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Xelma[®], an advanced wound treatment for venous ulcers: a European perspective

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Amelogenin (Xelma[®]) is an extracellular matrix (ECM) protein which provides a temporary extracellular matrix component for cell attachment which is thought to aid in the growth of granulation tissue when applied regularly to a wound. Clinical studies on venous leg ulcers using amelogenin as a therapeutic agent have established positive effects. This article looks at the results of using Xelma to treat 19 patients with a total of 25 non-healing venous leg ulcers. This study was funded by Mölnlycke Health Care, Gothenburg, Sweden.

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KEY WORDS

Amelogenin (Xelma[®])
Case studies
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In the normal processes of wound healing, damage to the integrity of the skin results in a complex series of events designed to restore structure and function. In normal healing these events occur in specific phases: inflammation, production of granulation tissue, matrix formation and remodelling. These processes overlap and involve interaction between a variety of cell types including inflammatory cells (neutrophils, macrophages and lymphocytes), fibroblasts, endothelial and epithelial cells. Biochemical messengers such as cytokines and growth factors, regulate cell proliferation, migration and the synthesis of the extracellular matrix (ECM) (Diegelmann and Evans, 2004).

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In chronic wounds such as venous leg ulcers (VLUs), diabetic foot ulcers and pressure ulcers, the normal healing process is delayed or prevented completely. It has been shown that ECM components in chronic wounds may be damaged and dysfunctional (Cook et al, 2000). This damage is thought to be due at least in part to the high levels of protease enzymes present in these wounds (Wysocki, 1996). The chronic inflammatory reaction seen in wounds such as VLUs results in a self-amplifying cascade with persistent elevated levels of pro-inflammatory cytokines and proteases that degrade the ECM components, growth factors and receptors that are essential for normal healing (Ågren et al, 2000; Schultz et al, 2005; Chen et al, 2007).

The incidence of chronic wounds varies according to age, health status and comorbidities such as diabetes, cardiovascular and neurological diseases. The most common chronic wounds are pressure ulcers, venous leg ulcers, arterial ulcers and diabetic wounds (Mustoe et al, 2006). About 1–2% of the whole population (Anderson, 2006) and 3–5% of the population over 65 years of age will suffer from a leg ulcer (Mekkes et al, 2003), with prevalence being 20 per 1,000 at the age of 80 years (Nelson, 2003). It is highly likely that the prevalence of such wounds is likely to rise as the population ages.

Risk factors for VLU development include: a family history of maternal venous insufficiency (Berard et al, 2002), a history of deep vein thrombosis, diabetes mellitus (DM), chronic heart failure or recent oedema, obesity, severe trauma to the leg and, for women, the number of pregnancies; Wipke-Tevis and Stotts, 1998a; Wipke-Tevis and Stotts, 1998b; Wipke-Tevis et al, 2000; Fowkes et al, 2001). VLUs constitute a serious clinical problem due to their high prevalence, morbidity and associated comorbidities, and mortality. They are associated with health-related quality-of-life (HRQoL) issues which impact upon the patients, such as ulceration, pain, malodour, itching, altered appearance, loss of sleep, limits in functionality and treatment expectations (Hareendren et al, 2005). VLUs are characterised by a cyclical pattern of healing and high recurrence rates (Nelson et al, 2006). There are major economic consequences on the healthcare system as a result of VLUs (Bouza et al, 2005) and their treatment is a heavy economic burden on health services in many countries.

The main treatment for VLUs is graduated compression (decreasing from toe to knee), either in the form of compression bandages or hosiery. However, it has been shown that only 65% of VLUs will heal after six months of treatment despite the use of high compression therapy (Barwell et al, 2004).

Recently a number of different therapeutic approaches have been developed that have targeted the dysfunction of the wound matrix. One such advanced treatment is Xelma® (Mölnlycke Healthcare, Gothenburg, Sweden). This gel consists of an ECM-biocompatible protein, amelogenin, dissolved in a propylene glycol alginate and water. When applied to the wound bed it provides a temporary extracellular matrix protein for cell attachment, thereby facilitating the restoration of the cellular and biochemical balance in non-healing wounds, which in turn promotes granulation tissue formation and normal wound healing. This advanced therapy has been shown to be successful in the treatment of some chronic wounds (Vowden et al, 2006; Vowden et al, 2007).

Method

This study involves an open non-randomised case study series, involving both in- and outpatients. The inclusion/exclusion criteria for the investigation are summarised in *Table 1*.

As the study involved case study evaluations, the inclusion/exclusion criteria were used as general guidelines to aid the clinicians in identifying patients who they believed would benefit from the use of Xelma. A hard-to-heal VLU was classified as having a wound surface area greater than 10cm² and a duration of longer than six months.

After being assessed for suitability, Xelma was applied to a clean wound bed on a weekly basis for up to a maximum of 12 weeks, although one patient had Xelma applied for 18 weeks because the investigator was seeing good results with Xelma at week 12 and did not wish to terminate the treatment. Dressing changes were undertaken when judged necessary by the investigator according to the needs of the patient. Compression therapy was also maintained according to the needs of the patient. The majority of patients had been treated with compression therapy for four weeks before inclusion in the evaluations to ensure that the wounds would not have responded to compression therapy alone.

Table 1

Criteria used to select patients for the assessment of Xelma

Inclusion criteria	Exclusion criteria
Patients aged 18 years or older	Known allergy/hypersensitivity to any of the components in the dressing
Signed informed consent	Patients who will have had difficulty understanding the treatment protocol
Patients with hard-to-heal VLUs that have not benefited from high compression bandaging or hosiery for at least four weeks before starting treatment with Xelma and having shown no sign of healing	Severe underlying disease that the investigator deemed may have interfered with treatment e.g. HIV, AIDS, cancer
ABPI > 0.8	ABPI < 0.8
	Infected wounds
	Wounds with high levels of exudate that are not being managed successfully by the dressings
	Bed-bound patients
	Patients unable to use a product of porcine origin

Assessments

Assessments of wound size, exudate level, patient satisfaction with treatment, and wound pain at dressing change were undertaken at the three participating centres:

- ▶▶ Hudpoliklinikken i Levanger, Norway (two patients plus data relating to nine patients from other clinics in Norway — 15 ulcers in total);
- ▶▶ Seinäjoen Keskussairaala, Finland (one patient — three ulcers);
- ▶▶ Wound Care Centre AZ, St Elisabeth, Zottegem, Belgium (four patients — four ulcers);
- ▶▶ Queen Elizabeth Hospital, London, United Kingdom (three patients — three ulcers).

Photographs of the ulcers were also taken and retained on file.

Ethics

The study was undertaken in accordance with the ethical guidelines of the 1964 Declaration of Helsinki, Amendment 1989.

Results

The efficacy of Xelma was assessed by treating 19 patients with a total of 25 hard-to-heal wounds. The results (*Table 2*) show that the success rate

with amelogenin therapy was high, with 76% of the ulcers either healed or reduced in size after treatment. Nine (36%) of the ulcers healed and 10 (40%) showed a significant improvement. Some of the ulcers healed after shorter periods of treatment than was recommended by the manufacturer and some continued to heal after their treatment had been completed. Due to the qualitative improvement of the wound bed following treatment with Xelma, a number of wounds went on to be grafted whereas before treatment with Xelma the wounds were thought not to be in a state in which any grafts would 'take' due to poor granulation tissue and vasculature. The progression to healing of one of the ulcers that healed is shown in *Figure 1*.

Nearly one-quarter of the ulcers did not show an improvement — either remaining unchanged (n=3; 12%) or deteriorating (n=3; 12%) during the treatment period. Those wounds associated with high levels of wound exudate developed skin maceration and, as a consequence, additional ulceration. These observations support the manufacturer's instructions

Table 2

Summary of VLU healing after treatment with Xelma

Patient No/ Location	Wound duration	Wound size (cm ²) start–end	Number of applications	Status	Comments
1. Norway	65 years	16.0–4.25	18	Improved	<i>Pseudomonas</i> spp. was discovered in the early stages of treatment, clinical infection with gram negative bacteria. However, the wound continued to heal. No antibiotics were used during treatment.
2. Norway	7 months	7.50–0.00	12	Healed	Hypergranulation tissue present in the initial stages of healing, <i>Pseudomonas</i> spp. present towards the end of healing. Treated with ciprofloxacin for 7 days in week 10.
3. Norway	5 years	5.20–0.00 4.32–0.00	6	Healed	
4. Norway	6 years	0.80–0.00 0.75–1.00	12	Healed Slightly bigger	Less pain was reported during treatment with Xelma Although one of the wounds got slightly bigger it looked qualitatively better.
5. Norway	3 years	13.5–0.00	8	Healed	
6. Norway	6 years	134.6–148	9	Deteriorated	Exudating wound. A low grade <i>Pseudomonas</i> spp. infection was identified as present before treatment with Xelma. Aquacel Ag and Acticoat were used in parallel. Patient had several antibiotic treatments before treatment with Xelma.
7. Norway	5 years	40.0–40.0	12	Unchanged	More granulation tissue initially, and ulcer improved during first 4 weeks of treatment. Thereafter wound increased slightly in size.
8. Norway	2 years	20.3–20.3	2	Deteriorated	Treatment with Xelma stopped because of high exudate level and <i>Pseudomonas</i> infection.
9. Norway	10 years	5.29–1.05	12	Improved	Almost healed after 9 treatments. Week 9 deterioration due to maceration because of sweating and infection.
10. Norway	2 years	3.22–1.20	11	Improved	
11. Norway	3 years	80–0.50 15–0.00	6	Improved Healed	Treatment with antibiotics one month before treatment with Xelma because of infection with <i>Staphylococcus aureus</i> .
12. Norway	1 year	8.68–0.00	10	Healed	The patient had a lot of pain before treatment with Xelma which was reduced during the assessment period
13. Finland	10 years	12–1.5 6.5–0 1.0–0	12 11 4	Improved Healed Healed	Wound 2 healed after 11 weeks of treatment, wound 3 healed after 4 weeks of treatment.
14. Belgium	35 years	20.6–14.5	12	Improved	Good healing progress. No pain at all.
15. Belgium	15 months	18.1–2.0	12	Improved	Less pain experienced between dressing changes. At the end of the Xelma treatment, <i>Pseudomonas aeruginosa</i> was still present
16. Belgium	4 years	27.8–52.1	10	Deteriorated	Patient withdrawn from study after 9 weeks of Xelma treatment. The wound was infected with <i>Pseudomonas aeruginosa</i> .
17. Belgium	3.5 years	22.3–26.7	12	Unchanged	Positive evolution at about 4 weeks after the start of Xelma treatment. Less pain than previous treatments.
18. UK	8 years	5.5–3.0	12	Improved	Last part of ulcer was epithelialising, thus allowing patient to be managed with compression hosiery for the first time in eight years.
19. UK	13 months	6.5–5.0	12	Improved	Xelma treatment kick-started the healing process and enabled the patient to be referred for skin grafting
20. UK	4 years	7.0–4.5	12	Improved	Almost healed, epithelialisation over most areas



Figure 1a. VLU in the right ankle region at baseline, before treatment with Xelma.



Figure 1b. VLU 3 weeks after starting treatment with Xelma.



Figure 1c. VLU 9 weeks after treatment initiation with Xelma. The wound is well on the way to healing.



Figure 1d. VLU after completion of study. The wound is completely healed.

Figure 1. Sequence of photographs of patient 2 demonstrating the progression to healing of a venous leg ulcer when treated with Xelma.

that Xelma should not be used on highly exuding or infected wounds. *Pseudomonas* colonisation/infection was present in some wounds after treatment had started, but this was treated with appropriate antibiotic therapy, and did not affect the wound's healing outcome. Systemic antibiotics are the standard first-line therapy in the treatment of infected wounds, with or without topical antimicrobials and cleansing or debridement.

According to the investigators, the overall impression of the product was positive; Xelma was easy to use and could be applied under standard dressing types and compression therapy, on a weekly basis. The treatment was not painful and in some cases patients reported alleviation of pain during treatment. Most importantly, Xelma was successful in initiating a healing response in wounds that had failed to heal when treated with standard therapies.

Discussion

The case study data presented here are in accordance with the findings of two randomised controlled trials in which Xelma was evaluated in the treatment of hard-to-heal VLUs (Vowden et al, 2006; Vowden et al, 2007). These clinical trials demonstrated significantly better healing in a sub-group of patients that had been treated with Xelma plus compression, compared with high compression therapy alone. The basis for the stimulation of healing in these hard-to-heal wounds can be conjectured to be that Xelma may provide cells with a surrogate extracellular matrix protein to which they can attach as well as providing a stimulus for cell proliferation, migration and synthesis of chemical messengers (Vowden et al, 2006) which would also aid in the initiation and progression of a 'normal' healing process.

Conclusion

Clinical experience from a number of

Key Points

- ▶▶ Non-healing venous leg ulcers (VLUs) have a dysfunctional extracellular matrix.
- ▶▶ About 1–2% of the population will suffer from a leg ulcer during their lifetime.
- ▶▶ Up to 20% of VLUs will not heal despite treatment with high compression therapy.
- ▶▶ VLUs are a significant burden on health agencies worldwide.
- ▶▶ Advanced treatments are needed to initiate healing in 'hard-to-heal' VLUs.
- ▶▶ Amelogenin (Xelma®) has been shown to be effective in treating VLUs.

case studies confirms that amelogenin can stimulate healing in some hard-to-heal venous ulcers. Wound exudate of moderate to substantial degree should be treated before starting amelogenin treatment. **WUK**

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Product REVIEW

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