Management of diabetic foot ulcers with a TLC-NOSF wound dressing

• **Objective:** To evaluate the efficacy, tolerance and acceptability of UrgoStart Contact (Laboratoires URGO), a new wound dressing impregnated with NOSF, as an MMP regulator in the management of neuropathic diabetic foot ulcers.

• **Method:** A multicentre, pilot, prospective, non-controlled open-label clinical trial. Adult patients with type 1 or 2 diabetes mellitus, suffering from a grade 1A (Texas classification), uninfected neuropathic foot ulcer, 1–15cm^2 in size and duration 1–24 months (mean 6.7 ± 5.2 months) were included in the study. The primary endpoint was the relative reduction of the wound surface area (%) at the end of the study. Secondary end-points included rate of complete healing, tolerability and acceptability of the dressing. Wound dressing was regularly changed at the investigator's discretion according to the wound status and volume of exudates. Patients were followed up every two weeks for a twelve weeks period. At each visit, patients underwent clinical assessments and ulcer surface area was measured by planimetry and photographs.

• **Results:** Thirty-four diabetic patients with a neuropathic foot ulcer were included but only 33 cases were analysed, as data were completely lost for one patient. At baseline, mean surface area was 2.7cm^2. At the 12-week visit, the median surface area reduction was 82.7% (mean reduction 62.7 ± 49.9%) and in 10 of the 33 analysed patients (30%), the wound was healed. Only two out of the seven documented local adverse events were deemed to be related to the tested dressing. According to the nursing staff, acceptability was considered as very satisfactory, particularly conformability and ease of use.

• **Conclusion:** The use of the new UrgoStart Contact dressing, combined with offloading and debridement, looks effective to promote the healing process of the neuropathic diabetic foot ulcers, with a good tolerance and acceptability.

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neuropathic diabetic foot ulcers; nano-oligosaccharide factor; wound dressing; multicentre clinical trial

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Despite many therapeutic advances over the past decades, healing rates of diabetic foot ulcers (DFUs) remain low, impacting on patient quality of life and costs.[1,2] Mechanisms of faulty wound healing in diabetic patients are complex, related to both intrinsic and extrinsic factors.[3] Recently, excessive production of matrix metalloproteases (MMPs), coupled with reduced expression of the tissue inhibitors of MMPs, has been emphasised as a key abnormality within the neuropathic DFU.[3–7] This imbalance may result in excessive degradation of extracellular matrix components, as well as an inappropriate local inflammatory response.

A number of medical devices that could reduce MMP activity in the wound bed have been developed, such as collagen/oxidised regenerated cellulose (ORC, Promogran, Systagenix Health Care). However, the results of randomised clinical trials (RCTs) comparing ORC with an inert dressing in both chronic venous ulcers,[8] and in DFUs,[9] were ambiguous, as the percentage of complete wound healing was not significantly different in the Promogran-treated patients compared with the control group.

A new dressing with anti-MMP properties has now been developed, based on a lipidocolloid technology (TLC) impregnated with nano-oligosaccharide factor (NOSF, UrgoStart Contact; Laboratoires URGO). TLC-NOSF is a dressing made of carboxymethylcellulose particles spread in a petroleum jelly network and impregnated with NOSF over a non-woven non-occlusive soft-adherent polyester layer. On contact with exudate, hydrocolloid particles form a gel that interacts with petroleum jelly to make a lipidocolloid film that creates a moist environment within the wound. This environment is claimed to promote healing and prevents the dressing sticking to the wound. Moreover, the TLC allows

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NOSF to recover the whole wound and to interact with MMPs, neutralising their activity.

In vitro studies using a dermal equivalent model have shown that TLC-NOSF was able to significantly reduce the activity of some MMPs, such as gelatinases (MMP2 and MMP9) and collagenases (MMP1 and MMP8),[10–12] that are involved in the chronicity of the DFU.[5–7] Clinically, TLC-NOSF was demonstrated to be significantly more effective in reducing wound surface area of venous leg ulcers compared with ORC in a 12-week European multicentre RCT.[13] To our knowledge, no other RCT about efficacy of TLC-NOSF has been published in the peer-reviewed literature.

Based on the evidence of these previous clinical trials, this study aimed to conduct a pilot, open-label clinical trial to estimate the general performance (efficacy, tolerability and acceptability) of this TLC-NOSF matrix in the local management of DFUs.

Method

This study was an open-label, non-controlled, pilot study conducted in 14 French hospital departments involved in the management of DFU. All participating centres were chosen because they have expertise on the diabetic foot and manage DFUs in a similar way, including wound debridement and offloading.

Participants

From May 2008 to June 2009, adult patients (>18 years) with type 1 or 2 diabetes mellitus were included if they presented with neuropathic foot ulceration, as defined by a Michigan neuropathy screening instrument (MNSI) score >3.[14] The presenting DFU had to be:

- 1–15cm^2 in size
- Located on the forefoot or midfoot
- Classified as grade 1A, according to the Texas University classification system.[15]

In addition, more than 50% of the wound surface had to be covered by granulation tissue. Ischaemia was ruled out by presence of pedal pulses, an ankle brachial pressure index (ABPI) ≥0.8, a toe systolic pressure >40mmHg, or a $TcPO_2$ value >40mmHg. Wounds with any clinical signs or symptoms of infection were excluded.

All patients received detailed information on the study protocol and gave written consent before entering the study.

Study protocol

Included patients were followed for a maximum of 12 weeks, or until full closure, defined as complete epithelialisation of the wound without drainage.

After cleansing the wound with saline, the TLC-NOSF dressing was applied directly to the wound bed, without a secondary dressing. UrgoStart Contact dressing (Laboratoires URGO) is a non-absorbent contact matrix impregnated with NOSF developed from TLC. It is indicated for the management of moderate to highly exuding wounds. However, its lipid component makes it non-adherent and usable in the light exuding wounds we treated in this study.

Patients were assessed at the hospital centres every 2 weeks. At every follow-up visit, a clinical examination was undertaken by the investigating physician, together with a wound tracing on an acetate sheet and photographs of the DFU, for documenta-

Table 1. Patient characteristics at baseline (n=33)

Age (years)	60.5 ± 10.4 (60) [34–78]
Gender (female/male)	7 (21%)/26 (79%)
BMI (kg/m^2)	32.6 ± 6.8 (32.8) [19.0–44.9]
Type of diabetes:	
• Type 1	4 (12%)
• Type 2	28 (85%)
• Other type	1 (3.0%)
Duration of diabetes (years)	17.5 ± 11.6 (16) [1–45]
HbA1c (%)	7.5 ± 1.1 (7.6) [5.5–10.0]
Presence of pedal pulses	28 (85%)*
Duration of DFU (months)	6.7 ± 5.2 (5) [1–20]
Wound area (cm^2)	2.70 ± 2.39 (1.95) [0.46–8.63]
Granulation tissue (%)	88.9 ± 15.3
Surrounding skin:	
• Healthy	10 (30%)
• Hyperkeratosis	21 (64%)
• Maceration	4 (12%)
Offloading (%)	32 (97%)
Local treatment prior baseline:	
• Alginate/Hydrofiber	13 (39%)
• Greasy gauze/contact layer	12 (36%)
• Hydrocellular	4 (12%)
• Silver dressing	2 (6.1%)
• Hyaluronic acid	2 (6.1%)

Results are given as number, or mean ± SD (median) [range]; BMI=body mass index;
*In five patients, one or both pedal pulses were not palpable, in three patients ABPI was 0.8, and in another patient $TcPO_2$ was 47mmHg. The fifth patient had a toe systolic pressure of 190mmHg, likely due to medial arterial calcification; peripheral Doppler ultrasonography was normal

tion. If necessary, a hospital nurse sharply debrided the wound and, together with the investigator, regularly educated the patient about potential foot problems and the importance of offloading.

Between visits, local care was delivered at home by a private nurse, according to instructions from the investigating centre, written on a special leaflet. The investigating clinician decided the frequency of dressing change, according to the quantity of exudate and the wound status.

At each dressing change, hospital and private nurses assessed the tolerability and acceptability of the dressing on a 4-point scale, by scoring the following parameters:

- Ease of application and removal
- Pain and bleeding on removal
- Conformability to the wound bed
- Maceration of the wound
- Adherence of the dressing to the wound bed.

Throughout the study period, each patient received standard foot-care, including offloading. If offloading devices were already worn by the patients before they entered into the study, they were encouraged to continue. All patients but one agreed to wear the offloading device; devices were not standardised, but were those usually prescribed in each centre, mainly half-shoes, known as Barouk's shoes in France.

The primary endpoint of the study was the relative reduction of the wound surface area (%) at the end of the study; wound surface area was calculated from the tracings by centralised planimetry, using a digital pen and dedicated software (StatMed). Secondary endpoints included healing rate and mean healing time, tolerability and acceptability of the dressing.

Statistical analysis

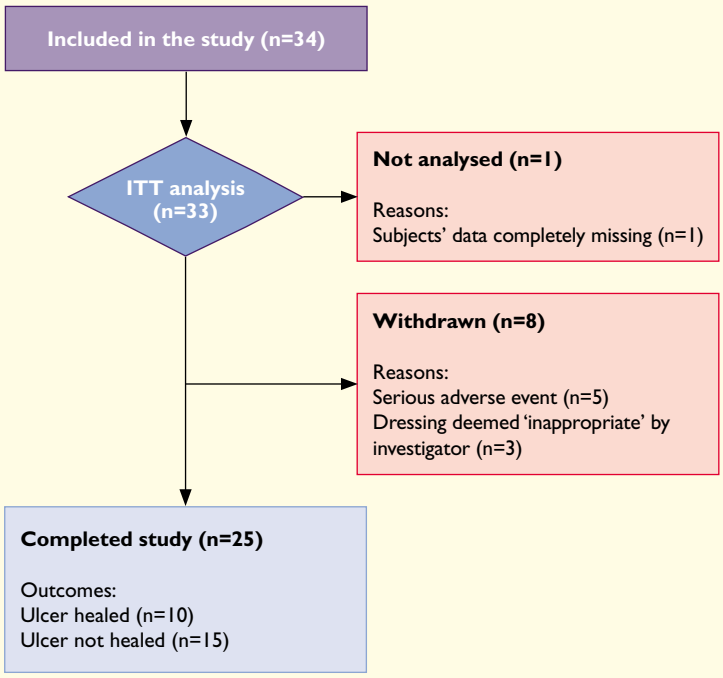
The statistical analysis was performed on an intention-to-treat (ITT) basis for both the primary and secondary endpoints of the study. If the patient withdrew or healed before the 12-week treatment period, the analysis took account of the last evaluation available (last observation carried forward).

Ethics

The study was conducted according to European Good Clinical Practices recommendations, the current French regulations and the principles of the declaration of Helsinki. The study was approved by the local French ethics committee (Comité de Protection des Personnes Sud-Mediterranée) and by the French Health Authority (AFSSAPS; registration no. 2008-A00060-55).

For ethical reasons, the investigating physicians were allowed to discontinue the study and change the dressing if they considered that the wound was aggravating and the TLC-NOSF dressing was no longer indicated; in these case, the dressing was recorded as 'inappropriate'. The type of dressing to replace UrgoStart was left to the investigator's discretion.

Fig 1. Flow of participants through the trial



Results

Thirty-four consecutive diabetic patients were included in the study. One patient was excluded from the ITT analysis due to completely missing data; therefore, the ITT analysis took account 33 patients; patient baseline characteristics are shown in Table 1. Each centre included between one and six patients. In five centres, a single patient was included, three centres included two patients, three others included three patients, two centres included four patients, and one centre included six patients.

As shown in the Fig 1, 25 patients (76%) completed the study according to the protocol (either full-closure or 12-week study period). At baseline, mean ulcer surface area was 2.7±2.4cm^2. Coverage of the wound by granulation tissue was 89±15% of the wound surface. At baseline, 97% (n=32) of the patients had an effective offloading system.

Healing

At the end of the study, 10 DFUs (30%) had healed, seven before the 12-week scheduled period and three on the week 12 visit. Median and mean (±SD) healing times were 58 days and 58.9±25.7 days, respectively. In 24 patients (73%), the wound

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Table 2. General adverse events

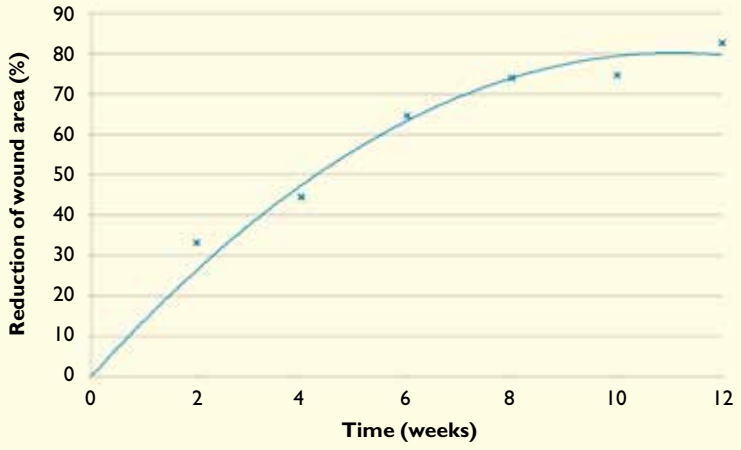
Description	Severity	Withdrawn	Outcome at end of study
Sepsis and acute renal failure	Serious (hospitalisation)	Yes	Unknown
Gastroenteritis	Serious (hospitalisation)	Yes	Cured
Worsening of the wound	Serious (hospitalisation)	No	Not resolved
Probable stroke	Serious (death)	Yes	—
Cellulitis	Serious (hospitalisation)	Yes	Cured
Skin and soft-tissue infection with pus discharge	Serious (hospitalisation)	Yes	Not resolved
Conjunctivitis after planed intervention for cataract	Serious (hospitalisation)	No	Cured but persistence of ocular smarting
Osteomyelitis of the foot	Serious (hospitalisation)	No	Cured
Hypoglycaemic coma	Serious (hospitalisation)	No	Cured
Bronchitis	Moderate	No	Cured
Tachycardia	Mild	No	Cured
Attack of acute gout (left hand)	Moderate	No	Cured

Table 3. Ease of application/removal of UrgoStart dressing

	Ease to apply	Ease to remove
Very easy	537 (56%)	857 (92%)
Easy	378 (39%)	66 (7.1%)
Difficult	36 (3.8%)	2 (0.2%)
Very difficult	6 (0.6%)	1 (0.1%)
Missing data	25	5

Each item was scored by nurses, using a 4-point scale, when dressing was applied (n=982) or removed (n=931) at home or during hospital visits

Fig 2. Median percentage reduction of ulcer area over the time



was considered as improving, according to the investigator's judgment, by week 12.

At week 12, the median and mean wound surface area were 0.47cm^2 and 0.92±1.47cm^2, respectively. Median reduction of the wound surface area was 82.7% at week 12, compared with baseline surface area, with a mean reduction of 62.7±49.9%. Median percentage reduction in ulcer surface area over the time is shown in Fig 2. In 14 of the 33 patients (42%), wound surface area decreased by more than 50% by week 4. In eight of those patients, the ulcer healed during the 12-week study period, while the surface area decreased by >95% in four of the six remaining patients.

Safety

Seven local adverse events were reported over the study duration. Two (maceration) were assessed as possibly or probably related to the dressing, while the five remaining adverse events were judged as not attributable to the dressing (were allergy to a topical cream, occurrence of a phlyctena, occurrence of a new ulcer, foot swelling and skin and soft-tissue infection).

Thirteen general adverse events occurred throughout the study, nine of them serious (Table 2), although none of these were considered to be related to the wound management or dressing by the investigators. In five patients, these serious adverse events led to treatment discontinuation. Four patients recovered with no after-effects and one had only minor local persistent trouble due to chronic conjunctivitis.

Finally, three other patients were withdrawn from the trial and switched to another dressing according to the investigator expertise, as the wound was considered to be not responding and the tested dressing

Table 4. Acceptability and tolerance of the TLC-NOSF dressing

	Bleeding on dressing removal	Pain on dressing removal	Maceration	Adherence to the wound	Exudation	Unpleasant odour
Absence	879 (95%)	887 (96%)	671 (73%)	887 (96%)	532 (58%)	864 (94%)
Mild	44 (4.8%)	0 (0%)	235 (25%)	37 (4.0%)	366 (40%)	54 (5.9%)
Moderate	2 (0.2%)	37 (4.0%)	15 (1.6%)	3 (0.3%)	17 (1.8%)	4 (0.4%)
Important	0 (0.0%)	3 (0.3%)	2 (0.2%)	0 (0.0%)	5 (0.5%)	0 (0.0%)
Missing data	6	4	8	4	11	9

Each item was scored by nurses, using a 4-point scale, when dressing was removed (n=931) at home or during hospital visits

Table 5. Conformability of the TLC-NOSF dressing to the wound

	Conformability
Very good	364 (40%)
Good	402 (45%)
Poor	128 (14%)
Very poor	7 (0.8%)
Missing data	81

Each item was scored by nurses when the dressing was applied (n=982)

no longer adequate. Overall, eight patients (24%) prematurely discontinued the study before the week 12 (Fig 1).

Tolerance and acceptability

In total, 982 applications of TLC-NOSF dressings were recorded, accounting for 2189 days of treatment, with 931 removals documented. An average of 2.5 dressings were applied per patient per week, equalling one new dressing every 2 days.

According to the nurses' opinion, application of the dressing was assessed as easy or very easy in 95.6% of cases and its removal in 99.1% (Table 3). Absence of bleeding or pain on removal was recorded in 95.0% and 95.7%, respectively (Table 4). Wound maceration and adherence of the dressing to the wound bed was judged as moderate or important in 1.8% and 0.3%, respectively (Table 4). Finally, conformability of the dressing when applied to the wound was considered as good or very good in 85.0% of cases (Table 5).

Discussion

The aim of this pilot, open-label clinical trial was to assess the overall performance (efficacy, acceptability and tolerance) of the TLC-NOSF wound dressing in grade 1A neuropathic DFUs.

In terms of efficacy, combined with good wound care, including offloading and regular debridement, use of the TLC-NOSF matrix was associated with a median relative reduction in the surface area of 82.7% (mean 62.7±49.9%) by the end of the 12-week follow-up period. Further, 30% of DFUs healed during the 12-week study period and 73% were considered to be improving.

The non-controlled design of this pilot clinical trial makes interpretation of the results difficult; however, these preliminary data look encouraging. An indirect comparison with the published data on DFU management has to undertaken very carefully, even if the characteristics of the wounds included in this trial and their prognostic indicators (size, duration, grade and absence of infection) were similar to those reported in other published trials.

Despite this, our results seemingly compare favourably with those from the literature. In a systematic review of 10 RCTs, Margolis et al. evaluated the healing rate of neuropathic DFUs treated with a control (gauze or a placebo).[16] The mean healing rate was 24.2% in 450 patients followed up for 12 weeks, and 30.9% for those (n=172) followed up for 20 weeks. All patients in the control groups received good standard wound care, similar to that given in our study. More specifically, the results of our study are similar to those obtained using ORC, another MPP inhibitor. In the study by Vin et al.[8] on non-infected chronic venous leg ulcers measuring between >2cm and ≤10cm at baseline, the median and mean wound reduction in ORC-treated patients were 54.4±10.9% and 82.4%, respectively. In a RCT comparing ORC and moistened gauze in the management of DFUs, Veves et al. showed a mean percentage of wound reduction of 64.5% in the ORC group.[9]

As wound protease activity is thought to have a detrimental effect on growth factors during the healing process,[17] and the TLC-NOSF matrix inhibits MMPs,[10–12] it is also interesting to compare the

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results of the present study with those on growth factor therapy in DFUs. Smiell et al. published a combined analysis of four randomised studies that evaluated the effects of a topical platelet-derived growth factor (PDGF) (becaplermin gel, Regranex) in DFUs.[18] Included ulcers were mostly small (median baseline size: 1.5cm^2) chronic, uninfected, full-thickness (category III/IV) ulcers, with a sufficient arterial blood supply; therefore, the inclusion criteria were comparable to those of the present study. After 20 weeks of treatment by platelet-derived growth factor (PDGF), the healing rate was estimated to be 50.2%, significantly higher than in the placebo group (36.3%; p=0.007).

Despite this, in the first study on PDGF, which involved 118 patients with neuropathic DFUs,[19] while the healing rate was 48% and 25% after 20 weeks of treatment in the PDGF and control group, respectively, this rate decreased to approximately 30% and 10% after 12 weeks of treatment. It is worth noting that this study enrolled diabetic patients with neuropathic ulcers similar to those of our study, except for a larger size (mean and median area 9cm^2 and 4.9cm^2 in the placebo group, respectively and 5.5cm^2 and 3.1cm^2 in the PDGF-treated group). Moreover, as in the present study, ulcers were sharply debrided and offloaded, as standard treatment protocol. Embil et al.[20] also conducted an open-label study to assess the efficacy of becaplermin in 134 chronic, uninfected, well-perfused, full-thickness (category III/IV) and superficial neuropathic DFUs. Mean ulcer area at baseline (2.71±2.30cm^2) was comparable to that in the present study and ulcers were offloaded and regularly debrided, if necessary. Becaplermin gel application resulted in complete healing in 57.5% of patients after 20 weeks of treatment, with a mean time to closure of 63 days.

Finally, in a more recent RCT involving 73 patients with grade 1A neuropathic DFUs,[21] the rate of wound closure with becaplermin was 28% after 12 weeks of treatment, with a mean healing time of 73 days. Despite the encouraging results from the studies of Steed[19] and Embil et al.,[20] this RCT would suggest using PDGF to heal neuropathic DFUs gives no decisive definite advantages over simpler and less costly approaches, such as dressings.

Anecdotally, our study confirms that percentage change in DFU surface area after 4 weeks of treatment is predictive of healing at 12 weeks, as shown by Sheehan et al.[22]

Regarding safety, two local adverse events were reported as possibly related to the tested dressing. This low incidence gives evidence for the good tolerance of the matrix, already reported in a previous trial on leg ulcers.[13] Therefore, the addition of the NOSF compound in the neutral TLC seems not to modify the tolerability of the neutral matrix, which has been reported as very satisfactory.[23] Serious adverse events were experienced by nine patients (27%), a percentage close to that reported by Embil et al. (22%) in becaplermin-treated patients,[20] and by Smiell et al.[18] in the combined analysis of the four randomised studies (24% in the PDGF-treated group, 25% in the placebo group and 28% in the group treated with good ulcer care alone). Moreover, as in the preceding studies, most of the serious adverse events were related to non-healing DFUs, or diabetic complications, and the majority were considered by the investigators as unrelated to the study dressing.

Finally, the dressing was well accepted by both nurses and patients, as its application and removal were judged easy and painless with a good conformability to the wound bed in the majority of cases.

Limitations

There are a number of limitations of this study. Notwithstanding its non-randomised, non-controlled, non-blinded design, this study included only a small number of patients, despite being a multicentre trial conducted in departments specialised in the management of DFUs. This specialisation could explain in part the difficulty experienced in recruiting patients into the study; those referred to specialised units generally have complicated DFUs, such as infected or ischaemia-associated wounds, while the protocol was aimed at the grade 1A, non-infected, non-ischaemic, superficial wounds. It might be surprising that our study tested TLC-NOSF wound dressing in superficial, mildly exuding ulcers, but these were chronic and recalcitrant, as shown by their long duration (median 5 months) and failure to respond to previous topical treatments. This suggests that these ulcers were stalled in a non-healing phase, possibly due to an excess of MPPs.

Another limitation of the study is a possible selection bias, despite including consecutive patients in the study, if they fulfilled the protocol criteria. Finally, as the wounds were not examined by the same observer in a single centre, with some subjective outcomes, and inter-rater reliability was not assessed, a judgment bias may be possible. Despite this, the investigators were part of an experienced staff, very homogeneous in their practice; moreover, at the initiation visit all members involved in the trial were trained.

Conclusion

This pilot clinical trial suggests that this new impregnated TLC-NOSF matrix (UrgoStart Contact) could be an interesting adjunct in the therapeutic strategy of these chronic wounds. It now remains necessary to consolidate these encouraging preliminary results with clinical data from a randomised controlled trial in patients with more complex and severe neuropathic DFU. ■