Use of a synthetic extracellular matrix protein in non-healing diabetic foot wounds

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This article reports a series of 10 non-healing chronic diabetic foot ulcers following treatment with a new synthetic extracellular matrix (SECM) protein gel, Xelma. During the treatment period, 80% of the previously static ulcers treated showed a reduction in area. These findings suggest that, in conjunction with off-loading, infection control and an adequate blood supply, SECM protein gels may be considered for the treatment of static ulcers, when traditional therapies have failed to achieve healing.

Diabetes-related foot complications are one of the most serious and expensive complications arising from diabetes (International Working Group on the Diabetic Foot, 2007), not only for health services, but also for the individual and society. The majority of lower-limb complications among those with diabetes begin with the formation of a foot ulcer, and non-healing ulcers are recognised as a strong predictor of amputation (Pecoraro et al, 1990; McInnes et al, 1998).

The pathology of non-healing diabetic foot wounds includes disturbances to growth hormones, proteases and the extracellular matrix (ECM; Harding et al, 2002). ECM is formed by functional and structural proteins that perform important roles in maintaining cellular and tissue structure during wound healing (Schultz et al, 2005). Disturbance of ECM production, and its degradation, have been associated with chronic wounds (Ravanti and Kahari, 2000).

Xelma (Mölnlycke Health Care, Dunstable) is a topical gel that delivers synthetic ECM (SECM) protein to the wound site. SECM protein facilitates cell attachment, creating conditions in the wound bed favourable for the restoration of cellular functions necessary for healing, including cell proliferation and migration, and the production of growth factors (Ravanti and Kahari, 2000). This case series assesses the effects of Xelma on a series of non-healing diabetic foot ulcers.

Method

Nine participants, with a total of 10 ulcers, were included in this case series. Ulcers were predominantly neuropathic in origin, with no overt signs of deep infection, such as pus,

Article points

1. Non-healing ulcers in people with diabetes increase the risk of amputation and are costly to individuals and health services.
2. Xelma is a biological treatment that delivers synthetic extracellular matrix protein to the wound site.
3. The overall response to the treatment was favourable in the static diabetic foot ulcers reported here.
4. When other treatments fail, more expensive therapies are worth considering.

Key words

- Non-healing foot ulcer
- Synthetic extracellular matrix protein
- Xelma

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Page points

1. Ulcers in this case series had persisted for 10 weeks or more prior to treatment with a topical gel containing synthetic extracellular matrix protein applied directly to the ulcer bed, which was applied weekly for up to 12 weeks.
2. At the end of the treatment period, two ulcers healed completely, six ulcers remained un-healed but reduced in area; two ulcers did not improve during the study period.
3. The percentage of ulcer area improvement varied between individuals, from 6–100%, with a median percentage reduction of 55% by study end.

soft-tissue swelling or bone involvement. Appropriate off-loading of ulcerated feet was undertaken. Devices used to off-load participants' feet included temporary sandals and boots with modified insoles, total-contact casts, pressure-relieving heel devices for ambulating and heel lifts for resting. All ulcers had persisted for 10 weeks or more prior to treatment with the SECM protein gel. Ulcers had been measured, using the Visitrak planimetry system (Smith and Nephew, Hull; McCardle et al, 2005), on at least two occasions before inclusion in this treatment group and showed no evidence of reduction in area.

Xelma was applied using the single-use sterile dispenser provided by the manufacturer directly to the ulcer bed at weekly intervals at the diabetic foot clinic; Mepilex (Mölnlycke Health Care) was used as a secondary dressing. Participants were reviewed weekly for re-application, and for wound debridement as required, for up to 12 weeks (as per the manufacturer's instructions). When the community team was required to change a participant's dressing between visits to the diabetic foot clinic, instructions were provided to ensure that only the secondary dressing was changed and that the wound bed was not cleansed or irrigated, as this could disturb the wound-healing cascade.

If, during the course of treatment, the ulcer regressed, showed signs of clinical infection, increased exudate production or healed, treatment with the SECM protein gel was discontinued immediately.

Table 1. Clinical characteristics of participants at baseline and following 12 weeks' treatment with Xelma.

Participants (*n*)	9
Ulcers (*n*)	10
Average age (years)	52.1
Sex (*n*, male:female)	8:1
Participants neuropathic to a 10 g monofilament level (*n*)	9
Baseline	
Median ulcer area (cm^2 [interquartile range])	1.9 (1.0–3.5)
Mean duration of ulcer (weeks [range])	16 (10–220)
Post-treatment with Xelma	
Median ulcer area (cm^2 [interquartile range])	0.8 (0.0–3.6)
Ulcers healed (*n*)	2
Ulcers unhealed (*n*)	7
Amputated (*n*)	1

Results

Case series

Clinical characteristics of the participants are summarised in *Table 1*.

At the end of the 12-week treatment period, two ulcers had healed completely (the case histories of these two participants are reported below) and six ulcers remained un-healed but had reduced in area (the responder group, *n*=8). Two ulcers did not improve during the study period (the non-responder group, *n*=2); one of these ulcers became infected, resulting in a below-knee amputation.

The responder group experienced a reduction in the median ulcer area, down from 1.9 cm^2 (interquartile range [IQR] 1.0–3.5 cm^2) at baseline to 0.8 cm^2 (IQR 0.0–3.6 cm^2) at study end. The percentage of ulcer area improvement varied between individuals, from 6–100%, with a median percentage reduction of 55% by study end.

Case history 1

Ms S, a 33-year-old woman with type 1 diabetes, presented with a neuropathic ulcer on the plantar aspect of her right foot (*Figure 1a*). The foot showed evidence of a previous episode of Charcot foot. A number of toes had been amputated, resulting in biomechanical problems. Ms S' immunosuppressive drug regimen, for pancreas and kidney transplants 4 years previous, were also impairing wound healing. At the time of her referral to the diabetic foot clinic, Ms S' ulcer had persisted for approximately 5 years without previous specialist treatment.

A number of interventions were attempted during the year following Ms S' referral to the clinic, including total contact casting,

hyaluronic acid dressings (as described by Young and Heinrichs, 2003), treatment with Dermagraft (Smith and Nephew, Hull), and a short admission to hospital. Ms S' ulcer remained unhealed and treatment with Xelma was commenced, as describe in the Methods section. The progress of the ulcer is charted in *Figure 2*. At the end of the 12-week treatment period, the ulcer was fully healed (*Figure 1b*). Ms S remained healed at the time of writing.

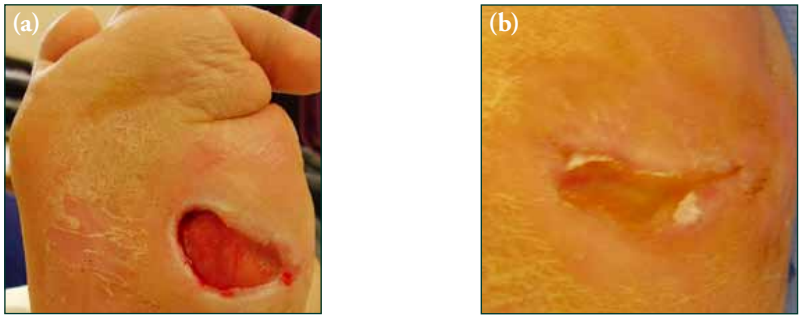

Figure 1. (a) Ms S' static diabetic foot ulcer prior to commencement of treatment with Xelma; (b) following 12 weeks of treatment, Ms S' ulcer healed.

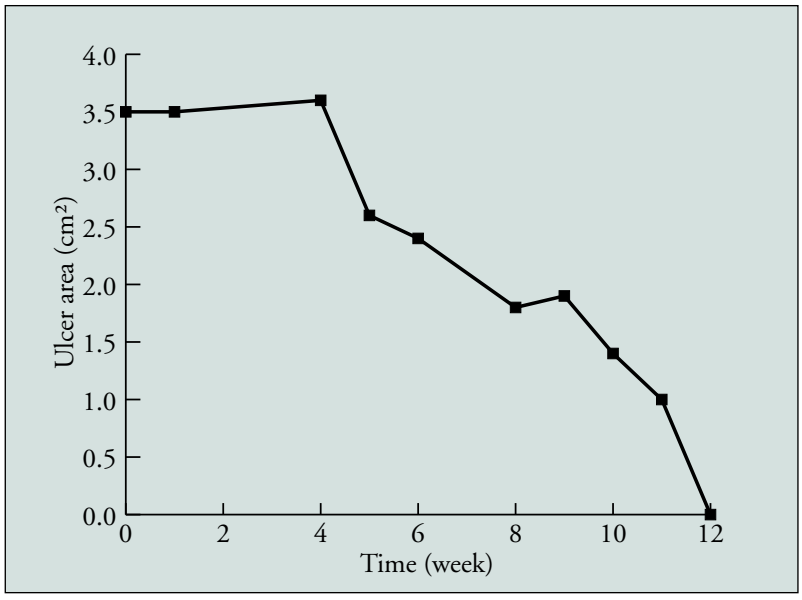

Figure 2. Graph of the area covered by Ms S' ulcer area during the 12 weeks of treatment with Xelma.

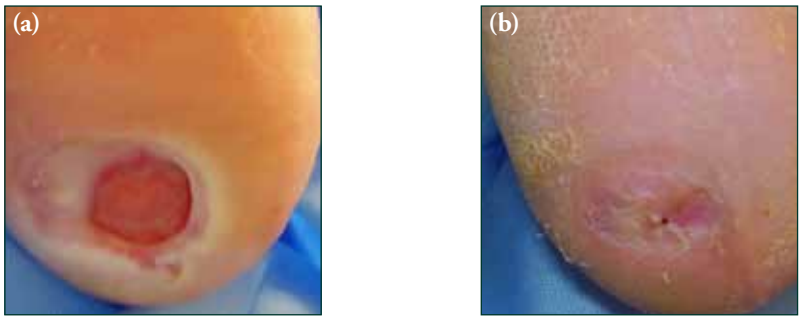

Figure 3. (a) Mr R's static diabetic foot ulcer prior to commencement of treatment with Xelma; (b) following 12 weeks of treatment, Mr R's ulcer healed.

Case history 2

Mr R is a 64-year-old man with type 2 diabetes who frequently uses a wheelchair due to significant motor and autonomic neuropathy. Mr R had been attending the diabetic foot clinic for 8 months with a static plantar neuropathic heel ulcer on his right foot (*Figure 3a*). A number of treatment modalities had been used to treat this ulcer, including larval therapy, various dressings (e.g. Hyalofil [ConvaTec, Gwent]), and pressure-relieving devices (e.g. Darko [Mobilis, Oldham]; Podud Boot [Procare, Guildford]; felt padding around the wound site).

Mr R appeared to be compliant with treatments, although an initial improvement in the ulcer was not maintained and the ulcer became static. Xelma was applied to Mr R's ulcer, as described in the Methods section. The wound quickly reduced in size, and healed within the 12-week treatment period (*Figure 3b*). However, 6 months after healing, Mr R's heel re-ulcerated and remained unhealed at the time of writing.

Discussion

Diabetic foot ulcers are often challenging wounds to heal, and each case needs to be assessed individually. The role of specialist diabetic foot clinics is to achieve rapid healing of foot wounds to reduce the risk of amputation associated with ulceration. However, even with appropriate off-loading, debridement and infection control under the care of a specialist diabetic foot clinic, and in the absence of vascular disease, a sub-set of diabetic foot ulcers fail to heal, and become static (Robson et al, 2000).

A number of biosynthetic advanced therapies have been licensed for use in the UK since the 1990s, such as Regranex (Janssen–Cilag, High Wycombe), Dermagraft (Smith

Page points

1. The synthetic extracellular matrix protein gel used here is a relatively expensive option, but the cost of the product must be weighed against the cost of a long-term non-healing foot ulcer, which is substantial.
2. Treatment with Xelma should be discontinued if an ulcer does not respond within the first 6 weeks of treatment.
3. The percentage of healing achieved during the study period could not be predicted from the baseline characteristics of the small group.
4. There is no single ideal wound dressing or treatment for diabetic foot ulcers, and novel therapies need to be considered when traditional wound care avenues have been exhausted.

and Nephew) and Vivoderm (Convatec, Gwent), but none have achieved regular use in the clinical setting (Young, 2007).

Xelma is a novel SECM amelogenin protein, designed to augment healing in static wounds (Mölnlycke Health Care, 2009). It is available in 0.5 mL and 1.0 mL individual syringes, coming in packs of six. A course of treatment for a foot ulcer typically requires 12 syringes, which, at £98 per 1.0 mL syringe and £56 per 0.5 mL syringe (Mölnlycke Health Care, 2009), makes Xelma a relatively expensive option. However, the cost of the product must be weighed against the cost of a long-term non-healing foot ulcer, which is substantial. Further, the manufacturer suggests that use of the product should be discontinued if an ulcer does not respond within the first 6 weeks of treatment (Mölnlycke Health Care, 2009). This can reduce the costs of therapy using this product, by limiting any ongoing use to those ulcers that respond within the first 6 weeks of treatment.

In this case series, two of the 10 ulcers failed to improve following 12 weeks of treatment. The other eight ulcers improved, but the percentage of improvement varied widely (healing between 6–100% of the original ulcer area by study end). The percentage of healing achieved during the study period could not be predicted from the baseline characteristics of the small group. However, the authors noted that those wounds that responded less dramatically during the 12-week treatment period did appear to continue to heal after the cessation of treatment with Xelma.

It should not be ignored that compliance with treatment regimens, including the wearing of off-loading devices or reducing ambulation, can be major factors in the progression to, or lack of, healing of diabetic foot ulcers (Armstrong et al, 2003). The authors found that the people included in this case series were eager to concord with the treatment requirements, and acknowledge that some of the success reported here may be attributable to this high level of concordance.

The authors conclude that Xelma was effective in the treatment of this series of static diabetic foot ulcers, successfully reducing the ulcerated area in eight out of 10 cases where other treatments had failed.

Conclusion

There is no single ideal wound dressing or treatment for diabetic foot ulcers. However, when traditional wound care avenues have been explored and the wound is not progressing, other options need to be considered, even those which might, at first consideration, appear expensive. ■

Conflict of interest statement

While Xelma for use in this study was provided by Mölnlycke Health Care, none of the authors or study participants were paid to perform the research reported here.

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