CLINICAL STUDY
VENOUS ULCERS

Xelma®

Extracellular matrix protein therapy

Effect of Amelogenin Extracellular Matrix Protein (Xelma) as an Adjunct Treatment to High Compression in Hard-to-Heal Venous Leg Ulcers: a Multi-Centre, Randomised Controlled Trial.

Peter Vowden MD, FRCS
Vascular Unit, Bradford Royal Infirmary,
Bradford, United Kingdom

Marco Romanelli MD PhD
Department of Dermatology,
University of Pisa,
Pisa, Italy

Patricia Price PhD
Wound Healing Research Unit,
Cardiff, United Kingdom

MÖLNLYCKE HEALTH CARE

Poster presented at the European Wound Management Association Conference, Glasgow, United Kingdom, 2-4 May 2007

CLINICAL & SCIENTIFIC EVIDENCE

CLINICAL & SCIENTIFIC EVIDENCE

Effect of Amelogenin Extracellular Matrix Protein (Xelma®) as an Adjunct Treatment to High Compression in Hard-to-Heal Venous Leg Ulcers: a Multi-Centre, Randomised Controlled Trial.

AUTHORS: Vowden P.[1] MD, FRCS; Romanelli M.[2] MD, PhD; Price P. PhD [3]. 1. Vascular Unit, Bradford Royal Infirmary, Bradford, United Kingdom. 2. Department of Dermatology, University of Pisa, Pisa, Italy. 3. Wound Healing Research Unit, Cardiff, United Kingdom. On behalf of the European Xelma Clinical Investigation team

INTRODUCTION

Extracellular matrix (ECM) proteins define the extracellular environment of living cells. Inappropriate matrix remodelling in chronic wounds results from the imbalance of proteinases and their endogenous inhibitors; this may compromise the function of the ECM, especially with respect to the sequence of filling the dermal defect! Xelma (Molnlycke Health Care) is an advanced wound care product containing amelogenin, an ECM biocompatible protein. When applied to the wound bed it provides a temporary matrix for cell attachment and promotes wound healing.

Therapy using amelogenin has already been shown to be successful in the treatment of periodontal wounds[2] Furthermore, clinical evaluations (a randomised controlled trial[3] and case studies[4]) have indicated the potential for amelogenin to assist in the healing of 'hard-to-heal' venous leg ulcers (VLUs).

OBJECTIVE

A comparison of hard-to-heal venous leg ulcers (VLUs) treated with high compression therapy alone versus high compression therapy with amelogenin protein.

METHODS

An open, randomised, comparative, parallel group multi-centre investigation with a 3-week run-in period. Patient eligibility for inclusion included adult, mobile patients with 'hard-to-heal' VLUs that had been treated with compression therapy for at least 1 month prior to screening. The ulcers had to be at least 6 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. At the end of the run-in period, additional criteria for eligibility, e.g. change in wound area of ±≥ 50% and a wound area < 8 and > 36 cm², were applied. Patients were randomised to treatment with amelogenin plus high compression bandaging, or high compression bandaging alone. All participants received a secondary dressing combination of Mepitel® and Mesorb® or Mepilex®, with high compression bandaging therapy one month prior to, during the investigational period of 3-weeks run-in and throughout the following 12 weeks of active treatment.

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

Statistical Analysis

The primary endpoint was the percent change in ulcer size from baseline to the last visit, analysed using Wilcoxon Mann-Whitney U-test, as was the number of improved patients with more than 50% ulcer area reduction using Fishers Exact Test between the groups at the final time point. The analysis of pain related to the disease and at dressing change, the rate of healed and improved patients, and comparisons of exudate levels were also analysed between the groups at the final time point using Fishers Exact Test. Multiple Logistic Regression was also calculated on the primary efficacy variable.

Table 1 Wound history at baseline. Data are presented as mean (SD)

Xelma (n = 42)		Control (n = 41)	
Age of ulcer (months)	Ulcer Size (cm²)	Age of ulcer (months)	Ulcer Size (cm²)
55.3 (62.7)	17.0 (9.1)	32.4 (27.8)	18.0 (9.0)

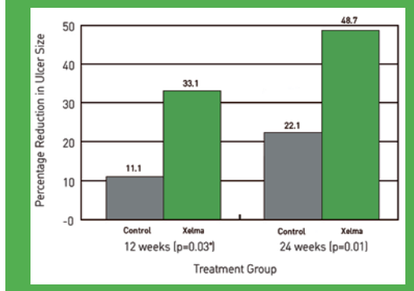


Figure 1. A Statistical Comparison (Control vs Xelma) of the % Reduction in Ulcer Size (Intention to treat) at 12 and 24 weeks.
*Multiple regression analysis for the baseline variables

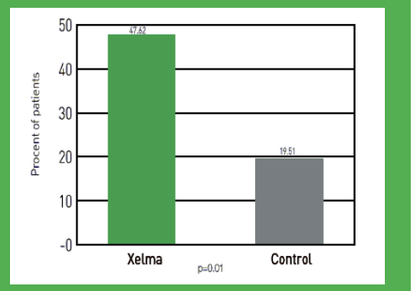


Figure 2. A Comparison between Xelma and Control of the Percentage of Patients With 50% or greater reduction in ulcer size at Week 12.

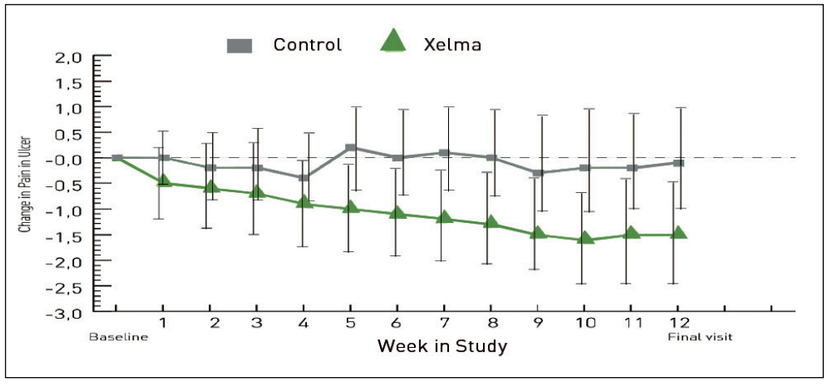


Figure 3. Mean (95% CLI) Change in Pain in Ulcer per Treatment and Week (ITT Population p = 0.01).

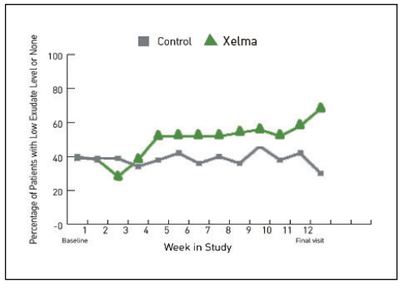


Figure 4. The Percentage of Patients With Low Levels of Exudate or None in the Xelma and Control Groups per Week (p=0.01 at week 12).

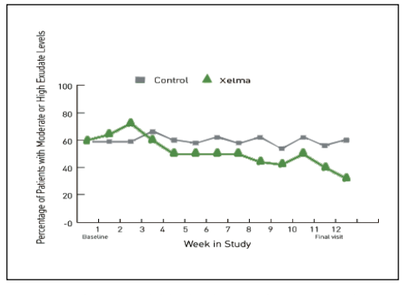


Figure 5. The Percentage of Patients with Moderate or High Exudate Levels in the Xelma and the Control Groups per Week.

The Intention to Treat (ITT) population included all the patients that received at least one treatment. In total, 42 patients were treated with amelogenin plus compression therapy, and 41 patients with compression alone.

Statistical Analysis

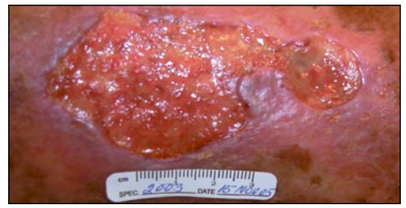
The primary efficacy analysis was the difference, although the difference was not significant, in the percent change ulcer size from baseline to the last visit between the two treatment groups. The results show (ITT data) that the mean percent change from baseline in wound size at the last visit for the amelogenin group was -33.11 (SD 49.69) % and for the control group was -11.07 (SD 46.55) % (p=0.06). Compensating for baseline characteristics by using a multiple regression test revealed a statistically significant (p=0.03) reduction in percent change in ulcer size in the amelogenin group. The mean and 95% CI for the difference between the amelogenin and the control was -22.04 (-43.08 -1.01) %, p=0.03. (Figure 1.).

The data relating to the reduction in ulcer size (Figure 2) illustrated a larger number of wounds with reductions of greater than 50% in the amelogenin group and, conversely, more wounds showed an increase in ulcer size in the control group. The overall healing rate was greater in the amelogenin treated group. The percentage of improved ulcers at the last visit was statistically significantly higher, 47.5% in the amelogenin group compared to 19.5% in the control group (p=0.01).

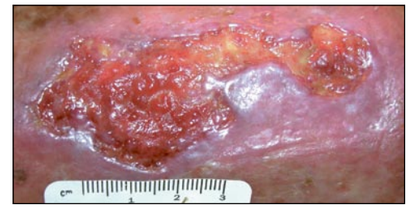
Pain was estimated using an ordinal scale with 11 steps; from 0 = none to 10 = unbearable pain[5]. The results showed that reduction in pain related to the disease and reduction in pain at dressing changes were more apparent in the amelogenin treated group. Statistical analysis showed that the amelogenin group had significantly greater ulcer pain reduction (p = 0.01); the mean and 95% CI for the difference in pain reduction between amelogenin and control at the final visit was -1.59 (-2.84 to -0.34) (Figure 3). The level of exudate was estimated as 'none', 'low', 'moderate' or 'high'. The results show (Figures 4 and 5) that in the amelogenin group, 'none' and 'low' exudate levels were recorded for 28 patients (66%); and in the control group for 15 patients (37%).

There were significantly (p=0.01) more patients in the amelogenin group with 'none' or 'low' exudate levels for much of the treatment period (Figure 4). Comparison between the two treatment groups with 'moderate' or 'high' exudate levels over the course of the twelve weeks study (Figure 5) shows that a reduction in the higher levels of wound exudate occurred in the amelogenin group, but not in the control group.

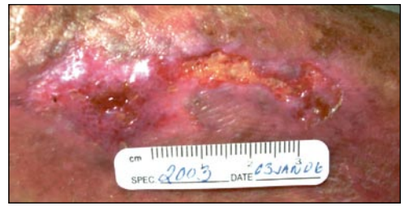
The total number of AEs in the two groups was similar; vital signs, weight and BMI did not reveal any safety issue in the investigation. The most commonly reported SAE/SADE was reported under the heading "Cardiac Disorders" and "Infections and Infestations" with single reports under each heading in both treatment groups. No consistent pattern of AEs evolved in the investigations suggesting good safety of the two treatments. A series of photographs of a VLU treated with amelogenin is presented (Photographs 1 to 4). This patient was female, Caucasian and 83 years old and presented with a VLU on the left leg that was 8 months old, there was no other underlying disease. At the start of the run-in period, the area of this wound was 17.9cm², This had reduced to 0.02cm² by week 9, effectively healed. The series of photographs demonstrates progression of healing as the wound fills with granulation tissue and epithelial cells cover the wound bed. At the final time point, complete healing has occurred and, visually, the scar tissue was good, with no evidence of hypertrophy or contracture.



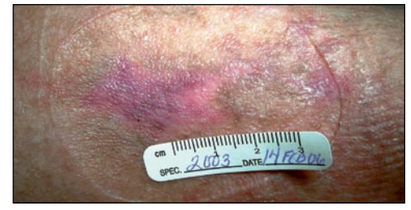
Photograph 1. VLU at beginning of run-in period (15th November 2005). Large clean wound (17.9 cm²).



Photograph 2. VLU at Baseline (7th December 2005). Still a large clean wound after run-in period.



Photograph 3. VLU at 4 weeks treatment (5th January 06). Significant healing with re-epithelialisation and granulation tissue formation. No maceration and skin adjacent to wound appears very healthy.



Photograph 4. VLU at 12 weeks treatment (4th February 06). Qualitatively an excellently healed wound, with little scar tissue or contracture.

CONCLUSION

The results from this investigation, carried out over 24 weeks including 3 months of follow-up, are in agreement with other clinical studies[3,4,6] which have demonstrated that the addition of amelogenin to high compression bandaging is statistically and clinically significantly beneficial to the healing of hard-to-heal VLUs, in the following areas:

- Reduction in ulcer size
- Improvement in the state of ulcers
- Reduced pain between visits and at dressing change
- Larger proportion of ulcers with no/low levels of exudate

The investigation indicates that amelogenin (Xelma) is safe and effective in the treatment of hard-to-heal venous leg ulcers that had failed to heal with standard therapy. These hard-to-heal venous leg ulcers present the worst case scenario in this indication, in that some patients had presented with these wounds many years previously, but no treatment was effective in initiating or maintaining a healing response. This study highlights the importance that, in order to be successful, the amelogenin must be applied to a clean/non-infected wound bed and preferentially in association with high compression therapy.

References: **2. Exposito M,** et al. Cochrane Database Syst Rev 2003; CD003875. **5. Hartrick C T,** et al. Pain Pract 2003; 3(4): 310-316. **4. Huldt-Nystrom T,** et al. SAR 2006; 4. **6. Romanelli M,** et al. Poster presentation. EWMA Symposium, Stuttgart, Germany 2005. **1. Schulz GS,** et al. World Wide Wounds 2005; August (www.worldwidewounds.com). **3. Vowden P,** et al. Wound Repair Regen 2006; 14 (3): 240-6.

Mölnlycke Health Care AB (publ)
Box 13080, SE-402 52 Göteborg, Sweden
Phone +46 31 722 30 00
www.molnlycke.com

MÖLNLYCKE
HEALTH CARE