

Collagen regeneration template in the management of full-thickness wounds: a prospective multicentre study

Objective: To evaluate the tolerance and healing rate of a collagen regeneration template in covering full-thickness wounds, including rate of adverse events.

Method: In this prospective, multicentre study, patients with a full-thickness wound underwent two-stage surgery consisting of implantation of a collagen regeneration template followed by a split-thickness skin graft (STSG). Patients were followed-up for 12 months. Adverse events arising from either the implantation or STSG were evaluated.

Results: Of the 33 patients included in the study, 29 completed the full follow-up period. During the study, 13 adverse events occurred at the treated wound site, as reported by 11 patients during follow-up. These included local infection (n=5), a diffuse infection (n=1) and non-infectious

seroma under the silicon layer (n=1). The mean percentage of take of the collagen template at 21±7 days after implantation was 81.2% of the treated surface. The mean percentage of take of STSG at 28 days after grafting was 84.4% of grafted surface. STSG was successful in 28 patients, but was completely rejected at 12 months for one patient. Mean functional score at 12 months, as evaluated by the treating surgeons, was 76.8/100 and mean aesthetic score was 62.7/100.

Conclusion: This study found use of a collagen regeneration template to be a safe procedure for the coverage of full thickness-wounds.

Declaration of interest: Professor Vincent Casoli acts as a consultant/medical expert for Symatase. The authors have no conflict of interest to declare.

collagen • complications • regeneration • skin wounds • wounds

The coverage of full-thickness wounds is a major challenge and the aim of dermal regeneration treatment is to restore skin function following trauma, surgical procedure or deep (third degree) burn.^{1,2} Full coverage of the wound must be achieved in order to: protect the major subdermal structures (bones, muscles, nerves, tendons, ligaments, vessels); restore normal mechanical function; restore thermal regulation and immunologic functions; and restore aesthetic appearance.

There has been increasing interest in the use of collagen regeneration templates. Primarily developed for use in burn management, their indications have widened due to their reported advantages including lower levels of morbidity or infection at the donor site and ease of application.³⁻⁵ The formation of the collagen layer provides a supple and non-adherent tissue which can support a split-thickness skin graft (STSG).^{6,7} The functional and aesthetic results are usually better than using only a STSG.⁸

A collagen regeneration template is a bilayered material consisting of a collagen matrix and a silicone

membrane.^{1,8-12} The collagen matrix is colonised by the patient's cells, mainly fibroblasts and endothelial cells, until it is eventually resorbed. The silicone membrane acts as an epidermis until new collagen is formed. The silicone membrane is then removed and replaced by a STSG.⁹

Aim

The aim of this study was to evaluate the feasibility and rate of adverse events related to a new collagen regeneration template, associated with a STSG procedure, to cover full-thickness skin defects.

The primary objective was to assess tolerance by recording any adverse events related to the use of the collagen regeneration template. Secondary objectives included the healing rate of the template at the time of STSG, at 28 days, and at six and 12 months post-STSG. Patient and surgeon satisfaction at 12 months and the quality of the reconstructed skin at six and 12 months were also recorded.

Method

Study design

This study was a prospective, longitudinal, multicentre clinical trial and was recorded on clinicaltrials.gov database (number NCT02089490). It was conducted with national ethical committee approval, requiring written informed consent, in accordance with the Declaration of Helsinki. The evaluated template was CE marked in 2013.

Between April 2014 and February 2016, patients of Bordeaux University Hospital and Montpellier University

*Jean-Maxime Alet,^{1,2} MD; Audrey Michot,^{2,3} MD; Emilie Desnouveaux,^{1,2} Project Manager; Marion Fleury,^{1,2} MD; Luc Téot,^{4,5} MD, PhD; Sergiu Fluieraru,^{4,5} MD; Vincent Casoli,^{1,2} MD, PhD

*Corresponding author email: jeanmaxime.alet@chu-bordeaux.fr

1 CHU de Bordeaux, Pole des spécialités chirurgicales, Service de chirurgie plastique brûlés main, F-33000 Bordeaux, France. **2** University of Bordeaux, F-33000 Bordeaux, France. **3** Institut Bergonié, F-33000 Bordeaux, France. **4** CHU de Montpellier, Service de chirurgie plastique brûlés, F-34295 Montpellier, France. **5** Université de Montpellier, F-34295 Montpellier, France.

Table 1. Components of the Vancouver Scar Scale

Score	Pliability	Vascularity	Pigmentation	Height
0	Normal	Normal	Normal	Normal
1	Supple	Pink	Hypopigmentation	<2mm
2	Yielding	Red	Hyperpigmentation	2–5mm
3	Firm	Purple		>5mm
4	Banding			
5	Contracture			

Hospital were recruited to the study. The inclusion criteria were patients aged ≥18 years, with a full-thickness skin wound (either third degree burn, surgical procedure or traumatic wound), geographically stable (not relocating during the study period), had agreed to a 12-month follow-up and signed the informed consent including for the taking and use of photographs.

Patients were excluded if they had any infectious signs at the wound location, a known predisposition to allergy and, in particular, to silicone or bovine collagen, had a life-threatening disease, any condition interfering with healing, an autoimmune disease, Creutzfeld-Jacob

Table 2. Patient demographic data and wounds characteristics

Patient number	Gender	Age (years)	Wound characteristics	Limb	Body part	Wound surface (cm ²)
1	Male	66	Traumatic	Lower	Foot	90
2	Male	57	Amputation stump issue	Lower	Leg	90
3	Male	75	Third-degree burn	Lower	Foot	72
4	Male	74	Traumatic	Lower	Foot	84
5	Male	48	Traumatic	Lower	Leg	195.4
6	Male	37	Third-degree burn	Lower	Thigh	360
7	Female	68	Necrotic	Upper	Hand	126
8	Male	19	Third-degree burn	Lower	Foot	150
9	Male	64	Amputation stump issue	Lower	Thigh	336
10	Female	30	Donor site	Lower	Leg	20.3
11	Female	31	Traumatic	Lower	Foot	12.2
12	Male	49	Traumatic	Lower	Leg	204
13	Male	65	Necrotic	Lower	Foot	408
14	Male	56	Traumatic	Lower	Foot	16
15	Female	44	Skin cancer removal	Upper	Shoulder	24.5
16	Female	21	Donor site	Upper	Forearm	323
17	Female	80	Necrotic	Lower	Leg	120
18	Male	49	Traumatic	Upper	Forearm	135
19	Male	30	Traumatic	Lower	Leg	84.5
20	Male	90	Skin cancer removal	Upper	Forearm	47.6
21	Male	72	Ulcer	Lower	Leg	26.4
22	Female	29	Donor site	Upper	Forearm	52.5
23	Male	38	Donor site	Lower	Leg	54
24	Male	34	Donor site	Upper	Forearm	255
25	Female	62	Skin cancer removal	Lower	Leg	46.8
26	Female	41	Donor site	Upper	Forearm	42.5
27	Male	85	Skin cancer removal	Lower	Leg	35
28	Male	67	Traumatic	Upper	Forearm	150
29	Female	53	Diabetic	Lower	Foot	7
30	Male	60	Diabetic	Lower	Foot	80
31	Male	72	Diabetic	Lower	Foot	17.5
32	Male	49	Amputation stump issue	Lower	Foot	15.8
33	Male	53	Amputation stump issue	Lower	Foot	35

CRT—collagen regeneration template; STSG—split-thickness skin graft; PID—povidone iodine dressing; NPWT—negative pressure wound therapy

Disease, if they were pregnant or already involved in another study.

According to the study protocol, once the patient enrolled during the inclusion visit (visit one) and was treated with the collagen regeneration template (visit two/day zero), five follow-up visits were performed (visits three to seven). Visit three took place between days three to seven and allowed evaluation of the treatment progress (template take/collagen regeneration/adverse events). Visit four (at 21 days) was the second operative time and consisted of removal of the upper silicone layer and STSG procedure. Collagen regeneration

template take and adverse events were assessed by the surgeon. Visit five, planned for 28±7 days, assessed STSG take. Visits six and seven, at six and 12 months respectively, allowed the evaluation of STSG take rate, and functional and aesthetic outcomes. Additional consultations were at the discretion of the surgeon. Adverse events were systematically recorded at each scheduled follow-up visit.

Collagen regeneration template

The template used in this study, NEVELIA (Symatase, Chaponost, France) is a bilayer matrix for dermal

First step surgery – CRT implantation				Second step surgery – STSG		
CRT size	Fixation	Wound dressing	Bolster dressing	Harvest site	Thickness (inch)	Type of skin graft
10x30	Stapling	PID	No	Thigh	0.100	Expanded
10X30	Stapling	NPWT	No	Thigh	0.100	Expanded
10X30	Stapling	PID	No	Thigh	0.100	Perforated
10X30	Stapling	PID	No	Thigh	0.100	Perforated
10X30	Stapling	PID	Yes	Thigh	0.100	Expanded
10X30	Stapling	PID	No	Thigh	0.100	Expanded
10X15	Stapling	PID	No	Thigh	0.100	Perforated
10X15	Stapling	PID	No	Thigh	0.100	Expanded
10X30	Stapling	NPWT	No	Thigh	0.120	Expanded
5X5	Stapling	PID	No	Thigh	0.120	Perforated
5X5	Stapling	NPWT	No	Thigh	0.200	Perforated
10X15	Stapling	PID	Yes	Thigh	0.160	Perforated
10X15	Stapling	PID	Yes	Thigh	0.400	Perforated
5X5	Stapling	PID	No	Thigh	0.110	Full
5X5	Sutures	PID	No	—	—	—
10X30	Stapling	PID	No	Thigh	0.100	Expanded
10X15	Stapling	PID	No	Thigh	0.100	Expanded
10X15	Stapling	PID	No	Thigh	0.120	Expanded
10X15	Stapling	PID	No	Thigh	0.120	Expanded
5X5	Stapling	PID	No	Arm	0.120	Full
10X15	Stapling	NPWT	No	Thigh	0.100	Full
10X15	Stapling	PID	Yes	Thigh	0.120	Full
10X15	Stapling	PID	No	Thigh	0.100	Expanded
10X15	Stapling	PID	No	Thigh	0.100	Expanded
10X15	Stapling	PID	No	Thigh	0.100	Full
10X15	Stapling	PID	No	Thigh	0.120	Perforated
10X15	Stapling	PID	Yes	Thigh	0.120	Expanded
10X15	Stapling	PID	No	Thigh	0.100	Expanded
5X5	Stapling	PID	No	Thigh	0.100	Full
10X15	Stapling	PID	No	Thigh	0.100	Full
5X5	Stapling	PID/NPWT	No	Thigh	0.100	Full
5X5	Stapling	PID	No	Thigh	0.100	Full
10X15	Stapling	PID	No	Thigh	0.100	Full

Table 3. Adverse events: collagen regeneration template follow-up

Complication type	Occurrence
Non-specific complication	
Pulmonary oedema	1/33 (3.0%)
Specific complication	
Local infection and fluid collection (including one haematoma)	5/33 (15.2%)
Diffuse infection and fluid collection	1/33 (3.0%)
Non-infectious fluid collection	1/33 (3.0%)

regeneration composed of a thin, stabilised lyophilised type I bovine collagen matrix (2mm in thickness) and an ultra-thin superficial silicone layer reinforced by polyester material. The collagen layer serves as a support for cell infiltration and is resorbed in 2–3 weeks during the natural dermal regeneration process. The silicone layer acts as a pseudo-epidermis, protecting the wound from the external environment during tissue reconstruction and is removed at the time of the STSG.⁹

Surgical procedure

The patients were operated on by senior plastic surgeons, under general or local anaesthesia, depending on the location of the wound and the clinical view of the anaesthetist. The coverage of full-thickness wounds using the collagen regeneration template was a two-step surgical procedure.

The wound was debrided until viable tissue was obtained, then irrigated with saline. A meticulous haemostasis without tourniquet was performed. The prehydrated collagen regeneration template was then cut to fit the wound size and placed on the wound in order to minimise wrinkling and air bubble entrapment under the device. It was then stabilised with sutures or staples. Dressings were used until the STSG procedure took place and consisted of either negative pressure wound therapy (NPWT) or povidone iodine gauzes. When collagen regeneration was obtained (based on the colour change (demonstrating the neo-dermis had colonised the matrix and the collagen was resorbed) to

Table 4. Adverse events: split-thickness skin graft follow-up

Adverse event type	Occurrence	Postoperative time appearance
Diffuse infection	1 (3.0%)	15 days
Fistula: heel	1 (3.0%)	15 days
Pressure ulcer: heel	1 (3.0%)	6 months
Seborrheic cyst	1 (3.0%)	6 months
Necrotic hypodermis recurrence with over-infection (<i>Pseudomonas aeruginosa</i>)	1 (3.0%)	12 months
Necrosis: heel	1 (3.0%)	12 months

peachy or vanilla from the initial white of the medical device, the silicone layer was removed and an autologous STSG (0.01–0.016 inch thickness) was applied. The use of antibiotics was at the discretion of the surgeon.

Data management and statistics

All data were analysed with Minitab statistical software (Minitab Inc., US). The complications were noted at each follow-up visit. The collagen regeneration template and STSG take rates were evaluated by visual observation and measured with a ruler.

The quality of the skin obtained was evaluated using the Vancouver Scar Scale (VSS).^{13,14} This validated scale gathers information related to vascularity, pigmentation, pliability and height of the skin (Table 1). Normal skin is represented by zero. Functional results were separately assessed using a visual scale, graded from zero (‘very disappointing’) to 100 (‘very satisfying’) by both the patient and the surgeon.

The description of quantitative variables was made with the mean, median, and standard deviation. For categorical variables, the frequencies and percentages were used. All data were analysed in an intention-to-treat (ITT) manner and when data was not available (due to loss of follow-up or patient withdrawn) it was recorded as equal to zero to avoid influencing the success rate.

Results

Patients

A total of 33 patients were included in the study, the majority of which were men (n=23; 69.7%). Mean age was 53.6 years (range: 19–90 years). Indications included full-thickness burn surgery (n=3; 9.1%) and reconstructive surgery (n=30; 90.9%), including nine (30%) traumatic wounds, six (20%) flap donor site coverage, four (13.3%) cancer wounds, four (13.3%) amputations, three (10%) diabetic feet, three (10%) necrotic chronic wounds and one (3.3%) ulcer. The majority were located on the lower limb (n=24; 72.7%), and the rest on the upper limb (n=9; 27.3%). The mean length and width of wounds were 11.7cm and 7.8cm, respectively, with a total mean grafted surface area of 112.6cm² (range: 7–408cm²). A patient withdrew their consent at one month to be included in another study related to their disease and a further two patients were lost at follow-up (one patient at six months, the other at 12 months). During the six months’ follow-up period, one patient died due to head and neck cancer evolution. The clinical study was completed by 29 patients. Demographic and wound characteristics are shown in Table 2.

Adverse events

Adverse events were recorded throughout the study and analysed according to the four medical phases:

- Intraoperative collagen regeneration template implantation
- Follow-up
- STSG procedure

- Postoperative skin graft follow-up.

During the first-step surgical procedure, one case of perioperative hypovolaemia occurred and was managed by blood transfusion of two units of packed red blood cells. No intraoperative issue related to the template use was reported.

From the time of collagen regeneration template implantation until the STSG procedure, seven adverse events of the treated wound site and one non-specific adverse event (pulmonary oedema) were recorded (Table 3). Among these specific adverse events, six (18.2%) were neo-collagen infections (five local and one diffuse) associated with a fluid collection under the template and one (3%) a non-infectious seroma located under the silicone layer. These infections occurred in treated skin cancer wounds (n=3), third-degree burns (n=2) and necrosis (n=2). They were successfully managed by cleaning and disinfecting the wound site with saline and povidone iodine, coupled with antibiotic treatment. However, removal of the collagen regeneration template was required in three patients due to localised infection with an accumulation of fluid under the matrix, impeding the take. However, the STSG was performed in these patients despite these complications.

During the second-step surgery, no intraoperative adverse event was recorded except in one patient where an exanthema localised on the trunk and upper limbs appeared on the day. After the STSG procedure, six postoperative adverse events of the treated site were reported (Table 4). All adverse events were assessed as being not directly related to the collagen regeneration template which had already been colonised by the patients' cells and resorbed.

Technical and performance results

The collagen regeneration template was easy to place in 30 (91%) patients, according to the results of the surgeon satisfaction questionnaire. In the remaining three patients, the handling of the collagen template was assessed as more difficult to place due to matrix rigidity in one case, and the presence of undesired folds in two cases, making it difficult to apply to large wounds. Once cut to the desired shape, the template was fixed by staples in 32 (97%) patients and sutures were used for one patient (3%). The mean percentage of take of the collagen regeneration template at visit 4 (21 days) was 81.2% of treated surface (Table 5). The integration of the collagen regeneration template failed (take rate <50%) in five cases, but without delaying the STSG procedure. In six patients, the presence of granulation tissue (three patients) or remnants of the template which had not completely resorbed (three patients) were observed at day 21 but did not prevent the STSG procedure.

STSG was performed at a mean time of 26.5 days. The inner thigh was the most common site (n=31; 93.9%) for harvesting the STSG. The mesh expansion technique was used in 14 (44%) patients.

The mean percentage of STSG take at visit five

Fig 1. Full-thickness wound of the dorsal aspect of the foot resulting from a quad bike accident (a). Placement of the collagen regeneration template to cover the wound using staples (b). Day 21 after collagen regeneration template placement; the change of colour to orange-peach indicates the optimal time for split-thickness skin grafting (STSG) (c). Day 21 after collagen regeneration template placement; removal of the silicone layer showing the new collagen layer (d). Day 21 after collagen regeneration template placement: aspect of the new collagen layer covering the wound (e). Placement of a 0.010 inch meshed STSG (1.5:1) (f). At 12 months, the patient is able to wear normal shoes (g)

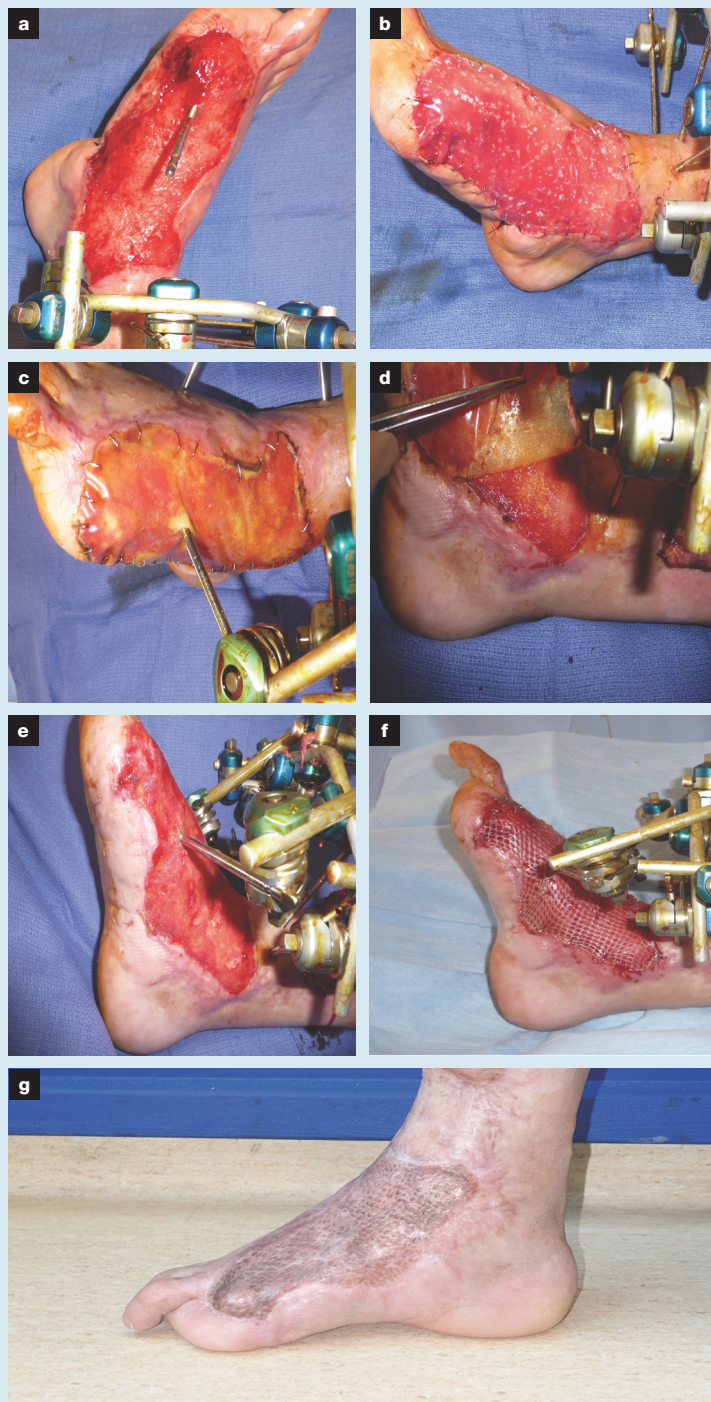


Table 5. Collagen regeneration template and skin graft take rate

Patient number	CRT take rate (%)	STSG delay (days)	STSG take rate (%)			
			Visit 4 (21 days)	Visit 5 (28 days)	Visit 6 (6 months)	Visit 7 (12 months)
1	60	18	85	100	100	
2	100	31	100	100	100	
3	90	23	50	100	100	
4	100	26	100	100	100	
5	70	25	75	100	100	
6*	0	21	85	100	0†	
7	100	22	100	100	100	
8	80	29	100	100	100	
9	100	26	100	100	100	
10	100	25	100	100	100	
11	100	29	70	100	100	
12	100	21	95	100	100	
13	100	21	90	100	100	
14	100	18	100	100	100	
15*	0	—	0†	0†	0†	
16	100	43	100	100	100	
17	0	54	90	100	100	
18	100	29	100	100	100	
19	100	25	100	100	100	
20*	50	30	95	0†	0†	
21	80	42	100	0	0	
22	0	25	100	100	100	
23	100	17	100	100	100	
24	100	36	100	100	100	
25	100	28	80	100	100	
26	100	17	80	100	100	
27*	80	34	30	0†	0†	
28	90	23	100	100	100	
29	80	23	90	100	100	
30	100	23	80	100	100	
31	100	21	10	40	80	
32	100	21	90	100	100	
33	100	21	90	100	100	
ITT	>50% of take rate	28 (84.8%)	—	29 (87.9%)	28 (84.8%)	28 (84.8%)
	<50% of take rate	5 (15.2%)	—	4 (12.1%)	5 (15.2%)	5 (15.2%)
	Mean	81.2%	26.5	84.4 %	86.1 %	84.2%

CRT—collagen regeneration template; STSG—split-thickness skin graft; *LFU—lost to follow-up/withdrawal; ITT—Intention to treat; †Missing data considered equal to 0

(28 days) was 84.4% of treated surface area, 86.1% at six months and 84.2% at 12 months. In three (9.1%) patients, the STSG take rate was <50% at visit 5 due to graft lysis as a consequence of localised infection, fluid accumulation or incorrect immobilisation. At 12 months, engraftment was successful in 27/29 patients who completed the study. With regards to the two other patients, one patient reached a graft take rate of 80%, and one patient underwent skin graft failure due to a recurrent healing issue with their chronic ulcer and underlying cardiovascular pathology.

Functional and aesthetic results

At six and 12 months, satisfaction with function and aesthetic appearance results were similar (Table 6). At 12 months, the mean functional scores, individually evaluated by the surgeons and patients, were 76.8% and 69.4%, respectively. The mean aesthetic satisfaction rates were 62.7% and 55.8%, respectively. The mean VSS score was 5.8 at six months and 5.9 at 12 months. The mean score for each component at 12 months was 1.8 for pliability, 1.5 for vascularity, 1.6 for height and 1.8 for pigmentation.

Clinical case

A 45-year-old man sustained a full-thickness wound on the back of his right foot (Fig 1) due to a quad-biking accident. The prehydrated collagen regeneration template was placed over the wound (Fig 2). At day 21, the colour had changed to orange-peachy (Fig 3), indicating that the collagen reconstruction was ready for the STSG (Fig 4 and 5). A 0.010 inch meshed STSG (expanded to 1.5 times the harvested surface) was placed over the wound (Fig 6). At 12 months, the healing was complete and the patient was able to wear shoes (Fig 7).

Discussion

Surgeons commonly have to deal with complex issues in covering wounds in patients with high-risk comorbidities, such as cardiovascular conditions or radiation therapy, contraindicating flap surgeries. This issue is frequently faced in lower limb trauma in older patients or in full-thickness defects associated with wide excisions of cancers. The number of adverse events was low and none led to systemic complications. This suggests that collagen regeneration template can be used even in poor surgical candidates to provide an efficient wound coverage.

Ease of use and satisfaction rates were also high, potentially making it a useful tool for young surgeons or surgeons who have a limited number of cases per year. All cases with insufficient percentage of take of the collagen regeneration template at three weeks were due to simple complications that did not require complex management. This would also indicate collagen regeneration template as a good option for surgeons with little experience of wound coverage or for surgeons outwith specialised centres. The surgical procedure is

similar to skin grafting. Furthermore, it does not prevent the progression to another, more complex surgery in a specialised centre in case of failure of the template.

The use of collagen regeneration template demands a learning wound dressing's management. NPWT could potentially have a beneficial wound healing effect as it allows a good contact between the wound bed and collagen regeneration template, reducing possible infection and need for dressing change.¹⁵ Nevertheless, it may also be hazardous in older patients, whose skin has reduced functionality due to ageing, as it may injure healthy skin, for example due to shear friction and impair the mobility of the patient.¹⁵

The reinforced silicone layer contributes to promoting the high rate of new collagen formation. This layer does not tear easily (a common issue when using staples), which leads to less granulating tissue forming. Furthermore, if the template take rate is low, as the silicone membrane stays in place, a moist environment is ensured, creating a suitable healing condition.

The results of this study are consistent with those of others available in the literature. Previous studies have reported similar rates of adverse events with other collagen regeneration templates. Adverse events reported in Dantzer et al.¹⁶ included haematomas (2%), neo-dermis infection (12.8%) and an STSG failure rate of 7%. In 2005, Groos et al.¹⁷ adverse events included collagen infection (13%), and an STSG failure rate of 9%. With a complete skin graft take of 84.6%, the failure rate in the Murray study is similar to that of our study.¹⁸ To our knowledge, our study is the only prospective study designed to assess these complications.

The functional results of this study are also comparable with the available data on collagen regeneration templates. A 2010 study¹⁹ showed a significant increase in functionality and patient satisfaction in deep burns of the hand. The thickness of the skin measured with ultrasound was not significantly different from a control group (healthy skin hand). The elasticity of the skin was also similar to intact skin. The retraction rate was also low.^{20,21} It has also been shown that the quality of the

scar was superior to that of STSG alone.²² Data about keloid scar formation after STSG was not found in the literature.

In our study, the findings of the VSS showed that patients were not as satisfied as the surgeons. This may be a reflection of auto-evaluation bias. Indeed, patients tend to evaluate their scar in a 'global' way, where their views may be influenced by other factors such as memories of an accident that caused the trauma. This may have influenced patients in their evaluation.

Scars are associated with functional and psychological complications, which can lead to long-term rehabilitation or depression, which represents an important cost for society (time out of work, expensive treatments). However, a common reported drawback of collagen regeneration template remains their cost.^{23,24} An improvement of these conditions, in addition to possible reductions in the cost associated with the complications of flap surgery, could counterbalance the initial elevated cost of collagen regeneration template. For example, the time of hospital stay is significantly decreased when using collagen regeneration template in deep burns involving more than 20% of the total body surface area in adults.²⁵ An economic evaluation should be considered.

Limitations

A limitation of the study was its single-arm characteristic, its small sample size and, furthermore, the collagen regeneration template could not be used on an infected wound or where the wound was an open joint.

Conclusion

The findings of this study add to the body of evidence advocating the safety of collagen regeneration template in wound healing. Future research should include comparative studies between flap surgeries and the use of collagen regeneration template, in terms of functional and aesthetic results and adverse events. It would also be worthwhile evaluating the use of NPWT in association with collagen regeneration template. **JWC**

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Reflective questions

- What types of wounds are best suited to treatment with a collagen regeneration template?
- What are the advantages and disadvantages of using a collagen regeneration template?
- Could collagen regeneration template and negative pressure wound therapy be used to treat the same wound? If so, describe how.

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