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Safety of Silk-elastin Sponges in Patients with Chronic Skin Ulcers: A Phase I/II, Single-center, Open-label, Single-arm Clinical Trial

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Background: Although traditional wound dressings such as collagen scaffolds promote granulation tissue formation, the efficacy of these dressings in chronic wounds is limited because of high susceptibility to bacterial growth. Biomaterials that can be applied to chronic wounds should have an anti-bacterial function. We previously reported that administering a silk-elastin solution that forms moisturizing hydrogels to wound surfaces of diabetic mice reduced bacterial growth and promoted granulation tissue formation compared with control or carboxymethyl cellulose hydrogels. We hypothesized that silk-elastin promotes wound healing in human chronic wounds by suppressing bacterial growth.

Methods: An open-label, clinical case series was conducted with a prospective, single-arm design at Kyoto University Hospital in Kyoto, Japan. In this study, 6 patients with chronic skin ulcers of any origin ($2 <$ ulcer area (cm^2) < 25) on their lower extremities were included; patients with critical ischemia were excluded. Silk-elastin sponges were applied and covered with a polyurethane film without changing the dressing for 14 days. Inflammation triggered treatment discontinuation due to fear of infection. The primary study endpoint was adverse events, including inflammation and infection.

Results: Poor hydrogel formation, possibly due to continuous exudation, was observed. No serious adverse events were noted. Two patients discontinued treatment on day 6 and day 7, respectively, due to inflammation, but they were not infected. The other 4 patients completed the 14-day silk-elastin sponge treatment without infection.

Conclusion: Silk-elastin sponge is safe for chronic skin ulcers, and its ability to promote wound healing should be determined by confirmatory clinical trials.
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INTRODUCTION

Chronic skin ulcers on the lower extremities such as venous leg ulcers and diabetic foot ulcers constitute significant healthcare problems. Venous leg ulcers account for approximately 70% of all leg ulcers and frequently recur; consequently, they significantly reduce patient quality of life.[1] An estimated 19%–34% of all diabetic patients will be affected with diabetic foot ulcers in their lifetime.[2] Moreover, more than half of diabetic foot ulcers become infected.[3] Lower-extremity ulcers can be extremely refractory: between one-quarter and half of them fail to heal over 6 months of conventional treatment.[4] One of the mechanisms of delayed wound healing in chronic ulcers is a high susceptibility to infection due to microangiopathy

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and immunopathy, including macrophage dysfunction.[5–9] Although traditional wound dressings such as collagen scaffolds promote granulation tissue formation, the efficacy of these dressings in chronic wounds is limited because of high susceptibility to bacterial growth.[5] Biomaterials that can be applied to chronic wounds should, therefore, have an anti-bacterial function.

Silk-elastins are artificial proteins that were developed by genetic engineering and biological production methods using *Escherichia coli*.[10] While there are several kinds of silk-elastins, 47K (SE-P47K)—a polymer that contains 12 repeats composed of a sequence of 4 elastin-like motifs, the V-to-K-replaced elastin-like motif, 3 more elastin-like motifs, and 4 silk-fibroin-like motifs—is water-soluble at room temperature and undergoes an irreversible sol-to-gel transition at 37°C at a concentration of 4 wt% or higher.[11–14] Although this temperature-mediated gelation process has permitted the use of this material in a variety of biomedical applications, the application of silk-elastin to wound healing has not been reported. Besides, not silk-fibroin but silk-elastin has the feature of sol-to-gel transition because the elastin-like motif allows the conformation to be flexible.

We have reported that applying an SE-P47K solution or sponge to pressure sores of *db/db* mice reduced bacterial growth and promoted granulation tissue formation compared with control or carboxymethyl cellulose hydrogels.[15,16] An in vitro study showed that SE-P47K promoted the migration of macrophages and fibroblasts and induced collagen production.[17] Therefore, we speculated that silk-elastin would accelerate wound healing in murine models of diabetes through the actions of macrophages and fibroblasts.

These non-clinical studies led us to hypothesize that silk-elastin reduces bacterial growth and promotes granulation tissue formation in human chronic wounds. Thus, we conducted an investigator-initiated first-in-human clinical trial that tested the safety and feasibility of the SE-P47K sponge for treating chronic wounds on the lower extremities. The primary endpoint was adverse events, including inflammation and infection. The secondary endpoints included the clinical outcomes, namely the effect of the sponge on chronic wound healing.

METHODS

Ethical Considerations

The study was performed in compliance with the ethical principles of the 1975 Declaration of Helsinki, the Act of Japan on Securing Quality, Efficacy, and Safety of Products Including Pharmaceuticals and Medical Devices, and the Ministerial Ordinance of Good Clinical Practice. The protocol was reviewed and approved by the Institutional Review Board of Kyoto University Hospital on 20 December 2017 (No. K038). The Japanese regulatory agency PMDA (Pharmaceuticals and Medical Devices Agency) was notified regarding this medical-device clinical trial on 4 January 2018. All recruited patients signed an informed consent form before participating in the study. The study was registered on the Japanese clinical trials registry called UMIN-CTR (University hospital Medical Information Network Clinical Trials Registry) under the number UMIN000030694.

Fig. 1. Photograph of the SE-P47K sponge.

Investigational Device

The investigational device was designated as the P47K-WAS or SE-P47K sponge. It was developed as previously described with some modifications and was provided by Sanyo Chemical, Kyoto, Japan. The density of SE-P47K in the sponges used in the study was 25 mg/cm^3. The device was 5-cm long, 5-cm wide, and 5-mm high (Fig. 1).

Study Design and Patients

We designed an investigator-initiated phase I/II, prospective, single-arm, open-label clinical trial to evaluate the safety and feasibility of the SE-P47K sponge for chronic skin ulcers that did not heal after 4 weeks of conventional treatments. The study was conducted at a single academic hospital (Kyoto University Hospital, Kyoto, Japan) between February and December 2018. Each individual was screened for eligibility on the basis of the inclusion and exclusion criteria in Table 1.

Procedures

A representative ulcer that was enrolled in the study is shown in Figure 2A (patient #6). The target ulcer was debrided in the operating room by using a scalpel, scissors, and a curette under local anesthesia combined with epinephrine (Fig. 2B). After hemostat and irrigation, an SE-P47K sponge was applied to the surface of the wound (Fig. 2C) and covered with a polyurethane film dressing (Fig. 2D). The day of application was set as day 1. Antibiotics were administered intravenously before and after the procedure. The study protocol permitted a single replacement of the sponge before day 5 due to hematoma, excessive exudation, and/or detachment of the sealing film dressing. An example of hematoma, which led to the replacement of the sponge on day 2 in patient #6, is shown in Figure 2E. When the device was replaced, the day of replacement was newly set to day 1. If there were no signs of wound inflammation (defined in the Assessment Methods section below), the film dressing was left in place for 14 days (Fig. 2F). The dressing was then removed on day 15, and the wound was washed. Figure 2G shows healthy granulation tissue after washing on day 15.

Table 1. Inclusion and Exclusion Criteria

Inclusion criteria
• The total wound size (long × short diameter) after 4 weeks of conventional treatment was still more than 50% of the wound size at the first visit
• The ulcer was located below the knee joint
• The wound area after debridement ranged from 2 cm^2 to 25 cm^2
• When the ulcer was covered by the sponge, it could be sealed by polyurethane film
• There were no other ulcers within 5 cm of the target wound
• There was no local infection in the wound
• The proportion of the area that exposed bone was <10% of the total wound area
• The skin perfusion pressure of the affected leg exceeded 30 mm Hg
Exclusion criteria
• The patient was < 20 years old when he/she consented to participate in the trial
• Women who were or could be pregnant
• Women who were nursing
• Women who did not consent to use contraception during the trial
• Patients with previous histories of allergy against silk, urethane, and other reagents used in the trial, including local anesthetics and disinfectant
• Patients with any of the following conditions:
○ Poorly controlled diabetes (≥10% of HbA1c in the latest laboratory findings within 28 days before enrollment)
○ Patient was receiving hemodialysis or peritoneal dialysis
○ Patient was being treated for malignancy
○ Patient required continuous systemic administration of steroids (dose exceeding an equivalent predonisolone dose of 10 mg/day)
• Patients participated in another clinical trial within 3 months before enrollment
• Patients participated in this trial and were administered the investigational device
• Patients who were not able to consent in writing to participate in the trial
• Patients who were considered by an investigator or sub-investigator to be inappropriate for inclusion in the trial

Study Endpoints and Assessment Methods

The study endpoints are presented in Table 2. Clinical signs of wound inflammation indicate the onset of wound infection and was therefore considered to be a trigger for treatment discontinuation. Wound inflammation is defined in Table 3 as a total daily wound inflammation score of ≥4. To determine daily wound inflammation scores, we checked the wounds every day for signs of inflammation. Redness, heat, swelling, and pain exacerbation were each scored 1. Increased exudate, cloudy exudate, and malodor were each scored 3. For example, a wound that exhibited both redness and a cloudy exudate had a score of ≥4, and its treatment was discontinued.

Safety and wound healing were assessed in both the patients who completed treatment and those who discontinued treatment. The baseline wound, final wound, and healthy granulation areas were measured by a central review committee by using digital images of the wounds, and the committee members were as follows: 1 experienced plastic surgeon who subjectively demarcated the healthy granulation area and 2 experienced plastic or dermatologic surgeons who confirmed the demarcated areas. The digital images were taken with a calibrator (Casmatch; Bear Medic, Tokyo, Japan). Their color and size were calibrated according to the manufacturer's instructions, and the size of the area was measured using a raster graphics editor (Adobe Photoshop; Adobe, San Jose, Calif.).

Statistics

The sample size was determined from the viewpoint of feasibility and was based on the 6-month registration period of this study and the number of patients with skin ulcers on the lower extremities in the electrical health record database of Kyoto University Hospital. In 2016, 45 patients were recorded to certainly or possibly have the disease. Assuming that 30% of the patients with this disease are refractory, we estimated that 6 patients could be recruited for this trial.

All continuous data were expressed as median (range). Categorical data were expressed as n (%). Statistical tests were not conducted, and therefore P values and confidence intervals were not calculated.

RESULTS

Six patients were enrolled and treated between 8 March and 27 December 2018. Significant protocol violations were not found with regard to any of the patients. Table 4 shows the demographic and clinical characteristics of the patients at enrollment.

The Feasibility of Treatment with SE-P47K Sponges for Human Skin Ulcers

In 5 of the 6 patients, the sponge was replaced once due to hematoma, excessive exudation, or detachment of seal (Table 5). Two patients (#1 and #3) did not complete the 14-day treatment due to mild inflammation on day 7 and day 6, respectively. Thus, 4 of the 6 patients were treated for 7 consecutive days and also completed the 14-day treatment. Consequently, the total sponge-treatment duration ranged from 6 to 17 days (Table 5).

The Safety of Treatment with SE-P47K Sponges for Human Skin Ulcers

Serious adverse events were not observed in any of the patients during the study period. Faults in the investigational device that could induce adverse events in the patients or investigators did not occur during the study period. A total of 14 non-serious adverse events occurred in 6 patients (Table 6).

Two patients (33% of the study sample) exhibited mild inflammation, an investigational treatment-related adverse event (defined in the Assessment Methods section above, Table 3) before day 15 (Table 6). One patient (patient #1) exhibited pain exacerbation and cloudy exudate on day 7, and her treatment was discontinued on the same day (Table 7). (**See figure 1, Supplemental**

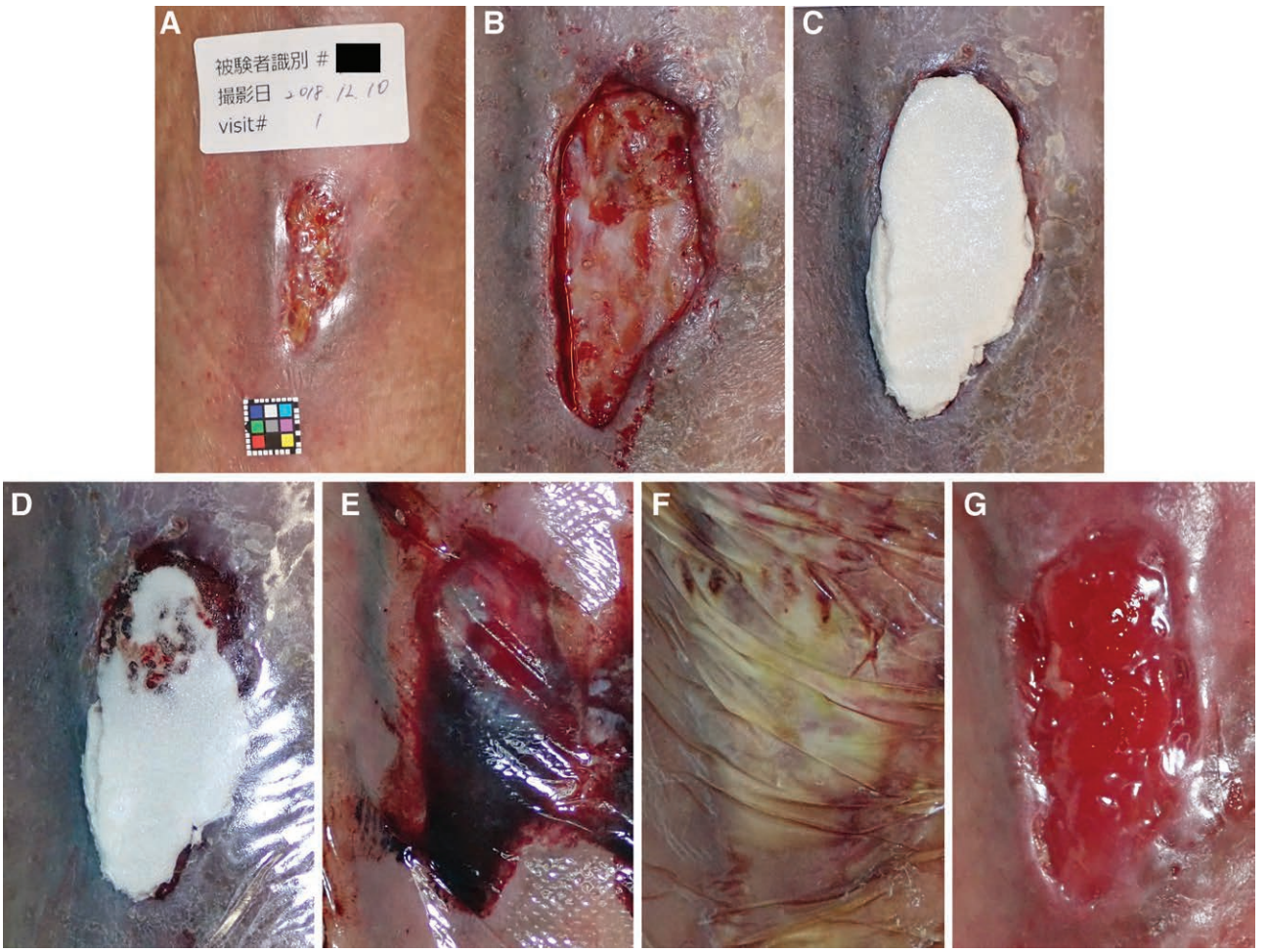

Fig. 2. An overview of the treatment course in a representative patient. A, Patient #6 had a venous stasis ulcer on his right lower leg that had started 1 year before enrollment. B, Debridement was performed under local anesthesia. C, The SE-P47K sponge was fitted into the defect. D, A polyurethane film was applied over the sponge. E, On day 2, excessive secretion of sanguineous exudate led to replacement of a new sponge and film dressing. F, Signs of inflammation were never observed, including on day 15. G, After removing the dressing and washing the wound, healthy granulation tissue was observed all over the wound surface but the wound size had increased.

Table 2. Study Endpoints

Primary endpoints
• Incidence of adverse events, which were defined as any untoward medical occurrence in a participant that did not necessarily have a causal relationship with the trial intervention
○ Serious adverse events were defined as any adverse event that resulted in (i) death or immediately threatened life, (ii) hospitalization or longer than anticipated stay in hospital, (iii) persistent or significant disability or incapacity, or (iv) a congenital anomaly or birth defect
Secondary endpoints
• Incidence of wound inflammation
• Frequency of patients who used the sponge for 7 and 14 consecutive days
• Proportion of the final wound area that was occupied by healthy granulation tissue
• Ratio of the final wound area relative to the wound area at enrollment

Table 3. Daily Scoring of Wound Inflammation and the Treatment Discontinuation Criterion

Score*	Symptoms
1	Redness, heat, swelling, pain exacerbation
3	Increased exudate, cloudy exudate, malodor
A total score of ≥4 represents wound inflammation that could indicate infection.	
Treatment was discontinued when the total daily score was ≥4	

*Each symptom in the righthand column is given the indicated score; for example, if the wound exhibits redness and heat on a specific day, it is scored 2 points. If the wound exhibits redness and increased exudate, it is scored 4 and the treatment is stopped.

Digital Content 1, which shows on day 1, the wound was debrided (A) and the sponge was applied. On day 6, cloudy exudate was observed (B). On day 7, the inflammation had increased to include pain exacerbation, and her treatment was therefore discontinued (C). **http://links.lww.com/PRSGO/B645.**) The other patient (Patient #3) demonstrated heat and increased exudate on day 6, and his treatment was discontinued on the same day (Table 7). However, neither patient demonstrated local infection after the dressing was removed; moreover, there was no elevation of white blood cell counts or C-reactive protein levels compared with baseline levels. The local

Table 4. Demographic and Clinical Characteristics of the Patients and Their Non-healing Ulcers

Patient #	Age/Sex	Background (Duration Since Onset)	Location (Side)	Size at First Visit, cm^2	Size at Enrollment, cm^2	Ratio of Wound Size, %*
1	50/W	SLE; PSL 7.5 mg/d (2 mo)	Lower leg (R)	8.5 × 3.5	7.4 × 3.2	80
2	69/M	Unknown; trauma (3 mo)	External malleolus (R)	1.8 × 1.3	1.8 × 1.2	92
3	64/M	Diabetes; metatarsal amputation (1 mo)	Dorsum of foot (L)	4.2 × 0.8	3.4 × 0.7	71
4	63/W	Venous stasis (1 y)	Dorsum of ankle (R)	1.7 × 0.7	1.8 × 0.8	121
5	54/M	Unknown; trauma (1 y)	Lower leg (R)	2.9 × 1.9	4.1 × 2.9	216
6	59/M	Venous stasis (1 y)	Lower leg (R)	3.6 × 1.9	3.2 × 1.4	66

*Ratio of wound size (%) = 100 × Size at enrollment (cm^2) / Size at first visit (cm^2).
M, man; PSL, prednisolone; R, right; L, left; SLE, systemic lupus erythematosus; W, woman.

Table 5. Course of Treatment

Patient #	Device Was Replaced before Day 5 (Cause)	Total Duration of Treatment (d)	Treatment Completion at 7/14 (d)
1	No	6	No/no
2	Yes (excessive exudate)	17	Yes/yes
3	Yes (detachment of seal)	6	No/no
4	Yes (hematoma)	16	Yes/yes
5	Yes (excessive exudate)	15	Yes/yes
6	Yes (hematoma)	15	Yes/yes

inflammation was mild in both patients, and the signs disappeared when the wound was irrigated. The remaining 4 patients (67%) completed the 14-day treatment. The ulcers of patients #4 and #5 displayed slight inflammation on day 8 and day 15, respectively (Table 7). None of the wounds showed local infection when the dressing was removed on day 15.

A Patchy Wound-healing Response Induced by SE-P47K Sponges

The median proportion of the final wound area on treatment completion/discontinuation that was occupied by healthy granulation tissue was 88% (range, 0%–100%). In 4 patients (67%), the healthy granulation area accounted for >85%. The remaining 2 patients (33%) developed granulation tissues, which were mostly judged to be not healthy (Table 8).

The median ratio of the final wound area on treatment completion/discontinuation relative to the baseline wound area was 125% (67%–158%). Thus, the wound became larger in 4 patients (67%). Two patients (33%) exhibited a reduction in the wound area (Table 8).

Table 7. Clinical Observations of Wound Inflammation during Treatment in Each Patient

Patient #	Symptom	Timepoint in Treatment
1	Pain exacerbation	Day 7
	Cloudy exudate	Day 7
3	Heat	Day 6
	Increased exudate	Day 6
4	Increased exudate	Day 8
5	Redness	Day 8
	Heat	Day 8
	Heat	Day 15

Case Presentations: Successful Gelation Depending on the Exudative State

Patient #2 was a case that showed good clinical outcomes. On day 1, the wound was debrided (Fig. 3A), and the sponge was applied. On day 15, after removing the dressing, a fibrin clot-like gel was found to be attached to the wound surface (Fig. 3B). After removing the gel, 89% of the wound was occupied with healthy granulation tissue, and the wound area had reduced to 75% (Fig. 3C and Table 8).

Patients #5 was a case that showed continuous exudation. (**See figure 2, Supplemental Digital Content 2,** which shows on day 1, the wound was debrided (A), and the sponge was applied. On day 2, exudate accumulated under the film dressing, and the dressing was removed (B). Two days after placing a new sponge, exudate was still being secreted by the wound (C). On day 15, none of the granulation tissues that had formed were healthy, and the wound area had enlarged (D). **http://links.lww.com/PRSGO/B646**.)

Table 6. Adverse Events during Treatment

Patient No.	Adverse Event	Level of Severity	Degree of Seriousness	Outcome	Relation to the Treatment
1	Pain after debridement	Mild	Non-serious	Recovered	Not related
	Wound inflammation	Mild	Non-serious	Recovered	Related
2	Pain after debridement	Mild	Non-serious	Recovered	Not related
3	Hypertension	Moderate	Non-serious	Recovered	Might be related
	Wound inflammation	Mild	Non-serious	Recovered	Related
	Ankle pain	Mild	Non-serious	Recovered	Might be related
	Contact dermatitis	Mild	Non-serious	Recovered	Might be related
4	Pain after debridement	Mild	Non-serious	Recovered	Not related
	Itchiness	Mild	Non-serious	Recovered	Not related
	γ-GTP elevation	Mild	Non-serious	Recovered	Not related
5	Itchiness	Mild	Non-serious	Recovered	Not related
	Contact dermatitis	Moderate	Non-serious	Recovered	Might be related
	Pain after debridement	Mild	Non-serious	Recovered	Not related
6	Itchiness	Mild	Non-serious	Recovered	Might be related

γ-GTP, gamma-glutamyl transpeptidase.

Table 8. Clinical Outcomes

Patient #	Baseline Wound Area (cm^2)	Final Wound Area (cm^2)	Healthy Granulation Area (cm^2)	Proportion of Healthy Granulation Area (%)*	Ratio of Wound Area (%)†
1	7.50	9.37	9.09	97	125
2	1.94	1.45	1.29	89	75
3	2.23	1.49	0.16	11	67
4	1.70	2.13	1.85	87	125
5	13.82	21.89	0.00	0	158
6	2.37	3.34	3.34	100	141
Median (range)				88 (0–100)	125 (67–158)

*Proportion of healthy granulation area (%) = 100 × Healthy granulation area (cm^2) / Final wound area (cm^2).
†Ratio of wound area (%) = 100 × Final wound area (cm^2) / Baseline wound area (cm^2).

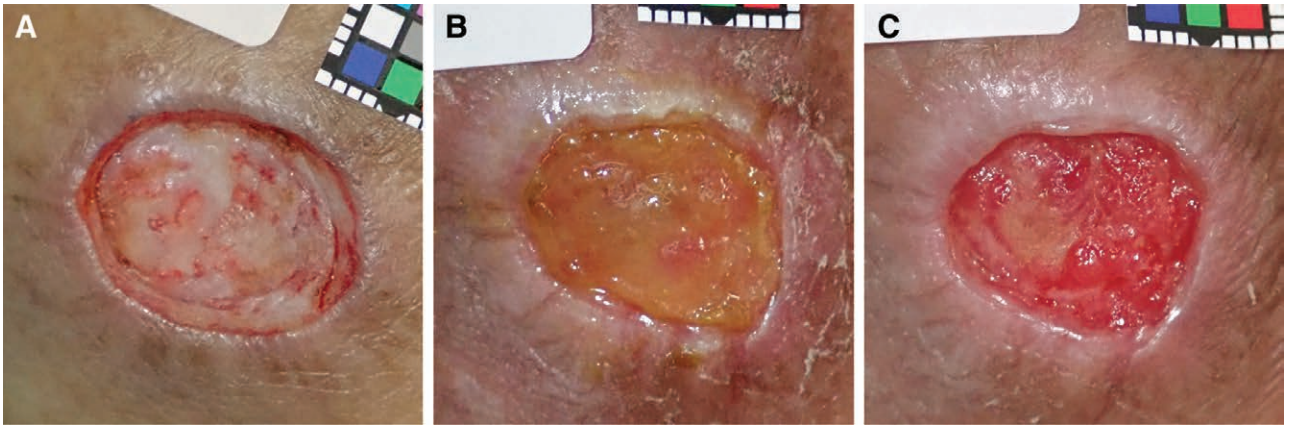

Fig. 3. Overview of the treatment course in patient #2, who demonstrated limited exudation, proper hydrogel formation, good granulation, and wound contraction. The patient had a non-healing trauma-induced wound on his right external malleolus that started 3 months before enrollment. A, The wound was debrided. B, When the dressing was removed on day 15, a fibrin clot-like gel was attached to the wound surface. C, After removing the gel, healthy granulation was observed.

DISCUSSION

In terms of feasibility, our study showed that the silk-elastin sponge had been held uneventfully in place for 14 days in four patients without promoting bacterial growth. Notably, this meant that the occlusive dressings never needed to be changed. Thus, this treatment may help surgeons to reduce the frequency of dressing changes, which in standard clinical practice should be performed every 3 to 7 days depending on the dressing products.[18]

In relation to patients #1 and #3, whose treatment was discontinued due to wound inflammation, a possible cause of inflammation is the excessive exudation that accumulated under the film dressing. In addition, continuous exudation may have diluted the concentration of the silk-elastin on the wound, thereby hampering full gelation. Only 62.5 μl of exudate is needed to convert 1 cm^2 of SE-P47K sponge into a 20% SE-P47K solution, which was validated by our animal experiments.[15,16,19] Therefore, SE-P47K sponge is appropriate for chronic wounds that have a relatively small amount of exudate. The immediate use of SE-P47K sponge after radical debridement should be avoided because excessive exudation may result in poor hydrogel formation. During the time until the exudate reduces after debridement, applying traditional wound care is recommended; 2–3 days after debridement, a silk-elastin sponge should be applied.

There are 2 obstacles to overcome in providing benefits with patients: the cost reduction and regulatory approval. The cost of producing recombinant proteins is higher than that of synthesizing natural compound derivatives such as carboxymethyl cellulose. The manufacturer is on the way to produce the protein at a high yield with a low cost. In the approval process for medical devices in Japan, PMDA requires beneficial clinical evidence of new materials. On the basis of these trial results, the manufacturer is now planning to initiate phase III clinical trials.

CONCLUSIONS

This prospective, single-arm, first-in-human clinical study was conducted to assess the safety, feasibility, and wound-healing properties of the 14-day SE-P47K sponge treatment. The sponge seemed to be a safe material for chronic wounds, but its efficacy needs to be explored by studies that employ a wound-treatment procedure that best limits exudation, thereby promoting proper hydrogel formation.

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