Optimal wound closure of diabetic foot ulcers with early initiation of TLC-NOSF treatment: post-hoc analysis of Explorer

Objective: In March 2018, the Explorer study, an international, double-blind, randomised controlled trial (RCT), established that adding a TLC-NOSF (UrgoStart Contact, Laboratoires Urgo, France) dressing to good local standard of care (SoC) significantly and substantially increases wound closure and reduces the healing time of neuroischaemic diabetic foot ulcers (DFU). Besides the TLC-NOSF treatment, the wound duration was the only other covariate that had an influence on the wound closure rate in the regression model used in the original study. The purpose of this work was to further document the impact of wound duration on the healing outcomes of the DFUs included in the Explorer study and to discuss complementary pragmatic observations on the TLC-NOSF effect.
Method: In this post-hoc analysis of the Explorer data, the wound closure rates by week 20 are reported for the global cohort (n=240, Intention-to-treat population) and for the treated (n=126) and control groups (n=114) according to DFU duration and location.
Results: For the combined group, wound closure rates decreased with the increase of wound duration at baseline (from 57% in wounds ≤2 months to 19% in wounds >11 months). Whatever the wound duration subgroups analysed, higher closure rates were reported in the TLC-NOSF group than in the control group. However, the maximal difference between the two treatments was reported in wounds with a duration of ≤2 months (71% versus 41%, 30 percentage points difference, Relative Risk 1.7, 95% Confidence Interval 1.1 to 2.8). Regarding wound location subgroup analyses, the outcomes were always in favour of the TLC-NOSF treatment, with closure rates ranging between 43% and 61% within the TLC-NOSF group, and between 25% and 40% within the control group.
Conclusion: This clinical evidence supports that treating DFUs with TLC-NOSF dressing and good SoC results in higher wound closure rates than with a neutral dressing and the same good standard of care, whatever the duration and the location of the treated wounds. However, the earlier the TLC-NOSF dressing is initiated in DFU treatment, the greater the benefits.
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diabetic foot ulcers • randomised controlled trial • sucrose octasulfate dressing • TLC-NOSF dressing • UrgoStart

Diabetic foot ulcers (DFU) are a serious complication of diabetes, which result from the development of lower limb neuropathy, most often associated with peripheral vascular disease (PVD).[1] DFUs are considered a major public health concern due to the high and growing prevalence of patients suffering from these wounds. At present, nearly half a billion people worldwide live with diabetes and this figure is expected to increase by 50% by 2045.[1] It is estimated that 19–34% of these patients will have a DFU during their lifetime.[2,3] The management of these chronic wounds requires special attention as they often lead to serious infection episodes and amputations which are correlated with a higher risk of mortality for patients.[4–8] Indeed, the occurrence of a DFU is a significant turning point in the history of patients with diabetes, as the survival of patients is estimated to be lower than those for several types of cancer, including prostate or breast cancer.[9] Until recently, no therapeutic tool added to adequate wound care and efficient offloading device had demonstrated any clear benefits in the management of DFUs.[10–12] No clinical evidence had supported the choice of one specific dressing over another in improving the closure rate of DFUs.[13–14]

However, in March 2018, a large, European, double-blind, randomised controlled trial (RCT), the 'Explorer' study, demonstrated for the first time that treating patients presenting with neuroischaemic DFU with a TLC-NOSF dressing (UrgoStart Contact, Laboratoires

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Urgo, France) significantly improves DFU outcomes compared with treating these wounds with a commonly used neutral contact layer.[15] The wound closure by week 20, the study primary outcome, was 48% in the TLC-NOSF group versus 30% in the control group (18 percentage points difference, adjusted odds ratio 2.6; p=0.002; intention-to-treat (ITT) population). Additionally, the estimated time-to-reach wound closure was reduced by 60 days (Kaplan Meier, p=0.029) due to the TLC-NOSF treatment, while the nature and incidence of adverse events were similar in both groups during the study period. The high level of evidence from this study and its substantial and consistent outcomes established the superiority of the benefits of the TLC-NOSF dressing[16] and supports its use in the management of DFUs, as recently recommended by the National Institute for Health and Care Excellence (NICE).[17] The effect of this treatment may be explained by its matrix metalloproteinase inhibitor (MMP) inhibition and angiogenesis properties,[18,19] as protease imbalance and poor tissue perfusion have been correlated with delay of the healing process in chronic wounds.[20–22]

Numerous factors are known to have an influence on DFU closure rate. The choice of the dressing is now, and for the first time, an additional one. In the Explorer study, the primary outcome was analysed with a binary regression model using six parameters as covariates. Besides the dressing treatment, the wound duration was reported to be the only other factor to significantly impact wound closure rate (adjusted odd ratio 0.3 for closure of wounds ≥6 months duration versus <6 months duration; p<0.0001).[15] Wound duration has long been reported as a risk factor affecting chronic wound closure prognosis.[23–25] Furthermore, recent publications still highlight the importance of an early detection, assessment and management of DFUs in order to improve closure rate and reduce the wound-associated complication risks such as infection or amputation.[26,27]

Due to the paucity of data available in the literature on neuroischaemic DFUs, we considered that it would be interesting to further document the relationship between wound duration and wound closure rate within the Explorer cohort. In addition, we propose to comment on the effect of the TLC-NOSF dressing in the various subgroups of patients categorised by wound location in response to health professionals' common interest in this issue. With this descriptive post-hoc analysis, we aim to offer complementary observations on the effect of TLC-NOSF.

Materials and methods

The Explorer cohort and the original clinical study

The detailed protocol and results of the Explorer study have been described in previous publications.[15,28] Therefore, in this article, we propose to summarise the main elements of its protocol and briefly describe the analysed cohort of patients.

The Explorer study was a European, double-blind RCT, aimed at demonstrating the efficacy of a TLC-NOSF dressing (UrgoStart Contact dressing) in the management of DFUs, compared with a control dressing (UrgoTul, Laboratoires Urgo), indistinguishable from the treatment dressing, over a treatment period of 20 weeks.

The UrgoStart dressing is a flexible contact layer composed of a polyester mesh impregnated with a lipidocolloid matrix containing sucrose octasulfate potassium salt (Technology Lipido-Colloid with Nano Oligo Saccharide Factor, TLC-NOSF). The potassium salt of sulfated oligosaccharides are known to have many biological activities such as inhibition of MMPs, interaction with growth factors and restoring their biological functions,[18,19] and the protease inhibiting and healing enhancer properties of the TLC-NOSF dressings have been established in chronic wounds such as DFUs, leg ulcers and pressure ulcers (PU).

In the original study, we calculated that 108 patients per group (216 patients in total) were needed to detect an 18 percentage points difference between the two groups with 80% power and an alpha risk of 5% (bilateral situation). Assuming a dropout rate of broadly 10%, we calculated that a sample size of 238 randomly assigned participants was required.

Adult patients with diabetes, referred for the management of a non-infected DFU, were recruited from 43 investigating centres across France, Spain, Italy, Germany and the UK, between March 2013 and March 2016. Glycaemic control, neuropathy and PVD of the patients were confirmed and critical severe ischemia was excluded. After a two week run-in period, 114 patients were randomly assigned to the control group and 126 to the TLC-NOSF group. A total of 37 patients (15%) dropped out during the treatment period of the study, without difference regarding their allocated group.

The 240 randomised patients were mostly male outpatients (mean age: 64.5, mean body mass index: 30.1kg/m^2) with type 2 diabetes (mean duration: 17.7 years) and hypertension (88%). Half of the global cohort already had complications related to diabetes (retinopathy 52%; nephropathy 41%; amputation history 61%; revascularisation history 48%). The most common DFU location was plantar (47%), and in the majority of cases, the wounds were superficial (81%), of usual area (median: 2.3cm^2), associated with hyperkeratosis (64%) and lasted for <6 months (median value: five months). Demographic characteristics and medical history of the randomly assigned patients, as well as their wound characteristics, were well balanced between the two groups at baseline. Throughout the whole study, good local care was provided to patients in both groups. Local care was aligned with DFU management guideline standards.[11,29,30] Patients received standardised offloading devices, to which they were highly adherent, reporting wearing the device 'every day' in 83% of the visits and 'as often as possible'

in 15%. Dressing changes and wound care were similarly performed two to three times per week, based on the clinical status of the wound (mean number of dressings: 3.1±1.8 per week). Surgical or mechanical debridement was performed in 86% of the visits and hyperkeratosis removal in 70% of them.

The primary outcome of the Explorer study was the proportion of patients with wound closure by week 20 in the ITT population. Wound closure was assessed by a local investigator and had to be confirmed at least 10 days after the first assessment of closure. The primary outcome was analysed with a binary logistic regression. Secondary outcomes and four sensitivity analyses, including a centralised blind review of the primary outcome by two experienced physicians not involved in the study, are reported in the original publication.[15]

The study protocol was approved by Ethics Committees in the related countries and the trial was conducted in compliance with the Declaration of Helsinki and the Good Clinical Practice guidelines. Every participant has signed an informed consent form. The trial was registered at ClinicalTrials.gov (NCT01717183).

Purpose and methods of the current analyses

The inclusion and exclusion criteria of the Explorer study aimed to select patients with neuroischaemic DFUs covering a large variety of characteristics. The original analysis was performed using a binary regression model including group (treatment or control), country, wound area (<5cm² or ≥5cm²), age (<70 years or ≥70 years), wound duration (<6 months or ≥6 months) and limb amputation history as covariates. However in the end, aside from treatment, wound duration was the only other factor to significantly impact on reaching wound closure in that model (adjusted odd ratio: 0.3 for closure of wounds ≥6 months duration versus <6 months duration; p<0.0001).

In this post-hoc analysis, the key questions were:

- How does wound duration impact wound closure rate in neuroischaemic ulcers?
- What were the wound closure rates reported according to wound duration distribution?
- Were higher wound closure rates reached with TLC-NOSF dressing, whatever the wound duration?
- Does the timing of the initiation of the TLC-NOSF treatment matter?
- What were the wound closure rates according to wound location?
- Were higher wound closure rates reached with TLC-NOSF dressing, whatever the wound location?

For these purposes, we used ITT population and reported the wound closure rates by week 20, as defined in the original study. Receiver operating characteristic (ROC) curve analyses were used to understand the prognostic potential of wound duration at D0 on complete closure by week 20. Quartile distributions of patients according to wound duration were determined in the global cohort, as in the groups of patients treated in the TLC-NOSF group and in the control group. Absolute differences of wound closure rates between groups and Relative Risks (RR) with their 95% Confidence Interval (CI) were calculated. In the Explorer

Fig 1. Examples of DFUs that had reached wound closure in the Explorer cohort. Patient 4170, a DFU of three-months' duration at initiation of the TLC-NOSF treatment (**a**). Patient 156, a DFU of four-months' duration at initiation of the TLC-NOSF treatment (**b**)

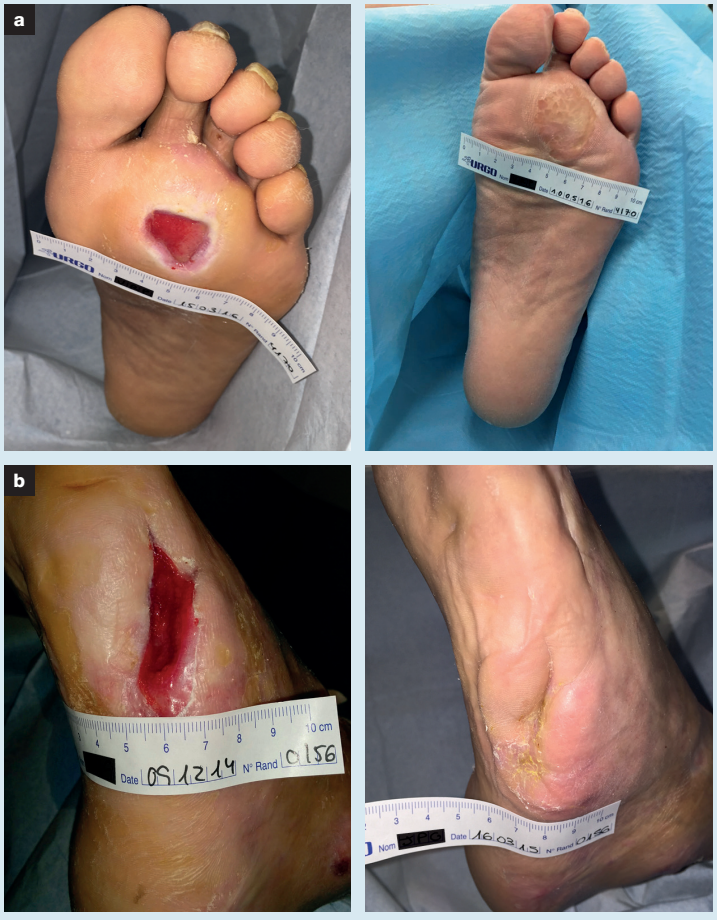


Fig 2. Predictive value of diabetic foot ulcer (DFU) duration for wound closure (receiver operating characteristic curve)

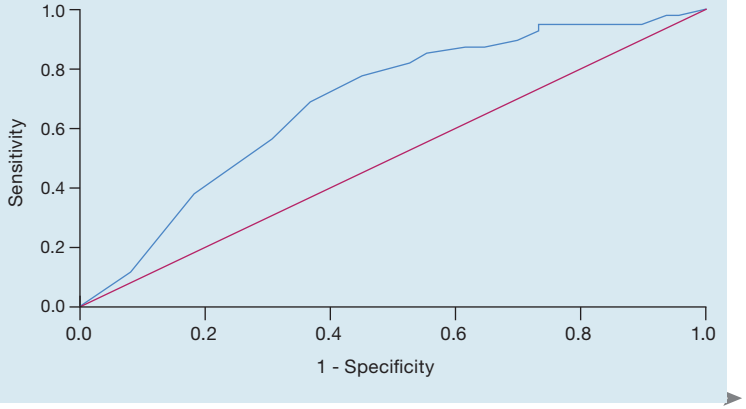


Fig 3. Wound closure rates by week 20 according to wound duration categories in the global Explorer cohort

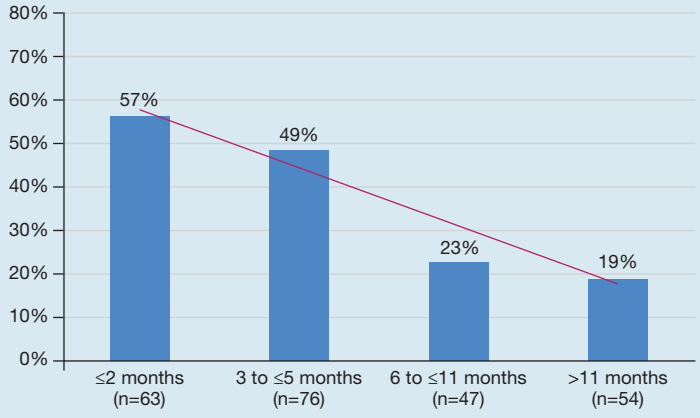
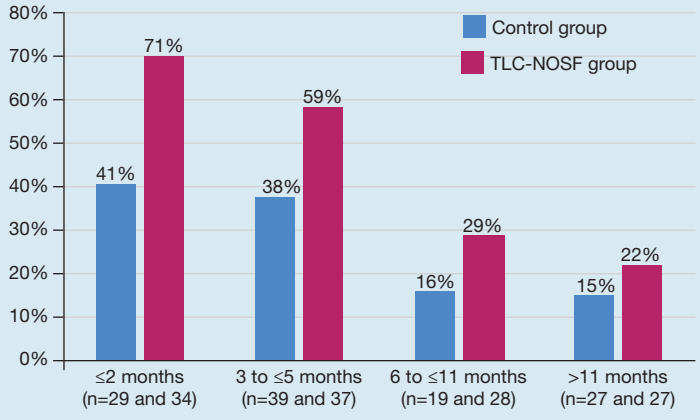


Fig 4. Wound closure rate according to wound duration categories and treatment



study, all DFU locations were allowed, except those on interdigital wounds (which are not suitable for accurate measurement of the wound area) and wounds on the Achilles tendon on the posterior part of the heel (to avoid confusion with PUs). In this post-hoc analysis, wound closure rates were reported for each wound location and all DFU locations other than plantar were pooled into one category for RR analysis, due to the low numbers of patients in most of the wound location subgroups. These analyses were merely descriptive and no formal statistical test has been performed as we were in a post-hoc situation and alpha risk inflation was very high due to multiple comparisons, thus precluding the relevance of any p-value. All calculations were performed using SPSS 18.0 software (IBM Inc., US).

Results

Impact of DFU duration on wound closure rate in the global Explorer cohort

In the Explorer cohort, the majority of patients had a DFU lasting for <6 months (139/240; 58%). Wound closure by week 20 was achieved in 73 (53%) of the 139 patients with a DFU lasting <6 months (Fig 1), but in only 21 of the 101 remaining patients (22%) who had a wound lasting ≥6 months. The older the DFU, the lower the closure rate (31 percentage points difference, 95%CI: −19 to 42).

Analysing the predictive value of wound duration at day zero on wound closure in the global Explorer cohort, the area under the ROC curve was 0.684 (95% CI: 0.615 to 0.752; p<0.001), indicating this parameter is an acceptable predictor of the outcome (Fig 2). According to this analysis, sensitivity and specificity of not observing closure by week 20 when the wound duration was of ≥6 months at baseline were respectively 0.792 (95%CI: 0.713 to 0.871) and 0.525 (95%CI: 0.442 to 0.608).

Categorising patients according to DFU duration quartiles (0–2 months, 3–5 months, 6–11 months and >11 months), wound closure rates continuously decreased with the increase of DFU duration at baseline (Fig 3). Wound closure was achieved in 36 (57%) of the 63 patients with a DFU lasting for ≤2 months, and in 10 (19%) of the 54 patients with a DFU lasting >11 months. This analysis by quartile duration confirmed that, regardless of the treatment received, the shorter the DFU duration, the higher the wound closure rate.

Impact of DFU duration on wound closure rate in the control and TLC-NOSF groups

When cross-analysing patients' distribution according to their DFU duration by quartiles and the treatment received, the absolute differences between wound closure rates were always in favour of the therapeutic strategy with the TLC-NOSF dressing, whatever the DFU duration was at baseline (Fig 4).

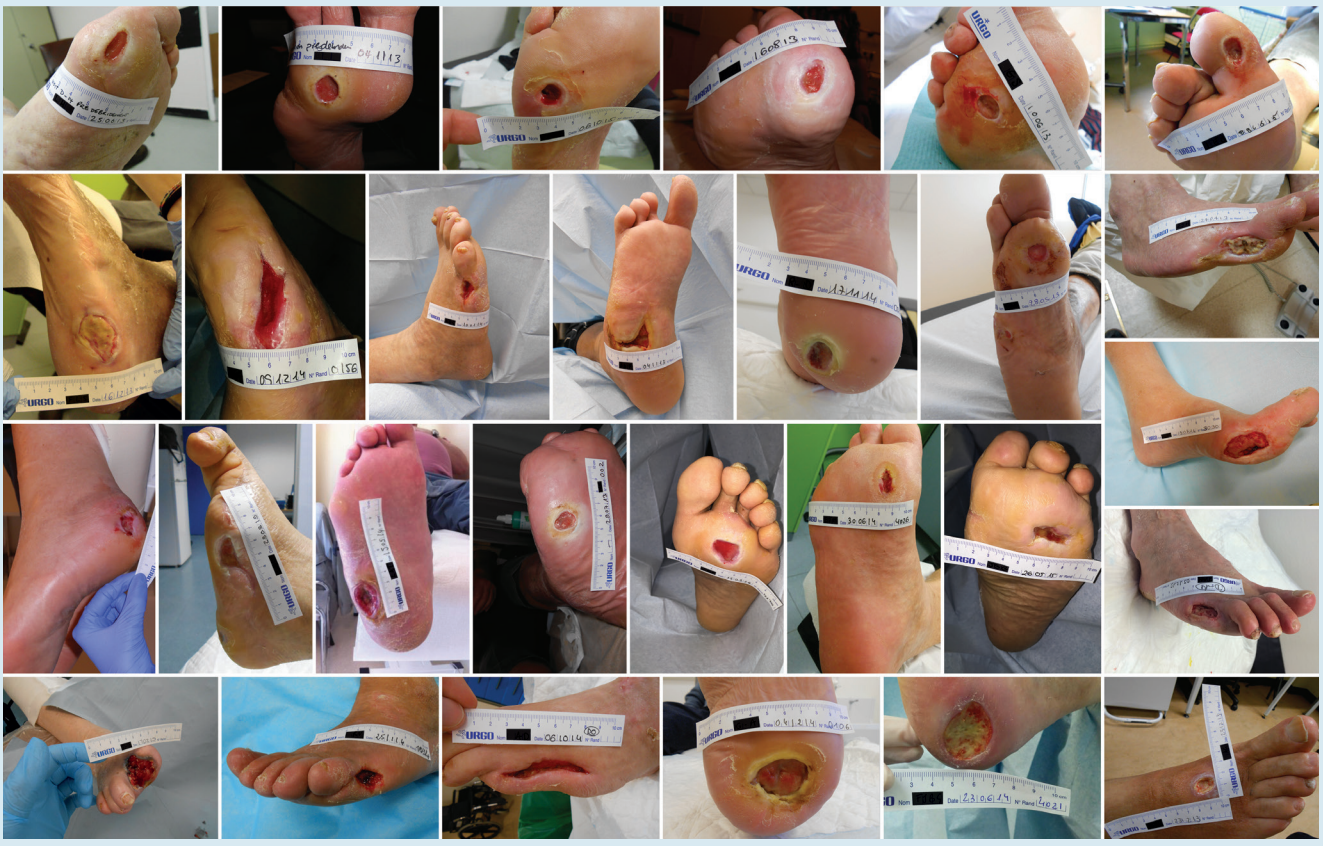
The RR for wound closure in the DFU duration quartile categories stayed within a relatively close range (1.7 for DFUs with a duration ≤2 months to 1.5

Table 1. Wound closure rates according to treatment groups and quartile categories of DFU duration

DFU duration categories	Control group (n=114)	TLC-NOSF dressing (n=126)	Absolute difference in percentage points	Relative Risk (TLC-NOSF/control) (95% CI)
≤2 months	12/29 (41%)	24/34 (71%)	30	1.7 (1.1–2.8)
3 to ≤5 months	15/39 (38%)	22/37 (59%)	21	1.6 (1.0–2.5)
6 to ≤11 months	3/19 (16%)	8/28 (29%)	13	1.8 (0.6–6.0)
>11 months	4/27 (15%)	6/27 (22%)	7	1.5 (0.5–4.7)

DFU—diabetic foot ulcer; TLC-NOSF—technology lipido-colloid with nano oligo saccharide factor; CI—confidence interval; data are expressed as n/N (%), unless otherwise indicated

Fig 5. The variety of the diabetic foot ulcers included in the Explorer cohort

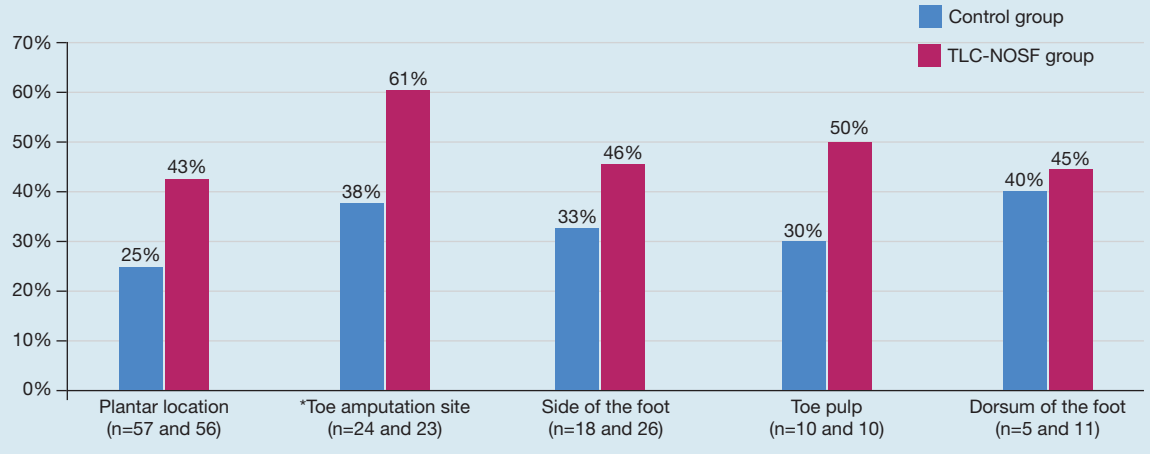


for DFUs with a duration >11 months). However the highest absolute difference was reported when the most recent DFUs were treated (Table 1). The 30 percentage points difference (71% versus 41%) in wounds with a duration of ≤2 months supports the initiation of the TLC-NOSF treatment as early as possible, for optimal impact.

Closure rates and DFU locations

As illustrated in Fig 5, a large variety of wounds have been included in the Explorer cohort. The wound locations, on the pulp of the toe, on the sole of the foot, on its side, on its dorsum, etc. were well balanced between the two groups at baseline, with plantar location being the most frequent location in both

Fig 6. Wound closure rate according to wound location and treatment



*The toe amputation site subgroup also included extensive wounds covering different locations

groups (47%) and the dorsum, the less frequent one (7%).

Analysing the subgroups of patients for each DFU location, higher closure rates were always reported in favour of the TLC-NOSF dressing, wherever the location sub-group considered (Fig 6).

The lowest wound closure rate with the TLC-NOSF dressing was reported in the plantar location subgroup (43% versus 25% in the control group, 18 percentage points difference) and the highest rate was reached in the toe amputation site subgroup (61% versus 38% in the control group, 23 percentage points difference). Within the control group, the lowest closure rate was also reported in the plantar location subgroup. The highest closure rate was reported in the dorsum subgroup (40%); however, as it only represents two patients out of five, this result must be taken with caution.

According to the RR analysis (Table 2), the beneficial effect of the TLC-NOSF treatment was consistent, wherever the location of the wound.

Table 2. Closure rates by week 20 according to ulcer location

DFU duration categories	Control	TLC-NOSF dressing	Absolute difference in percentage points	Relative Risk (95% CI)
Plantar	14/57 (25%)	24/56 (43%)	18	1.7 (1.0 to 3.0)
Other than plantar	20/57 (35%)	36/70 (51%)	16	1.5 (1.0 to 2.2)

DFU-diabetic foot ulcer; TLC-NOSF—technology lipido-colloid with nano oligo saccharide factor; CI—confidence interval ; data are expressed as n/N (%), unless otherwise specified

Discussion

The results from this post-hoc analysis based on the Explorer's data confirmed that, in the management of DFUs, wound duration matters. The TLC-NOSF treatment improved the wound closure rate compared with the neutral dressing, whatever the wound duration at baseline. However the sooner the treatment was initiated, the more substantial the outcome difference between the groups. The negative impact of wound duration on the closure of chronic wounds has long been established in the literature, whatever the local treatment evaluated.[23,24,31,32]

Chronic wounds, such as DFUs or leg ulcers, are characterised by impaired vascularisation, prolonged inflammation, increased levels of proteinases and defective cellular functions.[21] These defects, and in particular the excess of MMPs present in the wound tissue and fluid since the occurrence of the wound, create a deleterious environment that tend to impair the healing process and propel the wound into a vicious inflammatory circle.[20,21,33] The correlation between protease imbalance and wound delay has been notably well documented in patients with DFU. [20,22,34] Hence, inhibiting proteases has been suggested as a potential solution to enhance the healing process of chronic wounds.[20,21,35] The TLC-NOSF healing matrix is known to inhibit excess MMPs. The significant healing enhancer properties of the dressing may results from the restoration of impaired biological functions and the stimulation of angiogenesis through the migration and proliferation of endothelial cells.[15,18] The Explorer study was the first RCT that assessed and established the superiority of a dressing in the management of neuro-ischemic DFUs. Early initiation of the TLC-NOSF treatment resulted in the healing process finding its optimal trajectory, before the tissue environment of the DFU degrades any further.

Optimal healing outcomes with an early initiation of TLC-NOSF treatment had already been reported through previous studies in the management of chronic wounds.[36,37] In a pooled analysis of data from non-interventional studies, including several thousands of patients suffering from DFUs, leg ulcers or PUs, Munter et al. have reported shorter times-to-closure in real-practice when the TLC-NOSF dressing was prescribed as first-line treatment compared with when it was prescribed after using another primary dressing (70 days versus 104 days, p<0.001).[36] This result was consistent whatever the severity and the aetiology of the treated chronic wounds.[36] Increased wound area reductions and higher wound closure rates were also documented when the TLC-NOSF treatment was initiated in patients with wounds of shorter duration in two recent clinical trials conducted on the management of leg ulcers and reporting the consistent benefits of the dressing at different stages of the healing process (debridement and granulation stages) and until wound closure.[37]

Even based on a significant evidence of efficacy and supported by powerful and consistent clinical evidence, the implementation of new SoCs may still be challenging, due to the potential complexity of the procedure, or uncertainties regarding the cost-effectiveness of the treatment. The TLC-NOSF treatment is presented in the form of a dressing. Dressings have always been part of wound care, used in order to simply cover the wound and maintain a moist environment. Thus, the TLC-NOSF treatment integration in the global management of DFU does not require any additional workload, training or expertise from the health professionals, nor any more constraint for the patients.

Based on the clinical evidence from the Explorer study and the previous clinical trials conducted in DFUs and leg ulcers, the TLC-NOSF dressings have a similar safety profile to others dressings, and are judged easy to apply and well-accepted by both patients and health-care professionals.[15,18,37–41] Its cost-effectiveness has been previously demonstrated in the treatment of leg ulcers,[42] and according to NICE's estimation, using TLC-NOSF dressings to treat DFUs could be associated with a cost saving of £342 per patient after one year, and if 25% of people having treatment for DFUs were using TLC-NOSF dressings instead of a non-interactive dressing, the NHS in the UK could save up to £5.4 million each year.[17]

In the Explorer study, DFUs with a large variety of characteristics have been included, while the stratified randomisation insured well balanced groups at

baseline and the blinded caregivers provided the same standard of care in both groups throughout the 20-weeks' treatment period. Each sensibility analysis and subgroup analysis performed with the Explorer data confirmed the consistent superiority of the TLC-NOSF treatment compared with the control dressing, whatever the wound duration, location, area, age of the patients, or history of amputation. The beneficial outcomes reported in the Explorer study were also consistent with the previous clinical evidence gathered in the management of DFUs, with or without a PVD component, from non-comparative clinical trial and large non-interventional studies in real-practice.[36,41] In the Explorer study, some wounds presented with a location and characteristics representative of neuroischaemic DFU, and the confirmation of a vascular component of their aetiology could have seemed superfluous. For others, their appearance and plantar location could have mistakenly led to thoughts of purely neuropathic involvement, if their toe brachial pressure index (TBPI) and/or ankle brachial pressure index (ABPI) measurement had not been checked. According to recent literature, PVD, which is associated with lower probability of healing, longer healing times, higher probability of recurrence and greater risk of amputation, is now estimated to be present in a majority of patients with a DFU.[7,43–46] Early detection of DFUs and prompt referral by both the patient and health professional has been demonstrated to be crucial for optimal healing, reduction of amputation risk and of treatment cost.[5,25,47] First assessment by foot specialist comprehends in a holistic approach the identification of medical history and comorbidities of the patient, aetiology of the wound, biological and clinical exams, including an assessment of the foot perfusion which may lead to revascularisation if required, the investigation of local signs of infection, and the initiation of infection treatment if required, to avoid rapid deterioration of the DFU.[48] A patient-centric diagnosis should also identify the patient's lifestyle and individual needs. Optimisation of glycaemic control, offloading adherence, frequent maintenance debridement and appropriate selection of wound dressing constitute the SoC that influence the healing outcomes of DFUs.[48] Reinforcing and supporting the education of health professionals and patients to these and to the need for surveillance of DFUs and their complications is essential.[2,46–48] While new effective treatments and evidence-based treatment decisions can help to increase closure rate and gain time-to-closure in the management of these chronic wounds, additional efforts should be made to increase the early detection of DFUs and the prevention of their recurrence, notably by highlighting the importance of foot surveillance and hyperkeratosis removal.[2] Patients with diabetes may find it difficult to detect a new wound due to neuropathy and if a possible plantar wound location. They may also not fully understand the seriousness of their wound and the need to rapidly present it to a health professional. At the time of the initial visit, the wound duration, usually reported in months in the patient file, may not be very accurate and even underestimated. It is all the more crucial to implement a fast-track pathway for DFUs and encourage inclusive dialogue with the patient, their relatives and all health professionals involved, in order to ensure full consideration of the patient's needs and continuity of care.

Limitations

The main limitation of this post-hoc analysis is that it is merely descriptive, and there is an absence of a formal statistical test (no p-value was calculated). The effect of the TLC-NOSF treatment in the management of DFUs had been already established with the Explorer study's original publication. This work aimed to further document the consistency of the reported outcomes and to offer pragmatic observations to ease the implementation of this new cost-efficient treatment in current practice in order to achieve optimal benefits for patients and health-care systems.

Conclusion

This post-hoc analysis, based on the data from the Explorer study, confirms the consistency of the substantial benefits of the TLC-NOSF treatment in the management of DFUs, whatever the wound duration or location, and supports the early implementation of TLC-NOSF dressings as part of the global management of DFUs, as the sooner the initiation of the treatment, the more substantial the benefits in terms of wound closure. **JWC**

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Reflective questions

- Which type of wounds can be treated with the TLC-NOSF dressings?
- When the TLC-NOSF treatment should be initiated for optimal benefits?
- Which elements are included in the standard care of diabetic foot ulcers (DFU)?