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Quality of life in patients with leg ulcers: results from CHALLENGE, a double-blind randomised controlled trial

***S. Meaume**,[1] MD, Dermatologist and Geriatrician, Head of Geriatric Department and Wound Care Unit; **A. Dompmartin**,[2] MD, Dermatologist; **C. Lok**,[3] MD, Head of Dermatology Department; **I. Lazareth,**[4] MD; **M. Sigal**,[5] MD, Dermatologist, Head of Dermatology Department; **F. Truchetet**,[6] MD, Head of Dermatology Department; **A. Sauvadet**,[7] PhD; **S. Bohbot**,[7] MD**; On behalf of the CHALLENGE Study Group**

Corresponding author e-mail: sylvie.meaume@rth.aphp.fr

1 Rothschild University Hospital, Paris, France. **2** Dermatology Department, Clemenceau University Hospital, Caen, France. **3** South University Hospital, Amiens, France. **4** Department of Vascular Medicine, Saint-Joseph Hospital, Paris, France. **5** Victor Dupouy Hospital, Argenteuil, France. **6** Head of Dermatology Department, Beauregard Hospital, Thionville, France. **7** Clinical Research Department, Laboratoires URGO, Chenôve, France.

Quality of life in patients with leg ulcers: results from CHALLENGE, a double-blind randomised controlled trial

Objective: We recently showed the superiority of a matrix metalloproteinase (MMP) modulating dressing (foam impregnated with NOSF, nano-oligosaccharide factor) compared with a lipidocolloid matrix (TLC) control dressing in median wound area reduction (WAR). Here we report the results from the same study assessing the performance and safety of TLC-NOSF in the local management of venous leg ulcers (VLUs) or mixed leg ulcers and determining its impact on the patient's health-related quality of life (HRQoL).

Method: A superiority randomised double-blind controlled trial was conducted on patients presenting with a non-infected leg ulcer (VLUs or mixed leg ulcers) of predominantly venous origin (ABPI >0.8), with a surface area ranging from 5 to 50cm^2 and a duration of 6 to 36 months. Patients were randomly allocated to either the TLC-NOSF matrix foam (UrgoStart) dressing group or to the neutral TLC foam dressing group (UrgoTul Absorb). All received appropriate compression therapy and the wounds were assessed blindly (clinical examination, wound area tracing and photographic record) every 2 weeks for a period of 8 weeks, or until complete closure. A secondary endpoint, described here, was the patient's HRQoL, documented by the patient, through the EuroQol 5D tool (EQ-5D) questionnaire and visual analogue scale (VAS).

Results: In total, 187 patients were randomised to either the TLC-NOSF group (n=94) or the control dressing group (n=93). The two groups were well balanced at baseline with regard to wound and patient characteristics. 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 VAS score was better in the test group compared with the control group (72.1±17.5 versus 67.3±18.7, respectively), without reaching significance (p=0.072). Acceptability and tolerance of the two products were similar in both groups.

Conclusion: The double-blind clinical trial has demonstrated that the TLC-NOSF matrix dressing promotes faster healing of VLUs and mixed leg ulcers and significantly reduces the pain/discomfort and anxiety/depression experienced by the patients. These results suggest that acceleration of VLU healing could improve the HRQoL of the patients and reduced the emotional and social burden of these chronic wounds.

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venous leg ulcer • matrix metalloproteinase modulator • quality of life • randomised controlled trial • TLC-NOSF matrix dressing

Venous leg ulcers (VLUs) are estimated to affect 0.63–1.9% of the population.[1] The prevalence increases with age[2] and the recurrence rate is reported to reach 70% within three months of wound closure.[3,4] Despite the improvement of standard of care, including consistent compression therapy of the limb, debridement, infection control and local management with dressings ensuring a moist environment, wound healing of VLUs remians a challenge for the multidisciplinary team in charge.

Recent work in the UK has shown the resources required to manage leg ulcer and associated comorbidities cost the NHS £1.94 billion in 2012/2013.[5] Beyond cost burden, patients presenting with leg ulcers usually suffer from important health-related quality of life (HRQoL) impairments. These are defined as 'the functional effects of an illness and its consequent therapy upon a patient, as perceived by the patient'.[6] According to a recent review of 23 studies, chronic VLUs impact negatively on all areas of daily living.[7] Patients endure restricted mobility, anxiety, depression[8–11] and 17–65% of patients report severe or continuous pain.[12] Guidelines, as well as health professionals recognise the critical need to address, with the patients, the pain and HRQoL issues along with the clinical wound healing outcomes.[4,13] However, to date, it seems that such HRQoL issues receive inadequate attention during consultations and are only infrequently assessed in the clinical trials evaluating wound treatments.[7]

***S. Meaume**,[1] MD, Dermatologist and Geriatrician, Head of Geriatric Department and Wound Care Unit; **A. Dompmartin**,[2] MD, Dermatologist; **C. Lok**,[3] MD, Head of Dermatology Department; **I. Lazareth**,[4] MD; **M. Sigal**,[5] MD, Dermatologist, Head of Dermatology Department; **F. Truchetet**,[6] MD, Head of Dermatology Department; **A. Sauvadet**,[7] PhD; **S. Bohbot**,[7] MD**; On behalf of the CHALLENGE Study Group**
Corresponding author e-mail: sylvie.meaume@rth.aphp.fr
1 Rothschild University Hospital, Paris, France. **2** Dermatology Department, Clemenceau University Hospital, Caen, France. **3** South University Hospital, Amiens, France. **4** Department of Vascular Medicine, Saint-Joseph Hospital, Paris, France. **5** Victor Dupouy Hospital, Argenteuil, France. **6** Head of Dermatology Department, Beauregard Hospital, Thionville, France. **7** Clinical Research Department, Laboratoires URGO, Chenôve, France.

Table 1. Analysis of the primary end point of the CHALLENGE randomised controlled trial

		TLC-NOSF (n=93)	(TLC n=94)	p-value
Relative WAR (%)	mean±SD	45.2±47.9	21.4±81.0	0.002
	median (range)	58.3	31.6	
Absolute WAR (cm²)	mean±SD	6.9±11.4	2.5±11.9	0.003
	median (range)	6.1	3.2	
Healing rate (mm²/day)	mean±SD	13.32±24.56	4.54±23.20	0.005
	median (range)	10.83	5.15	

WAR–wound area regression; TLC-NOSF–lipido-colloid nano-oligosaccharide factor

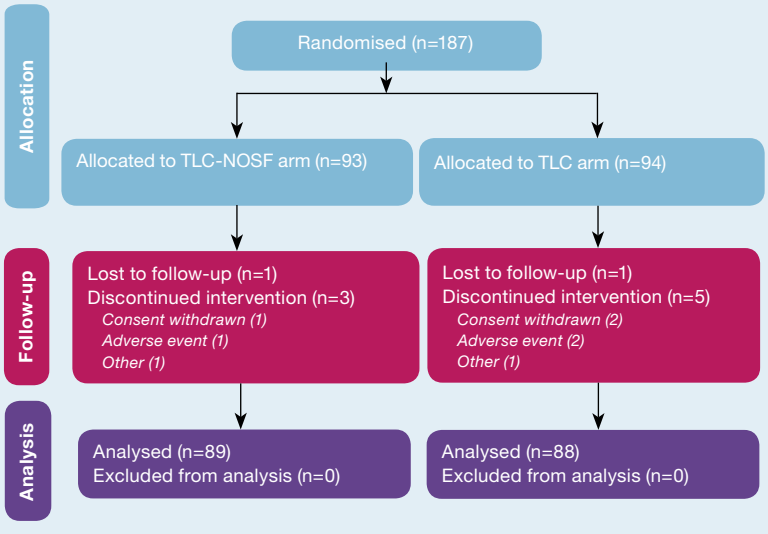
The majority of chronic leg ulcers occur as a consequence of chronic venous insufficiency, caused by venous reflux and/or valve incompetence or obstruction.[14] The precise chain of events that links the high venous pressure with skin breakdowns and the chronic wound is not fully understood,[15,16] but it may involve genetic and environmental factors, sustained venous hypertension, changes in local microcirculation, leukocyte activation and inflammation, and cytokine and MMP dysregulations.[17–20] A mechanism that has been correlated to the chronicity of wounds is the overexpression of matrix metalloproteinases (MMPs, particularly MMP-2 and MMP-9) in chronic wound tissue and exudates.[21–24] This elevated and persistent proteolytic activity triggers extracellular matrix (ECM) degradation and growth factor inactivation, which delays the tissue repair[25–27] while the ulcers are stalled in the inflammatory phase.[28] Therefore, it was postulated that interventions capable of reducing the excessive protease levels may help to produce an anti-inflammatory effect and benefit wound healing.[17,29]

The lipido-colloid nano-oligosaccharide factor (TLC-NOSF) matrix dressings have been designed to improve the local treatment of chronic ulcers. The nano-oligo-saccharide factor (NOSF), a compound with MMP-modulating properties[30,31] incorporated into a lipidocolloid matrix (TLC) has been used in the local management of chronic wounds of various aetiologies[32–34] The ability of the TLC-NOSF matrix in reducing the activity of MMPs, in particular of gelatinases (MMP-2 and MMP-9) and of collagenases (MMP-1 and MMP-8), has been demonstrated *in vitro*.[30,31] In a dermal equivalent model, this MMP-modulating effect was reported along with a stimulation of the proliferation and migration of endothelial cells.[31]

Based on these preclinical results, the TLC-NOSF matrix dressing was evaluated, in a European randomised controlled trial (RCT),[35] against a recognised MMP modulator dressing indicated in chronic wound local management, the Promogran matrix (an oxidised regenerated cellulose/collagen matrix).[25,36,37] A total of 117 patients were randomly allocated to a 12-week treatment with either the TLC-NOSF matrix dressing or with the oxidised regenerated cellulose/collagen dressing, while all of them receiving compression therapy. After the 12 weeks of treatment, the TLC-NOSF matrix showed significant superior healing properties compared with the ORC matrix, with a higher wound area reduction (WAR) and a higher percentage of wounds reaching the 40% WAR endpoint. This outcome was also obtained in a significant shorter median period of time than in the oxidised regenerated cellulose/collagen group.

In order to consolidate these first RCT results, another prospective multicentre double-blind RCT was performed to evaluate the efficacy of the TLC-NOSF matrix dressing compared to a neutral foam dressing, in the local management of VLUs: the 'CHALLENGE' trial. The wound healing outcomes of this clinical trial have been previously published.[38] In brief, in the 8-week study, the results of the primary endpoint efficacy showed the TLC-NOSF matrix effect was more substantial regarding: the relative WAR, when compared with the control group. The median

Fig 1. Distribution of patients



relative WAR was 58.3% in the TLC-NOSF group and 31.6% in the control group (p=0.002). Concordance with venous compression therapy system was confirmed in both groups, without significant difference and the type of compression applied was also similar in both groups.

There were two secondary endpoints. The mean absolute WAR was 6.9±11.4cm^2 (median: 6.1cm^2) at the last planimetry in the TLC-NOSF group compared with 2.5±11.9cm^2 (median: 3.2cm^2) in the control group (p=0.0038 Mann-Whitney U test). The mean wound healing rate was significantly higher in the TLC-NOSF group than in the control group: 13.32±24.56mm^2/day (median: 10.83) and 4.54±23.20mm^2/day (median: 5.15), respectively (p=0.0056 Mann-Whitney) (Table 1). At the end of the evaluation 13 leg ulcers (6 in the test group and 7 in the control group) were completely healed.

Sub-analyses were performed using the three known prognostic factors of the wound healing process: duration (12-month threshold), surface area (10cm^2 threshold) and recurrence of the treated wound (yes/no).[39] Whatever the prognostic factor used and the prognostic value of the sub-groups analysed, the median values of the WAR at the final evaluation were always higher in the TLC-NOSF group than in the control group. Furthermore, the results in the TLC-NOSF group were less influenced by the prognostic factors than in the control group, with more homogeneous results between the subgroups (median values ranging from 55 to 63% in the TLC-NOSF group versus 19 to 41% in the control group).

Here, we aim to present and discus the HRQoL data from the same study to offer a well-deserved focus on the impact of the two treatments on the patients' HRQoL.

Table 2. EuroQuol (EQ-5D) health questionnaire

EQ-5D-3L descriptive system	
By placing a tick in one box in each group, please indicate which statements best describe your health today:	
Mobility	
I have no problems in walking about	❑
I have some problems in walking about	❑
I am confined to bed	❑
Self-Care	
I have no problems with self-care	❑
I have some problems washing or dressing myself	❑
I am unable to wash or dress myself	❑
Usual activities (e.g. work, study, housework, family or leisure activities)	
I have no problems with performing my usual activities	❑
I have some problems with performing my usual activities	❑
I am unable to perform any usual activities	❑
Pain/discomfort	
I have no pain or discomfort	❑
I have moderate pain or discomfort	❑
I have extreme pain or discomfort	❑
Anxiety/depression	
I am not anxious or depressed	❑
I am moderately anxious or depressed	❑
I am extremely anxious or depressed	❑

Materials and methods

This prospective randomised controlled double-blind trial was conducted in France in 2009–2010, through 45 centres involving hospital vascular physicians, internal medicine physicians, dermatologists and some wound care units. Initially, all investigating teams were trained on the Good Clinical Practice (GCP) guidelines and on the standard procedures required to assess the wound (mini Doppler, planimetric and photography records, all provided by the sponsor).

The patients recruited were in patients and out patients, of either sex and aged ≥18 years old, who were informed of the study protocol and provided written consent for participation. Patients were educated to compression system therapy and had agreed to be concordant, wearing their compression bandages every day along with the study dressing, as long as their open ulceration was present.

Patients were eligible for inclusion if having a venous or mixed leg ulcer with an ankle brachial pressure index (ABPI) between 0.8 and 1.3, a surface area between 5 and 50cm^2 and duration between 6 and 36 months. The wound bed had to be covered with >50% with granulation tissue at baseline without black necrotic tissue on the ulcer surface, and to be spaced by >3cm, from any edge, to another wound located on the same limb. If a patient presented with several ulcers located on the same limb at the inclusion visit, the investigator selected the wound which had best met the selection criteria (target ulcer) for clinical evaluation.

Patients excluded from the study were those having:

- Hypersensitivity to one of the components of the wound dressings
- Poor health which could lead to the patient withdrawal before the end of the study period
- Malignant wound degeneration or a neoplastic lesion treated by radiotherapy, chemotherapy, immunosuppressive drugs or high dose corticosteroids
- A clinically infected ulcer requiring a systemic antibiotherapy

- A history of deep or superficial vein thrombosis within the three previous months
- Having undergone surgery directly related to the venous insufficiency within the two months before inclusion
- Planned ulcer surgery during the trial period.

Study endpoint

The patients' HRQoL was assessed using the EQ-5D, documented by the patient in presence of the physician, at baseline and at the end of the treatment period.

The EuroQuol quality of life questionnaire (EQ-5D).

The EQ-5D is standardised to provide a simple, generic measure of health outcomes in clinical appraisal. Developed by the EuroQol Group, the questionnaire is used in Europe for the assessment of the impact of chronic wounds on the patient's HRQoL.[40–47] This tool is valid, reliable, sensitive to change and can discriminate between health states.[40] It is designed for self-completion by respondents, is cognitively undemanding, and takes a few minutes to complete. It consists of two pages: the EQ-5D descriptive system and the EQ visual analogue scale (EQ-VAS).

The EQ-5D descriptive system comprises five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The respondent is asked to indicate his/her health state by ticking in the box against the most appropriate statement in each of the five dimensions (Table 2). The EQ-VAS records the rated health on a 20cm vertical, VAS with endpoints labelled as 'the worst health you can imagine' (0) and as 'the best health you can imagine' (200). The respondent simply 'marks a cross on the scale to indicate how his/her health is today' and then 'writes the number he/she marked on the scale in a box'.

Tested dressings

The two dressings met the double-blind clinical trial requirements, with the only difference the NOSF dressing in the TLC matrix, in the TCL-NOSF dressing. The control TLC dressing (UrgoTul Absorb) has exactly the same composition, but free of the NOSF compound. While appearance, shape, colour, odour and packaging were identical. Before the study, a jury, independent of the trial, has assessed and confirmed that the dressings were undistinguishable.

The tested dressings were recommended to be changed every 2 to 4 days, depending on the clinical aspect of the wound and the level of exudate. Saline solution was used to wash and clean the wound. Compression therapy, according to the clinical procedures of the centres, was mandatory throughout the study period. The documentation of the compression system therapy, mono- or multi-layer applied at the convenience of the investigating physician, was required at each dressing change in the nursing care diary. Any other local treatment (such as antibiotics and antiseptics) had to be notified in the nursing care diary.

Table 3. Baseline patient's characteristics, including the visual analogue scale (VAS) and 5-dimension EuroQol (EQ-5D) scores

	TLC-NOSF (n=93)	TLC (n=94)
Gender (female/male) (n)	62/31	60/34
Age (year) (mean ± SD)	72.6±13.0	74.4±12.1
BMI (kg/m^2) (mean±SD)	30.5±8.7	30.1±6.9
BMI>30kg/m^2 n (%)	40 (43.0%)	40 (42.6%)
High blood pressure	64 (68.8%)	64 (68.1%)
Heart disease n (%)	31 (33.3%)	34 (36.2%)
Diabetes n (%)	13 (13.8%)	17 (18.1%)
History of deep venous thrombosis n (%)	40 (43.0%)	32 (34.0%)
History of venous leg ulcer n (%)	67 (72.0%)	69 (73.4%)
Patient status: outpatient n (%)	75 (80.6%)	77 (81.9%)
ABPI (mean±SD)	1.05±0.14	1.03±0.12
EQ-5D		
Mobility (mean±SD)	1.56±0.52	1.59±0.51
Self-care (mean±SD)	1.25±0.48	1.27±0.49
Usual activities (mean±SD)	1.55±0.62	1.50±0.60
Pain/discomfort (mean±SD)	1.82±0.60	1.95±0.52
Anxiety/depression (mean±SD)	1.53±0.64	1.61±0.63
VAS (mean±SD)	65.84±17.68	65.63±17.38

SD—standard deviation; ABPI—ankle–brachial pressure index; VAS—visual analogue scale; TLC-NOSF—lipidocolloid nano-oligosaccharide factor; BMI–body mass index

Study design

Once an ABPI measurement was taken (Dopplex D900, Huntleigh Healthcare, Cardiff, UK) and the selection criteria validated, patients were randomly allocated, according to the centralised randomisation, to either the TLC-NOSF or the TLC dressing. The randomisation list was established by an independent company (Vertical Paris, France), using a computer programme. The list was balanced by block of two and stratified by centre. The investigators did not have any access to the randomisation code.

At baseline, the patient's demographic characteristics, his/her major medical and surgical history and the general treatments were documented. The characteristics of the target lesion (duration, location, aetiology, clinical condition of the wound and the state of the surrounding skin) were assessed by the investigating physician. After debridement and cleansing of the wound, a planimetric record of the

Table 4. Baseline ulcer characteristics

	TLC-NOSF (n=93)	TLC (n=94)
Duration months (mean±SD)	15.6±9.1	15.12±8.7
Median (range)	12 (3–35)	12 (6–36)
Duration >1 year n (%)	54 (58.1%)	49 (52.1%)
Recurrent ulcer n (%)	51 (54.8%)	49 (52.1%)
Perilesional skin		
Healthy n (%)	35 (37.6%)	43 (45.7%)
Erythematous n (%)	34 (36.6%)	37 (39.4%)
Periwound eczema n (%)	23 (24.7%)	15 (16.0%)
Wound bed aspect*		
% granulation tissue (mean±SD)	71.4±17.9	72.8±17.0
% sloughy tissue (mean±SD)	28.6±17.9	27.2±16.8
Wound size		
Wound area cm^2 (mean±SD)	17.0±15.6	16.6±15.8
Median (range)	12.9 (2.3–86.9)	10.5 (2.7–85.3)
Area>10cm^2 n (%)	54 (58.1%)	48 (51.1%)

SD—standard deviation; ABPI—ankle–brachial pressure index; VAS—visual analgue scale: n–number; TLC-NOSF–lipidocolloid nano-oligosaccharide factor; *Percentage of wound area covered by granulation tissue or sloughy tissue (colorimetric scale)

wound surface was traced and a photograph (three mega pixel camera, at least) was taken, according to the standard procedures provided in the protocol. The patient's HRQoL was assessed through the EQ-5D questionnaire. For each patient included in the trial, the studied dressings were applied according to the manufacturer instructions for an 8-week period maximum or until healing, first occurred. At the final evaluation, the investigator conducted a second HRQoL assessment using the EQ-5D, in addition to a complete clinical assessment, planimetric and photographic records.

Statistics

Statistical analyses were conducted by an institution (Vertical), independent from the study sponsor, in accordance to a statistical analysis plan, approved by the different parties involved in the trial.

Data analyses were conducted with SPPS 18.0 software, on an intention-to-treat (ITT) population, defined as all randomised patients presenting at least one follow-up planimetry after the initiation visit. Bilateral tests were used and a $p<0.05$ was considered significant. The comparability of the two groups resulting from the randomisation was checked at baseline using appropriate tests (Student's t test, non-parametric Mann-Whitney test, Chi-squared test), according to the distribution and the nature of the variables (continuous or categorical). Non-parametric Mann-Whitney test was used to compare the dressing performances, on primary and secondary endpoints. For the local tolerance (occurrence of adverse events), Chi-square test was used and odds ratio was calculated with 95% confidence intervals (CIs). Scales variables have been presented by their means±SD, their median and range values.

Ethics

All patients enrolled gave written consent to participate, after receiving full disclosure and written information regarding the study objectives and conduct.

This clinical trial was conducted according to the European Good Clinical Practice (GCP) recommendations, the principles of the declaration of Helsinki and French regulations. The trial started after the French National Security Agency of Medicines and Health Products (AFSSAPS, Registration number 2008-A1573-32) and the French Medical Ethics Committee of Paris Ile de France VIII (IDF8 Ambroise Paré University Hospital) gave their approval.

Results

From March 2009 to July 2010, a total of 187 patients were recruited: 94 and 93 patients were randomly allocated to the TLC-NOSF dressing or to the control dressing, respectively.

As described in Fig 1, 94.6% of the study population (177 patients) were followed up until week 8 or until complete re-epithelialisation of their wound (89/93 patients in the TLC-NOSF group and 88/94 patients of the control group). A total of ten patients (4 in the TLC-NOSF group and 6 in the control group) prematurely and definitively discontinued the study treatment before week 8. The mean duration of patient follow-up was similar in both groups: 54.1±9.2 days in the TLC-NOSF group and 53.2±11.4 days in the control group, with a median value of 56 days for each treatment group. Globally, 895 medical evaluations (444 and 451 in the TLC-NOSF and control groups) and 3547 nursing care operations (1804 and 1743 in the TLC-NOSF and control groups) have been performed during this clinical trial.

Baseline characteristics

No significant difference was observed at baseline between the two treatment groups for demographics or leg ulcers characteristics (Tables 3 and 4). Of those recruited, 81% (152/187) were outpatients. The mean age of population was 73.5±12.6 years. Patients were predominantly female (65.2%) and overweighed with a mean body mass index (BMI) of 30.3±7.9kg/m^2. The large majority of the patients (72.7%) presented a history of VLUs, 38.5% had a history of deep venous thrombosis and 16% were diagnosed with diabetes. Patients were presenting a mean ABPI value of 1.04±0.13 (range 0.8–1.5) and nearly 92% of them were wearing a compression therapy system before randomisation. The included leg ulcers had a mean duration of 15 months (median: 12 months) and were recurrent in

53.5% of the cases. The mean wound surface area of the ulcers was 16.8±15.7cm² and 54.4% of patients presented an ulcer area >10cm². If considering the number of wounds presenting more than one year duration and more than 10cm² at baseline in the two groups, they were very similar (p=ns, for each parameter). The wound bed was appropriately debrided (no necrotic tissue and 72.1±17.4% of wound area covered with a granulation tissue). Only 41.7% of the treated wounds presented with a healthy periwound skin.

At baseline, the EQ-5D questionnaire was completed by 184 of the 187 patients. The profiles were very similar in both groups, with no significant difference in any of the five dimensions (Table 3). Pain was the most impaired dimension, with 11% of the total number of patients expressing a significant pain issue (extreme pain/discomfort) while the 'self-care' dimension was the least impacted. The 20cm VAS scores were also similar in both groups, with values of 65.8±17.7mm and 65.6±17.4mm in the TLC-NOSF and control groups, respectively.

Health-related quality of life

At the last visit, the HRQoL questionnaire was completed by 158 patients (80 from the study group and 78 from the control group). Pain/discomfort and anxiety/depression scores improved in both groups, but these scores were significantly better in the study group (Table 5). For the pain/discomfort dimension, the documented values were 1.53±0.53 versus 1.74±0.65 (p=0.022). The patients have reported 'no pain or discomfort' in 48.8% and 37.2% of the TLC-NOSF group and control group, respectively and 'extreme pain or discomfort' in 1.3% and 11.5%, of the groups, respectively. For anxiety/depression, the documented values were 1.35±0.53 versus 1.54±0.60, p=0.037). The patients noted 'I am not anxious or depressed' in 67.5% and 51.3% of the TLC-NOSF group and control group, respectively and noted 'I am moderately anxious or depressed' in 30.0% and 43.6% of the two groups, respectively. In particular, only 1 of 80 patients (1.3%) in the study group still reported significant pain compared with 9 patients out of 78 in the control group (11.5%, p=0.009, Fisher's exact test). As reported in the Table 5, no difference was noted for the three other dimensions of this questionnaire (mobility, self-care, usual activities). The final EQ-VAS score was also higher in the test group (72.1±17.5 versus 67.3±18.7 in the control group) without reaching the statistical threshold in this study (p=0.072).

Safety, acceptability

During the 8-week treatment period of the study, no serious adverse event related to the dressings has been reported. A total of 66 local adverse events (LAEs) reported in both groups, occurred in 29 and 27 patients, in the test and control groups, respectively.

Among the 34 LAEs of the TLC-NOSF group, 10 were considered to be potentially related to the tested dressing whereas, in the control group, 13 of the 32 LAEs were considered to be treatment related. For each group, the description of these LAEs is given in Table 6. The adverse events most often encountered throughout the trial consisted of periwound eczema, mainly already reported at baseline, before the initiation of the treatment. For 11 and 12 patients in the test and control groups, the occurrence of the LAEs represented the main reason for treatment discontinuation.

Regarding the acceptability of the two treatment groups, a total of 3547 nursing treatments (1804 in the test group and 1743 in the control group) were documented over the 8-week study period and a similar dressing change frequency was documented in the both groups: 6±3 times every two weeks. As described in Table 7, ease of application, conformability, ease of removal and pain and bleeding at removal were very similar with the two dressings.

Table 5. EuroQuol quality of life dimensions (EQ-5D) at the final visit

Dimension score (mean±SD)	TLC-NOSF	TLC	p-value
Mobility	1.55±0.52	1.56±0.52	0.86
Self-care	1.23±0.44	1.27±0.55	0.55
Usual activities	1.54±0.61	1.51±0.59	0.74
Pain/discomfort	1.53±0.52	1.74±0.65	0.02
Anxiety/depression	1.35±0.53	1.54±0.59	0.03
VAS (mean±SD)	72.1±17.5	67.3±18.7	0.07

SD—standard deviation; VAS—visual analogue scale; TLC-NOSF—lipidocolloid nano-oligosaccharide factor

Table 6. Number and nature of local adverse events

	TLC-NOSF (n=94)		Control (n=93)	
Local adverse events (LAE)	Number of LAE	% of patients	Number of LAE	% of patients
Perilesional skin irritation	2 (2)	2.16%	4 (2)	4.26%
Pain	1 (0)	1.08%	0 (0)	-
Periwound eczema	14 (4)	15.05%	9 (5)	9.57%
Overgranulation	3 (2)	3.23%	2 (0)	2.13%
Infection	7 (1)	7.53%	6 (0)	6.38%
Others	7 (1)	7.53%	11 (6)	11.70%
Total	34 (10)		32(13)	

Within brackets: Number of events considered by the investigators as probably/certainly related to the tested dressings; TLC-NOSF—lipidocolloid nano-oligosaccharide factor

Discussion

This double-blind RCT has documented that treating patients suffering from VLUs and mixed leg ulcers with a TLC-NOSF matrix as a primary wound dressing, associated with an effective compression therapy, was

Table 7. Characteristics of study dressing application and removal

		Treatment group					
		TLC-NOSF (n=1677)		TLC (n=1606)		Total (n=3283)	
		n	%	n	%	n	%
Ease of application	Very easy	1350	80.5%	1264	78.7%	2614	79.6%
	Easy	300	17.9%	316	19.7%	616	18.8%
	Difficult	5	0.3%	8	0.5%	13	0.4%
	Very difficult	2	0.1%	0	0.0%	2	0.1%
	MD	20	1.2%	18	1.1%	38	1.2%
Conformability	Very good	892	53.2%	878	54.7%	1770	53.9%
	Good	720	42.9%	654	40.7%	1374	41.9%
	Poor	24	1.4%	22	1.4%	46	1.4%
	Very Poor	2	0.1%	10	0.6%	12	0.4%
	MD	39	2.3%	42	2.6%	81	2.5%
		TLC-NOSF (n=1694)		TLC (n=1622)		Total (n=3316)	
Ease of removal	Very easy	1240	73.2%	1218	75.1%	2458	74.1%
	Easy	405	23.9%	372	22.9%	777	23.4%
	Difficult	16	0.9%	1	0.1%	17	0.5%
	Very difficult	1	0.1%	0	0.0%	1	0.0%
	MD	32	1.9%	31	1.9%	63	1.9%
Pain at removal	None	1435	84.7%	1408	86.8%	2843	85.7%
	Minor	193	11.4%	158	9.7%	351	10.6%
	Moderate	19	1.1%	8	0.5%	27	0.8%
	Marked	5	0.3%	0	0.0%	5	0.2%
	MD	42	2.5%	48	3.0%	90	2.7%
Bleeding at removal	None	1466	86.5%	1442	88.9%	2908	87.7%
	Minor	164	9.7%	107	6.6%	271	8.2%
	Moderate	3	0.2%	3	0.2%	6	0.2%
	Marked	3	0.2%	0	0.0%	3	0.1%
	55	58	3.4%	70	4.3%	128	3.9%

MD–missing data; TLC-NOSF—lipidocolloid nano-oligosaccharide factor

able to significantly improve their wound healing trajectory.[38] Besides, as assessed in this clinical trial, this efficacy on the wound healing process has led to a substantial improvement of the patient's HRQoL.

Due to the unresolved challenge that hard-to-heal ulcers represent for health professionals, patients and payers, the selection criteria of this clinical trial have been chosen to evaluate the effect of the TLC-NOSF matrix on VLUs with bad prognostic (i.e. with a surface area >5cm² and a duration >6 months).[48–51] Consequently, the mean characteristics of the included ulcers were of long duration (15 months), large area (16cm²) and high rate of recurrence (50%). In the CHALLENGE RCT, groups were similarly concordant to compression therapy and well-balanced at baseline and similar cares applied in both groups throughout the study period.

A limitation of the trial was the duration of the treatment, too short to observe any difference on the complete wound closure outcome. However, based on the linear regression analysis of the median values of WAR over the 8-week follow-up, the time to complete closure was estimated at 90 days for the TLC-NOSF dressing group and at 180 days for the control group.

According to the French national health insurance database (SNIIRAM) database, developed on the basis of 110,000 outpatients treated for leg ulcers in real-world, the mean time to closure is estimated around 210 days.[52] The time to healing reported in the control group of the CHALLENGE RCT compared with the one from big data analysis (180 versus 210 days) are similar, especially as the slight difference might be explained by the optimal and holistic management implemented in the VLU-specialised centres involved in this investigation (appropriate compression therapy and support of patients' high adherence). Similarly, it is consistent with the data documented in real world surveys on TLC-NOSF dressings (90 versus 112 days).[53] In the 'Reality Study', clinical data of patients presenting a chronic wound treated with the TLC-NOSF matrix in real-life practice, collected from eight French and German large surveys involving 2792 investigators, were pooled into a global analysis.[53] Additionally, as in the CHALLENGE RCT, the pooled data of the Reality Survey suggested that the TLC-NOSF dressings may reduce the healing time of chronic wounds, independently from the presence or not of risk factors of poor healing prognosis.

In a survey performed on 241 patients, Jull reported that a VLU reduces patients health status by approximately 10% and reduces HRQoL to a similar extent as other common chronic conditions, such as arthritis and diabetes.[54] Guidelines recommend evaluating the impact of these wounds and their therapies on the patient HRQoL.[4] To our knowledge, the RCT reported here is the first double-blind RCT to explore the impact of two tested therapeutic strategies on the HRQoL in patients with hard-to-heal VLUs.

In the field of HRQoL assessment, two types of instruments can be used: disease-specific ones and generic ones. In VLUs, disease-specific instruments includes the NHPQ (Nottingham Health Profile Questionnaire),[55] the CWIS–Cardiff Wound Impact Schedule,[56] the FLQAwk (Freiburg Life Quality Assessment for Wounds),[57,58] the CCVLUQ–Charing (Cross Venous Leg Ulcer Questionnaire),[59] the VLU-QoL (Venous Leg Ulcer Quality of Life),[60] and the Hyland instrument.[61,62] These can be adapted to a specific illness but their popularity in practice is usually country-dependent. Among the generic instruments, the Short Form Health Survey (SF-36) with its adaptations SF-12 and SF-6D[62,63] and the EQ-5D[64–68] are most used to evaluate the impact of VLUs on HRQoL. The EQ-5D and the SF-12 are recognised as responsive[62,66,67] and the EQ-5D is recommended by policy decision-makers, such as the National Institute for Health and Care Excellence (NICE).[69]

The EQ-5D, because of its conciseness and relative simplicity was selected in this clinical trial. After the 8-week treatment, a significant improvement has been reported in the TLC-NOSF group for two of the five dimensions of the EQ-5D questionnaire: pain/discomfort and anxiety/depression and the p-value of the VAS was not far from a significant level (p=0.07). A similar improvement in HRQoL arising from a reduction of VLU area had been described by Herberger in a cross-sectional study on 530 patients recruited in the metropolitan area of Hamburg.[57] These findings are in agreement with those reported by Furtado et al.[64] an health perceived improvement of patients (evaluated through the EQ-5D questionnaire) after a 12-week treatment period of VLUs, which showed more specifically marked results in the bodily pain and depression-anxiety dimensions. The two dimensions of pain and anxiety were also documented by Palfreyman[65] as the most frequent symptoms reported (80% and 65%, respectively) in a self-completed postal questionnaire including the EQ-5D sent to a cohort of 266 patients with a history of VLUs. According to a cross-sectional study, published by Guarnera et al. conducted on 381 patients with VLUs, pain also emerged as the most significant factor affecting HRQoL in patients.[70] A direct correlation between pain and HrQoL was noted, which was worst for leg ulcers with a longer duration and a larger area. Furthermore, in another cross-sectional study on 141 outpatients in Netherlands, it appears that pain, present in 85% of the patients, was not only affecting the patient's HRQoL, but was likely to also affect the healing of the leg ulcers.[71] The impact of the TLC-NOSF treatment on the patient HRQoL reported in the CHALLENGE trial are also in line with the results observed in patients treated with TLC-NOSF dressings, in real life. The 'Trajectoire survey' is a French observational survey involving 1005 outpatients with non-healing VLUs treated with TLC-NOSF dressings.[72] The promotion of the healing process with the TLC-NOSF matrix showed then an improvement of HRQoL of the treated patients who experienced less pain/discomfort and anxiety/depression, as well as greater mobility, following treatment with TLC dressings including TLC-NOSF; the patients were also more able to perform their usual day-to-day activities.

Through all these elements, it appears that HRQoL, mostly affected by the pain and anxiety dimensions, is linked to the healing process. The literature considers that the type of neutral wound dressing applied beneath the compression system (as the one used in the control group of the CHALLENGE trial) does not affect the ulcer healing[73] and states that despite their potential specific characteristics, no superiority in terms of wound healing efficacy could have been demonstrated between the different neutral foam dressings available for the management of VLUs.[74,75] While other alternatives could be considered to accelerate the healing process of VLUs, as there is some evidence that modulating MMPs may be effective in improving healing rates,[4,17] the assessment of the impact of these new strategies on the HRQoL should be examined.

In this clinical trial, if considering the acceptability parameters for both patients and care givers, they were very similar for the two study dressings. Additionally,

both dressings had a very similar local safety profile, if considering the occurrence of LAEs. It can be concluded then that the TLC-NOSF matrix in the dressing does not impair the characteristics of the nursing care or modify the safety profile of the tested foam dressing compared with the control dressing.

Limitations

The main limitation of the data regarding HRQoL is the choice of this questionnaire among all others. We explained why we used the non-specific, EQ-5D, but we could have choosen others which are more specific to wounds and specifically VLUs.

Conclusions

This double-blind randomised controlled trial has established that the TLC-NOSF matrix dressing, a MMP-modulator dressing, in conjunction with standard of care promotes a faster healing of VLUs than standard care alone, and significantly improves HRQoL, notably on the pain/discomfort and anxiety/depression dimensions, with probably consequences on emotional and social aspects. Assessment of HRQoL is a relevant outcome in clinical research,[76] so health professionals should take account of wellbeing as part of the holistic treatment plan in order to maximise patient outcomes. **JWC**

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Reflective questions

- Have you introduced a health related quality of life (HRQoL) assessment tool in your daily practice to evaluate the impairment of the HRQoL when a patient presents with a leg ulcer?
- What questionnaires exist to monitor HRQoL and which would be the most useful for your practice?
- What are the advantages and disadvantage if the different assessment tools


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