim of the first RF passes applied with pressure is to introduce electricity into the dermis so that the current can have a stimulating effect on tissue and collagen formation. Collagen develops during the healing phase of micro-wounds formed by electricity absorption, which generates a thermal effect. In the case of hypertrophic scars, treatment is started by using the RF rolling wheel to make four criss-cross passes on the lesion, without pressure. Then, the external part of the scar, and the surrounding healthy tissue, is treated by making four criss-cross passes with firm pressure of the rolling wheel. The aim is to create microchannels in the epidermis of the scar while RF application with pressure on the neighboring area aims to induce collagen formation via an electrical thermal effect for tissue tightening.

Once this action is completed, the retinoic acid (atrophic scars) or triamcinolone (hypertrophic scars) is applied, followed by application of the ultrasound module (Impact™). The hammer-like effect produced by the sonotrode enables the transport of the retinoic acid or triamcinolone to the area previously treated by the RF iPixel™ roller, thus increasing the penetration of the compounds into the dermis.<sup>7,9</sup> The ultrasound is applied perpendicularly to the skin surface, in continuous contact with it, with a circular (concentric-eccentric) motion. Treatment is carried out for a period of 2–6 min, depending on the number and size of lesions, to enable the transepidermal penetration of the retinoic acid (Isotrex gel 0.05%; Stiefel España GSK, Madrid, Spain) in the case of atrophic scars, or triamcinolone (Cemalyt cream 1 mg/g; Labs Alcalá Farma SL, Madrid, Spain) when the lesion treated is hypertrophic.

The power for the RF iPixel™ treatment was set at 60 W. The Impact™ ultrasound device has a pulse modulation control that emits an output power of 40 W, with impacts ranging from 10% to 100% in intensity. The output frequency is 27.5 kHz, with variations of 10–100 Hz (acoustic pressure pulse vibration rate per second).

Treatments were carried out under topical anesthesia using a cream containing lidocaine (Lambdalina®; Laboratory Isdin, Barcelona, Spain). During treatment, cold air was used (Cryo V; Zimmer MedizinSysteme GmbH, Ulm, Germany) set on Program 5, which corresponds to a flow rate of 600 L/min. The nozzle was pointed directly over the tip of the RF handpiece, following its movement. Cold air flow at this speed reduces pain or discomfort produced by the passes of the RF tip.

When the treatment was finished and for the following 3 days, a calendula-based moisturizing cream was applied to the treated areas three times per day.

## Evaluation of clinical results

Clinical evaluation was performed using photographs viewed on a computer screen. The photographs were taken by the physician performing the treatment, before treatment and at 6 months after the end of treatment, using the same camera (Nikon CoolpixP50, 12.1 megapixels; Nikon Corp., Tokyo, Japan), with the same settings, lighting and patient positioning.

Two independent dermatologists, blinded to the treatment, viewed the photographs of the scars out of order, without knowing whether or not they had been treated. Both dermatologists were asked to score the severity of the lesions on a 6-point grading scale (0–5) on which a score of 0 points corresponded to absence of a scar and a score of 5 points indicated a severe scar. The scores obtained before and after treatment were compared using the Mann–Whitney *U*-test.

The same dermatologists were then shown the photographs of the scars in order, in pairs showing the scars before and after treatment. They were asked to score the level of attenuation or reduction of the scars on a scale of 0–100%, where 0% refers to the initial aspect of the scar and 100% represents the appearance of the surrounding skin. The percentage of attenuation was calculated as the average of the percentages given by both evaluating dermatologists.

The level of patient satisfaction was measured using the terms “very dissatisfied”, “dissatisfied”, “somewhat satisfied”, “satisfied” and “very satisfied” after each patient had been presented with photographs taken before and at 6 months after treatment.

## Evaluation of histological results

Biopsies of the scars were taken before treatment and at 6 months after the last treatment session, under local anesthetic (lidocaine 1%, without a vasoconstrictor), using a 2.5-mm punch. The initial and final biopsies were taken from different points on the scar. Samples were fixed in a 4% buffered neutral formaldehyde solution and embedded in paraffin. Histological sections of approximately 5 μm in thickness were stained with hematoxylin and eosin, and examined using a conventional light microscope (Olympus BX 40; Olympus Corp., Tokyo, Japan). An independent expert dermatopathologist viewed the samples in pairs (×125 magnification) before and after treatment, in order to observe potential histological changes.

## Results

### Clinical results

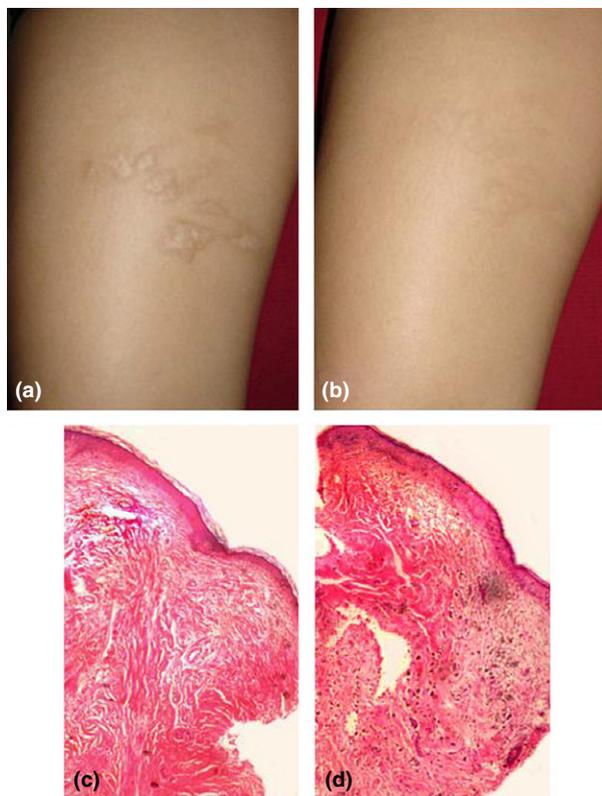
All patients completed the study without complications. Varying degrees of erythema and edema were observed in the hours following each treatment session. In a few cases, very fine scabs were observed, which disappeared within

a few days. No hyperpigmentation or other adverse effects were observed.

The scars improved significantly. The mean severity of the lesions was 4.12 points before treatment and 2.55 points at 6 months after treatment ( $P < 0.0001$ ). Table 1 shows the main characteristics of the patients and the scars, the percentages of attenuation achieved according to the independent evaluating dermatologists, and the means of both their scores. The mean percentage of attenuation for all scars was 67% (range: 50–75%). There were no demonstrable differences in results among patients or between types of scar. None of the scars disappeared.

Images (a) and (b) in Figs 1–6 show clinical results in Patients 1, 4, 6, 9, 11 and 12. The attenuation percentages observed in the images ranged from 55% (Fig. 4) to 75% (Figs 3 and 6).

Of 14 patients, two stated that they were dissatisfied, one somewhat satisfied, four satisfied and seven very satisfied. Thus, when patients had been shown the comparative photographs taken before and after treatment, 79% of patients stated that they were satisfied or very satisfied.



**Figure 1** Patient 1. Atrophic scars on the right leg after a burn, showing (a) the initial scar, and (b) the scar after treatment. Histopathology of biopsies obtained from (c) the initial scar and (d) the scar after treatment. (Hematoxylin and eosin stain; original magnification [c, d]  $\times 125$ )

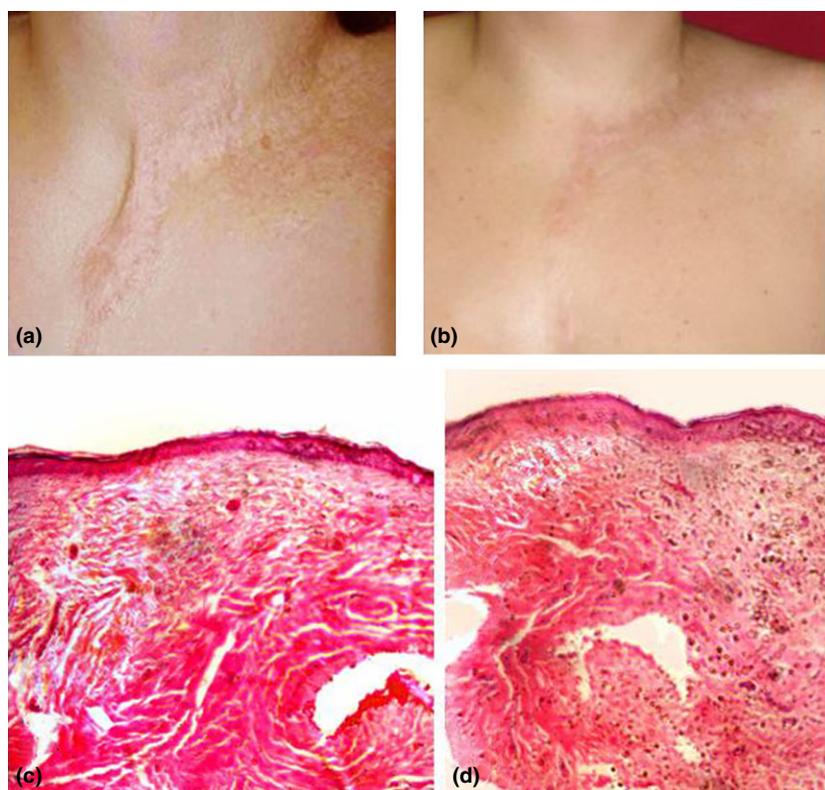
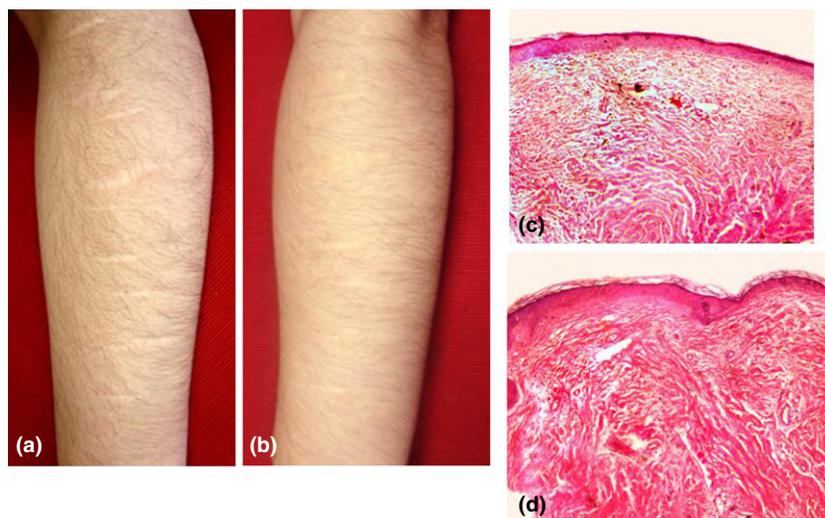
### Histological results

The atrophic scars showed a thin epidermis with few cell layers and a dermis with broad interfibrillar spaces. After treatment, the epidermis took on a more undulating and multicellular form, and the dermis, particularly the superficial dermis, presented more abundant and compact fibers, with inflammatory infiltrate. The hypertrophic scars showed pseudonodules of fibers in the dermis, a large part of which broke up. Images (c) and (d) in Figs 1–6 show histological findings in biopsies obtained from scars before treatment and at 6 months after treatment, respectively. Findings in the rest of the biopsies were similar.

Figure 1(c), which refers to an atrophic scar, shows keratin with a normal structure, a thin epidermis with few cell layers, a lack of epidermal crests, and a dermis with fibers arrayed in parallel and interlaced, with broad interfibrillar spaces. After treatment (Fig. 1d), observation reveals an absence of keratin, an epidermis with multiple cell layers and a dermis with abundant collagen, compacting of fibers, particularly below the dermo-epidermal junction, and discrete inflammatory infiltrate. Figure 2(c), which also corresponds to an atrophic scar, shows a thin layer of keratin, a flat epidermis formed by few cell layers, a lack of epidermal crests and a dermis with lax and broken fibers with spaces between them and characteristics of elastosis. After treatment (Fig. 2d), observation shows normal keratin, a discretely undulating epidermis with multiple layers and a dermis with fibers arrayed in a more homogeneous pattern that is more similar to that of normal skin. Figure 3(c, d) shows similar changes.

Figure 4(c), of a hypertrophic scar, shows a broad, flat epidermis formed by multiple cell layers, with a thin layer of keratin. The superficial reticular and papillary dermis show pseudonodules caused by compacted fibers, with few interfibrillar spaces. Observation after treatment shows an undulating epidermis made up of several cell layers, covered with a thin layer of keratin (Fig. 4d). The dermis has taken on a better-structured architecture, with residual scar tissue in the middle dermis and an inflammatory infiltrate. Figure 5(c), which refers to a hypertrophic scar, shows a broad, flat epidermis without keratin, and a compact dermis formed by multiple fibers in a nodular pattern, with almost no spaces between them. After treatment, observation shows a somewhat undulating epidermis with a smaller number of cell layers, covered with a thin layer of keratin (Fig. 5d). The arrangement of the fibers has been restructured, with collagen made of finer fibers and with no pseudonodular formations. Figure 6(c), which refers to a hypertrophic scar, shows a keratinized epidermis with several cell layers, with no dermal papillae, and compact, tightly spaced fibers in the reticular

**Figure 2** Patient 4. Atrophic scars on the left arm caused by self-inflicted cuts, showing (a) the initial scar, and (b) the scar after treatment. Histopathology of biopsies obtained from (c) the initial scar and (d) the scar after treatment. (H&E stain; original magnification [c, d]  $\times 125$ )



**Figure 3** Patient 6. Atrophic scars caused by a burn on the neck, showing (a) the initial scar, and (b) the scar after treatment. Histopathology of biopsies obtained from (c) the initial scar and (d) the scar after treatment. (H&E stain; original magnification [c, d]  $\times 125$ )

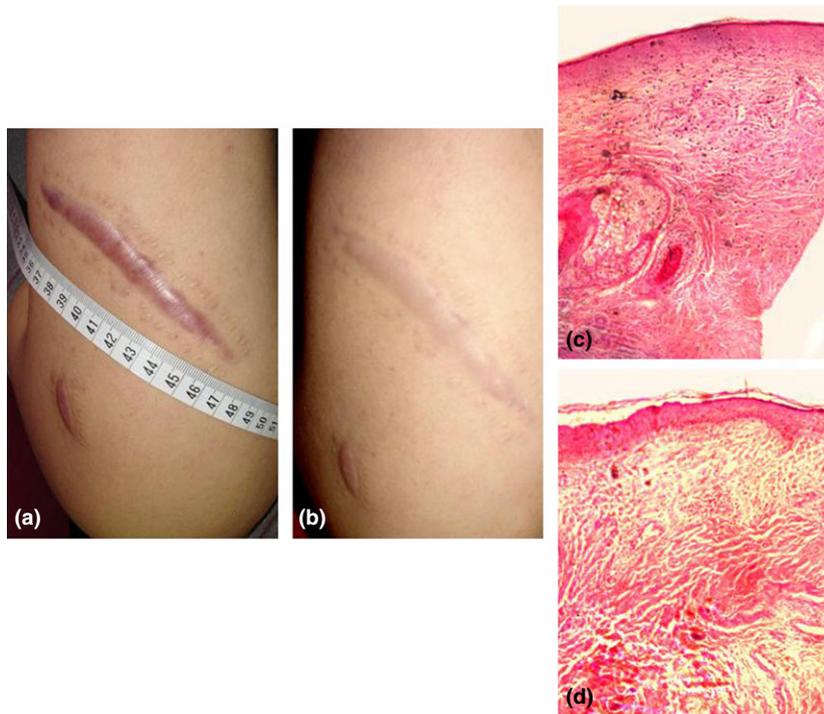
dermis. Observation after treatment shows a somewhat thinner and undulating epidermis, with a laxer dermis and larger inter-fibrillar spaces (Fig. 6d).

## Discussion

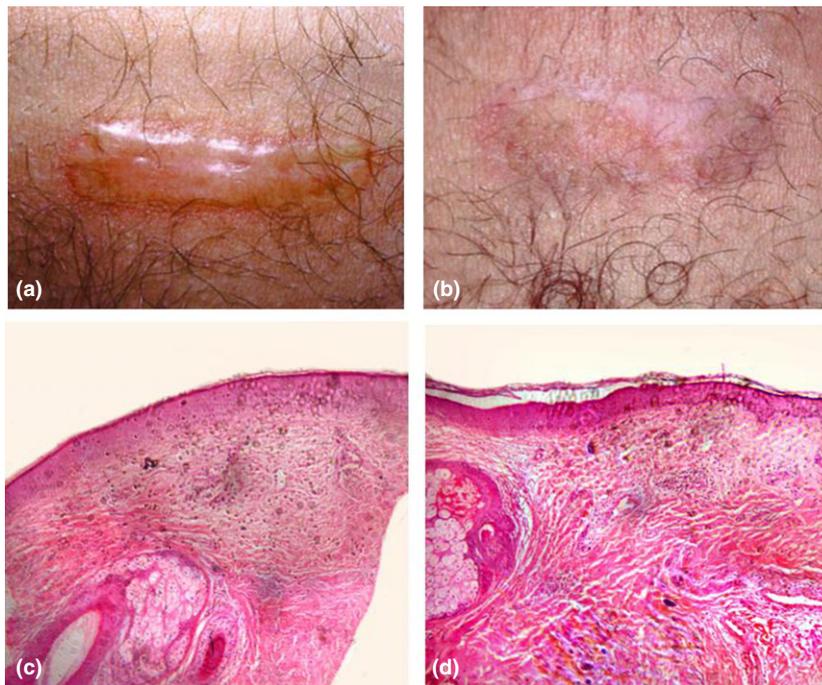
The results obtained confirm the efficacy of the method for attenuating or reducing scars, which supports the findings of previous studies.<sup>5-8</sup> We determined that it is possi-

ble to treat extensive scars, both atrophic and hypertrophic, with satisfactory results and without the complications inherent in other methods. Here, we show six percentages of attenuation corresponding to six sets of images of very different scars, which are representative of the sample and illustrative of the results achieved.

The first study of hypertrophic scars treated with Legato and triamcinolone suggested that some scars could disappear with a single treatment session, whereas other,



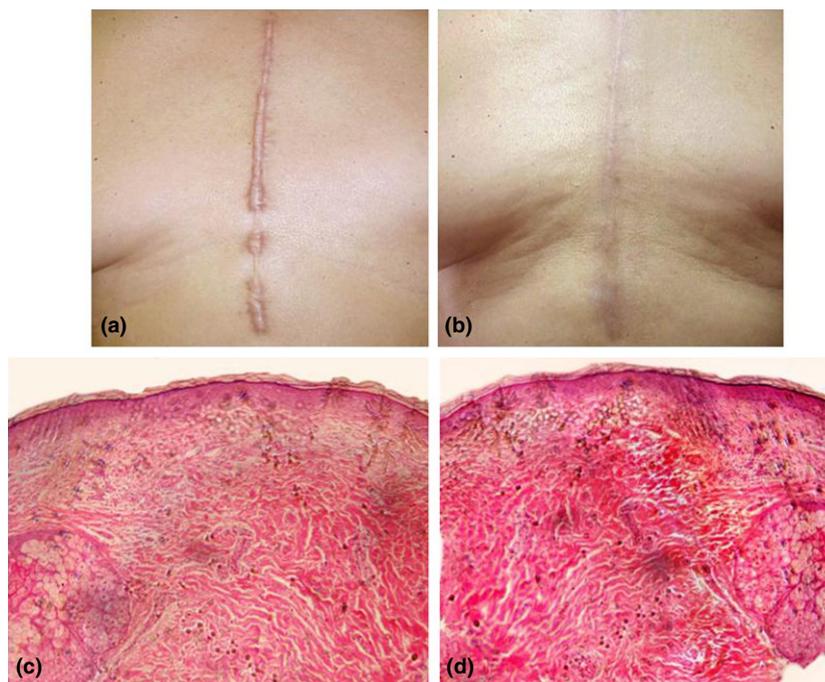
**Figure 4** Patient 9. Hypertrophic scars after abdominal surgery, showing (a) the initial scar, and (b) the scar after treatment. Histopathology of biopsies obtained from (c) the initial scar and (d) the scar after treatment. (H&E stain; original magnification [c, d]  $\times 125$ )



**Figure 5** Patient 11. Hypertrophic scar on the thorax after excision of a sebaceous cyst, showing (a) the initial scar, and (b) the scar after treatment. Histopathology of biopsies obtained from (c) the initial scar and (d) the scar after treatment. (H&E stain; original magnification [c, d]  $\times 125$ )

more refractory scars almost disappeared after a maximum of four sessions.<sup>6</sup> Given this possibility, we designed this study with the expectation of removing almost 100% of all the scars over six treatment sessions. This expectation was not met, but the clinical reduction of the scars has been estimated at a mean of 67% for all patients.

The MEDLINE literature shows no cases of extensive atrophic scars treated with Legato. The few studies published focus on the treatment of acne scars<sup>7</sup> and stretch marks.<sup>5,8</sup> Our results suggest that atrophic scars, caused by burns and trauma, may achieve better attenuation than hypertrophic scars. However, no statistically significant



**Figure 6** Patient 12. Hypertrophic scar on the thorax after heart surgery, showing (a) the initial scar, and (b) the scar after treatment. Histopathology of biopsies obtained from (c) the initial scar and (d) the scar after treatment. (H&E stain; original magnification [c, d]  $\times 125$ )

differences were found between the results for atrophic and hypertrophic scars, respectively.

In the treatment of hypertrophic scars, some authors have reported good results with injected triamcinolone,<sup>11–13</sup> whereas atrophic scars appear to improve with the application of iontophoresis with retinoic acid (tretinoin).<sup>14–16</sup> In a previous study of atrophic and hypertrophic acne scars, we obtained attenuations of almost 60% by transepidermal delivery of cosmeceuticals with bioactive components and whitening substances (allantoin, bisabolol, sodium hyaluronate, glycosaminoglycans, dipotassium glycyrrhizate, vitamin B complex, vitamin C, and low molecular weight peptides).<sup>7</sup> Based on the results of this trial, using a homologous methodology, we cannot conclude whether retinoic acid or triamcinolone are superior to the cosmeceuticals we used previously.<sup>7</sup> We believe that most of the therapeutic effect is attributable not to the transepidermally delivered substance, but to the conjunction of epidermal microablation and thermal stimulation of the dermis effected by this RF technology and the introduction of the drug during treatment. The ultrasound also appears to play an important role: we have observed several cases of epidermal shedding demonstrating a cause–effect relationship when the ultrasound is applied.<sup>17</sup>

In this study, we describe the first histological results of scars treated with Legato, verifying regenerative changes to the scar tissue in the epidermis and dermis, with good clinical and anatomopathological correlation. The microscopy images show consistent structural differences in

images obtained, respectively, before and after treatment, in which the initial signs characteristic of scar tissue are less evident at 6 months after treatment. The final histology results are also closer to those of normal skin.

The principal limitations of this study are its small sample size, the variability in the type, morphology and extent of scars, the lack of discrimination of the effects of each of the treatments applied separately, and the lack of information on effects achieved in fewer treatment sessions. Our initial objective was to determine whether it was possible to eliminate scars of very different characteristics and extents by applying more than the two to four sessions that are usually carried out for eliminating scars and stretch marks using this method, as reported in the literature.<sup>5–8</sup> Moreover, the evaluation of clinical results is always difficult as a result of the subjectivity of evaluators. Readers may use the pairs of photographs provided to determine a pattern of improvement that aligns with the percentages of reduction in the scars, as judged by the evaluators (Table 1).

A great number of methods have been used to treat scars. These include ablative and non-ablative laser therapy, autologous fat transfer, dermabrasion, chemical peels, injectables, subcision, iontophoresis and combination therapy. In expert hands, ablative lasers may, in some cases, achieve good and rapid results, but postoperative recovery involves discomfort and some of the adverse effects may be considerable and difficult to treat, particularly cases of prolonged erythema, hyperpigmentation, scarring and infection.<sup>14,18</sup> Some doubt exists

regarding the long-term maintenance of the effects of dermabrasion and autologous fat transfer.<sup>14</sup> Common problems with the other methods include pain or discomfort during treatment, the need for multiple sessions to achieve good results, and the length of time after treatment before improvement is observed.<sup>14</sup>

In conclusion, based on our experience with other therapies, the procedure described herein is an innovation of notable clinical interest in the treatment of scars. It makes it possible to treat multiple scars at the same time, regardless of their etiology, size, characteristics, or site, with good results, good predictability, and without the complications that may arise with laser treatments. Further studies are required in patients with specific types of scar, in larger samples, in order to determine the real scope of these preliminary results, and to better establish indications for the method and the recommended number of sessions.

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