

# Treatment of Hard-to-heal Chronic Venous Ulcerations with Amelogenin. The Norwegian Experience.

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## INTRODUCTION

Healing in Chronic Venous Ulcers (CVU) is problematic – 20% of all venous ulcers do not heal successfully after standard treatment (e.g. compression therapy). It has been shown that non-healing CVUs, e.g. which have not healed in six months, or measure 10cm<sup>2</sup> and larger, are associated with a reduced ability to heal.<sup>1,2</sup> A possible reason for this might be damage to the ulcer connective tissue matrix that prevents the fibroblasts from receiving proper stimulus to migrate and produce growth factors. Amelogenin is an extra cellular matrix (ECM) protein which is thought to act as a surrogate scaffold and aid in the growth of granulation tissue when applied regularly to a wound. Clinical studies on CVUs using amelogenin as a therapeutic agent have established positive effects and stimulation of healing.<sup>3</sup> A series of case studies are presented supporting the use of Xelma as an advanced therapy for the treatment of specific wound types.

## METHODS AND PATIENTS

In this survey, 12 patients (15 CVUs) received weekly amelogenin therapy (Xelma™ Mölnlycke Healthcare AB) up to a maximum of 18 weeks, unless the wounds healed earlier, or if there were no signs of improvement after 6 weeks of treatment.

Inclusion criteria:

- Non-infected CVUs
- ABPI index > 0,8
- Ulceration > 6 months
- Lack of response to compression treatment
- Venous insufficiency

Throughout the treatment period, the progress of each patient's wounds were measured as follows:

- Wound size
- Exudate level
- Fibrin content
- Patient satisfaction
- Pain (VAS)

Compression therapy was maintained according to the patients' normal requirements.

## RESULTS

The results of this preliminary evaluation of Xelma (summarised in Table 1.) showed that over the treatment period a large proportion of the ulcers healed or showed a reduction in size, and that 2 ulcers continued to heal after their treatment had been completed. Only a small proportion of ulcers remained unchanged (3) or deteriorated (2). Pseudomonas colonization/infection was present in some wounds after therapy had been started, but this was treated with appropriate antibiotic therapy, and did not

affect the successful healing outcome of the wounds. The treatment was generally well tolerated, however 2 ulcers with high levels of wound exudate developed skin maceration (not related to Xelma) and, as a consequence, additional ulceration. The inclusion of these wounds in the study support the manufacturer's instructions that the product should not be used on highly exuding or infected wounds. Some of the ulcer scars presented with distinct edges with small indents. Several patients reported a relief of pain during treatment, no patients reported increased pain.

**TABLE 1. SUMMARY OF CLINICAL RESULTS**

	Wound duration	Baseline wound area	Baseline wound exudate	Total no. applications	Final wound size	Status	Comments
<b>Patient 1 Male</b> (age 86)	65 years	5.0 x 3.2cm	0/+	18	2.5 x 1.7cm	Improved	Pseudomonas spp present in early stages of treatment. The wound continued to heal after Xelma treatment had been stopped.
<b>Patient 2 Female</b> (age 77)	7 months	5.0 x 1.5cm	+	12	0	Healed	Initial hypergranulation. Wound infected with Pseudomonas spp 2 weeks before end of treatment. Treated with Ciprofloxacin 500mg x 2 for 7 days.
<b>Patient 3 Female</b> (age 70)	5 years	4.0 x 1.3cm 2.4 x 1.8cm	++	6	4.0 x 2.1cm 2.0 x 2.8cm	Healed* Healed*	Non-compliant patient. Removed compression-bandages during therapy. Ulcer got infected with pseudomonas during therapy. *Both ulcers healed 4 weeks after cessation of Xelma treatment.
<b>Patient 4 Female</b> (age 80)	6 years	0.8 x 1.0cm 0.5 x 1.5cm	+	12	1.0 x 1.0cm	Unchanged Healed	Less pain. Probably inadequate compression therapy before starting Xelma.
<b>Patient 5 Male</b>	3 years		0/+	8	0	Healed	
<b>Patient 6 Male</b> (age 44)	6 years	134.6cm <sup>2</sup>	++	9	148.0cm <sup>2</sup>	Deteriorated	Exudating wound. Pseudomonas infection during Xelma treatment. Aquacel Ag /Acticoat used in parallel.
<b>Patient 7 Female</b> (age 75)	5 years	Ca 8 x 5cm	0/+	12	Ca 8 x 5cm	Unchanged	Increased amount of granulation tissue. Wound increased in size slightly.
<b>Patient 8 Female</b> (age 77)	2 years	20.3cm <sup>2</sup>	+++	2	20.3cm <sup>2</sup>	Deteriorated	Treatment with Xelma stopped because of high exudate level and Pseudomonas infection.
<b>Patient 9 Male</b> (age 68)	10 years	2.3 x 2.3cm	0/+	12	1.5 x 0.7cm	Improved	Almost healed after 9 treatments, then deterioration due to maceration of skin and infection with Staph.Aureus.
<b>Patient 10 Female</b> (age 81)	2 years	2.3 x 1.4cm	0/+	11	1.5 x 0.8cm	Improved	
<b>Patient 11 Female</b>	3 years	10.0 x 8.0cm 3.0 x 5.0cm	+++	6	1.0 x 0.5cm	Healed	
<b>Patient 12 Male</b> (age 58)	1 year	3.1 x 2.8cm	++/+++	10	0	Healed	The patient had a lot of pain prior to treatment with Xelma.

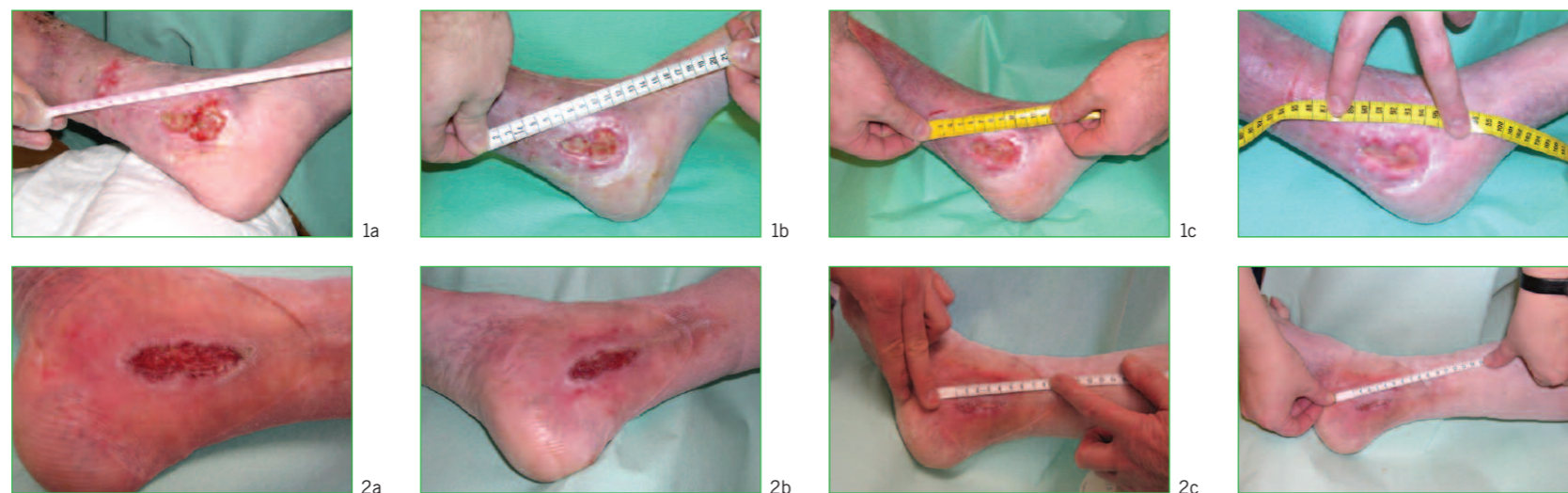


Figure 1a – 1d shows photographs of the sequential progress of wound healing in Patient 1 (VLU) treated with a total of 18 applications of Xelma.

Figure 2a – 2d shows photographs of the sequential progress of wound healing in Patient 2 (VLU) treated with a total of 12 applications of Xelma.

## DISCUSSION

In this study the success rate with amelogenin therapy was high, approximately 70% of the ulcers demonstrated a positive effect of either healing or a reduction in size after treatment. As expected from the manufacturer's instructions for use, the response was poor in ulcers with high levels of exudate. The likely explanation for this may be that the high levels of wound exudate washed out the amelogenin; it is thought that amelogenin requires at least 15 minutes' exposure to the wound bed in order to be effective. Treatment of infection, inflammation and heavy wound exudate prior to the amelogenin therapy is vitally important for an optimal effect. Scar tissue observed after therapy with amelogenin sometimes differs clinically from regular scar tissue, in that the forming of epithelia occurs on the surface of a thin layer of granulation tissue. Little is known of the quality of this scar tissue, or whether it is comparable to ordinary scar tissue in terms of strength and durability.

## CONCLUSION

Our clinical experience confirms that amelogenin can stimulate the healing of difficult to treat venous ulcers. Wound exudate of moderate to substantial levels should be treated before starting amelogenin treatment.

## References

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2. Margolis DJ, et al. Wound Rep Regen 2004; 12(2): 163-168.
3. Vowden P, et al. Wound Repair Regen 2006; 14(3):240-6.