A breakthrough in the management of neuro-ischaemic diabetic foot ulcers
Declaration of Financial Interests or Relationships

Speaker Name: Emilio Galea

I have the following financial interest or relationship(s) to disclose with regard to the subject matter of this presentation:

• I derive an income from URGO Medical associated with this presentation
Diabetic Foot Ulcers and Vascular Insufficiency: Our Population Has Changed, but Our Methods Have Not

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Based on an analysis conducted at the Diabetic Foot Clinic, King's College Hospital in London, there is some preliminary evidence that the prevalence of neuroischemic ulcers has been rising since the 1990s from approximately one-third of patients to over 50%, therefore becoming the most common etiology of DFUs.
Outcomes in Neuroischemic versus Neuropathic Diabetic Foot Ulcers

- DFU patients with ischemic or neuro-ischemic disease have a much higher probability of amputation
Standard of Care (SOC) of DFU is based on…

- **DEBRIDEMENT / HYPERKERATOSIS REMOVAL**
- **VASCULAR ASSESSMENT**
- **OFF-LOADING**
- **INFECTION MANAGEMENT**
- **EFFECTIVE LOCAL TREATMENT (EVIDENCE BASED MEDICINE)**
Conclusion

Neuroischaemic DFU is a life-threatening pathology with rapid rise in the prevalence and incidence which can affect a considerable proportion of diabetic patients. Currently, there is no satisfying treatment for this population, and any demonstration of wound healing improvement, even of modest in amplitude, might be regarded as a major therapeutic progress.
Suxrose octasulfate dressing versus control dressing in patients with neuroischaemic diabetic foot ulcers (Explorer): an international, multicentre, double-blind, randomised, controlled trial

Michael Sridhar, Iain G Littlejohn, Luziana Reis-Maia, Jacob N Timms, Jose-Maria Montes, Jean-Michel Seguier, Spain, Italy, Germany, and UK. 188 eligible participants were recruited or randomised aged 26 years or older with diabetes and a mean amputation risk index level greater than or equal to grade C or B. Participating centres were randomised to excitatory or control dressing. All ulcer centres had to be trained in macrolactone dressing, which had been shown to be effective in treating patients with nonhealing diabetic foot ulcers.

Methods: We did a randomised, double-blind clinical trial (dual-cam) to 19 hospitals with 119 diabetic foot ulcers treated in Spain, Italy, Germany, and the UK. Eligible participants were randomised on a 1:1 ratio to or control dressing, or macrolactone dressing. Participants were randomly assigned to macrolactone dressing with a computer-generated randomisation procedure. Forced randomisation of study centers and randomisation was used to ensure a 1:1 ratio in the two groups. Both groups underwent a similar treatment program, except for the dressing. Participants were assigned to a dressing arm after randomisation, which consisted of a single dressing with no further dressing. The primary outcome, assessed by a blinded reviewer, was percentage of patients who had no further dressing at 9 months.

Findings: Between March 2, 2015, and March 2, 2015, 188 participants were randomly assigned to macrolactone dressing (115) or control dressing (73). At 9 months, wound closure occurred in 72 participants (62.6%) in the macrolactone dressing group and 54 patients (74%) in the control dressing group (12 percentage points difference, 95% CI 0.01-0.27, p=0.047). In both groups, the mean difference was anesthetized in the 30-month follow-up. In both groups, 12 patients (9%) in the macrolactone dressing group and 10 patients (7%) in the control dressing group had no further dressing after 30 months. At 30 months, patients in the macrolactone dressing group were 2.5 times more likely to have no further dressing at 30 months than those in the control dressing group. Of 12 patients (10%) in the macrolactone dressing and 9 in 10 (74%) patients in the control dressing group (9 percentage points difference, 95% CI 0.01-0.27, p=0.047). In both groups, the mean difference was anesthetized in the 30-month follow-up. In both groups, 12 patients (9%) in the macrolactone dressing group and 10 patients (7%) in the control dressing group had no further dressing after 30 months. At 30 months, patients in the macrolactone dressing group were 2.5 times more likely to have no further dressing at 30 months than those in the control dressing group.

Interpretation: A macrolactone dressing significantly improved wound closure in nonhealing diabetic foot ulcers without adding safety after 10 weeks of treatment along with standard care. These findings suggest the use of macrolactone dressing as a local treatment for nonhealing diabetic foot ulcers.

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A HIGHLY ANTICIPATED CLINICAL TRIAL

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D.R. Shanahan


"...might be regarded as a major therapeutic progress."

"...makes this an ambitious, double-blind, randomised controlled trial."
The EXPLORER RCT in Europe

A European collaboration to build the Protocol: the Explorer Board

- France  Dr Jacques MARTINI  (Toulouse, France)
- Germany  Pr Ralph LOBMANN  (Stuttgart, Germany)
- Italy  Pr Alberto PIAGGESI  (Pisa, Italy)
- Spain  Pr Jose-Luis LAZARO MARTINEZ  (Madrid, Spain)
- UK  Pr Michael EDMONDS  (London, UK)

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- Dr Jean-Louis RICHARD  (†) (France) for his contribution in the conception of the trial
- Pr David ARMSTRONG (USA) and Pr Antonia PEREZ-MARTIN (France) for their contribution regarding the vascular part of the Protocol
The EXPLORER RCT

| Objective | To demonstrate that TLC-NOSF wound dressing is superior to the same dressing without TLC-NOSF, in the local treatment of neuro-ischaemic DFU |
| Design    | Randomised, double-blind, controlled trial in two parallel groups |
| Treatment arms | 2 treatment arms with a total of 240 patients |
| Indication | Neuro-ischaemic DFU |
| Primary endpoint | Complete wound closure* rate after 20 weeks of treatment with the studied wound dressings |
| Investigation center | 43 centres in France, Germany, Italy, Spain and the UK |
| Duration | 20 weeks treatment with 12 weeks follow-up |
| Aetiological treatment | Both arms were treated with standard of care, including off-loading |

*Complete wound closure is defined as 100% reduction in DFU surface area with full epithelialization of the target DFU, without exudates and has to be confirmed 2 weeks later (Wx+2) by the investigator.
What is the Mode of Action of the Treatment evaluated in the EXPLORER study?

Beyond the underlying aetiology of Diabetic Foot Ulcers, two key local factors significantly impair wound healing from the beginning.

1. A prolonged inflammatory phase with increased levels of Matrix Metalloproteinases (MMPs)\(^1\), which are present from the beginning of the wound and destroy essential extracellular matrix (ECM) components

2. An impaired neovascularisation\(^2\) leading to defective granulation tissue formation

→ In addition to the aetiological treatment such as off-loading, local treatment is needed to act on these local impeding factors.
What is the Mode of Action of the Treatment evaluated in the EXPLORER study?

UrgoStart is composed of a unique TLC-NOSF Healing Matrix (NOSF* impregnated in a TLC healing matrix), which acts locally in the wound, on 2 key factors significantly impairing wound healing:

1. Inhibition of excess Matrix Metalloproteinases (MMPs) \(^1\): KSOS has been shown to inhibit MMPs\(^1\). Since MMPs are the main enzymes implicated in the extracellular matrix (ECM) degradation, their inhibition will result in a reduction of proteolytic destruction of essential ECM components\(^2,3\).

2. Restoration of neovascularisation by reactivating vascular cells proliferation and migration \(^1,4\): KSOS has a unique structure that interacts with growth factors, particularly those acting on vascular cells \(^1,4\). Thus, it promotes proliferation and migration of vascular cells, restoring neovascularisation.

➔ UrgoStart, in addition to aetiological treatment, acts on 2 key local factors impeding wound healing. Therefore more wounds can be closed and the time to healing is reduced.

\(^1\)NOSF (Nano OligoSaccharide Factor) = KSOS (potassium sucrose octasulfate)

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The EXPLORER RCT. Diagram

Randomised, double blind, controlled and stratified trial, conducted in 2 parallel groups

1 Run-in period

- Patient consent
- Validation of inclusion and exclusion criteria
- Prescription of an off-loading system

Diagram:
- D-14
- D0
- MO

Legend:
- D0: Baseline assessment
- MO: Outcome assessment
The EXPLORER RCT. Diagram

Randomised, double blind, controlled and stratified trial, conducted in 2 parallel groups

1 Run-in period

- Patient consent
- Validation of inclusion and exclusion criteria
- Prescription of an off-loading system

2 Randomisation (D0) + Treatment period (D0 – W20)

- Δ Wound surface area D_{-14} vs W_0 ≤ 30%
- No infection (whatever wound, whatever limb)
- Off-loading compliance confirmed
- HbA1c ≤10% (if not available at D-14)
The EXPLORER RCT. Diagram

Randomised, double blind, controlled and stratified trial, conducted in 2 parallel groups

1 Run-in period
   - Patient consent
   - Validation of inclusion and exclusion criteria
   - Prescription of an off-loading system

2 Randomisation (D0) + Treatment period (D0 – W20)
   - Δ Wound surface area D-14 vs W0 ≤ 30%
   - No infection (whatever wound, whatever limb)
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   - HbA1c ≤10% (if not available at D-14)

3 Follow-up: Ancillary study
   - All the patients will participate to the follow-up study. In case of wound closure, at any time of the follow-up, the epithelialisation will be assessed two weeks after.
Neuro-ischaemic DFU with adequate arterial blood supply on the target limb, based on Ankle Brachial Pressure Index (ABPI) and the level of Toe or Ankle pressure (STBP or SABP) (mild to moderate ischaemia)

DFU Grade I-C or II-C (University of Texas Diabetic Wound Classification*)
- Grade I-C: ischemic, non-infected superficial ulceration
- Grade II-C: ischemic, non-infected ulcer that penetrates to tendon or capsule

RESULTS
60% more DFUs healed by 20 weeks were observed in the TLC-NOSF group compared to an advanced neutral dressing.

Wound closure: Defined as 100% epithelialization with no drainage and confirmed two weeks later by the investigators.
TLC-NOSF shortened the mean time to closure by 60 days.

Mean time to closure (days)

Data are given as mean ± SE (95% CI). Median value are not given as the control group did not reach 50% of wound closure.

Estimation is limited to the largest survival time if it is censored. Confirmed closure population.
“THE SOONER, THE BETTER”

73%
More

Wounds closure when wound duration is less than 2 months

Percentage of Wound Closure by Week 20

Wound closure: Defined as 100% epithelialization with no drainage and confirmed two weeks later by the investigators.
CONCLUSION (Explorer study)

Treating neuro-ischaemic DFU with TLC-NOSF leads to:

✓ A significant superiority on wound closure rate: 18 pts difference vs. control
✓ 60% more patients healed with TLC-NOSF treatment vs. a neutral dressing
✓ the sooner the treatment is used, the greater the results
✓ A significant reduction of time to closure: 60 days
✓ Positive outcomes in all sub-groups (duration/surface/location of the wounds)
✓ A highly favorable benefit/risk ratio
HOW TO IMPLEMENT TLC-NOSF IN YOUR DAILY PRACTICE

«Sucrose octasulfate dressing could be considered as the new standard of care» according to the Lancet position.

✓ Neuroischemic DFUs / All DFUs??
✓ First-line treatment until wound closure
PATHWAY FOR DIABETIC FOOT ULCERATION

FPT: Foot Protection Team; MDFT: Multidisciplinary Foot Team

TLC-NOSF included in >25 protocols in Europe
THANK YOU FOR YOUR ATTENTION