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New insights into therapy by mathematical analysis: Recalcitrant granulated improved more than sclerotic venous leg ulcers with amelogenin treatment☆

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ABSTRACT

Background: Chronic wounds are both time consuming as well as costly. A new therapeutic option for those wounds might be amelogenin, which supplies a temporary matrix to the fibroblasts and keratinocytes.
Objective: To prove the hypotheses for a divergent therapeutic outcome, we treated granulated vs. sclerotic chronic venous leg ulcers with amelogenin (Xelma®) 1×/week for 5–8 weeks.
Methods: The analysis of the treatment was performed by applying a recently published mathematical model. This model can predict and evaluate different wound treatment methods by treating only few patients which is even more practicable for diseases with different influencing factors within patients groups because it is easier to collect only a small homogenous number of patients than multiple.
Results: We treated 12 granulated vs. 16 sclerotic ulcerations. 5 (42%) of the granulated ulcerations with a mean initial wound area of 18.3 cm^2 showed optimal wound healing (>90% epithelization). The average area of new epithelia was 11.9 cm^2.

Nine (56%) of the sclerotic ulcerations showed optimal wound healing with an initial wound area of 7.5 cm^2 and a total average area of 4.1 cm^2 with new epithelia. For comparison of those groups, we extrapolate to a hypothetic mean sclerotic wound area of 18.3 cm^2 analogue to the granulated ulcerations. This calculates to a mean neoepithel of only 6 cm^2 for sclerotic ulcerations. Further on, we calculated about 2% of the wound area that proliferated in contrast to about 3% in granulated wounds.
Conclusions: Although sclerotic ulcerations show higher growth rates, Xelma® seems to be more effective in granulated ulcerations. For larger sclerotic ulcerations the mean maximal covered wound area with neoepithelia is reduced to about 33% in contrast to 65% in granulated ulcerations.

1. Introduction

The majority of chronic ulcerations are venous or venous-arterial leg ulcers which account for about 50–70% of chronic ulcerations [1,2]. A particular challenge is a subgroup of wounds that do not heal despite optimized wound treatment and sufficient compression therapy. In the past years, the focus has been placed on the importance of the extracellular matrix (ECM) for wound healing [3]. In 2008, we reported on a small case series involving the clinical effects of an amelogenin containing hydrogel (Xelma®) [4].

Amelogenin is produced by ameloblasts and is normally found in developing embryonal tooth enamel in different mammals. Amelogenin is a hydrophobic 20 kDa protein that, because of its bipolar characteristics, can aggregate under physiological conditions to larger stable hydrophobic ECM structures and build up a surrogate matrix [5]. This temporary matrix should provide growth structures for the fibroblasts, stimulate their migration and adhesion and finally lead to healing of the wound [6,7]. This supports the hypothesis that there may be a divergent result after treatment of granulated or sclerotic ulcerations and especially that sclerotic ulcerations may benefit more from the treatment because of their reduced potential to build up granulation tissue [8,9]. Additionally, we tried to analyse whether there is a correlation between pain intensity (measured via the visual analogue scale) and response to treatment.

The evaluation of the treatment was carried out by using a recently published mathematical formula for predicting and evaluating different wound treatment methods [10]. Mathematic modelling is not the same like a statistical analysis. For mathematic modelling, it is not necessary to treat many patients but only a few of about 15 patients with measurements once or twice a week.

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With this data, it is possible to adapt the healing trajectories to the reviewed group and to compare the results. To collect small numbers of patients are even more practicable for diseases with inhomogenity within their groups instead of the multiple for statistical analysis, e.g. leg ulcers with many different influencing factors like divergent persistence of ulcer durations or divergent ulcer areas and so on. Also, this method seems possible for analysis for maybe more hazardous treatment regimes, because it is not necessary to expose many patients with the therapy to see a difference.

2. Patients

2.1. Conditions

All patients were suffering from at least one or more chronic venous leg ulcers that had been recalcitrant under various kinds of treatment. Allocation to one of the two groups was performed by a wound treatment specialist according to the clinical appearance of the wound.

In the group with granulated ulcerations (G), there were 8 patients with a total of 12 recalcitrant wounds and, in the group with sclerotic ulcerations (S), there were 7 patients with a total of 16 ulcerations. We treated all wounds with amelogenin once a week for at least 5 and for a maximum of 8 weeks corresponding to the clinical improvement and willingness of the patient (details see Table 1a).

2.2. Definitions

A "granulated wound" was defined as one with a wound ground completely or almost completely (>80%) covered by newly formed soft vascular pink or red granulation tissue.

A "sclerotic wound" was defined as one with a wound ground covered only marginally – or not at all – with granulation tissue (<0%). Instead of this, the wound ground was hard, firm and indurated like a scar.

We included only wounds dating back to ≥6 months that were under continuing adequate and causative treatment but showed recalcitrant wound healing, which means that all patients (n = 15) were obliged to carry out consistent and sufficient compression therapy, and it was required that the wound dressing used before starting amelogenin treatment (at least >4 weeks for amelogenin treatment) had not improved wound status. These wounds we considered to be "recalcitrant wounds".

3. Materials and methods

Xelma® consists of a mixture of 3% amelogenin in propylene glycol alginate and water. It totally degrades within one week. It is a hydrogel with a transparent, slightly yellowish appearance that is of lower viscosity at room temperature and higher viscosity at refrigerator temperature. Xelma® was appropriately stored in the refrigerator at a max. of 8 °C throughout the complete treatment period.

Wound area was measured two dimensionally with Image Access (Version Enterprise 10, Imagic Bildverarbeitung AG, Glattbrugg, Switzerland) by photographs that were taken during the treatment period.

3.1. Basics of the mathematic model

To allow a better understanding of the context, we would like to recapitulate some elementary points of our mathematical model. In this model, we suggest that an area of fibroblasts and keratinocytes at the edge of the wound is activated to proliferate by the treatment provided to the wound. At a later stage, we assume that intercellular interaction puts the proliferating cells under stress. This will influence the further growth rate of the cells. They compete against each other, e.g. in terms of nutrition. Finally, cell growth will stagnate although the wound area might not be totally covered with neoepithelia. This hypothesis results in the following growth function [10]:

$$P(t) = \frac{K \cdot P_0}{a \cdot P_0 + (K - a \cdot P_0) \cdot e^{-\beta \cdot K \cdot t}} \tag{1}$$

$P(t)$ characterizes the area of neoepithelia in cm^2 at time point t, P_0 defines the area of cells in cm^2 that proliferate from the edge of the wound at the beginning of treatment t = 0, K represents the initial wound area in cm^2, and β defines the growth rate and parameter a takes the stress situation into account which varies from ulceration to ulceration.

$$t \to \infty \text{ leads to } P(\infty) = \frac{K}{a} \quad \text{and} \quad \frac{P(\infty)}{K} = \frac{\text{maximal neoepithelia}}{\text{wound area}} = \frac{1}{a}, \tag{2}$$

respectively, which represents the maximal wound coverage.

Only the parameter of the wound area at the time point t = 0 is measurable directly at the beginning of treatment. All other parameters have to be calculated and adapted to the equation by

Table 1a
Data of the included patients and their ulcerations.

	Granulated	Sclerotic
Patients	8	7
Female:male	5:3	4:3
Mean age of the patients	65 years (minimum 53, maximum 73)	65 years (minimum 49, maximum 86)
Ulcerations	12	16
Mean ulcer duration	28 months (minimum 9, maximum 84)	24 months (minimum 6, maximum 69)

Table 1b
Results of the ulcerations and their observed and calculated healing course under therapy with Xelma®.

	Granulated	Sclerotic	Sclerotic (extrapolation)
Evaluated ulcerations	9	6	–
Healed (>90% wound coverage)	5 (42%)	9 (56%)	–
Mean ulcer area (cm^2)	18.3 (minimum 0.8, maximum 59)	7.5 (minimum 3.8, maximum 13)	18.3
Mean wound coverage[a]	64%	55%	33%
Insufficient effect	3 (25%)	7 (44%)	–

[a] Wound coverage = $\frac{\text{area of neoepithel}}{\text{wound area}}$.