Original Contribution

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An innovative regenerative treatment of scars with dermal micrografts

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Summary

Background Pathological scars occur following injuries and are often considered esthetically unattractive. Several strategies have been attempted to improve these types of scars using both surgical and nonsurgical methods. The most common treatments include cryotherapy, intralesional corticosteroid injections, 5-fluorouracil, bleomycin, interferon, and verapamil.

Aims In this study, we aim to investigate the effectiveness of dermal autologous micrografts in the treatment of pathological scars resulting from burns, trauma, or any iatrogenic source.

Methods We used a new clinical practice called Rigenera Protocol to obtain autologous micrografts which were in turn injectable in the patients.

Results A significant improvement was observed in appearance and texture of the exaggerated scars in all cases following already 4 months of autologous micrograft treatment We have also shown that these micrografts are composed of mesenchymal stem cells and in addition, histological evaluation verified restoration of the structural layers immediately below the epidermis and a horizontal realignment of collagen fibers in the papillary dermis.

Conclusion Our results clearly demonstrate the optimal outcomes obtained following treatment with dermal micrografts on exaggerated scars with different etiologies. However, further studies are required to confirm the efficacy of this new technique.

Keywords: Rigenera, keloid, hypertrophic scars, micrograft, mesenchymal stem cells

Introduction

Hypertrophic scars and keloids are aberrant excessive forms of pathological wounding with an excess of extracellular matrix (ECM), which appears to be mainly driven by fibroblasts.[1] Keloids and hypertrophic scars pose a clinical challenge in scar-related cosmetic dysfunctions and are highly prevalent in trauma and burns.[2] Several methods have been implemented to improve hypertrophic scars using both surgical and nonsurgical approaches. Among these, the most common treatments include cryotherapy,[3] intralesional corticosteroid injections,[4] 5-fluorouracil,[5] bleomycin,[6] interferon,[7] and verapamil.[8] In addition to conventional treatments, other authors have used unconventional

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therapies or innovative approaches such as interleukin-10 [9] and botulin toxin type A.[10] Laser therapy is an emerging minimally invasive treatment that has recently gained attention. Laser and light-based treatment modalities may achieve favorable patient outcomes. Clinical studies using CO_2 laser are more prevalent in current literature, and a combination regimen may be an adequate ablative approach.[11] Adding light-based treatments, such as photodynamic therapy (PDT) [12] or pulsed light,[13] to laser treatment regimens may enhance patient outcomes. Moreover, regenerative medicine is an emerging field in plastic surgery. The discovery of adipose stem cells as regenerative therapy is highly favorable.[14] However, identifying an optimal universal treatment for all types of scars still remains a challenge.

Autologous micrografts in turn injectable in the patients may be obtained by a new clinical device (called Rigenera) which allows mesenchymal stem cells to be obtained from the same donor and acceptor, thus avoiding complications related to implants to nonautologous micrografts. This procedure can be easily and safety used during intervention both in the operating room and in ambulatories. This device is currently used in the oro-maxillo-facial field as shown in recent studies,[15,16] but it may be applicable in other clinical fields including plastic surgery, dermatology, and orthopedics. Moreover, in a recent study, we have shown the efficacy of dermal micrografts in the management of postoperative complex wounds [17] and post-traumatic lesions.[18] In medical practice, Rigenera is based on the use of Rigeneracons medical device (Human Brain Wave, Italy), a biological disruptor of human tissues, able to produce autologous viable micrografts to repair or regenerate tissue.

In this article, we aim to display the efficacy of dermal micrografts in the treatment of pathological scars of different etiologies.

Materials and methods

Subjects and regenerative treatment

The inclusion criteria are based on the pathological scar classification according to Table 1. The first patient, 36-year-old woman with no relevant medical history was affected by postburns hypertrophic scars on the face and neck. The patient presented with predominant simultaneous tissue lacerations in the neck area during attempts to release superficial tissues with expanders. The second case describes a 28-year-old woman with no relevant medical history, presenting with hypertrophic scars of the knee and lower limbs following a road accident. The third case is a 32-year-old man with no relevant medical history, presenting with post-CO_2 laser treatment keloids in the scapular region and shoulder (Table 2).

These patients were treated with Rigenera system, using the Rigenera machine and Rigeneracons, a mechanical disruptor of human connective tissues (Human Brain Wave, Italy) (Fig. 1a). Rigeneracons is a newly marketed medical device based on the Medimachine-based method.[19] Rigeneracons is able to disrupt small pieces of human connective tissue using a grid provided by hexagonal blades filtering cells and components of extracellular matrix with an approximate cut-off in a 50 micron. To this purpose, seven pieces of underarm dermis measuring 2 cm^2 were removed from the patient (Fig. 1b) and inserted in the Rigeneracons with the addition of 1 mL of saline solution per piece and disaggregated for 90 s (Fig. 1c). After disaggregation, 7 mL of autologous micrograft (Fig. 1d) was collected and subsequently used to treat the scars. The skin was disinfected with Citrosil®, and micrografts were injected by microponfi technique with a hypodermic needle 30G × 6 mm to 45 degrees along the fold of the skin scars. In the first patient, we injected 1 mL of micrograft into the scar of the left eyebrow, 2 mL into the scar of the right side of the forehead, and 4 mL into the scars on the neck and chin. In the second patient, we injected 2 mL micrograft into the scars of the knee and 3 mL into the scars of the lower limbs. In the third patient, we injected 2 mL of micrograft for shoulder scars, 4 mL for scapular scars.

No further medication was prescribed to the patients. The patients were followed up for 24 months after the intervention with no additional treatment during the follow-up evaluation. Clinical assessments of the trea-

Table 1 Inclusion criteria based on the scar classification

Mature scar
A light-colored, flat scar
Widespread hypertrophic
Scar that forms commonly after a burn and appears as a widened red, elevated, and sometimes itchy scar. Can tend to regress spontaneously. This scar can be similar to a minor keloid if not regress spontaneously.
Minor keloid
A focally raised, itchy scar extending over normal tissue. Possible development up to 1 year after injury or burn and with no spontaneous regression. Surgical excision is often followed by recurrence
Major keloid
Large, elevated (>0.5 cm) scar, possibly painful or pruritic, extending over normal tissue. Spreading can continue over years.

Adapted from Devlin-Rooney *et al.* Nurs Stand, 2005[27] and from Mustoe *et al.* Plast Reconstr Surg, 2002[28].

Table 2 Summary information about patients' scar

	Age	Etiology	Scar classification	Location	History of scar	Time from treatment
Patient 1	36	Burns	Hypertrophic scar	Face	Any treatment	1 year
Patient 2	28	Accident road	Hypertrophic scar	Knee Lower limb	Any treatment	1 year
Patient 3	32	CO_2 laser	Keloid	Scapular region Shoulder	Any treatment	1 year

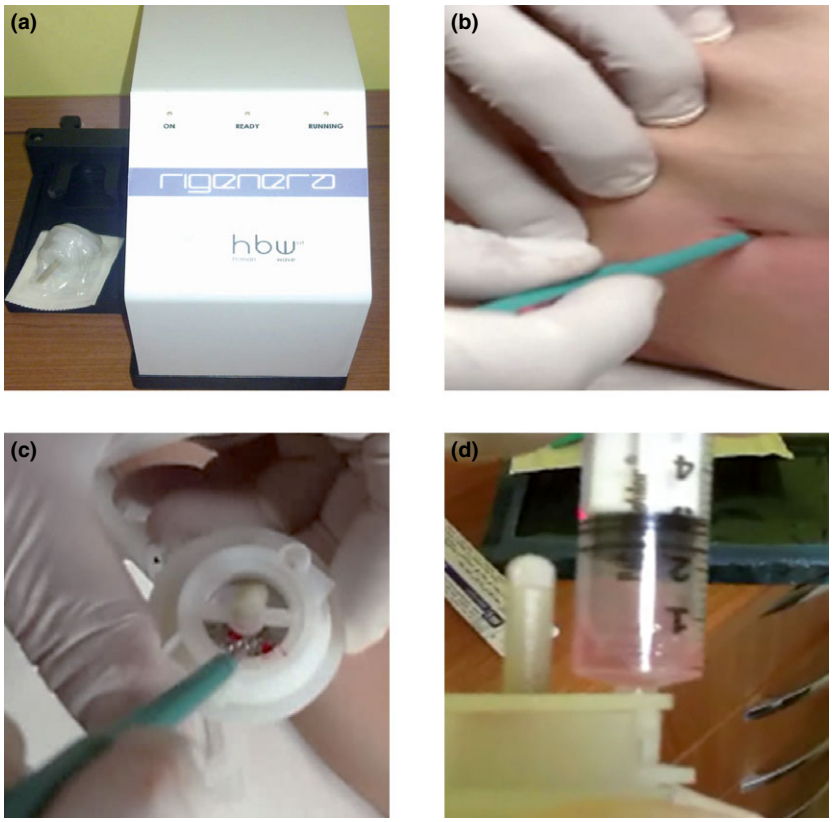

Figure 1 (a) Rigenera system composed of Rigenera machine and Rigeneracons. (b) Collection of dermis pieces by underarm. (c) The dermis pieces were inserted in the Rigeneracons medical device to be disrupt after addition of saline solution in order to collect micrografts. (d) Collection of micrografts including cell suspension, growth factors, and components of extracellular matrix of tissue of starting.

ted scars compared with baseline pretreatment photos were performed independently by two masked physician evaluators pre-operatively, immediately postoperatively and at 4 months intervals, using the following scale: 0, <25% improvement; 1, 26–50% improvement; 2, 51–75% improvement; 3, 76–90% improvement; and 4, >90% improvement.

Subjective scar assessment scale

The Vancouver Scar Scale (VSS) is the most well-known scar assessment method. It assesses four variables: scar color (vascularity), scar height (thickness), pliability, and surface texture (pigmentation) (Table 3). The pathological scars were evaluated before and after treatment with the VSS.

Flow cytometry

The cell suspension obtained by Rigeneracons was characterized by flow cytometry analysis (FACS) using a panel of antibodies which is generally employed to identify the mesenchymal cells. The following antibodies were used: anti-CD117 PE (c-kit) (Miltenyi –Biotech, Calderara di Reno, Bologna, Italy), anti-CD34 FITC and PE (Miltenyi-Biotech), anti-CD90 FITC (Miltenyi-Biotech), and

Table 3 Vancouver Scale Scar before the treatment with Rigenera protocol

	Scar characteristics
Vascularity	Normal
	Pink
	Red
	Purple
Pigmentation	Normal
	Hypopigmentation
	Hyperpigmentation
Pliability	Normal
	Supple
	Yielding
	Firm
	Ropes
	Contracture
Height	Flat
	<2 mm
	2–5 mm
	>5 mm

anti-CD105 PE (Miltenyi-Biotech). A FACS Vantage (Becton & Dickinson, Mountain View, CA, USA) was used.

Histological staining

Pathological scar samples were fixed in formalin or stored at −80°C. The specimens fixed in formalin were then dehydrated in alcohol and clarified in xylene and paraffin-embedded. Sections (5 μm thick) were stained with hematoxylin-eosin and observed under light microscopy.

Ethic and informed consent

This study respects all ethical requirements in its objectives and methodologies in compliance with the International codes of practice: The Nuremberg code, the Helsinki agreement, and the conventions of the Council of Europe on Human Rights and Biomedicine and EU legislation: 2001/83/EC, 86/609/EEC, and FP7 Decision nr 1982/2006EC. Written informed consent was obtained from the patients. Human biological samples are necessary to test human cells, which possess unique biological characteristics. The participants of our study have agreed to the publication of clinical images and of scientific treatment. We have obtained written consent from the patient. This study was approved by our Internal Ethical Board (Second University Ethical Board).

Results

Before treatment, we evaluated scar color (vascularity), scar height (thickness), pliability, surface texture (pigmentation), using the Vancouver Scar Scale. Table 4 shows that autologous micrografts injection revealed improvements in pigmentation, pliability, height, and vascularity. In fact, after autologous micrografts injections, we observed a significant improvement in appearance and texture of keloid scars both on the forehead, left eyebrow (Fig. 2a–b), neck, and chin (Fig. 2c–d) at 6 months compared to baseline conditions for the first patient. In the second patient, we also observed an improvement in scar appearance and color (Fig. 3c–d) compared to baseline conditions (Fig. 3a–b). A significant improvement was also noted in the esthetic aspect of the pathological scars in the third patient at 24 months follow-up (Fig. 4a–d).

Clinical observation has documented diminished scar bulk with a reduction in scar height and textural improvement. Moreover, the patients presented with skin pigmentation improvement and pliability in overall appearance. Mean patient and investigator scores for skin texture improvement after 1 month correlated with scales 2 and 3 and at the end of the follow-up correlated with scales 3 and 4 (Table 5). The patients appreciated the cessation of scar-related symptoms such as pruritus and burning. The improvement was mainly attributed to the fact that no additional dressing was required.

The phenotype of the cells obtained by Rigeneracons was studied by examining specific antigens for mesenchymal stem cells. In particular, we focused our attention on a population of stem/progenitor cells expressing the following markers: c-kit, CD34, CD90 (Thy-1), CD105. The flow cytometric analysis detected the presence of a cell population that we had previously identified[20]: cells positive for CD34 (82%), CD90 (82%), and CD105 (52%) (Fig. 5a–b) markers of the mesenchymal stemness. Moreover, from 2 mm^3, we isolated approximately 80 000 cells and the cellular vitality was 92% (data not shown), which demonstrates a positive outcome following mechanical fragmentation. In addition, approximately 70–80% of these cells were mesenchymal stem cells.

Table 4 Vancouver Scale Scar after 24 months from treatment with Rigenera protocol for Patients

	Baseline	24 Months follow-up
Vascularity	Red/Purple	Normal
Pigmentation	Hyperpigmentation	Normal/Hypopigmentation
Pliability	Firm/ropes	Normal/Supple
Height	2–5 mm	Flat

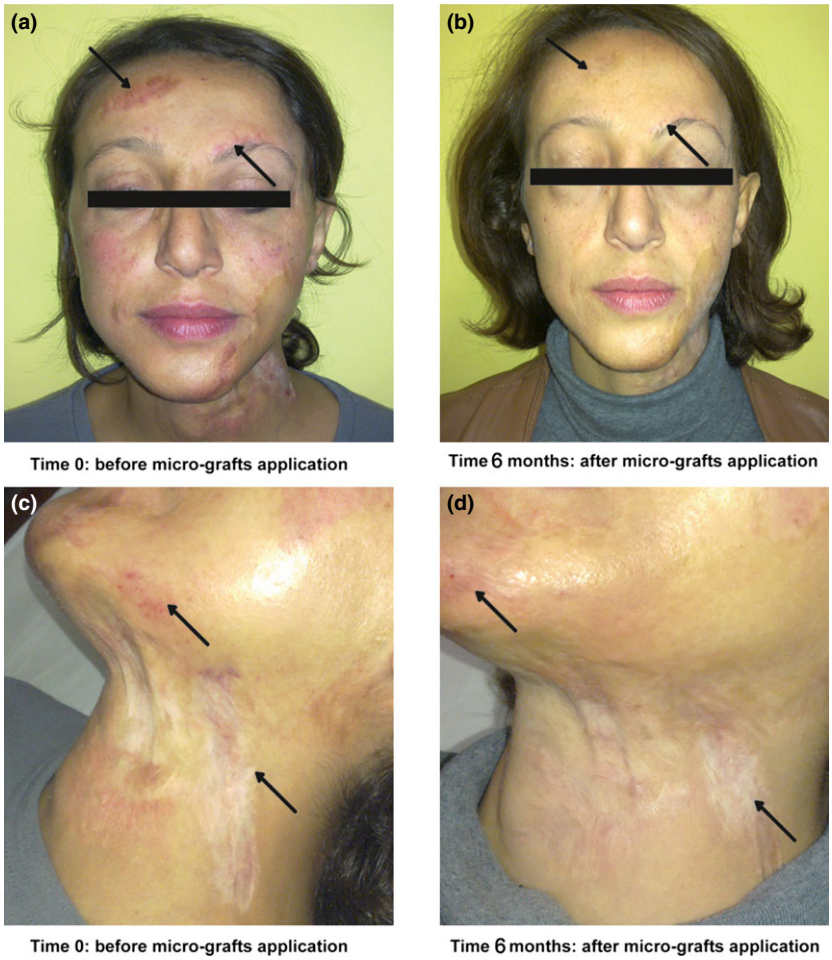

Figure 2 Images of pathological scars on forehead and left eyebrow (a–b) and neck and chin (c–d) before and after 6 months from autologous micrografts application as indicated in the text.

Baseline biopsy specimen of pathological scars showed (i) a considerable thickening of the skin and of the stratum corneum (Fig. 6a); and (ii) a morphological and structural disorder of the layers immediately below the epidermis (Fig. 6b). New collagen formation was observed at twelve months post-treatment showing restoration of the structural order of the layers immediately below the epidermis and a horizontal realignment of collagen fibers in the papillary dermis with normalization in polarity of keratinocytes (Fig. 6c–d).

Discussion

Our results demonstrate the potential efficacy of dermal autologous micrografts, used alone, to treat exaggerated scarring as a result of burns or traumatic injuries. Numerous studies have investigated effective treatments for exaggerated scars, but the efficacy of these treatments has not been clearly defined. The methods used to improve hypertrophic scars vary from surgical to nonsurgical methods and from conventional and nonconventional therapies. In many cases, intralesional treatments, such as the triamcinolone acetonide injection, play an important role in the improvement of these lesions suppressing vascular endothelial growth factor and inhibiting fibroblast proliferation to induce scar regression.[5] Preliminary clinical trials suggest a superior effect when steroids and 5-fluorouracil (5-FU) are injected together, in fact the 5-FU is classified as an antineoplastic agent and has recently been demonstrated to induce fibroblast apoptosis without necrosis and to inhibit TGF-β signaling in collagen I production. In addition to the 5-FU, the triamcinolone acetonide can be combined with bleomycin yielding optimal results. Bleomycin is a cytotoxic polypeptide

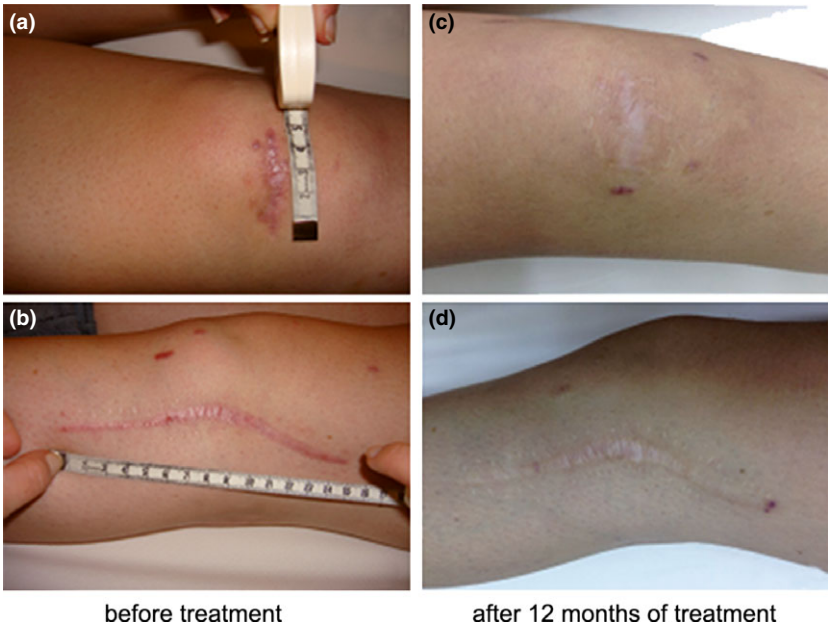

Figure 3 Images of pathological scars before (a–b) and after 12 months (c–d) from micrografts application.

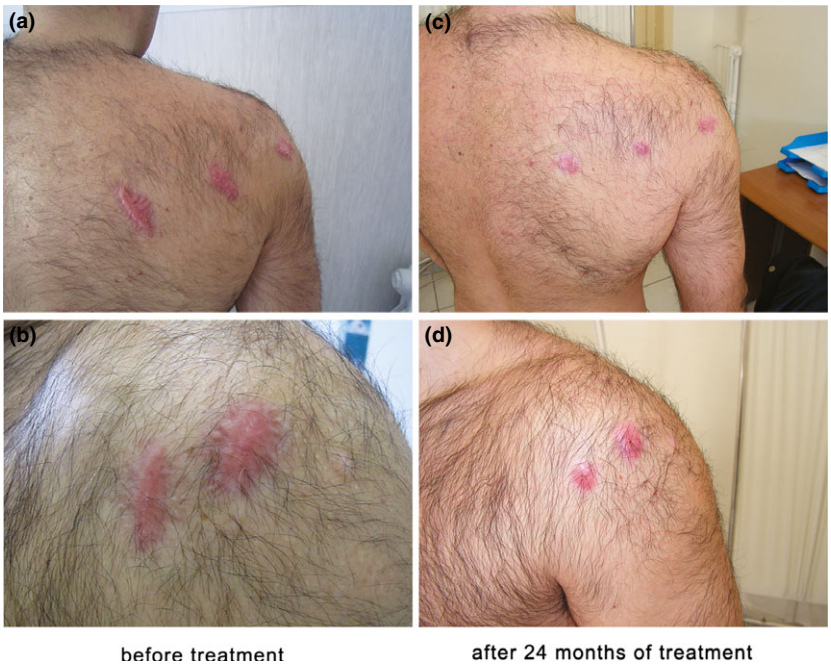

Figure 4 Images of pathological scars before (a–b) and after 24 months (c–d) from micrografts application.

with antitumor properties, and it is used as a systemic chemotherapeutical agent, and its effect in the treatment of hypertrophic scars may be explained by the inhibition of collagen synthesis by human dermal fibroblasts or stimulated by the presence of TGF-β or the increase of fibroblast apoptosis.[6] Moreover, verapamil can be used alone or in combination with triamcinolone acetonide, promoting procollagenase expression, inhibiting the synthesis of ECM, and increasing collagenase.[8]

Table 5 Mean improvement scores for patients and investigator evaluations

Variables	6 Months follow-up	12 Months follow-up	24 Months follow-up
Skin texture			
Patient	3	4	5
Investigator	4.1	4.5	5
Pigmentation			
Patient	2	3	4
Investigator	3.36	3.87	4.5
Smoothing			
Patient	3	3	4.5
Investigator	4	4.45	4.8
Overall appearance			
Patient	3	4	5
Investigator	3.78	4	5

New potential treatment approaches are progressing, and new combinations of treatment options have been proposed, such as the use of different lasers to improve scars in combination with other therapies including CO_2 laser, argon lasers, and Nd:YAG lasers,[21] but these therapies have not always yielded satisfactory results. Furthermore, some authors have evaluated carbon dioxide laser in the treatment of keloids showing a significant immediate and prolonged clinical improvement in skin tone and texture, in association with dermal remodeling after histologic examination of biopsied tissue.[11] The pulse dye laser has also been reported to produce long-term improvements in the appearance of hypertrophic scars. The basic mechanism is due to action on vascular proliferation, essential for the growth of collagen.

Nevertheless, other regenerative treatments have been proposed for improvement of scars. In addition to laser treatments, fat grafts,[22] platelet rich plasma (PRP),[23] and AdipoLASER [24] have been suggested. In particular, adipose stem cells present in the fat grafting may have a regenerative effect in the management of difficult wounds, regeneration of local soft tissue defects, and scar treatment. Moreover, PRP is rich in growth factors that stimulate cell proliferation and cell differentiation for tissue regeneration. PRP can also promote the proliferation of adipose stem cells to reduce healing time and aid the wound healing process. For this reason, some authors[25] have studied the synergic effect of fat graft, PRP, and CO_2 laser with remarkable results.

Recent reports suggest that mesenchymal stem cells (MSCs) represent a new antifibrotic treatment strategy. They attenuate wound inflammation and reprogram resident cells to favor tissue regeneration and inhibit fibrosis, influence host cells, and regulate the stem cell niche through differentiation and/or paracrine signaling mechanisms.[26]

Our hypothesis is that effectiveness of dermal micrografts could be related to the immunomodulatory effect of MSCs which secrete a combination of growth factors and cytokines to promote wound repair. In fact, the combination of growth factors and cytokines successfully induces angiogenesis, reduces inflammation, and promotes fibroblast migration and collagen production. In line with these data, previous *in vitro* studies have shown a high cell viability of micrografts obtained from different samples, such as the periosteum, cardiac atrial appendage biopsy, lateral muscle of eyeball, and adipose tissue.[14, 20] In addition, we reported a high positivity for micrografts derived from periosteum samples to several mesenchymal lineage markers, including CD90, CD105, and CD73.[20] Furthermore, we hypothesize that these micrografts are also characterized by components of extracellular matrix and growth factors derived from disaggregated human tissue able to repair lesions. Major advantages of this cellular therapy are as follows: (i) cells can be isolated from patients and autologously transplanted without the host's immune response, and (ii) using advanced technology, a single isolation can provide a repository of cells for the patients. On this basis of these findings,

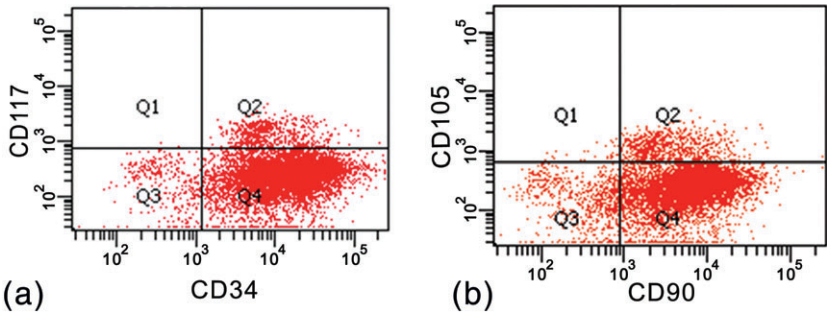

Figure 5 FACS evaluation. Cell characterization was carried out using mesenchymal cell line markers as CD34, CD90, CD105, and CD117.

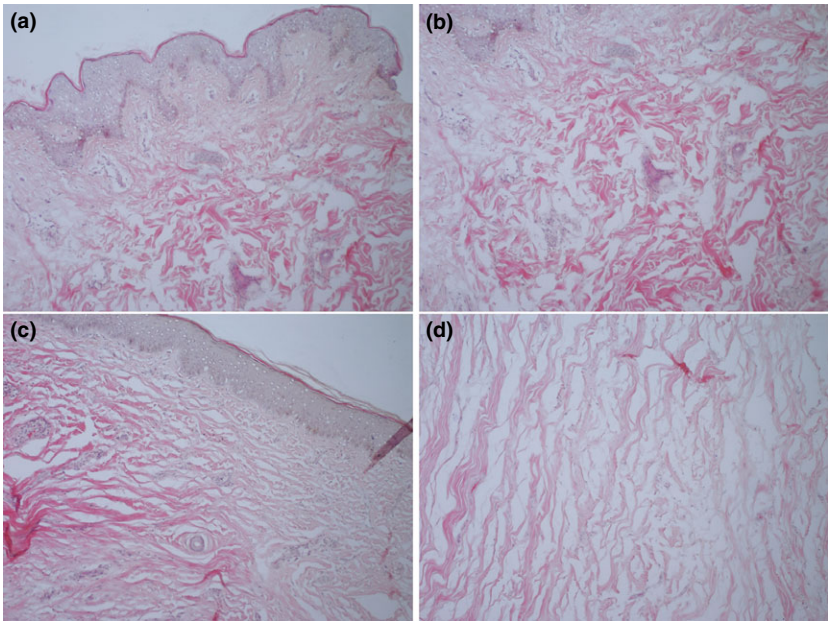

Figure 6 (a) H&E staining in the pre-operative biopsy specimen of pathological scars, representing the skin and the stratum corneum (Original magnification 100); (b) H&E staining in the pre-operative biopsy specimen of pathological scars, displaying a morphological and structural disorder of the layers immediately below the epidermis (Original magnification 200); (c) H&E staining twelve months after Rigenera treatment, with evident thinning of the stratum corneum (Original magnification 150); (d) H&E staining twelve months after Rigenera treatment, displaying a restoration of the structural order of the layer immediately below the epidermis and an horizontal realignment of collagen fibers in the papillary dermis (Original magnification 100).

these cells respond favorably to the local inflammatory and hypoxic conditions of the pathological scar environment, and they support important healing events that can be attributed to the secretion of anti-inflammatory proteins.

Prevention and treatment of abnormal scarring represents a challenge in the medical field. Different techniques have been used to treat hypertrophic scars and keloids, but failure and recurrence rates remain unacceptably high. The authors have used single micrograft injection, with no additional treatment during the follow-up evaluation. The permanent and stable effect of dermal micrograft following a single application led to an absence of recurrence rate. In conclusion, although the number of reported cases is limited, we reveal the efficacy of Rigenera protocol in the management of exaggerated scars, encouraging a new therapeutic approach based on the considerable regenerative potential of the human MSCs. However, further studies and cases are needed to confirm this potential.

Conflict of interest

Author L.T. has received payment for manuscript preparation (data collection and analysis) and support for study/meeting travel. Author A.G. is a board member of HBW Company. Other authors (F.S., F.D.F., and G.A.F.) declare that they have no conflict of interest.

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