Evaluation of two fibrous wound dressings for the management of leg ulcers: Results of a European randomised controlled trial (EARTH RCT)

• **Objective:** To evaluate the performance (efficacy, safety and acceptability) of a new micro-adherent absorbent dressing (UrgoClean®) compared with a hydrofiber dressing (Aquacel®) in the local management of venous leg ulcers, in the debridement stage.

• **Method:** A non-inferiority European randomised controlled clinical trial (RCT) was conducted in 37 centres, on patients presenting with venous or predominantly venous, mixed aetiology leg ulcers at their sloughy stage (with more than 70% of the wound bed covered with slough at baseline). Patients were followed over a 6-week period and assessed weekly. The primary judgement criteria was the relative regression of the wound surface area after the 6-week treatment period. Secondary endpoints were the relative reduction of sloughy tissue and the percentage of patients presenting with a debrided wound.

• **Results:** Altogether, 159 patients were randomised to either UrgoClean (test group; n=83) or Aquacel (control group; n=76) dressings. Regarding the wound healing process predictive factors (wound area, duration, ABPI value, recurrence), at baseline, the two groups were well balanced, for both wound and patient characteristics. Compression therapy was administered to both groups and after a median 42-day treatment period, the percentage of relative reduction of the wound surface area was very similar (-36.9% vs -35.4% in the UrgoClean and control groups, respectively). When considering the secondary criteria at week 6, the relative reduction of sloughy tissue was significantly higher in the UrgoClean group than in the control group (-65.3% vs -42,6%; p=0.013). The percentage of debrided wounds was also significantly higher in the test group (52.5% vs 35.1%; p=0.033).

• **Conclusion:** This 'EARTH' RCT confirmed that the UrgoClean dressing has similar efficacy and safety compared to Aquacel. However, UrgoClean also showed better autolytic properties than the control group in the management of venous leg ulcers at the sloughy stage. The new UrgoClean dressing therefore represents a promising therapeutic option within the current range of autolytic dressings available.

• **Declaration of interest:** This study was sponsored by a grant from the pharmaceutical company Laboratoires Urgo. S. Bohbot and O. Tacca are employees of Laboratoires Urgo. S. Meaume, J. Dissemond and G. Perceau have received monetary compensation as presenters for Laboratoires Urgo. Data management and statistical analyses were conducted independently by Vertical (Paris, France).

chronic wound; sloughy tissue; multicentre randomised trial; hydrofiber; UrgoClean

The healing of chronic wounds is a dynamic physiological process that proceeds in a succession of phases, namely debridement, granulation and epithelialisation.[1] Debridement can be defined as the removal of all material considered barriers to the wound healing process including necrotic and devitalised tissue, slough or any other type of bioburden from a wound.[2]

The debridement procedure, an essential part of chronic wound care management,[3] is considered to be the most efficient and effective way of achieving the wound bed preparation.[4] It facilitates the removal of wound-healing barriers and will lead to the improvement of wounds.[5] The most direct form of debridement is surgical excision, but for patients who are poor candidates for this procedure or who have limited access to a surgeon, other types of debridement like mechanic, enzymatic, autolytic or biologic can be used.[6]

This initial phase, managed by these non-surgical procedures, will last a few weeks and can reduce the time taken for wound closure to be reached.[7] Among the different types of non-surgical debridement, autolytic debridement allows for selective elimination of necrotic tissue through the release of the body's endogenous proteolytic enzymes like collagenase, elastase, myeloperoxidase and activation of

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Continued on page 106

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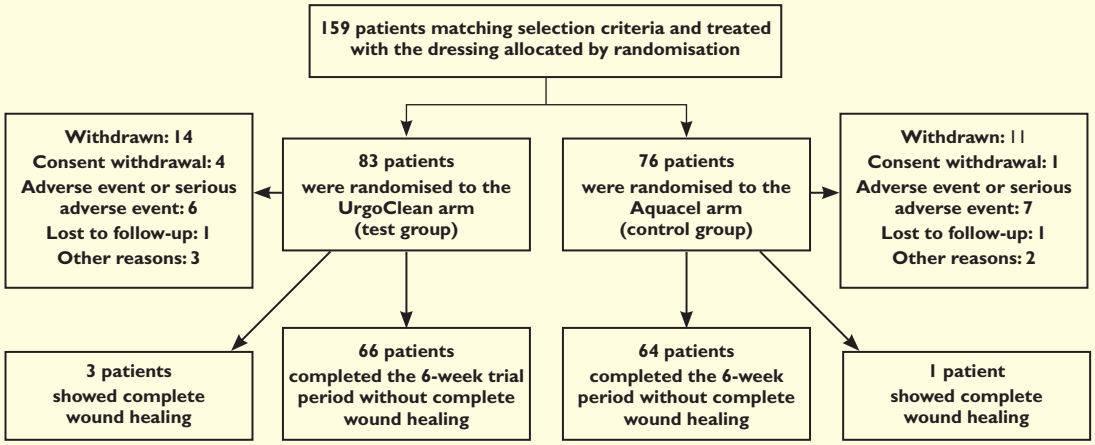
Fig 1. Patient disposition



phagocytes.[6,8] This method is considered to be one of the easiest and safest methods of debriding wounds.[2] It is therefore often chosen as first line treatment, as it represents the most selective form of debridement, sparing healthy tissue, managing wound exudate and providing a moist environment.[9]

Some current modern wound dressings are specific to this debridement phase. Alginates or hydrofibre dressings based on carboxymethylcellulose (CMC) can be used particularly on exuding wounds with hydrogels when the wounds are dry.[10,11] The hydrofiber dressing Aquacel is recognised for its therapeutic benefit in the healing process of chronic wounds, due to its autolytic properties.[12–14] Recently, an absorbent and micro-adherent cohesive dressing UrgoClean, composed of polyacrylate fibres and coated with a lipido-colloid layer known to promote the cutaneous healing process,[15,16] has been specifically developed for the desloughing phase of the healing process. A pilot clinical trial was conducted with this new dressing on 50 patients over a 6-week period, to manage chronic exuding wounds (venous leg ulcers and pressure ulcers) at their debridement stage.[17] Promising results were documented regarding the desloughing properties and the positive role of this dressing in the healing process, with good acceptability for both patients and nursing staff. The open-label character of this trial was the main limitation of this pilot study. These results were therefore to be consolidated through a randomised clinical trial, comparing the promotional healing effect of this dressing (UrgoClean) with that of a therapeutic reference dressing (Aquacel) in the local treatment of venous leg ulcers from their debridement stage.

Method

This open-label, multicentre, controlled, randomised clinical trial (RCT) was conducted in France, Germany and UK, from May 2011 until August 2012. The evaluations were carried out in 37 active investigating centres specialising in dermatology, vascular medicine and gerontology. Among the 37 active centres, 31 were hospitals investigating centres and only 6 centres were private physician investigators. All investigating teams were trained on the Good Clinical Practice guideline (GCP) at the initial visit. All local procedures were recorded by health-care professionals, including detailed information on dressing removal and application and the compression system applied.

The patients recruited for this clinical trial included adult hospitalised patients and outpatients presenting with a venous or mixed aetiology leg ulcer with a predominantly venous origin. This was validated by ensuring the ABPI (Ankle Brachial Pressure Index) was between 0.7 and 1.3 for the target limb at baseline. Written informed consent was obtained prior to the trial. Patients were to be followed by the same investigation team throughout the entire period of the study treatment and agreed to wear an effective venous compression system combined with the study dressings. Ulcer duration had to range between 3 and 36 months and baseline wound area had to range between 3 and 30cm^2 with sloughy tissue covering 70% or more of the wound surface area. If a patient presented with several ulcers located on the same limb at the inclusion visit, the investigator selected one wound (target ulcer) for the evaluation, which best met the selection criteria. The other wounds were treated as per the investigating centre's standard procedures.

The exclusion criteria included ulcers where clinical infection was suspected, an ulcer completely or partially covered with black necrotic tissue or completely dry, malignant wound degeneration, poor

Table 1. Baseline patient's characteristics

	Treatment group		
	UrgoClean n=83	**Aquacel n=76**	**p**
Gender			
- Female n (%)	60 (72.3%)	42 (55.3%)	0.025
- Male n (%)	23 (27.7%)	34 (44.7%)	
Age (years)			
mean ± SD	73.7 ± 12.2	73.7 ± 12.4	0.99
[min; max]	[35.5; 96.9]	[40.8; 97.0]	
median	75.1	77.2	
Height (cm)			
mean ± SD	167.2 ± 10.4	169.9 ± 10.8	0.102
[min; max]	[150.0; 190.0]	[140.0; 198.0]	
median	165.0	169.5	
Weight (kg)			
mean ± SD	82.3 ± 25.3	82.7 ± 21.6	0.0926
[min; max]	[40.0; 163.0]	[41.0; 140.0]	
median	79.5	78.5	
BMI (kg/m²)			
mean ± SD	29.2 ± 7.8	28.5 ± 7.0	0.569
[min; max]	[15.6; 50.3]	[19.5; 50.8]	
median	27.6	26.6	
Out-patients (n/%)	77 (92.8%)	72 (94.7%)	ns
Major medical history (n/%)			
- High Blood pressure	57 (68.7%)	51 (67.1%)	ns
- Heart disease	26 (31.3%)	26 (34.2%)	
- Diabetes	12 (14.5%)	12 (15.8%)	
- Deep vein thrombosis (DVT)	29 (34.9%)	30 (39.5%)	
- Venous surgery	34 (41.0%)	29 (38.2%)	
Ankle Brachial Pressure Index (ABPI)			
mean ± SD	1.05 ± 0.14	1.02 ± 0.15	0.57
[min; max]	[0.70; 1.30]	[0.70; 1.30]	
median	1.07	1.00	

Table 2. Baseline VLU characteristics

	Treatment group		
	UrgoClean n=83	**Aquacel n=76**	**p**
Ulcer surface area (cm²)			
mean ± SD	10.77 ± 11.13	12.66 ± 15.18	0.37
[min; max]	[2.17; 73.41]	[0.89; 86.36]	
median	7.56	6.61	
Ulcer duration (months)			
mean ±(SD	12.74 ± 9.67	15.57 ± 11.43	0.24
[min; max]	[3; 36]	[3; 36]	
median	10	12	
Recurrency n(%)	45 (54.2%)	32 (42.1%)	0.09
Wound Bed aspect (%)			
- Sloughy tissue			
mean ± SD	82.75 ± 10.84	80.65 ± 10.11	0.21
[min; max]	[70; 100]	[70; 100]	
median	80.0	80.0	
- Granulation tissue			
mean ± SD	17.25 ± 10.84	19.34 ± 10.11	0.21
[min; max]	[0; 30]	[0; 30]	
median	20.0	20.0	
Peri-lesional skin condition n (%)			
- Healthy	16 (19.3%)	26 (34.2%)	0.033

health status, current treatment with radiotherapy, chemotherapy, immunosuppressant drugs or high doses of oral corticosteroids and any patient who had presented with deep vein thrombosis in the 3 months prior to inclusion.

Study design

Once the selection criteria had been validated and the ABPI measurement taken with a mini Doppler (Dopplex D900, Huntleigh Healthcare, Cardiff, UK), patients gave their written informed consent to participate in the trial. They were then randomly allocated by centralised randomisation to either the test dressing (UrgoClean) or the control dressing (Aquacel) for a 6-week period.

At the inclusion visit, demographic parameters and the patient's medical, surgical and leg ulcer history were documented by the investigating physician. A detailed wound status was precisely recorded (location, duration, peri-lesional skin condition, clinical aspect of the wound bed using a colorimetric scale), a wound area tracing (planimetry) and a wound photograph was taken, according to the standard procedures provided by the sponsor.

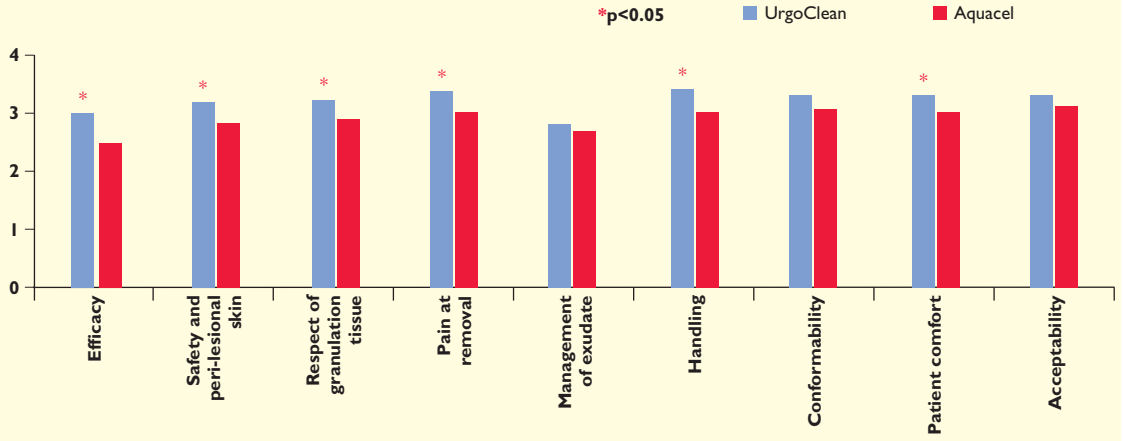
Clinical examination, which included tolerance (from the occurrence of adverse events and side effects) was performed by the investigating physician, until the sixth week of follow-up. It was conducted on a weekly basis during the first 4 weeks and then again at week 6. Five clinical evaluations following the inclusion visit were therefore conducted over the 6-week treatment period. An effective compression bandage system was linked to the trial dressings; the choice of system being left to the investigator and the patient's compliance was confirmed.

Throughout the study, the acceptability of the two dressings and the characteristics of the nursing treatments (focusing on the debridement details), were assessed. This was performed by the investigating team at the scheduled protocol visits or between two visits by private nurses, using open-ended questions.

At the final clinical evaluation (week 6), or earlier if the study treatment was prematurely discontinued, the investigator conducted a Quality of Life assessment using the EuroQol-5D Questionnaire [EQ-5D™]. A Global Performance Score (GPS) between 0 and 36 was given. The higher the score, the better the performance of the dressing considered by the investigator. Investigators evaluated the performance of the dressing at the end of treatment. This GPS was calculated on the basis of nine questions using a qualitative scale of five points (very poor, poor, fair, good, very good).

All nursing treatments were carried out by the care givers in the trial, in accordance with the manufacturer's instructions for the study dressing. A specific letter and procedure information were provided to

Fig 2. Each parameter value (score from 0 (very poor) to 4 (very good)) of the Global Performance Score



all carers explaining the protocol and giving advice on completing the nursing care diary.

Endpoints

Efficacy, the primary study endpoint, was assessed through the measurement of the wound surface area by the investigator at each clinical evaluation until week 6. Wound area reduction (WAR in %) was the selected judgment criteria. All acetate tracings were blinded and centrally measured by two non-participating clinicians using digital software (Universal DeskTop Ruler™).

The secondary end-points focused on the comparison of the autolytic properties of the dressings. These included:

- the clinical status of the treated wounds (% of granulation and sloughy tissue on the wound bed)
- the percentage of debrided wounds at the last assessment available (defined as a wound with 70% or more of its surface area covered by granulation tissue)
- the characteristics of the debridement
- the GPS, local tolerance (occurrence of local adverse events)
- the dressing change frequency and a number of acceptability parameters (e.g. ease of application and removal, conformability, bleeding on removal, adherence to the wound bed).

Tested dressings

The test dressing, UrgoClean (Laboratoires URGO, Chenôve, France), is a non-woven pad made of highly absorbent and cohesive polyacrylate fibres (polyacrylate polymers form the envelope of the fibres which contain an acrylic central core). The pad is coated with a soft-adherent, lipidocolloid layer, designed to be in contact with the wound bed and surrounding skin. The UrgoClean dressing provided was a single size 10x10cm, batch number E2032.

The control dressing, Aquacel hydrofiber (ConvaTec Limited, Deeside, UK), available in a single size 10x10cm, is indicated for chronic exuding wounds (pressure ulcers, leg ulcers, diabetic foot ulcers) and acute exuding wounds (abrasions, lacerations, incisions, graft donor sites and first and second-degree burns).

For both trial dressings, saline solution was used during local treatments, throughout the whole study period. Other local applications (pastes, corticosteroids) were permitted for use around the lesions and this was fully documented in the case report form. The dressings were applied directly to the wound bed. The frequency of the wound dressing change was prescribed by the investigator dependent on the level of exudate and the clinical aspect of the wound. The use and nature of the secondary dressing was left to the discretion of the investigator.

Randomisation

Randomisation was balanced by blocks of four and stratified by the level of ABPI (0.7–0.9, and ≥0.9)

Table 3. Analysis of the primary endpoint in the intention-to-treat (ITT) and per-protocol (PP) populations

	ITT population		PP population	
	UrgoClean	Aquacel	UrgoClean	Aquacel
Patients (n)	80	74	72	72
Wound area reduction (%)	34.1%	34.4%	36.9%	35.4%
Difference (%)	0.4%		-1.5%	
Upper limit of unilateral 95%CI	11.3 %		9.9%	
Standard deviation	5.5		5.8	
Non-inferiority margin -12%	p<0.025		p=0.01	

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Table 4. Number and types of local adverse events

	Treatment group		Total population		
Type of local adverse event n (%)	**UrgoClean n=83**	**Aquacel n=76**	**n=159**	**UrgoClean Definitive discontinuation**	**Aquacel Definitive discontinuation**
Pain	1 (1.2%)	5 (6.6%)	6 (3.8%)	1	3
Eczema	4 (4.8%)	1 (1.3%)	5 (3.1%)	1	1
Infection	1 (1.2%)	1 (1.3%)	2 (1.2%)	1	-
Ulcer worsened / extended	-	1 (1.3%)	1 (0.6%)	-	1
Hypergranulation	-	1(1.3%)	1 (0.6%)	-	-
Pruritus	1 (1.2%)	-	1 (0.6%)	-	-
Patients with documented local adverse events	7 (8.4%)	8 (11.8%)	15 (10.1%)	3	5

and by centers. Treatment allocation was disclosed after investigators called the coordinating centre.

Statistics

Statistical analyses were conducted by an institution (Vertical, Paris), independent from the study sponsor, according to a previously approved statistical analysis plan. Analyses were conducted using SPSS 18.0 software (IBM Inc.). An unblinded database and the allocated dressings were identified as 'A' or 'B' and treatment disclosure was performed after the final statistical report had been written.

The intent-to-treat (ITT) population was defined as all randomised patients with at least one follow-up planimetry value and the per-protocol (PP) population as all patients with a wound area measurement till the fourth week of follow-up, at least.

Baseline comparability of groups was verified by using Student t-test or the non-parametric Wilcoxon test for continuous variables, and chi-squared test for categorical variables.

Non-inferiority (NI) of the tested dressing versus the control dressing was assessed by using the unilateral upper limits of the 95% confidence interval of wound area regression difference (tested – control). A non-inferiority margin of 12% was pre-specified and corresponded to half the difference previously detected in a double-blind trial, which compared an active dressing to a visually identical dressing without the active ingredient, on venous leg ulcers.[18] NI was first tested using the PP population followed by the ITT population. NI was considered to be established if both tests provided similar conclusions.

All the analyses of the secondary endpoints were conducted on the ITT population. Secondary colorimetric parameters were compared using univariate analysis of variance. This took ABPI levels (between 0.7-0.9 and ≥0.9) as stratum and the baseline area as the covariate. The GPS, ranked 0–36 (the higher the score, the more satisfactory the performance of the dressing), was compared with the use of the Student t-test. Emergent local events were descriptively reported.

Sample size

This study was designed to document the non-inferiority of the test dressing, UrgoClean, compared with the control dressing, Aquacel, on the WAR value, after 6 weeks of treatment. Applying a non-inferiority margin of 12% and a standard deviation (σ) of 30%, 78 subjects were necessary in each group (i.e. 156 patients in total) with a power level at 80%.

Ethical approval

This clinical trial was conducted in compliance with the European Good Clinical Practice recommendations with the principles laid down in the Declaration of Helsinki (1975) and the specific regulations of the three involved countries. This clinical trial was initiated following approval from the French Agency for the Safety of Health Products (AFSSAPS Registration number 2011-A00141-40) and also the French Medical Ethics Committee of Paris Ile de France VIII (IDF8. March 2011).

In the UK, the National Health Service Research Ethics Committee (NHS-REC) South West-Exeter issued consent (No.11/SW/0292) for the initiation of this clinical trial, which was sent to the Local Ethics Committees (L-REC) of the different investigating centres.

In Germany, the approval (No. 11-4813-BO) was issued from the 'Ethik-Kommission der Medizinischen Fakultät der Universität Duisburg-Essen' and in accordance with German regulations, the ethics committee for each selected investigating centre, gave approval.

All patients enrolled submitted their written consent to participate in the trial, having received full disclosure and written information regarding the study objectives and conduct.

Results

A total of 159 patients were recruited and randomised into the clinical trial over a period of 15 months, from May 2011 to July 2012; 83 patients and 76 patients in the UrgoClean and Aquacel groups, respectively. One hundred and thirty four patients (84% of the study population) were followed up until week 6 or until complete re-epithelialisation of their wound. A total of 25 patients, 14 in the test group and 11 in the control group) prematurely and definitively discontinued the study treatment prior to week 6 for reasons other than complete re-epithelialisation of their wound, as described in Fig 1. The ITT analysis therefore included 154 patients in total (80 and 74 patients in the test and control groups, respectively) and the PP analysis, 144 patients (72 patients in each treatment group).

As defined in the protocol of the study, 5 patients have been excluded from the ITT analysis because they did not undergo any clinical evaluation of follow-up after inclusion. Amongst these 5 patients, 3 have presented an adverse event making the follow-up impossible and 2 patients could not be contacted for follow-up.

Table 5. Characteristics of study dressings application

Application parameters for the study dressings		Treatment group			
		UrgoClean		Aquacel	
		n	%	n	%
Ease of dressing application	Very easy	669	70.0%	592	66.0%
	Easy	285	29.8%	300	33.4%
	Difficult	2	0.2%	4	0.4%
	Very difficult	-	-	1	0.1%
	Total	956	100%	897	100%
Conformability during dressing application	Very good	623	65.6%	501	56.5%
	Good	295	31.1%	366	41.3%
	Poor	9	0.9%	15	1.7%
	Very poor	22	2.3%	5	0.6%
	Total	949	100%	887	100%
Type of secondary dressing	None	59	6.3%	6	0.7%
	Gauze/pad	623	66.7%	655	71.6%
	Hydrocellular	63	6.7%	115	12.6%
	Other	190	20.3%	139	15.2%
	Total	935	100%	915	100%

Baseline characteristics

More than 94% of the patients involved in the trial were outpatients and the two treatment groups were well balanced at baseline for both patient and leg ulcer characteristics (Tables 1 and 2). Among all the documented baseline parameters, no significant difference was observed between the two groups, except for gender distribution (more female patients in the test group) and the status of the peri-lesional skin.

The population was predominantly female with a mean age of 73.7±12.3 years presenting with a mean body mass index (BMI) of 28.9kg/m^2. The most associated comorbidities were high blood pressure (68%), cardiovascular disease (32%) or diabetes (15%). Deep venous thrombosis or previous venous surgery was associated with 37% and 39% of the total population and the recurrence of the treated ulcers was noted for 54% and 42% of the ulcers, in the test and control group, respectively (p=ns).

At baseline, if considering the total population, mean ABPI was 1.03±0.14, the mean surface area of the target ulcer was 11.68±13.21cm^2 (median 7.18cm^2) and the mean duration of the treated ulcers was 14.10±10.61 months (median 10 months). Approximately half the ulcers were located on the maleolus of both groups, with their wound bed covered with sloughy tissue on more than 80% of the surface area. Less than one third of the patients peri-lesional skin was considered to be 'healthy'. A significant difference was noted between the two groups for this criterion (peri-lesional skin was considered to be more altered in the test group than in the control group (p=0.033). Altered peri-lesional skin mostly presented as an erythema in about 60% of the patients in each group, or eczema in about 25% of the patients. Prior to the patients inclusion in the study, a venous compression system was prescribed for nearly 82% of the patients, irrespective of the group and study numbers between groups were well balanced between single or multi-layer compression systems.

Primary endpoint – efficacy

The mean duration of patient's follow-up was similar in the two groups: 37.7±11.8 days and 38.5±10.7 days in the test and control groups, respectively, with a median value of 42 days in each group.The non-inferiority hypothesis for this primary endpoint (relative reduction in wound surface area) was considered for the PP population. After 6 weeks of treatment, the surface area of the treated wounds was reduced by 36.9% in the UrgoClean group and 35.4% in the Aquacel group.

In order to conclude unambiguously that the test dressing was non-inferior in comparison to the control dressing, a complementary analysis was conducted on the ITT population on which it was noted that the wound surface area was reduced by 34.1% in the test group and by 34.4% in the control group after 6 weeks of treatment. As described in Table 3, and regarding the values of the one-sided 95%CI and the level margin of 12%, the non-inferiority hypothesis is accepted for the UrgoClean dressing (p=0.01 and p<0.025 for the PP and ITT populations, respectively). A venous compression system was linked with

Table 6. Characteristics of study dressings removal

Removal parameters for the study dressings		Treatment group			
		UrgoClean®		Aquacel®	
		n	%	n	%
Ease of removal	Very easy	624	63.9%	439	47.2%
	Easy	337	34.5%	429	46.1%
	Difficult	14	1.4%	56	6.0%
	Very difficult	1	0.1%	6	0.6%
	Total	976	100.0%	930	100.0%
Pain on removal	None	638	66.0%	576	62.0%
	Minor	150	15.5%	208	22.4%
	Moderate	111	11.5%	108	11.6%
	Marked	68	7.0%	37	4.0%
	Total	967	100.0%	929	100.0%
Bleeding on removal	None	850	88.0%	655	71.1%
	Minor	90	9.3%	183	19.9%
	Moderate	25	2.6%	70	7.6%
	Marked	1	0.1%	13	1.4%
	Total	966	100.0%	921	100.0%
Dressing adherence on removal	None	617	63.3%	336	36.2%
	Minor	266	27.3%	316	34.0%
	Moderate	85	8.7%	222	23.9%
	Marked	6	0.6%	55	5.9%
	Total	974	100.0%	929	100.0%
Dressing fragmentation on removal	None	832	86.0%	696	77.1%
	Minor	102	10.5%	134	14.8%
	Moderate	33	3.4%	68	7.5%
	Marked	-	-	5	0.6%
	Total	967	100.0%	903	100.0%

the study treatments in the course of the trial; 97.1% of the documented care operations for the test group vs. 94.8% for the control group. The use of a single-layer or multilayer compression system was well balanced between the two groups.

Secondary endpoints

The data recorded at each clinical evaluation was used to calculate the relative reduction of sloughy tissue (with respect to baseline) in each group, over the 6-week treatment period with the study dressings. Considering at baseline, the wound surface area was covered by 82.6% and 80.8% of sloughy tissue, in the test and control groups, respectively, the Relative Reduction was 65.3% in the UrgoClean group vs 42.6% in the Aquacel group after 6 weeks treatment. This difference of 22.6 points was statistically significant (p=0.013).

A wound is considered debrided when its surface area is covered by less than 30% of sloughy tissue at any given clinical evaluation. The percentage of debrided wounds in the test group was significantly higher than that in the control one; 52.5% vs 35.1%, respectively, (p=0.033, Mantel-Haenszel test). In order to ensure that the observed autolytic properties of each dressing were attributed correctly, at each clinical evaluation scheduled in the protocol, the investigator documented whether or not the wound underwent mechanical debridement. On the 575 documented clinical evaluations (293 and 282 for the test and control groups, respectively), mechanical debridement was associated with 63% of the treatments, for each group.

A curette was used in more than 70% of treatments in both groups and a scalpel in about 20% of the cases; this mechanical debridement was deemed to be 'very easy/easy' in 73.8% of the treatments in the test group vs. 75.8% in the control group). The pain felt by the patient during debridement was 'moderate/marked' in 27.9% of the test group compared to 28.6% in the control group and the time devoted to mechanical debridement was generally less than 10 minutes in both treatment groups. No difference was therefore documented regarding the characteristics of the mechanical debridement operations between the groups during the course of the trial.

The trial investigators considered the performance of the test dressing to be superior to that of the control dressing based on the subjective Global Performance Score (30.1±3.9 and 27.4±5.8 for the test and control groups, respectively; p=0.002), as six of the nine parameters were considered better in the test group (Fig 2).

Local tolerance of the study dressings

A total of 16 local adverse events (LAEs) were reported by 15 patients and were considered to be potentially related to the study dressings. Seven LAEs reported by 7 patients in the UrgoClean group and 9 LAEs by 8 patients in the Aquacel group. For each group, the description of these LAEs considered to be treatment-related is given in Table 4. The two adverse events most often encountered throughout the trial consisted of pain and eczema which represented the main reasons for treatment discontinuation. The tolerability results therefore show that the two study dressings have a similar safety profile.

The investigating physician also evaluated the condition of the peri-lesional skin at each visit scheduled in the protocol. At baseline, 19.3% vs 34.2% of the test and control group, respectively, (p=0.033) was considered to be 'healthy'. At the end of the treatment with the allocated dressings, an improvement in the condition of the peri-lesional skin was noted in the test group (healthy in 44.3%), whereas the condition of the peri-lesional skin in the Aquacel group showed no change (healthy in 42.0 %).

Acceptability of the study dressings

A total of 1930 nursing treatments (988 in the test group and 942 in the control group) were documented over the 6-week study period. As described in Table 5, ease of application and conformability of the two primary study dressings were very similar. They were covered with gauze or a pad in more than 66% of the dressing treatments.

Considering the removal characteristics of the two dressings (Table 6), a real trend in favour of the UrgoClean group was documented, noted 'very easy' in about 64% of patients, compared to 47% in the control groups. No bleeding was noted in 88% and 71% of treatments in the test and control groups, respectively. Non-adherence to the wound bed was noted for more than 63% of the UrgoClean dressing changes, whereas Aquacel had non-adherence in only 36% of the treatments conducted. However, no statistical tests were performed to compare the acceptability parameters of the dressings. A high proportion of patients completed the European quality of life questionnaire EuroQolTM-5D (84.9%) during the final evaluation or when the study treatment was discontinued. No statistically significant differences between the two study groups were identified in each of the five parameters considered (mobility, self-care, daily activities, pain-discomfort and anxiety-depression). A similar mean number of dressings were used per week in the two treatment groups: 4.0±1.77 and 4.4±1.84 in the test and control groups, respectively (p=0.325).

Discussion

This EARTH clinical trial was conducted in three European countries. Its primary objective was to evaluate the efficacy of two dressings: UrgoClean (test group) and Aquacel (control group), in the local management of venous leg ulcers or mixed aetiology leg ulcers predominately of venous origin, from their debridement phase. Prior to this Earth clinical investigation, the test dressing developed by the promoter of the trial was subject to an exploratory, non-comparative clinical study in the local management of chronic wounds in the debridement phase (50 patients presenting with leg or pressure ulcers).[17]

The promising findings of this initial pilot study appeared to be similar to those reported in literature for the reference alginate and hydrofibre dressings, indicated and widely used for the local treatment of chronic, exuding wounds.[12–14,19] However, the non-controlled nature of this first study prompted Laboratoires Urgo to undertake a supplementary clinical trial to demonstrate objectively the performance of this new dressing in the wound healing process of chronic wounds.

The European EARTH clinical trial was a controlled, randomised, multicentre trial, undertaken to provide a clinical demonstration of the non-inferiority of the test dressing in comparison to a reference dressing, in the management of exuding leg ulcers. The primary endpoint of this trial was the reduction of the treated wound surface area after 6 weeks of treatment with either dressing, expressed as a percentage of the wound area reduction. The Aquacel hydrofiber dressing is recognised by the French National Authority for Health as being of therapeutic benefit for all phases of the healing process.[20] This choice is further supported by clinical trials showing this dressing to be effective and well tolerated in the local management of chronic wounds (leg ulcers) from the debridement phase.[12–14] The high level of absorbency and marked gelling capacity of the hydrofibre dressing offer autolytic properties conducive to local debridement which are atraumatic to the wound and therefore painless for the patient.

A total of 159 patients were included in this clinical trial and divided into two groups (83 and 76 patients in the UrgoClean and Aquacel groups, respectively). Patient demographics and wound characteristics were well balanced at baseline. No differences between the two groups were reported concerning factors widely recognised as being predictive of chronic wound healing, e.g. initial wound area, wound duration, and the recurrent nature of the wounds.[21,22] Treatment lasted for a median duration of 42 days in both groups. Dressings were changed a median of 3.8 times each week, with very similar management of the venous disease in both groups. There was excellent patient compliance with the venous compression systems, which was very similar in the two groups. The clinical results obtained were subjected to ITT and PP analysis.

The ITT analysis showed that after 6 weeks of treatment the surface area of the wounds had reduced by 34.1% in the UrgoClean group and by 34.4% in the Aquacel group. Within a 12% margin, it may be considered that non-inferiority had been demonstrated with a two-sided 95% CI ($p<0.025$). The PP analysis showed that after 6 weeks of treatment, the surface area of the wounds had reduced by 36.9% in the UrgoClean group and by 35.4% in the Aquacel group. Within a 12% margin, it may be considered that non-inferiority had been demonstrated with a two-sided 95% confidence interval ($p=0.01$). These two strict ITT and PP analyses yielded very similar conclusions. The non-inferiority of the test dressing in terms of efficacy, in comparison to the reference dressing, was therefore clearly demonstrated with a very high level of confidence.

This result for the principal endpoint is fully consistent with literature reports of randomised studies conducted on the hydrofibre dressing in the management of leg ulcers during the debridement phase.[12,13,23] Similarly, the conclusions arising from this study are consistent with those of various competent European authorities (French, British and Spanish) concerning the performance of different types of neutral dress-

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ings, where no differences have been demonstrated in terms of wound closure rate.[10,23,24] The recently-developed Urgo dressing, which has already been made available to clinicians in several European countries, also gave identical principal endpoint results in this clinical trial to those documented in the pilot study conducted on the same indications.[17]

Concerning the secondary endpoints of the Earth trial following 6 weeks of treatment, the autolytic debridement capacities of the UrgoClean group were significantly greater than those in the control group when analysing the relative reduction of sloughy tissue (p=0.013) and the percentage of debrided wounds (p=0.033). It can therefore be assumed that the autolytic debridement effect (reduction of fibrin covering the bed of the wound) is attributed to the dressings assessed in this clinical trial. This is supported by the fact that the number of associated mechanical debridement operations (using a dermal curette or scalpel), which could have interfered with or biased the results, were similar in the two study groups. Mechanical debridement was employed in 63% of all wound care treatments by clinicians and was conducted with the same ease and length of time for both dressings.

It has recently been reported that the clinician's assessment of sloughy tissue covering the wound bed, by simple visual examination, is both relevant and acceptable despite its subjective nature, even when compared to an assessment made by specific software.[25] This initial debridement phase (removal of sloughy tissue) only lasts a few weeks and is an essential precursor to the appropriate healing process. If managed correctly, it can reduce the time to closure of these chronic and often recurrent wounds[6,26] as sloughy tissue causes peri-lesional hypoxia, inhibiting the growth of granulation tissue and potentially delaying re-epithelialisation.[27]

As expected in the protocol hypothesis, no difference was observed between the two groups from a healing efficacy endpoint (WAR) by the end of the 6-week treatment period. However, the investigating physicians considered the test dressing superior to the reference dressing in terms of efficacy, when using a subjective Global Performance Score at the end of the treatment (p=0.001). This may be related to the fact that they believed the debridement achieved in the test group to be superior to that of the control group.

Concerning the treatments carried out during the trial (close to 1000 treatments in each group), a favourable trend emerged in favour of the test group UrgoClean for the parameters of acceptability. In particular, the test dressing was very easy to remove (63.9% vs. 47.2%), doubtless due to its non-adherence to the wound bed (63.6% vs. 36.2%). There was also less bleeding and less dressing fragmentation in the test group, though no statistical tests were conducted on these qualitative variables. Although the open-label nature of this trial means that these subjective data should be interpreted with caution, it should be noted that this favourable trend is consistent with the Global Performance Scores attributed by the investigators at the end of the trial. These scores showed that the acceptability parameters evaluated by the physicians (patient comfort, tolerance of peri-lesional skin, pain on removal, etc.) were significantly in favour of the UrgoClean group (p<0.05).

Regarding the safety profile, both study dressings were well tolerated with only rare, non-specific adverse effects presented (7 and 9 adverse effects for the test and control dressings, respectively). This is consistent with published clinical data for the Aquacel dressing[12–14] and those of the pilot study conducted on the UrgoClean dressing.[17] It should be noted that peri-lesional skin had substantially improved by the end of the trial in the test group, but not in the control group. This corroborated the findings of other clinical trials or observational studies on dressings with the same lipido-colloid technology as the test dressing.[15,16,28]

Conclusion

This EARTH European clinical trial has confirmed that the test dressing UrgoClean is similar in terms of efficacy to the control dressing Aquacel, based on the healing process. However, the autolytic debridement capacity of the test dressing was superior to that of the control dressing, as was its acceptability, documented during nursing treatments. The UrgoClean dressing, now available for health care professionals, should therefore be considered as a strategic, therapeutic approach for the management of chronic exuding wounds from their debridement phase. ■

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