



54951491

Relais Request No. REG-24813981

Customer Code

88-1823

Delivery Method

Ariel

Request Number

RZSAB11824 FXBK99 COPYRT

Scan

Date Printed: 03-Jan-2008 16:04

Date Submitted: 02-Jan-2008 17:33

5072.695000

TITLE: JOURNAL OF WOUND CARE.

YEAR: 2008

VOLUME/PART: J WOUND CARE 2008; 17 (1): 17-23

PAGES:

AUTHOR:

ARTICLE TITLE:

SHELFMARK: 5072.695000

REGULATORY AFFAIRS DEPARTMENT

Ariel Address: Phil.Davies@Molnlycke.com

Your Ref :RZSAB11824 FXBK99 COPYRT|ROMANELLI ET AL|EFFECT OF AMELOGENIN...|J WOUND CARE
2008; 17 (1): 17-23**DELIVERING THE WORLD'S KNOWLEDGE****This document has been supplied by the British Library****www.bl.uk**

The contents of the attached document are copyright works. Unless you have the permission of the copyright owner, the Copyright Licensing Agency Ltd or another authorised licensing body, you may not copy, store in any electronic medium or otherwise reproduce or resell any of the content, even for internal purposes, except as may be allowed by law.

The document has been supplied under our Copyright Fee Paid service. You are therefore agreeing to the terms of supply for our Copyright Fee Paid service, available at :

www.bl.uk/services/document/edd.html

Effect of amelogenin extracellular matrix protein and compression on hard-to-heal venous leg ulcers: follow-up data

• **Objective:** To undertake a follow-up of patients with hard-to-heal venous leg ulcers (VLUs) who had participated in a randomised controlled trial in which they had been treated with either compression therapy in combination with amelogenin extracellular matrix protein or compression therapy alone for 12 weeks or until their ulcers had healed, whichever occurred first.

• **Method:** Patients were randomised to receive either high compression therapy plus amelogenin (n=42) or high compression therapy alone (n=41) for a period up to and including 12 weeks. The method and initial findings are detailed in an earlier paper. Twelve weeks after the final visit, the patients were followed up and the wounds were re-evaluated.

• **Results:** The initial results demonstrated clinically and statistically significant benefits for the patients in the amelogenin group. The results of the follow-up showed that the successful healing response had been maintained. Significantly more patients continued to show a reduction in ulcer size from baseline in the amelogenin-treated group versus the control group ($p=0.02$), and there was a statistically significant ($p=0.01$) larger reduction in the amelogenin-treated group. This group also had a significantly ($p=0.02$) higher percentage of patients with decreases in wound size. The overall number of patients with healed wounds was greater (n=9) in the amelogenin-treated group than in the control group (n=3). Pain continued to be significantly reduced in the amelogenin-treated group compared with the control group ($p=0.001$).

• **Conclusion:** Amelogenin therapy in conjunction with high compression therapy was beneficial in the treatment of hard-to-heal VLUs when compared with treatment with high compression alone. These beneficial effects were maintained post-treatment and were identified at follow-up.

• **Declaration of interest:** This study was funded by Mölnlycke Health Care, Göteborg, Sweden.

amelogenin; extracellular matrix; compression therapy; venous leg ulcers

An advanced wound-care treatment consisting of an extracellular matrix (ECM) biocompatible protein, amelogenin (Xelma, Mölnlycke Health Care), has been developed for use in the treatment of hard-to-heal wounds such as venous leg ulcers (VLUs). When applied to the wound bed of these recalcitrant ulcers, it is thought that amelogenin provides a temporary matrix for cell attachment and thereby helps promote healing in wounds that have been shown to have a deficit in extracellular matrix components.¹ This deficit has been shown to be a consequence of inappropriate matrix remodelling resulting from the imbalances of proteinases and their endogenous inhibitors. Ultimately, this deficit in the ECM may compromise its function with respect to the process of wound healing, where it plays a key role.²⁻⁴

Amelogenin has been shown in a number of clinical studies to be successful in the treatment of hard-to-heal VLUs and that it can also help to stimulate

the healing process in hard-to-heal VLUs that meet certain prognostic criteria.⁵⁻⁷ These criteria have been established in the literature as being an aid to identifying ulcers that have a low chance of healing, and include factors such as ulcer size (eg, size greater than 10cm² and duration longer than six months).⁵ A recent clinical study has highlighted that amelogenin treatment in conjunction with high compression can successfully be used to treat patients with VLUs that fall within this group.⁶

A subsequent study was set up to compare two treatment regimens: amelogenin plus high compression therapy versus high compression therapy alone in a patient population that met the criteria of hard-to-heal VLUs.⁷ Importantly, the mean duration of the study ulcer at baseline was 55.3 months (SD 62.7) in the amelogenin-treated group and 32.4 months (SD 27.8) in the control group ($p=0.56$). The mean ulcer size at baseline was 17.0 cm² (SD 9.1) in the amelogenin-treated group and 18.0 cm² (SD 9.0) in the control group. These data highlight the fact

M. Romanelli, MD, PhD, Consultant Dermatologist, Department of Dermatology, University of Pisa, Italy;

E. Kaha, MD, Surgeon, Orthopedic and Clinical Research Center, West Tallin Central Hospital, Estonia;

H. Stege, MD, Associate Professor, Department of Dermatology, University of Düsseldorf, Germany;

J.W. Wnorowski, PhD, MD, Head of Dermatology Ward, Clinic of Dermatology, Hospital St Lazarza, Warsaw, Poland;

P. Vowden, MD, FRCS, Consultant Vascular Surgeon, Professor of Wound Healing Research, Vascular Unit, Bradford Royal Infirmary, UK;

H. Majamaa, MD, PhD,
Head of the Department
of Dermatology,
Satakunta Central
Hospital, Pori, Finland;
J.L. Lazaro, Podiatrist,
Professor, Chief of
Diabetic Foot Unit,
Universidad Complutense
de Madrid, Spain.
Email: m.romanelli@med.
unipi.it

References

1 Schulz, G.S., Ladwig, G., Wysocki, A. Extracellular matrix: review of its roles in acute and chronic wounds. *World Wide Wounds* 2005. www.worldwidewounds.com/2005/august/Schulz/Extrac-Matrix-Acute-Chronic-Wounds.html (accessed 23 July 2007).
2 Gailit, J., Clark, R.A. Wound repair in the context of extracellular matrix. *Curr Opin Cell Biol* 1994; 6: 5, 717-725.
3 Tomic-Canic, M., Ågren, M.S., Alvarez, O.M. Epidermal repair and the chronic wound. In: Rovee, D.T., Maibach, H.I., eds. *The epidermis in wound healing*. Boca Raton: CRC Press, 2004: 25-57.
4 Ågren, M.S., Werthen, M. The extracellular matrix in wound healing: a closer look at therapeutics for chronic wounds. *Int J Low Extrem Wounds* 2007; 6: 2, 82-97.
5 European Wound Management Association. Position document: Understanding compression therapy. Medical Education Partnership, 2003.
6 Vowden, P., Romanelli, M., Peter, R., et al. The effect of amelogenins (Xelma) on hard-to-heal venous leg ulcers. *Wound Repair Regen* 2006; 14: 3, 240-246.
7 Vowden, P., Romanelli, M., Price, P. Effect of amelogenin extracellular matrix protein and compression on hard-to-heal venous leg ulcers. *J Wound Care* 2007; 16: 5, 189-195.

that the ulcers included in the study were long-standing and hard-to-heal.

The first part of this study presented clinically and statistically significant results in favour of those patients that had been treated for up to 12 weeks with amelogenin therapy. Overall, this study showed that the addition of amelogenin to high compression bandaging was significantly beneficial to the healing of hard-to-heal VLU. In summary, the results showed significantly larger reductions in wound size, more patients showing improved ulcers, lower pain between study visits and at dressing change, and a larger proportion of patients demonstrating low degrees of exudate in the amelogenin-treated patients (Table 1). The study also showed few adverse events, with no significant differences between the amelogenin-treated group and the control group. The conclusion of the study therefore was that amelogenin therapy was safe and beneficial in the treatment of hard-to-heal VLU that had failed to heal with standard therapy.

The treatment of these VLU with amelogenin was terminated either at 12 weeks or when the ulcers healed, whichever occurred first, and the patients whose ulcers had not healed resumed their standard therapy (eg, compression with an appropriate primary/secondary dressing). After a further 12 weeks, all patients were followed-up and the following parameters were evaluated:

- Percentage change in ulcer size from baseline
- Number of improved ulcers
- Change in ulcer size
- Pain related to the disease and at dressing change.

In addition, the ulcers were photographed to provide a permanent record of healing progression.

The data relating to this follow-up, in conjunction with the results from the first part of this study (that is, the active treatment phase) are presented in this paper.

Method

A detailed description of the methodology for this study has been published previously.⁷ In summary, it was designed as an open randomised comparative parallel-group multi-centre investigation with a three-week run-in period to ensure that a population of true non-healing ulcers was included in the trial. Patient eligibility for inclusion included adult, mobile patients with hard-to-heal VLU that had been treated with compression therapy for at least one month before screening. The ulcers had to be at least six months old, with a surface area at inclusion of at least 10cm², but not exceeding 30cm², and not demonstrating excessive exudate or signs of infection. Additional exclusion criteria after the run-in period were wound reduction or enlargement of ≥50% in the three-week run-in period and ulcer area <8cm² or >36cm². Patients were randomised to treatment with

amelogenin plus high compression bandaging (one treatment of amelogenin per week), or high compression bandaging alone (control group). All participants received a secondary dressing combination of Mepitel and Mesorb or Mepilex (all Mölnlycke Health Care), with high compression bandaging therapy one month before, during the investigational period of three weeks run-in and throughout the active treatment period (12 weeks, or until the ulcers healed, whichever occurred sooner).

At the end of the active treatment phase, amelogenin therapy ceased and, if their ulcers had not healed, patients resumed treatment with standard therapy (compression with appropriate primary/secondary dressings). After a further 12 weeks, the patients were followed-up and wound size and the number of ulcers that had healed were documented.

Ethics committee approval was sought and obtained in all participating centres. The study was conducted according to the European Standard EN ISO: 14155 Clinical Investigations with Medical Devices.

Investigated product

Xelma is a sterile extracellular matrix protein for topical application, consisting of amelogenin proteins dissolved in a propylene glycol alginate and water.

Statistical evaluation

Percentage change in ulcer size from baseline to the follow-up visit, and pain were analysed using multiple logistic regression. The numbers of healed and improved ulcers were analysed using Fisher's exact test between the groups at the final time point. Pain was analysed using the non-parametric Wilcoxon Mann-Whitney U-test.

Results

The results of the first part of the study have been published previously and are summarised in Table 1. The primary efficacy analysis in this study was the percentage change in the ulcer size from baseline to final visit (or last observation carried forward) and the results (intention-to-treat data) are presented in Fig 1 for both the final visit and the follow-up visit data. The results are consistent between the time points and within the groups. They show significant differences in the percentage change in ulcer size from baseline between the amelogenin-treated group and the control group (p=0.03 and p=0.02 for the final visit and follow-up visit data respectively), with greater reductions in ulcer size in the amelogenin-treated group (33% at final visit and 48.7% at follow-up visit) compared with the control group (11.1% at final visit and 21.1% at follow-up visit). At the follow-up visit, the mean (95% CI) for the difference between the amelogenin-treated

8 Hartrick, C.T., Kovan, J., P., Shapiro, S. The numeric rating scale for clinical pain measurement: a ratio measure. *Pain Pract* 2003; 3: 4, 310-316.

Table 1. Summary of final visit data

Measurement objective	Result	p value
Study design	Open randomised comparative parallel-group multi-centre investigation comparing amelogenin plus high compression (n=42) with high compression alone (control) (n=41) in the treatment of hard-to-heal venous leg ulcers	
Percentage reduction in ulcer size	Percentage reduction in ulcer size was significantly greater in the amelogenin-treated group (-33.11) compared with the control group (-11.1)	p=0.03
Ulcer improvement	Number of ulcers showing improvement (eg. more than 50% reduction in ulcer size) was significantly greater in the amelogenin-treated group compared with the control group.	p=0.01
Pain	Compared with the control group, the amelogenin-treated group was associated with significantly lower levels of:	
	<ul style="list-style-type: none"> * ulcer-related pain p=0.01 * pain at dressing change p=0.02 	
Exudate	Compared with the control group, more patients demonstrated none or very low levels of exudate in the melogenin-treated group	p=0.01

group and the control group was -27.61 (-48.67 to -6.55). There was a statistically significantly larger percent reduction in ulcer size in the amelogenin-treated group (p=0.02).

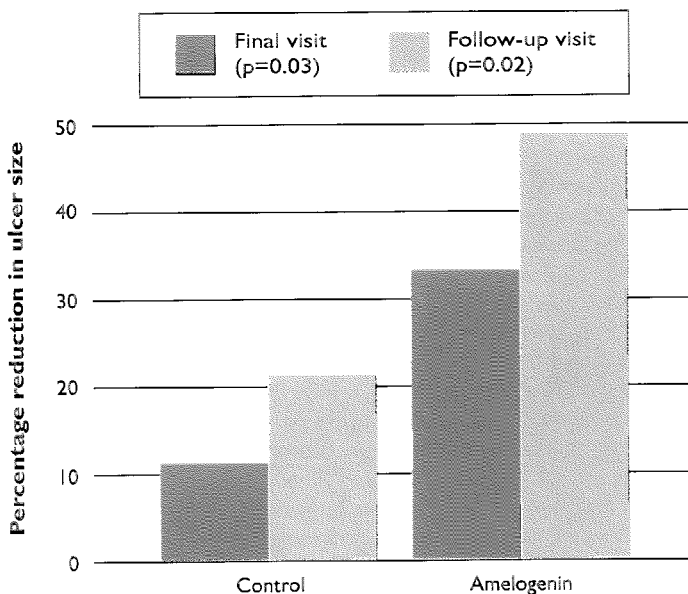
The proportion of patients with healed and improved ulcers was analysed. At the follow-up visit, the number of patients with healed and improved ulcers in the amelogenin-treated group was nine (21%) and 24 (57%), respectively. The corresponding values in the control group were three (7%) and

14 (34%) respectively.

The data relating to the change in ulcer size at final visit showed that the amelogenin-treated group had significantly more wounds with reductions in area between 50% and 100% than the control group (p=0.01). This trend was also observed at the follow-up visit, which found a significantly (p=0.02) higher percentage of patients with decreases in wound size in the amelogenin-treated group. Conversely a significantly higher percentage of patients in the control group showed increases in wound size (Fig 2). Additionally, at the follow-up visit, the change in ulcer size from baseline was significantly different in the amelogenin group (mean -6.9 [SD 7.2]) versus the control group (mean -3.5 [SD 9.5]) (p=0.03). Overall, the number of healed patients at the follow-up visit was greater in the amelogenin-treated group (n=9) than in the control group (n=3).

Pain was evaluated as related to the disease or to the ulcer, and measurement was undertaken using an ordinal scale from 0 (no pain) to 10 (unbearable pain).⁸ The results showed that reduction in pain related to the disease and dressing changes was more apparent in the amelogenin-treated group than in the control group. A summary of the statistical results relating to the pain analysis is presented in Table 2. The data on pain related to the disease show that the amelogenin-treated group, in comparison with the control group, had significantly greater ulcer pain reduction from baseline to final visit and at follow-up (p=0.01 and p=0.001 respectively) (Fig 3). Similarly, the data on pain related to the dressing change show that the amelogenin-treated group, in comparison with the control group, had significantly greater ulcer pain reduction from baseline to final visit and at follow-up (p=0.02 and p=0.001 respectively).

Fig 1. Percentage reduction in ulcer size at final visit and follow-up



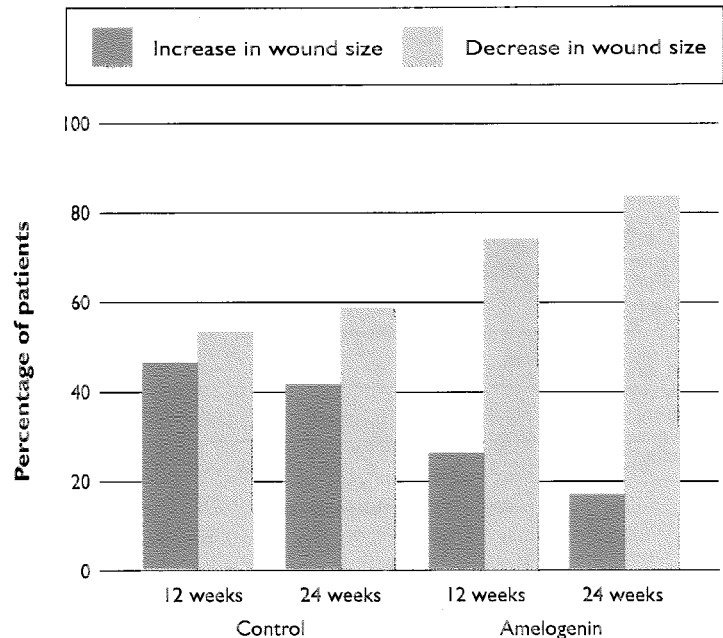
Discussion

Amelogenin is an extracellular matrix protein originally derived from porcine enamel matrix of developing teeth.⁹ The chemical characteristics of amelogenin, which give it bipolar properties, and its amino acid sequences enable the protein to self-assemble into large hydrophobic aggregates that under physiological conditions resemble a stable ECM.⁶

It has been shown that the ECM in chronic wounds is abnormal. For example, it has been reported that fibronectin, an ECM component that plays a pivotal role in acute wound healing, is absent at the base of chronic ulcers.¹⁰ This deficiency may impair cellular migration and signalling, thus causing interference with the fundamental mechanisms of wound healing.⁴ The cause of this dysregulation is thought to be excessive levels of proteases (present as a result of prolonged inflammation) degrading both the old and newly-forming ECM. The formation of a surrogate ECM by amelogenin provides the basis for its use in the treatment of chronic wounds such as VLUs.

There are a variety of wound treatments now available that appear to target the ECM therapeutically: a recently undertaken review of these products has shown that they have been associated with varying degrees of success.⁴ A review of the literature does, however, provide a sound basis for the use of amelogenin as a treatment of chronic wounds that have failed to heal. Experimental data have highlighted a number of mechanisms to which the success of the protein can be attributed. For example, the fibroblast, the primary cell involved in wound healing, synthesises ECM as a precursor to healing. In some studies, fibroblasts and other cells treated with amelogenin have demonstrated an augmentation of fibroblast-driven collagen matrix remodel-

Fig 2. Wound area changes in amelogenin and control groups at final visit (12 weeks) and follow-up (24 weeks)



ling, increased dermal contraction and fibroblast proliferation.¹¹ In terms of growth factors, it has been demonstrated that amelogenin can increase the synthesis of transforming growth factor-beta 1 (TGF-β1)¹¹ and can increase levels of vascular endothelial growth factor (VEGF).¹² In a variety of *in vitro* models, amelogenin has been shown to enhance angiogenesis, a key component of the normal wound healing process.¹³⁻¹⁵

9 Kim, N.H., Tominaga, K., Tanaka, A. Analysis of eosinophilic round bodies formed after injection of enamel matrix derivative into the backs of rats. *J Periodontol* 2005; 76: 11, 1934-1941.

10 Herrick, S., Ashcroft, G., Ireland, G., et al. Up-regulation of elastase in acute wounds of healthy aged humans and chronic venous leg ulcers are associated with matrix degradation. *Lab Invest* 1997; 77: 3, 281-288.

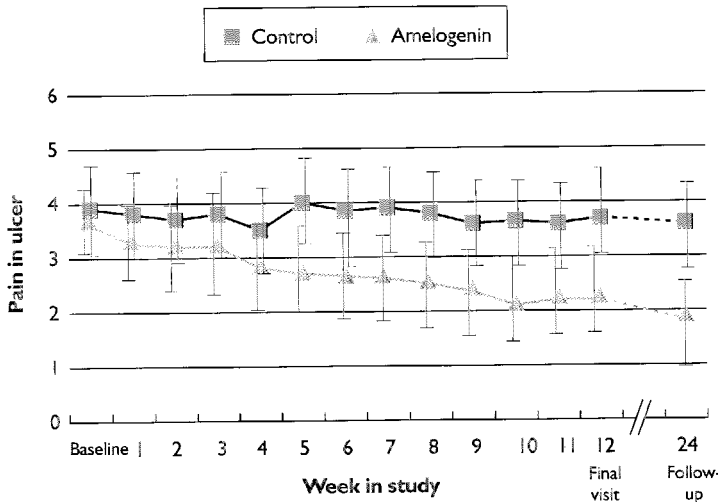
11 Grayson, R.E., Yamakoshi, Y., Wood, E.J., et al. The effect of the amelogenin fraction of enamel matrix proteins on fibroblast-mediated collagen matrix reorganization. *Biomaterials* 2006; 27: 15, 2926-2933.

12 Mirastschijski, U., Konrad, D., Lundberg, E., Lyngstadaas, S.P., Jorgensen, L.N., Agren, M.S. Effects of a topical enamel matrix derivative on skin wound healing. *Wound Repair Regen* 2004; 12: 1, 100-108.

Table 2. Summary of reduction in pain scores

	Reduction from baseline Mean (SD)		Mean difference (95% CI)	p value
	Amelogenin (n=42)	Control (n=41)		
Related to disease				
Final visit	1.6 (3.1)	0.1 (3.1)	-1.59 (-2.54 to -0.34)	0.01
Follow-up	2.1 (2.8)	0.2 (3.0)	-1.92 (-3.05 to -0.69)	0.001
Mean pain at dressing change				
Final visit	1.6 (2.1)	0.7 (2.9)	-1.35 (-2.54 to -0.16)	0.02
Follow-up visit	1.7 (2.4)	0.3 (3.0)	-1.83 (-2.98 to -0.69)	0.001

Fig 3. Mean (95% CI) disease-related pain scores per treatment and week (LOCF) based on ordinal scale from 0 (no pain) to 10 (unbearable pain)



13 Yuan, K., Chen, C.L., Lin, M.T. Enamel matrix derivative exhibits angiogenic effect in vitro and in a murine model. *J Clin Periodontol* 2003; 30: 732-738.

14 Schlueter, S.R., Carnes, D.L., Cochran, D.L. In vitro effects of enamel matrix derivative on microvascular cells. *J Periodontol* 2007; 78: 1, 141-151.

15 Drinkwater, S.L., Smith, A., Sawyer, B.M., Burnand, K.G. Effect of venous ulcer exudates on angiogenesis in vitro. *Br J Surg* 2002; 89: 6, 709-713.

16 Romanelli, M., Ellervee, T., Jarve, H., et al. Amelogenin (Xelma®) in hard-to-heal venous leg ulcers, an open regime investigation. Poster presentation. European Wound Management Association Conference, Prague, Czech Republic, 2006.

17 Meuleneire F. A preliminary evaluation of an advanced therapy (Xelma) for the treatment of hard to heal wounds: venous leg ulcers and diabetic foot ulcers. Poster presentation. European Wound Management Association Conference, Glasgow, United Kingdom, 2007.

These experimental data are supported by the positive results seen in clinical studies on patients with hard-to-heal VLUs,^{6,16} diabetic foot ulcers¹⁷ and pyoderma gangrenosum.¹⁸ Subsequent to those studies, this clinical study was aimed at targeting a specific patient population with hard-to-heal VLUs. The primary objective was to measure the difference in percentage change in ulcer size from baseline to the final visit and subsequently at follow-up. The results show unequivocally that the ulcers treated with amelogenin and high compression had significantly greater reductions in size than the comparator control group of high compression alone, both at final visit and follow-up. The significance values at follow-up were also greater than those calculated for the final visit, indicating a widening gap between the two groups. These data suggest that amelogenin aided in the initiation of a healing response in the ulcers but, more importantly, this response appeared to have been maintained after treatment, with a continuing reduction in ulcer size. There was also a tendency towards more improved ulcers in the amelogenin-treated group that was significantly different from the control at final visit.

The beneficial effects of amelogenin are apparent from the data presented in Fig 2. For the control treatment at both 12 and 24 weeks, the proportion of wounds increasing in size was close to the proportion decreasing, in each case approximately 40% deteriorated over the treatment period. For amelogenin the relative proportion were approximately 20% increasing and 80% decreasing in size. This response, considering the 'hard to heal' nature of

the ulcers involved, was statistically significant ($p=0.02$). The number of deteriorating wounds in the control group fell between final visit and follow-up. Even after cessation of treatment, ulcers in the amelogenin-treated group showed less deterioration than the control group, and a continuation of the healing process.

This study shows that the ulcers of nine (21%) patients in the amelogenin-treated group were fully healed during the follow-up period of the trial, which compares with only 3 (7%) in the comparator control group.

Perhaps as a consequence of healing being initiated in the ulcers, pain associated with the ulcer and with dressing changes were also significantly lower ($p=0.001$ for both parameters) in the amelogenin-treated group than the control group. Pain is probably the major contributing factor that affects patients' well-being and quality of life. Virtually all patients with a VLU suffer with some pain associated with the condition and it has been highlighted by clinical authorities as an area that requires immediate attention.

Qualitatively, healing of the amelogenin-treated ulcers was very good. This is highlighted in the sequence of photographs of two patients (Fig 4). These photographs show excellent healing rates expressed during amelogenin therapy (weeks 6 and 12) that were maintained after treatment had been terminated and up to the follow-up (week 24). Patient 206 demonstrated ulcer size reduction, whereas patient 204 was virtually healed at week 12. The follow-up pictures support the excellent quality of the healed tissue, with no contraction or hypertrophic scarring, and healthy peri-wound skin.

From a clinical perspective, this and previously undertaken studies have been invaluable in identifying in what state the ulcer is required to be before amelogenin is applied. For example, because amelogenin protein is applied topically to the surface of the wound bed, it must be predominantly clean and free from eschar and slough. This is because it is thought that any dead tissue might physically prevent the protein from integrating into the wound bed target tissue. Thus, in ulcers presenting with large areas of dead tissue, it is recommended that debridement is undertaken to produce a clean wound bed before starting amelogenin therapy.

In this study, one of the exclusion criteria was the presence of infection in any of the ulcers; if present it had to be treated (using systemic or topical antibacterial agents) before inclusion in the study. However, high levels of pathogenic bacteria such as *Pseudomonas* species may be present and colonise VLUs which may develop into wound infection.¹⁹ It is suggested that if a wound infection does develop during amelogenin treatment, then topical or systemic antibacterial therapy should be

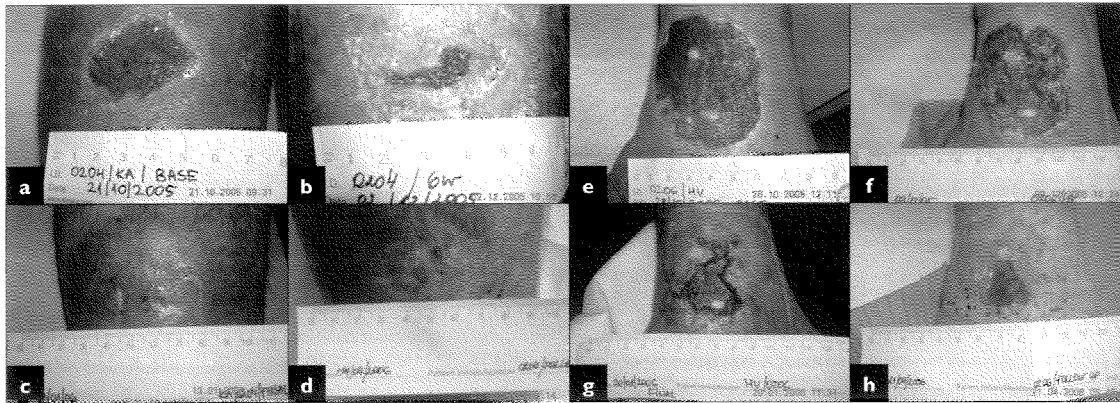


Fig 4. Photographs of ulcers before and after treatment with amelogenin (a-d); male patient, three-year-old ulcer; at baseline 9.5cm²; at 12 weeks 0.1cm²; at 24 weeks healed (e-h); male patient, seven-month-old ulcer; at baseline 32cm²; at 12 weeks 6.7cm²; at 24 weeks 4.3cm²

undertaken according to standard practice, but there is no requirement to delay treatment with amelogenin.

VLUs can produce large amounts of exudate. This may be as a result of infection (eg, commonly seen with *Pseudomonas* infections), ineffective or absent compression, or it may be merely as a result of the healing process. For example, it is thought that the stimulation of healing by amelogenin may result in a corresponding increase in the angiogenic response,^{14,15} increasing the local wound bed blood supply which would account for the raised levels of exudate. Again, this symptom was part of the exclusion criteria, thus any patient that exhibited high levels of exudate had to be managed and controlled, preferably by the use of compression, before amelogenin was applied to the wound. A transient increase in exudate levels was observed in the amelogenin-treated group, but only in the early stages of treatment. Overall, ulcers treated with amelogenin were associated with statistically significant decreases in exudate levels

Ultimately, the aim of the treatment is to heal the ulcers. As has been indicated, the patients evaluated in this study were from a population described as 'non-healing'. In many patients the ulcers had been present for years with no positive responses to the standard treatment regimes, including high compression, which is recognised as the 'gold standard' in the treatment of VLUs. These patients are a heavy burden on the health service and a treatment that will actually heal such wounds will not only provide significant benefits to patients and their carers, but ultimately allow much-needed resource to be allocated elsewhere within the health service.

Amelogenin therapy may be more costly initially when it is compared with the more traditional dressings that are available to treat these ulcers. In order, therefore, to be cost-effective, amelogenin

therapy must be targeted at the population of VLUs that will not respond to standard treatment, estimated to be about 20%.²⁰ It is this sub-group of VLUs that is most burdensome on the health service, requiring greater treatment resources. It is important to identify such patients as early as possible. This will prevent them being treated inappropriately with dressings and therapies that will not serve to heal or alleviate the condition. Prognostic indicators such as the ulcer size being greater than 10cm² and of duration greater than six months have been referenced in the literature.⁵ This study has shown that these prognostic indicators are valid and can be used to improve treatment by using different treatment modalities. An additional indicator that ulcers may not heal is if they have not shown a significant improvement (eg, wound reduction greater than 40%) over a period of three to four weeks.²¹

Conclusion

The results of this clinical study have demonstrated that amelogenin therapy in conjunction with high compression was statistically and clinically better in the treatment of patients with hard-to-heal VLUs than high compression alone. The criteria for identifying suitable patients and the requirements of the wound before treatment have been elucidated and can be used as the basis for the use of amelogenin therapy. In addition, when the balance of healing a VLU with a relatively costly advanced treatment, such as amelogenin, is compared with maintaining a patient with a VLU over the remaining period of a patient's life (which may be many years), and taking into account the contributing factors of better quality of life with regards to, for example, pain reduction, then with the successes seen in this study, the advanced amelogenin treatment should be viewed as a cost-effective treatment for VLUs. ■

18 Dini, V., Bertone, M., Barbanera, S., et al. The use of amelogenin in pyoderma gangrenosum. Poster presentation. European Wound Management Association Conference, Glasgow, United Kingdom, 2007.

19 Bowler, P.G., Duerden, B.I., Armstrong, D.G., et al. Wound microbiology and associated approaches to wound management. *Clin Microbiol Rev* 2001; 14: 2, 244-269.

20 Rippon, M., Davies, P., White, R., et al. The economic impact of difficult-to-heal leg ulcers. *Wounds UK* 2007; 3: 2, 58-69.

21 Phillips, T.J., Machado, F., Trout, R., et al. Prognostic indicators in venous ulcers. *J Am Acad Dermatol* 2000; 43: 4, 627-630.

DOCUMENT SUPPLY

Boston Spa, Wetherby
West Yorkshire LS23 7BQ
www.bl.uk

Please note the following:

This is the best copy available

This article has a very tight binding

Some pages within the original article are advertisements and have therefore not been sent

Advertisement pages: 19.....

Some pages within the original are blank and have therefore not been sent

Blank pages:

The article you require is on different pages to those that you quoted