Taking up the challenge — neuroischaemic diabetic foot ulcers

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ABSTRACT

Diabetic patients are at a high risk of amputations with most of these debilitating and life-threatening procedures being preceded by ulcers. Risk factors for the development of a foot ulcer in the diabetic patient include long diabetes duration, the presence of peripheral neuropathy, peripheral vascular disease, a history of any prior foot ulcer, and prior amputation. Moreover, recent medical forecasts have shown that neuroischaemic diabetic foot ulcers (DFUs) are on the increase worldwide. Health care professionals have a pivotal role to provide optimal management of DFUs, leading to a reduction in amputation rates. A TLC-NOSF (TLC-sucrose octasulfate) dressing has been shown in various clinical and observational studies that it may well play a key role in the local management of these wounds. The Explorer Study, conducted over six years in five European studies, has provided health care professionals with robust clinical evidence and it has been shown to have the potential to improve health outcomes and strengthen health systems by providing more efficient and cost-effective care.

Keywords: Chronic wounds, diabetic foot ulcers, neuroischaemic diabetic foot ulcers, TLC-NOSF, Explorer Study.

AIMS

The aims of this paper are threefold:

- To discuss the severity of the problem of diabetic foot ulcers (DFUs), mainly neuroischaemic and its implications, while exploring the complexity of these types of wounds.
- To evaluate the effectiveness of TLC-NOSF (Technology Lipido-Colloid — Nano OligoSaccharide Factor) in the management of chronic wounds through results of previously published randomised controlled trials (RCTs) and explore the methods and results of a recent RCT regarding the specific management of neuroischaemic DFUs.
- To assess the reactions regarding the Explorer Study and how the results may affect the way DFUs are managed.

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INTRODUCTION

Diabetes has been stated as the most common cause of non-traumatic lower limb amputations[1] and understanding mortality rates of these non-traumatic amputations sheds an appalling truth on the severity of the consequences of DFUs[2]. In his blog, David Armstrong aptly stated that “Perhaps the reason these sobering data are so sobering is because the 'hole' is a window on the 'whole'. In other words, the ulcer on the foot is likely a better predictor than any of the other end organ diseases because it is an amalgam of all of those complications in one place”[2]. The data referred to comes from a study conducted by Brennan *et al.*, who concluded that 1-, 2-, and 5-year survival rates were 80.80%, 69.01% and 28.64%, respectively[3], while it was also presented that people with a history of a DFU, have a 40% greater 10-year mortality than people with diabetes alone[4].

The facts about DFUs are really ‘sobering’ and these have highlighted the importance of acting as early as possible to avoid further complications, such as amputations. The earlier recognition of the high-risk foot and the timely treatment is said to save both the limbs and lives of diabetic patients[5]. DFUs require aggressive management involving a coordinated interprofessional team[5]. Appropriate management of DFUs cannot be overstressed, making it vital that clinicians are able to make informed, evidence-based decisions on the optimal management strategy[6].

THE NEUROISCHAEMIC DFU.

The annual population-based incidence of DFUs ranges from 1.0% to 4.1%, with a lifetime incidence that may be as high as 25% globally[7], with lifetime prevalence that is now estimated to be 19–34%[8]. The presence of peripheral vascular disease (PVD) is a strong predictor of non-healing foot ulcers[9], with diabetic patients being more at risk, as they have more severe disease in the distal arteries than those without diabetes[10]. This is mainly attributed to the issue that diabetes mellitus is concomitant with advanced atherosclerosis, with extended arterial wall calcifications and occlusions in lower limb arteries[11].

In the 1980s, it was suggested that neuropathy was the main factor responsible for foot ulceration in diabetes[12]; however, this is contrasted by more recent suggestions that there has been a noticeable increase of foot ulcers with underlying

PVD, with 52.3% of all ulcers being neuroischaemic, 36% neuropathic, and 11.7% purely ischaemic[13]. Neuroischaemia is the result of a combination of the effects of both neuropathy and ischaemia[14] and develops ulcers on the margins of the foot and toes, often located at sites of pressure from poorly fitted shoes[15] with pressure going unperceived due to the co-existing neuropathy[16]. It is not clearly understood why there is this increase of neuroischaemic and ischaemic ulcers in diabetic patients; however, it has been speculated that this is mainly due to better diagnostic methods and stricter diagnostic criteria as well as an increased awareness on the role of ischaemia to foot ulceration, leading to better systematic screening and diagnosis of PVD[6].

Management of the neuroischaemic foot has been identified as treating the underlying disease processes, relief of pressure (off-loading), debridement and hyperkeratosis removal, revascularisation when possible and management of inflammation and infection[17-19].

Although neuroischaemic ulcers have been established today as the most common DFUs, no clinical studies have ever assessed the performances of any device or procedure in a cohort of patients exclusively presenting with neuroischaemic ulcers[20] and, thus, no device or drug has demonstrated efficacy in neuroischaemic DFU treatment[21].

THE NEUROISCHAEMIC DFUs AND THEIR MICRO-ENVIRONMENT

The complexity of neuroischaemic ulcers has been recently explored in greater detail and issues such as fibroblast dysfunction, poor neo-vascularisation and high levels of metalloproteinases (MMPs) have been identified as prolonging the inflammatory process and delaying healing[22].

MMPs are part of the structurally related, protein-degrading enzymes that require calcium ions for structural conformation and zinc ions in their active site for function[23]. Their main purpose in wound healing is tissue degradation — they are usually produced in response to tissue injury and are not normally present in detectable levels in healing and non-injured tissue[24]. They degrade substances in the extracellular membrane (ECM) in order to facilitate migration of cells, deposition of new ECM as well as the development of new tissue[24]. The activity of MMPs is controlled at three basic levels: (1) at the gene level by transcriptional control; (2) at the molecular level by requiring factors to convert the proenzyme form to the active form; and (3) through local secretion of endogenous enzyme tissue inhibitors of metalloproteinases (TIMPs)[23,24].

MMPs appear to be elevated in chronic wounds and they may play a role in determining the chronicity of these wounds[25]. There is a significantly higher degradation of epidermal growth factor in chronic wounds and chronic wound fluid has 30-times greater MMP activity when compared with acute wound fluid[26].

Neovascularisation is important for wound healing as it involves the growth of new capillaries to form granulation tissue[27]. In diabetics, angiogenesis is decreased, with subsequent poor formation of new blood vessels and decreased entry of inflammatory cells and their growth factors[28]. Moreover, growth factors essential for wound healing have been found to be reduced in experimental diabetic wounds models[29]. Vascular endothelial growth factor (VEGF), which plays an important role in neovascularisation by stimulating angiogenesis as well as influencing wound closure and epidermal repair, granulation tissue formation, and the quality of repair, is also deficient in diabetic wounds as shown in an experimental and clinical model[30]. In chronic wounds, the formation and release of growth factors may be prevented. Growth factors may be sequestered and unable to perform their metabolic roles, or degraded in excess by cellular or bacterial proteases[31].

MANAGEMENT OF CHRONIC WOUNDS WITH A TLC-NOSF DRESSING

Sucrose octasulfate has been previously used in the management of gastro-duodenal ulcers[32]. However, 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[33,34]. Sulfated oligosaccharides have many biological activities such as inhibition of matrix metalloproteases and interaction with growth factors and restoring their biological functions[35-37]. Furthermore, nano-oligosaccharide factor (NOSF, sucrose octasulfate) is an innovative compound derived from the same chemical oligosaccharide family of sucrose octasulfate that has demonstrated MMP-inhibiting properties and clinical efficacy. It promotes healing in leg ulcers, pressure ulcers, DFUs and recurring wounds[33,34].

The efficacy of NOSF was tested *in vitro* and was shown that technology lipido-colloid (TLC)-NOSF significantly reduces the activity of MMPs, such as gelatinases (MMP2 and MMP9) and collagenases (MMP1 and MMP8) as well as stimulates the proliferation of fibroblasts, favouring wound healing and stimulating the formation of extracellular matrix by increasing collagen synthesis and hyaluronic acid synthesis[38-42]. Initially, two clinical studies testing TLC-NOSF (UrgoStart® — Urgo Medical) were conducted: The Wound Healing Active Treatment (WHAT) study[43], and the Challenge Study[44]. The WHAT study was an open, two-arm, parallel group, 12-week randomised trial conducted in 22 French hospital units and 5 UK wound specialised centres, with the intention to show non-inferiority or superiority of the NOSF matrix compared with a collagen-ORC dressing (PROMOGRAN™ Matrix Wound Dressing — Acelity). Both patient populations (117 patients were randomised: 57 and 60 patients in the NOSF matrix and control groups) had similar characteristics and venous leg ulcers (VLUs) at baseline. VLUs included in this clinical trial were considered as difficult-to-heal wounds: the mean age of the population was >70 years, ulcers were

present for 11 months on average and 61% were recurrent and the baseline mean ulcer area was superior by 10 cm^2. Regarding the primary objective (wound area reduction), the TLC-NOSF dressing reduced the wound surface area by 54.4% compared to 13.0% with the collagen-orc dressing during the 12-week period (p=0.0286). The healing rates were 5.5 mm^2/day with TLC-NOSF and 1.5 mm^2/day with collagen-orc (p =0.029). TLC-NOSF also reduced the size more wounds by >40%: 56.1% versus 35.0% with collagen-orc (p =0.022). Moreover, TLC-NOSF was found to have a better safety profile than collagen-orc. The Challenge Study was a controlled, randomised, phase 3, multi-centre, double-blind clinical trial. Overall, results clearly demonstrated a significant superiority and a sustained effect of the test dressing versus the control when considering relative and absolute wound area reduction over the eight-week treatment. The primary study outcome was the relative wound area percentage of wound area reduction, and the secondary objectives were absolute wound area reduction, healing rate, and percentage of wounds with >40% surface area reduction. One hundred and eighty-seven patients were randomly allocated to treatment groups. Screened patients were of both sexes, over 18 years of age (with no upper age limit), and were being managed for a VLU. Median wound area reduction was 58.3% in the TLC-NOSF dressing group and 31.6% in the TLC control group, with a difference: –26.7%; 95% confidence interval: –38.3 to –15.1%; p=0.002). All other efficacy outcomes were also significant in favour of the TLC-NOSF dressing group. Clinical outcomes for patients treated with the TLC-NOSF were shown to be superior to those patients in the control group (TLC without NOSF), suggesting a strong promotion of the healing process. Furthermore, a more recent publication reported the results from the same study assessing the performance and safety of TLC-NOSF in the local management of VLUs or mixed leg ulcers and determining its impact on the patient's health-related quality of life (HRQoL)[45]. In the HRQoL questionnaire (EQ-5D), the pain/discomfort and anxiety/depression dimensions were significantly improved in the TLC-NOSF group versus the control one (pain/discomfort: 1.53±0.53 versus 1.74±0.65; p=0.022, and anxiety/depression: 1.35±0.53 versus 1.54±0.60, p=0.037). The visual analogue scale score was better in the test group compared with the control group (72.1±17.5 versus 67.3±18.7, respectively). Acceptability and tolerance of the two products were similar in both groups.

Interestingly, a 2014 cost-effectiveness analysis derived from the clinical study 'Challenge' from the perspective of the German statutory health care system was performed using a decision tree model for a period of eight weeks[46]. In the treatment model, effect-adjusted costs of €849·86 were generated after eight weeks for treatment of the patients with VLUs with TLC-NOSF versus €1335·51 for the comparator, resulting in an effect-adjusted cost advantage of €485·64 for TLC-NOSF. In linear sensitivity analyses, the outcomes were stable for varying assumptions on prices and response rates, showing superior cost-effectiveness of the TLC-NOSF when compared with the similar neutral foam dressing without any active component (TLC without NOSF).

Moreover, an analysis by pooling the data from real-life observational studies on chronic wounds treated with TLC-NOSF wound dressings was conducted to determine whether the clinical trials' results translate into routine management of such wounds[47]. Pooled data from eight European observational studies (10,220 patients with various chronic wounds) were analysed to see if the clinical data from RCTs could be extrapolated to daily practice. Time to complete wound closure and time to 50% reduction in pressure ulcer scale for healing score using the Kaplan–Meier model (estimation of average time to closure) and subgroup analysis (depending on the Margolis severity score) were assessed.

In total, data from 10,220 patients were included, with 7903 leg ulcers (LUs), 1306 DFUs and 1011 pressure injuries (PIs) The overall closure rate was 30.8% [95% confidence interval (CI): 29.9–31.7%]. Overall, the average time to complete closure was 112.5 days [95% CI: 105.8–119.3] for LUs, 98.1 days [95% CI: 88.8–107.5] for DFUs and 119.5 days [95% CI: 94.6–144.3] for PIs. Based on a subgroup analysis of the French cohort, time to closure is substantially shorter for wounds treated with the TLC-NOSF dressing as a first-line intervention compared with those where it has been prescribed as a second-line intervention.

MANAGEMENT OF NEUROISCHAEMIC DFU WITH TLC-NOSF DRESSING

An initial pilot, prospective, multi-centre, non-controlled pilot, open-label trial of TLC-NOSF was conducted to test it in the management of DFUs[34]. The cohorts (n=34) included adults with a grade 1A (Texas classification) uninfected neuropathic foot ulcer 1–15 cm^2 in size with a duration of 1–24 months (mean 6.7±5.2 months). The primary endpoint was relative reduction in wound surface area (%). The results showed an 82% median surface reduction by week 12. Ten patients' DFUs (31.3%) had healed during this period[34]. These results seemingly compare favourably with those from the literature achieved after a systematic review of 10 RCTs. The investigators concluded that TLC-NOSF matrix (UrgoStart® Contact) could be an interesting adjunct in the therapeutic treatment of these chronic wounds.

The announcement made in 2013 by Urgo Medical of the pioneering Explorer Study into the efficacy of UrgoStart® Contact for treating DFUs was an exciting development in the management of these potentially devastating wounds[48]. It was established that there was a lack of firm evidence for the efficacy of dressings in the local management of DFU. The Explorer study was designed to make a major contribution to the evidence base in this field[48]. As such, it was expected that this study will bring a much-needed element of clinical consistency to the decision-making process in this challenging arena[48].

The Explorer Study[33] set out to test the efficacy of TLC-NOSF dressing versus a control (TLC dressing without NOSF) dressing in patients with neuroischaemic DFUs. This was the first study to assess the efficacy of a dressing in individuals with diabetes and confirmed neuropathy and PVD. The double-blind trial was conducted in five European countries across 43 hospital centres with specialised diabetic foot clinics using a multidisciplinary approach. The eligible 240 participants were inpatients or outpatients, aged 18 years or older with diabetes and a non-infected neuroischaemic DFU >1 cm^2 and of grade IC or IIC (University of Texas Diabetic Wound Classification system). The participants were randomly assigned using a computer-generated randomisation procedure to treatment with either a sucrose octasulfate wound dressing (UrgoStart®) or a control dressing without sucrose octasulfate (UrgoTul®) for 20 weeks. The two cohorts received the same standard of care for a two-week screening period before randomisation and throughout the 20-week trial and then were assessed two weeks after randomisation, then monthly until week 20 or occurrence of wound closure. The primary outcome, assessed by intention-to-treat, was the proportion of patients with wound closure at week 20. The noteworthy result of this study showed that wound closure occurred in 60 patients (48%) in the sucrose octasulfate dressing group versus 34 patients (30%) in the control dressing group (18 points difference, 95% CI 5–30; adjusted odds ratio 2·60, 95% CI 1·43–4·73; p=0·002). The assessed mean time to closure was 60 days (95% CI 47–75) longer in the control dressing group than in the TLC-NOSF dressing group. A greater reduction in absolute wound surface area and in relative wound surface area, and a faster wound re-epithelialisation wave were recorded in the TLC-NOSF cohort than in the control group by week 20. Also of note is that, in the TLC-NOSF group, 65% (46/71) of wounds with a duration of <6 months, closed compared to just 25% (14/55) of wounds ≥6 months. This strongly suggests that earlier adaption of UrgoStart®, in addition to accepted standards of care, for example, offloading, debridement, affords better results. The Explorers concluded that: "A sucrose octasulfate dressing is effective and safe, and its use is easy to implement by all health-care professionals. This dressing could form an important part of modern multidisciplinary management of neuro-ischaemic diabetic foot ulcers."

The use of several offloading devices was considered a limitation of this study. It was decided to use several devices rather than one specific device due to the practices of the 43 centres with different experience with and access to specific devices.

Reactions to the Explorer RCT have been very positive. Pr Fran Game (NHS, UK) was quoted as saying that "the results are certainly more encouraging than findings for most interventions that have been reported to date"[49]. However, Dr Edmonds emphasises that the findings are relevant to patients with neuroischaemic DFUs and not critically ischaemic feet, for which urgent revascularisation is required[49]. Furthermore, DFA stated that "Overall, the methodological rigour of this study really sets the standard for future wound dressing studies to achieve. With the quality of this study and its findings we dare say that the new International Guidelines (launched at the International Symposium on the Diabetic Foot in May 2019) will feature a new recommendation, something like 'to heal a neuroischaemic diabetic foot ulcer consider using a sucrose octasulfate impregnated dressing."[50]

CONCLUSION

Quality research needs to be translated into the clinical environment to ensure that health care professionals have sound clinical evidence upon which to base their clinical management. The application of evidence-based practice has been shown to have the potential to improve health outcomes and strengthen health systems by providing more efficient and cost-effective care. The Explorer Study has provided health care professionals who face the challenge of neuroischaemic DFUs in their daily practice with the evidence that can be a paradigm shift in how these hard-to-heal wounds are managed. It has been shown in the RCTs quoted, that, together with evidence-based standard of care, UrgoStart® is a safe and reliable option in the management of chronic wounds in general. Moreover, the Explorer Study has provided clinicians with robust evidence regarding the benefits and efficacy of UrgoStart® in the management of diabetic neuroischaemic foot ulcers.

DISCLAIMERS

The author is the International Medical Director of URGO Medical. The RCTs discussed regarding TLC-NOSF in this paper are suggested to be unbiased publications by independent authors.

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