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 (cm²) < 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.

(Plast Reconstr Surg Glob Open 2021;9:e3556; doi: 10.1097/GOX.0000000000003556; Published online 28 April 2021.)

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. An estimated 19%–34% of all diabetic patients will be affected with diabetic foot ulcers in their lifetime. Moreover, more than half of diabetic foot ulcers become infected. Lower-extremity ulcers can be extremely refractory: between one-quarter and half of them fail to heal over 6 months of conventional treatment. One of the mechanisms of delayed wound healing in chronic ulcers is high susceptibility to infection due to microangiopathy.

Disclosure: All the authors have no financial interest in relation to the content of this article.

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and immunopathy, including macrophage dysfunction.\textsuperscript{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.\textsuperscript{3} 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.\textsuperscript{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.\textsuperscript{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 \textit{db/db} mice reduced bacterial growth and promoted granulation tissue formation compared with control or carboxymethyl cellulose hydrogels.\textsuperscript{15,16} An in vitro study showed that SE-P47K promoted the migration of macrophages and fibroblasts and induced collagen production.\textsuperscript{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.

**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.
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).

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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

Table 1. Inclusion and Exclusion Criteria

| Inclusion criteria                                                                 | Exclusion criteria                                                                 |
|-----------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|
| • The total wound size (long x short diameter) after 4 weeks of conventional treatment was still more than 50% of the wound size at the first visit | • Patient required continuous systemic administration of steroids (dose exceeding an equivalent predonisolone dose of 10 mg/day) |
| • The ulcer was located below the knee joint                                      | • Patient was being treated for malignancy                                          |
| • The wound area after debridement ranged from 2 cm² to 25 cm²                    | • Poorly controlled diabetes (≥10% of HbA1c in the latest laboratory findings within 28 days before enrollment) |
| • When the ulcer was covered by the sponge, it could be sealed by polyurethane film | • Patient was receiving hemodialysis or peritoneal dialysis                         |
| • There were no other ulcers within 5 cm of the target wound                      | • Patient was being treated for malignancy                                          |
| • There was no local infection in the wound                                        | • Patient required continuous systemic administration of steroids (dose exceeding an equivalent predonisolone dose of 10 mg/day) |
| • The proportion of the area that exposed bone was <10% of the total wound area   | • Patients who were not able to consent in writing to participate in the trial     |
| • The skin perfusion pressure of the affected leg exceeded 30 mm Hg                | • Participants 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 were 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.).

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

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).

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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
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).

**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 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, cm² | Size at Enrollment, cm² | Ratio of Wound Size, % |
|-----------|---------|----------------------------------|-----------------|--------------------------|-------------------------|------------------------|
| 1         | 50/W    | SL; PSL 7.5 mg/d (2 mo)          | Lower leg (R)   | 8.5 × 3.5                | 7.4 × 3.2                | 80                     |
| 2         | 69/M    | Unknown; trauma (1 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         | 65/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                     |

*aRatio of wound size (%) = 100 × Size at enrollment (cm²) / Size at first visit (cm²).

M, man; PSL, prednisolone; R, right; L, left; SL, 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                         |

### 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               |
| 2           | Wound infection        | Mild              | Non-serious           | Recovered| Related                   |
| 3           | Pain after debridement | Mild              | Non-serious           | Recovered| Not related               |
| 4           | Hypertension           | Moderate           | Non-serious           | Recovered| Might be related          |
| 5           | Wound infection        | Mild              | Non-serious           | Recovered| Related                   |
| 6           | Ankle pain             | Mild              | Non-serious           | Recovered| Might be related          |
| 7           | Pain after debridement | Mild              | Non-serious           | Recovered| Related                   |
| 8           | Contact dermatitis     | Mild              | Non-serious           | Recovered| Might be related          |
| 9           | Itchiness              | Mild              | Non-serious           | Recovered| Not related               |
| 10          | γ-GTP elevation        | Mild              | Non-serious           | Recovered| Not related               |
| 11          | Itchiness              | Mild              | Non-serious           | Recovered| Related                   |
| 12          | Contact dermatitis     | Moderate           | Non-serious           | Recovered| Might be related          |
| 13          | Pain after debridement | Mild              | Non-serious           | Recovered| Not related               |
| 14          | Itchiness              | Mild              | Non-serious           | Recovered| Might be related          |

*γ-GTP, gamma-glutamyl transpeptidase.
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 cm² 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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ACKNOWLEDGMENTS

This study was supported by the AMED Acceleration Transformative Research for Medical Innovation (ACT-M)
program (Grant No. JP18im0210207 and JP20he1302037). The expense of the external audit was partly provided by Sanyo Chemical Co., Ltd. The investigational devices were provided by Sanyo Chemical Co., Ltd. for free. Sanyo Chemical Co., Ltd. did not participate in the conduct of the clinical trial, the data analysis or interpretation, the writing or review of the manuscript, or the decision to submit the manuscript for publication. The authors thank Drs. Shigehiko Suzuki, Susumu Saito, Masayuki Yokode, and Tatsuya Ito for planning the project; Dr. Kayoko Enomoto, Ms. Mieko Watanabe, and Mr. Kazutaka Tagishi for quality control of the trial; Drs. Hisashi Motomura, Hiroshi Naitoh, and Takao Tachibana for participating in the central committee reviewing of the wounds; and Drs. Jan Arata, Takashi Nomura, and Yoshiki Ueno for participating in the safety monitoring committee.

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