Reviewing the evidence for using TLC-NOSF dressings

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In 2018, the now seminal Explorer Study was published in *The Lancet Diabetes & Endocrinology*, attracting the attention of many wound care professionals (Edmonds et al, 2018). The Study's findings swayed a number of healthcare facilities in Europe to include Technology Lipido-Colloid (TLC) Nano Oligosaccharide Factor (NOSF) technology in their clinical protocols for the management of diabetic foot ulcers (DFUs). Particularly, after TLC-NOSF was included in National Institute of Health and Care Excellence (NICE) medical technologies guidance where it was suggested that if TLC-NOSF was used in 25% of diabetic foot ulcer (DFU) patients, the NHS could save up to £5.4 million per year (NICE, 2019a). However, it was the inclusion in the International Working Group for the Diabetic Foot (IWGDF) guidelines later that year that resulted in a more noticeable reaction to this modality (IWGDF, 2019). This article gives an overview of the literature published that evaluated the use of TLC-NOSF dressings.

In 2018, the author published the article 'A Breakthrough in the Management of Neuro-Ischaemic Diabetic Foot Ulcers' in this journal (Galea, 2018), in which he discussed the findings of the double-blind randomized control trial, now commonly referred to as the Explorer Study (Edmonds et al, 2018), which assessed the efficacy of a Technology Lipido-Colloid–Nano-Oligosaccharide Factor (TLC–NOSF) dressing versus a control (TLC dressing without NOSF) dressing in patients presenting with neuro-ischaemic diabetic foot ulcers (DFUs). The study was conducted in five European countries across 43 hospital-centres with specialized diabetic foot clinics using a multidisciplinary approach. TLC, which was developed by Urgo Medical, comprises of a matrix containing hydrocolloid and lipophilic substances (McGrath et al, 2014). This technology allows the formation of a lipido-colloid gel when in contact with wound exudate to support moist wound healing (McGrath et al, 2014) leading to the promotion of the healing process. *In vitro* studies have shown that TLC aids the wound healing environment by enhancing proliferation of fibroblasts, which has the potential to stimulate extra cellular matrix production and encourage formation of granulation tissue (Bernard et al, 2005; Bernard et al, 2009; McGrath et al, 2014). NOSF is an innovative compound derived from the chemical oligosaccharide family that has demonstrated matrix metalloproteinases (MMP)-inhibiting properties and clinical efficacy and it has been shown that it promotes healing in leg ulcers, pressure ulcers, DFUs and recurring wounds (Richard et al, 2012; White et al, 2015). Apart from inhibiting MMP, this molecule has been shown to accelerate epithelial wound healing by increasing the bio-availability of certain growth factors which, in turn, has been demonstrated to have a crucial role in angiogenesis during the proliferative stage of wound healing (Edmonds et, 2018). Now let's take a look at other publications that evaluated this treatment modality.

Post-hoc analyses

In June 2019, a post-hoc analysis of the Explorer data was published *"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"* (Lázaro-Martínez et al, 2019). It was stated that *"regardless of the treatment received, the shorter the DFU duration, the higher the wound closure rate",* which suggests that the earlier the ulcer is treated by standard of care and an early adaptation of TLC-NOSF, as discussed in the Explorer study, the better the clinical outcomes. The authors concluded that there was a decrease of wound closure rates with the increase of the baseline ulcer duration; however, data was always in favour of the therapeutic strategy with the TLC-NOSF dressing, whatever the DFU duration was at baseline. The absolute difference in percentage points was noticeable in wounds with a duration of ≤2 months were there was a difference of 30% (71% versus

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"Consider the use of the sucrose-octasulfate impregnated dressing in non-infected, neuro-ischaemic diabetic foot ulcers that are difficult to heal despite best standard of care".

41%) between the study groups. While in patients with wounds that were >11 months, the difference was 7% (15% versus 22%), which represents an increase of 35% of healed patients. The authors' conclusion resonates these results by stating that the evidence supports that the earlier the TLC-NOSF and good standard of care is initiated, whatever the location and duration, the better the results and benefits (Lázaro-Martínez et al, 2019).

International guidelines, recommendations and pathways

International guidelines

After 2 years of intensive work by groups of experts of the International Working Group on the Diabetic Foot (IWGDF), Nicolaas et al put together a set of evidence-based documents, which are projected to serve as a basis for national guidelines (IWGDF, 2019). These guidelines are based on a series of systematic reviews on the prevention and management of diabetic foot disease, provide guidance in six chapters, namely:

- Prevention of foot ulcers in persons with diabetes
- Offloading foot ulcers in persons with diabetes
- Diagnosis, prognosis and management of peripheral artery disease in patients with a foot ulcer and diabetes
- Diagnosis and treatment of foot infection in persons with diabetes
- Interventions to enhance healing of foot ulcers in persons with diabetes
- Classification of DFUs (IWGDF, 2019).

In the intervention chapter, the guidelines suggest: *"Consider the use of the sucrose-octasulfate impregnated dressing in non-infected, neuro-ischaemic diabetic foot ulcers that are difficult to heal despite best standard of care".* Many thought this to be a weak/moderate recommendation, which might be attributed to the fact that currently there is only one randomized control trial (RCT) on TLC-NOSF of patients with DFU; however, it was probably taken in consideration due to the high level of the evidence. One could suggest that TLC-NOSF was looked at as a breakthrough treatment that showed positive outcomes in neuro-ischaemic DFUs as this is the first time that a particular dressing was recommended by the IWGDF.

The IWGDF in collaboration with D-Foot International have also produced a pathway for early referral which would reduce the risk of adverse clinical outcomes, such as delayed healing and increased risk of amputation (D-Foot International, 2018). This clear and simple pathway tries to tackle the long existing problem of late referral *"to help identify the most vulnerable patient by adopting a holistic approach in the patient's initial assessment, with comorbidities and the clinical assessment of the ulcer"* (Meloni et al, 2019). What is interesting is that use of TLC-NOSF is also suggested in the local wound care section (D-Foot International, 2018). This pathway can be adapted to conform with legislation in different countries and has already been tailored for use in the UK, Spain and Germany (Meloni et al, 2019).

Guidance in the UK and Europe

NICE is an independent public health body of the Department of Health in the UK. It is the prime source for evidence-based recommendations, including guidelines, technology appraisal guidance and pathways that have the aim to improve outcomes for people using the NHS and other public health and social care services (Atkin, 2019). NICE now also evaluates new medical devices in order to determine whether these should be adopted in practice and provide value for money to health services in the UK, their findings are then published in their Medical Technologies Guidance (MTG) section. In 2019, NICE gave its recommendations on using UrgoStart (a soft-adherent foam dressing with TLC-NOSF) to treat DFUs and leg ulcers and included a useful section on tools and resources to help clinicians put these into practice (NICE, 2019b). Some of the main statements that come from these recommendations are:

- UrgoStart dressings should therefore be considered as an option for people with DFUs or venous leg ulcers after any modifiable factors such as infection have been treated.
- Using UrgoStart dressings to treat DFUs is associated with a cost saving of £342 per patient after 1 year
- Potential cost savings mainly come from better healing with UrgoStart dressings. If 25% of people having treatment for DFUs use UrgoStart instead of a non-interactive dressing, the NHS may save up to £5.4 million each year.

It is of note that the NICE guidance considers TLC-NOSF in all DFUs rather than only in neuro-ischaemic.

NICE reviewed clinical evidence that supported the use of UrgoStart treatment range and demonstrated significant efficacy in reducing healing time both in DFUs but also in venous leg ulcers (VLUs). Apart from the Explorer

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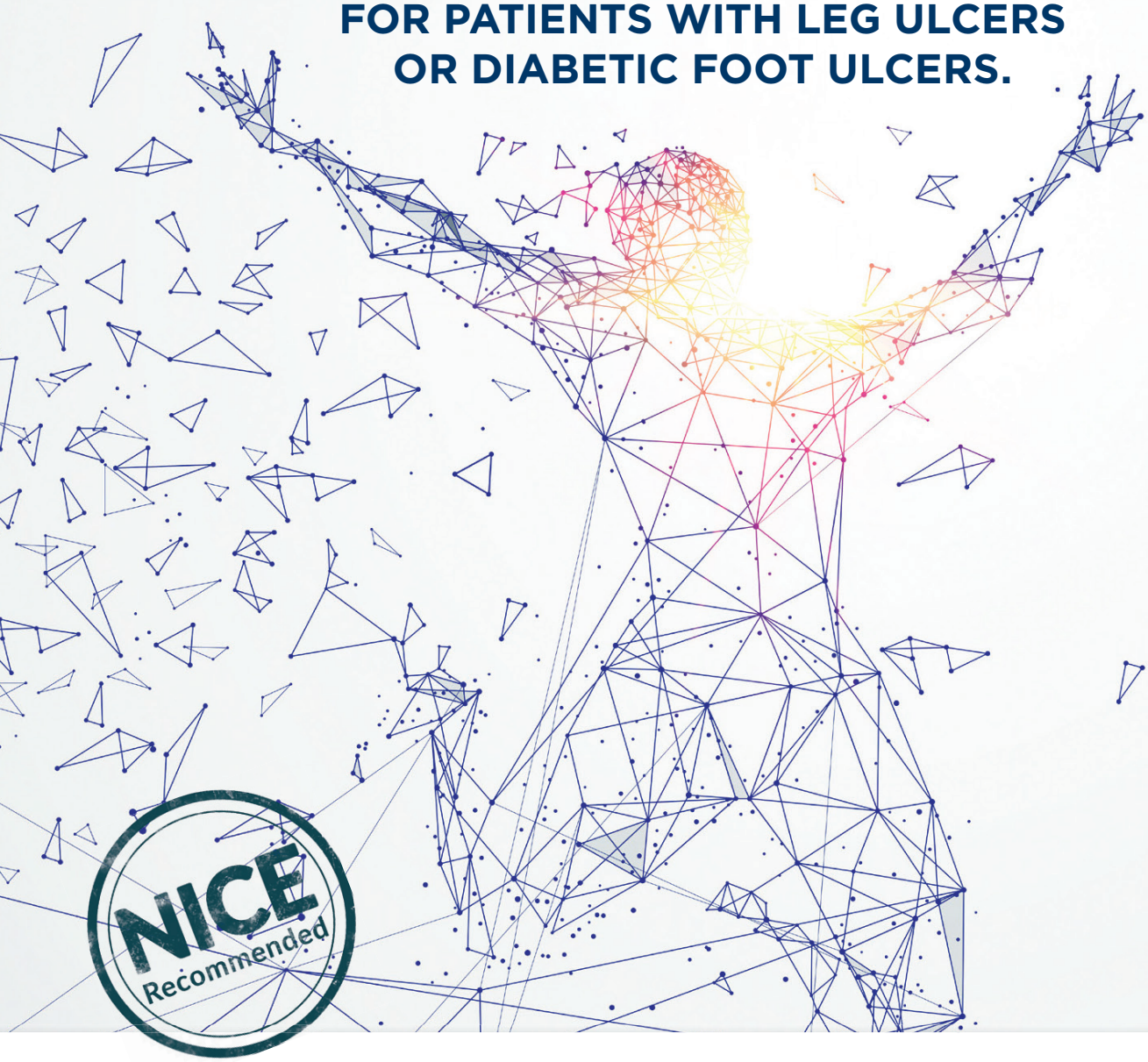

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NICE now recommends UrgoStart for the treatment of venous leg ulcers and diabetic foot ulcers.[1]

UrgoStart dressings are proven to reduce healing time for patients, improving patients' quality of life, and are associated with significant cost savings for the NHS compared to non-interactive dressings.[2–5]

Implement UrgoStart into your clinical practice for all of your patients with leg ulcers and diabetic foot ulcers. Initiate UrgoStart treatment from day 1 to maximise healing outcomes.[6]

1. UrgoStart for treating leg ulcers and diabetic foot ulcers, https://www.nice.org.uk/guidance/mtg42, January 2019; **2**. Münter KC, Meaume S, Augustin M, Senet P, Kérihuel J.C. The reality of routine practice: a pooled data analysis on chronic wounds treated with TLC-NOSF wound dressings. J Wound Care. 2017; 26(2): S4-S15. Erratum in: J Wound Care. 2017; 26(3): 153; **3**. Meaume S, Truchetet F, Cambazard F *et al*. A randomized, controlled, double-blind prospective trial with a Lipido-Colloid Technology-Nano-OligoSaccharide Factor wound dressing in the local management of venous leg ulcers. Wound Repair Regen. 2012; 20: 4, 500-5114; **4**. Meaume S, Dompmartin A, Lazareth I, Sigal M, Truchetet F, Sauvadet A, Bohbot S. Quality of life in patients with leg ulcers: results from CHALLENGE, a double-blind randomized controlled trial. Journal of Wound Care. 2017; 26: 4, 368-379; **5**. Edmonds M, Lázaro JL, Piaggesi A, *et al*. Sucrose octasulfate dressing versus control dressing in patients with neuroischaemic diabetic foot ulcers (Explorer): an international, multicentre, double-blind, randomised, controlled trial. Lancet Diabetes & Endocrinol. 2018 Mar;6(3),186-196; **6**. Rayman G, Edmonds M, Lázaro-Martínez JL, Martini J, Lobmann R, Bohbot S, Piaggesi A. Sucrose Octasulfate Dressing versus Neutral Dressing in Patients with Diabetic Foot Ulcer: Results of a Prospective, European, Randomised, Double-blind, Controlled Trial ('Explorer'). EWMA Krakow. May 10th 2018. Oral presentation.

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Study, the recommendations refer also to the other two RCTs that were conducted using the same technology, namely the Challenge Study (Meaume et al, 2012), a controlled, randomized phase 3 multi-centre double-blind clinical trial carried out in 45 centres in France, where greater reduction in wound surface area was achieved with the TLC-NOSF dressing than the neutral dressing (58.3% versus 31.6%, respectively, p=0.0021) (Meaume et al, 2012) and the Wound Healing Active Treatment (WHAT) study that was an open-label control trial conducted in 27 centres in the UK and France where patients with leg ulcers of venous or mixed origin were given 12 weeks of treatment with TLC-NOSF or collagen/oxidised regenerated cellulose (CORC) (Schmutz et al, 2008). The TLC-NOSF dressings reduced wound surface areas by 54.4% compared to 13.0% with the CORC dressings during the 12-week period (p=0.0286) (Schmutz et al, 2008).

This data is also supported by the Reality Study (Münter et al, 2017). Its authors analyzed pooled data from eight observational studies conducted in France and Germany to see if there is concordance with the RCTs that had compared control groups with TLC-NOSF dressings (UrgoStart) in order to determine if such results are also observed in the daily routine practice of managing patients with wounds. The authors assessed the time to complete wound closure and time to 50% reduction in pressure ulcer scale for healing score (the PUSH Score) using the Kaplan–Meier model (estimation of average time to closure) and subgroup analysis (depending on the Margolis severity score). The studies included a total of 10,220 patients with various chronic wounds. The overall closure rate was 30.8% and the average time to complete closure was 111 days with UrgoStart, compared to 210 days with other treatments. Again, the time to closure was shorter if UrgoStart was used as first-line rather than second-line treatment (Münter et al, 2017).

Conclusions

David Sackett explained evidence-based practice as *"the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients"* (Sackett et al 1996). The TLC-NOSF modality has behind it robust evidence, such as the Explorer Study, which led to the inclusion of TLC-NOSF in international and national guidelines and protocols in the management of patients suffering from diabetic foot disease.

The evidence confirms better healing times for chronic wounds when managed with TLC-NOSF. Faster healing due to the TLC-NOSF compound introduced in a good standard of care has been associated with a reduction of pain, discomfort, anxiety and depression. It has been found to improve the overall health-related quality of life of wounded patients by reducing emotional and social burden of these chronic wounds (Meaume et al, 2017).

Reduction of healing time needs to be one of most important objectives for wound care specialists, and the evidence points towards the need to have TLC-NOSF in your tool-box to be able to achieve this goal. WAS

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