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First Clinical Pilot Study on critical ischemic leg ulcers with Matrix Therapy ReGeneraTing Agent (RGTA®) technology

Abstract

Patients with non-healing leg ulcers due to severe limb ischemia and who cannot or no longer undergo vascular surgery, have high morbidity and amputation risks. A device derived from a technology of water soluble engineered biodegradable nano-polymers mimicking heparan sulphates, produced promising results in preclinical models of chronic wounds. We studied 14 chronic lower-extremity ulcers in 12 patients (median age, 71) $TcPO_2$<30 mmHg and ABPI<0.5. At baseline, mean ulcer surface area and duration were 14.15 cm^2 and 7 months respectively. The device was used twice a week and perfectly tolerated. After 4 weeks ulcer size reduction was 35% (p<0.001) (primary outcome). Increasing to 53% (p<0.001) at 8 weeks as 5 ulcers healed. Pain relief was also noted. RGTA (ReGeneraTing Agents) treatment was prolonged for 6 patients the third months and 2 healed (total 58% patients healed). Follow up for 9 patients indicated that 8 were alive at 12 months, with no ulcer reopening nor amputation nor death linked to treated ulcers. Matrix protection therapy induced significant ulcer healing to full and stable closure in patients with severe ischemia for whom no other treatment options were available. This unique, simple to use and promising technology provides a new opportunity for unmet therapeutic needs.

Keywords: Matrix Therapy, RGTA, CACIPLIQ20, ischemic ulcers, clinical trial

INTRODUCTION

Chronic leg ulcers in patients with peripheral arterial disease often require amputation.[1] Within 1 year of a diagnosis of critical limb ischemia, 25% of patients require major amputation, 25% require minor amputation, and 25% die.[2] In the US, 100,000 lower-limb amputations are performed each year because of non-healing ulcers.[3] Diabetes is the most common underlying disease in patients requiring amputation. Thus, among patients with diabetic foot ulcers, about 15% require lower limb amputation.[4,5] In 2008 in the US, an estimated 57,000 amputations were performed for critical limb ischemia and hospitalisation costs were evaluated at $3.1 billion.[6]

The main reason for amputation is the persistence of lower-extremity ulcers despite optimal multidisciplinary management. After evaluation of limb perfusion using ultrasonography Doppler and arteriography, angioplasty with or without stenting or bypass surgery is performed if feasible. However, in some patients vascular surgery is not or no more feasible or not followed by lasting ulcer healing. When limb ischemia is severe with a transcutaneous partial pressure of oxygen ($TcPO_2$) below 30 mmHg and an ankle brachial pressure index (ABPI) below 50%, healing is considered highly unlikely and amputation is usually performed in the event of life-threatening complications. These patients are therefore rarely included in controlled trials. The technology used in this study consists in inducing extra-cellular matrix repair by providing nano-sized biodegradable glycanase-resistant polymers in situ. These polymers are engineered to mimic heparan sulphates (HS), which they replace in the damaged tissue, thereby restoring the matrix scaffold. In addition, the polymers protect heparin-binding growth factors, cytokines, and chemokines from proteolysis. These effects allow the normal tissue repair process to take place. *In vivo* evidence of the tissue repair and regeneration effect of these nanobiopolymers has been obtained in preclinical models of acute ischemia of the leg[7] and myocardium[8] and in a model of necrotic skin ulcers[9], hence these heparan sulfate-mimicking nanobiodegradable engineered polymers were named ReGeneraTing Agents or RGTA.

The objective of this prospective pilot study was to evaluate a specifically adapted RGTA based class 3 device trade named CACIPLIQ20®, for the treatment of chronic lower-extremity ulcers due to Leriche and Fontaine Stage IV peripheral arterial disease in patients who were not or no more candidates for revascularisation surgery.

METHODS

This prospective uncontrolled pilot study of safety and efficacy in human patients was approved by our institutional review board in July 2006. At that time, French law did not require registration of clinical studies evaluating medical devices with the health authorities. Therefore, no authorization number was given. However, we informed the French health authorities of the study. Written informed consent was obtained from all patients before study inclusion.

Medical device and modalities of use. We studied the medical device CACIPLIQ20® (CE mark N°0499), which is a kit consisting of a vial of RGTA (carboxymethyl glucose sulphate polymer) in 5 ml of sterile saline solution, a sterile gauze pad in a blister pack and sterile forceps. The vial is completely emptied onto the gauze pad left in the opened blister and the pad is then placed on the wound bed using the forceps. Before application of the RGTA-impregnated gauze pad, the ulcer was thoroughly debrided by mechanical elimination of dead tissues, exudates, bacterial film, and fibrin, using a scalpel if needed and followed by washing with large amounts of sterile saline solution. The RGTA-impregnated gauze pad was positioned so that it covered the entire wound bed. The pad was left on the wound bed for 5 minutes then removed, as recommended by the manufacturer. The ulcer was covered with a non-adherent vaseline bandage to avoid damage to newly formed skin during dressing changes. The CACIPLIQ20® application was repeated every 3 or 4 days.

Patients. Patients consistent with our inclusion and exclusion criteria were recruited at the Henri Mondor Teaching Hospital in Créteil, France, over the 13-month period from

Case #	Age, years Sex	Ulcer location	Ulcer duration (Months)	Ulcer sizeat base-line, (cm^2)	Aspect at base-line	Appearance after 4 weeks	% SR after 8 weeks	Healing after 12 weeks	Comments	Followup (Months)	Alive at last follow-up	Healed ulcer
1	87 M	Foot, medial aspect	12	0.5	100%F	90%G 10%F	50%	Stopped	Left the study after 8 weeks, AHT	Lost to follow-up		
2	86 F	Foot, medial edge	6	0.45	100%F	20%F 80% G	80%	Healed	Hypertension, myocardial infarction, AHT	24	Yes	Yes
2	Heel		6	1.05	30%F 70%G	Healed	100%				Yes	Yes
3	85 F	Lef, medial aspect	10	9.1	10%F 90%G	90%G 10%F	20%	Stopped	Bacterial infection between 4 and 8 weeks.HTA Healed later	24	Yes	Yes
4	83 M	Foot, sole	2	5.6	30%F 70%G	100% G	50%	Not healed	Renal dialysis, died months after study completion from unrelated causes, HTA	16	No	No
5	88 M	Big toe, lateral aspect	> 18	0.99	100%F	70%F 30%G	0%	Not healed	Died from cachexia, HTA, Smoker	2	No	
6	93 F	Lateral malleolus	4	73.8	20%F 80%G	95%G	15%	Healed Other slowly healing ulcers, HTA	Lost to follow-up			
7	74 M	Foot, lateral edge	> 12	2.4	100%G	100%G 62% SR	100%			24	Yes	Yes
8	63 M	Heel	7	0.7	20%F 80%G	100%G	30%	Not healed	Bacterial infection, bladder carcinoma, HTA	24	Yes	No
9	62 M	Stump ulcer	1	49	20%F	100G 70% SR	100%		Diabetes	12	Yes	Yes
9		2 weeks after femoral amputation		15	80%G	78% SR	100%			12	Yes	Yes
10	89 F	RF Amputation of big toe	>12	0.6	50%F 50%G	100%G	100%		HTA	Lost to follow-up		
11	78M	Transmeta-tarsal amputation	1	41.2		90% G 42% SR	56%	Not healed		24	Yes	Yes
12	62 M	RF, Toe amputation	2	24		30% SR stopped the treatment			Amputation of 4 toes 3 months later then healed with CACPLIQ20® (out of the study). HTA. Diabetes, Smoker.	24	Yes	Yes
Total	Mean					1 healed, 13	Remain 12	Remain 8		8 alive at		

Table 1. Patients included in the study and wound evolution after CACIPLIQ20® treatment M, male; F female; F, fibrin; G, granulation tissue; SR, Surface Reduction, RF Right Foot, F Fibrine, G Granulation.

November 2006 to December 2007. Patients were eligible for the study if they had Stage IV peripheral arterial disease (Leriche and Fontaine classification) documented by two evaluations done at least 1 week apart by two different investigators and either at least one chronic lower-extremity ulcer or a chronic ulcer related to amputation, with "chronic" being defined as 2 months' duration at least, with no evidence of healing. Ankle systolic pressure lower than 70 mmHg or toe systolic pressure lower than 30 mmHg on the affected side was required, as well as arteriographic and Doppler evidences of severe peripheral arterial disease in the relevant territory obtained within the last 3 months. In addition, patients had to have an ABPI below 50% and a $TcPO_2$ below 30 mmHg. Before study inclusion, the case of each potentially eligible patient was discussed at a meeting of physicians and surgeons. Only patients who were deemed ineligible for revascularisation surgery were included. Non-inclusion criteria were as follows: age younger than 18 years, pregnancy, breastfeeding, woman not using effective contraception, eligibility for revascularisation surgery, participation in another trial within the past 4 weeks, social or psychological factors deemed to carry a high risk of poor adherence to the study treatment, mental disorders likely to prevent the patient from expressing pain, and inability or unwillingness to provide informed consent. Furthermore, as required by French law we did not include patients without health insurance.

Baseline evaluation. For each patient, we recorded age, sex, co-morbidities, and characteristics of the ulcer (including duration). Systolic blood pressure was measured at the brachial artery and ankle and the values were used to compute the ABPI. $TcPO_2$ was measured, when possible, near the ulcer.

Study treatment and monitoring time points. CACIPLIQ20® was applied every 3-4 days until complete healing or for up to 10 weeks. The impregnated gauze pad with CACIPLIQ20® solution was then applied to the wound for 5 minutes as established on preclinical models.[10] After removal of the gauze, the wound was covered by a non-adherent dry secondary dressing. Extensive debridment is a key step to give access to the bed of the wound in order to have full effect of CACIPLIQ20®. The study treatment consisted in CACIPLIQ20® applications twice a week for 1 month.

Patients whose lesions were not completely healed at the end of the first month could request a second month of treatment, and patients with persistent lesions after two months could request a third month of treatment. The effects of the treatment were evaluated at the following time points: day 3, week 1, week 2, week 3, and week 4, then every 4 weeks until week 12.

Other treatments. Patients continued their usual treatments including antiplatelet and anticoagulant regimens. Analgesics were given in doses that ensured pain relief in the recumbent position. Infusions of prostacyclin or its derivatives were not allowed during the week before study treatment initiation and were avoided whenever possible during the study treatment. No topical preparations containing silver or other metal ions or iodine were used, as they inactivate CACIPLIQ20®. Neither negative pressure therapy nor hyperbaric therapy was allowed during the study treatment.

Follow up. As most patients returned for the treatment of their vascular disorders and check, follow up was possible.

Endpoints. The primary efficacy criterion was the percentage of ulcer healing computed by dividing the ulcer surface area at week 4 by the surface area at baseline. Ulcer surface area was calculated by multiplying the longest ulcer diameter by the shortest ulcer diameter, measured by holding a graduated disposable ruler near the ulcer.

Secondary efficacy criteria were (i) the percentage of ulcer healing assessed as described above at the following time points: week 1, week 2, week 3, week 8, and week 12; (ii) analgesic consumption assessed by patient interview at weeks 4 and 8; and (iii) need for amputation.[11] Analgesics were classified according to the WHO pain relief ladder (http://www.who.int/cancer/palliative/painladder/en/).

Statistical analysis: The paired Student t-test was used to assess differences in ulcer surface area between time points. Values of *p* smaller than 0.05 were considered significant.

RESULTS

Patients *(Table 1).* We included 15 patients with a median age of 71 years (range, 49-93 years). Among them, three had diabetes, which was well controlled. One patient died after two weeks from metastatic cancer, one patient requested an amputation after one week, and one patient left the study after one week. These patients were excluded from the analysis. Two patients each had two ulcers, yielding 14 ulcers for the analysis. Of the patients with two ulcers, one had the second ulcer develop after the first healed, and the other had two ulcers simultaneously but at different sites. Therefore, the ulcers in these patients were handled as independent events.

At baseline, mean ulcer surface area was 14.15 cm^2 (range, 0.5-73 cm^2) and mean recorded ulcer duration was 7.5 months (1-18 months) *(Table 1).* Table 1 reports ulcer locations and appearance. Two patients (#9 and #11) had amputation stump ulcers with a time from amputation to study treatment initiation of less than 1 month.

Ischemia was assessed after angiography, Doppler measures, $TcPO_2$ and ABPI. *Table 2* reports the last two values for each patient. Two of the recruited patients had $TcPO_2$ above 30% or ABPI above 0.5 but fulfilled all other recruitment conditions and were not candidate to vascular surgery.

Safety. No adverse effects of CACIPLIQ20® were recorded. Moreover, some patients reported a feeling of relief a few minutes after each application, although no specific records of this effect were kept.

Ulcer surface area *(Figures 1 and 3).* The percentage of healing at 4 weeks versus baseline (primary efficacy criterion, *Figure 2*) was statistically significant (35%, $p<0.001$). At 2 weeks, healing was already significant versus baseline (19%, $p<0.02$). CACIPLIQ20® treatment consistently decreased the surface area covered with fibrin and increased the surface area of granulation tissue. *Table 1* reports changes in ulcer appearance at 4 and 8 weeks and *Figure 1* ulcer healing progression at 2 and 4 weeks. Of the 14 ulcers, 12 showed evidence of healing at 2 weeks *(Figure 1a),* and one ulcer was completely closed at 4 weeks *(Figure 1b).*

All patients with persistent ulcers at 4 weeks chose to continue the study treatment. The percentage of healing continued to increase, to 53% at 8 weeks ($p<0.001$, *Figure 2*), when four more ulcers were closed (5/14, 36%) *(Figure 3).* Two patients showed no improvement (#5 and #8); among them, one died 2 months later from cachexia syndrome and the other had bladder cancer.

A third month of treatment was requested by 6 patients (6 ulcers) of the 8 patients (8 ulcers) with persistent ulcers at week 8. At week 12, two additional ulcers were closed. Thus, 7 of 14 ulcers were closed at 3 months (50%).

Follow up. It was possible to follow 9 patients of the initial 12 for two years. 8 were still alive at 12 months and 6 at 24 months. There was no reopening of the closed ulcer and none →

Case #	Age, years, Sex	$TcPO_2$ (mmHg)	APBI
1	87 M	NA	0,6
2	86 F	28	0,4
3	85 F	7	NA
4	83 M	21	0,5
5	88 M	17	0,4
6	93 F	NA	NA
7	74 M	8	NA
8	63 M	16	0,2
9	62 M	27	NA
10	89 F	69	0,4
11	78 M	53	0,8
12	62 M	NA	0,5

Table 2. Vascular parameters of the patients treated with CACIPLIQ20®. Values of the $TcPO_2$ and ABI of the patients that were treated with CACIPLIQ20® are represented in this table. All patients have undergone an angiography and Doppler to characterise their ischemic condition. Following all these analyses, none was a candidate for revascularisation at the moment the study was performed. NA: not available for clinical reasons (amputation, pain).

→ of these patients was amputated as a consequence of the ulcer. Out of the 6 patients with persistent ulcers at week 12, one patient experienced healing of the ulcer and was still alive after 2 years; the remaining three patients had no change in ulcer size or appearance after study treatment discontinuation. None required amputation for the CACIPLIQ20®-treated ulcer. One underwent amputation of the other leg and two died from causes unrelated to the ulcer.

Pain and analgesic consumption. *Table 3* shows changes in analgesic use expressed by assigning 1 arbitrary unit (AU) to step 1 analgesics, 2 AU to step 2 analgesics, and 3 AU to step 3 analgesics. At baseline, 11 patients were taking analgesics. Among them, 4 were taking class 3 analgesics and 7 class 2 analgesics, yielding 27 AU. The AU number was 14 at 4 weeks (51.8%) and 11 (60% of baseline) at 8 weeks.

DISCUSSION

In this study of patients with chronic lower-extremity ulcers due to limb ischemia ($TcPO_2$<30mm, ABPI<0.5) who were not eligible for revascularisation surgery, the percentage of ulcer healing at 4 weeks was statistically significant versus baseline (35%). As these patients had not responded to conventional wound care before the study, no healing was expected to occur without the studied treatment. Furthermore, 7 (50%) of 14 ulcers healed completely with 1 to 3 months of CACIPLIQ20® treatment. All ulcers showed evidence of healing except in one patient with severe cachexia who died shortly after study completion.

This high rate of ulcer healing in patients with severe ischemia and no response to conventional wound care is consistent with

	No (0 arbitrary units)	Class 1 (1 arbitrary units)	Class 2 (2 arbitrary units)	Class 3 (3 arbitrary units)	TOTAL (arbitrary units)
T0	1	0	7	4	27
4 weeks	5	2	3	2	14
8 weeks	7	1	1	3	11

Table 3. Painkilling class treatment. Evolution of the painkilling class treatment as determined by the sum of the patients of the painkilling class analgesics multiplied by the corresponding arbitrary unit.

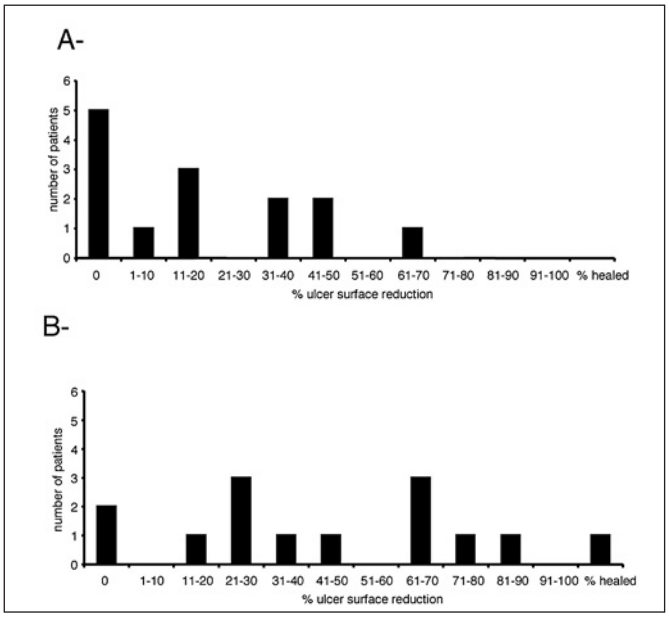

Figure 1. Ulcer surface reduction after 2 (A) and 4 (B) weeks of CACIPLIQ20 treatment The percentage of ulcer surface reduction was calculated by dividing the ulcer surface area at 2 or 4 weeks by the ulcer surface area at baseline.

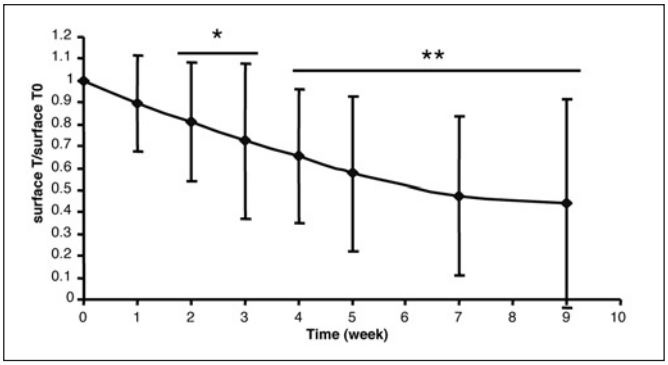

Figure 2. Changes in ulcer size during CACIPLIQ20® treatment. Mean ulcer surface area at each time point divided by ulcer surface area at baseline is shown for each treatment week. The vertical bars show the SDs *p<0.05 versus baseline (T0). **p<0.001 versus baseline (T0).

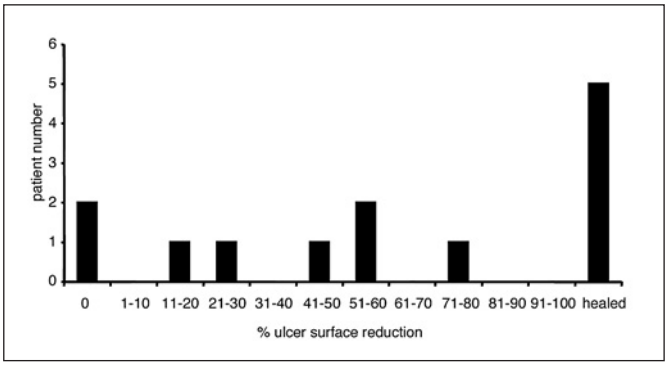

Figure 3. Ulcer surface area reduction after 8 weeks of CACIPLIQ20 treatment. The percentage of ulcer surface reduction was calculated by dividing the ulcer surface area at 2 or 4 weeks by the ulcer surface area at baseline.

preclinical studies of RGTA on ischemic muscles and chronic necrotic skin ulcers.[7,9] CACIPLIQ20® induced healing despite low $TcPO_2$ and ABPI values. Granulation tissue started to form rapidly after treatment initiation on ulcers that had shown no regenerative activity for months.

Recommendations for using CACIPLIQ20® must be followed carefully. Thorough debridment is crucial. More specifically, fibrin must be removed, as fibrinogen binds heparin via numerous heparan binding sites and would therefore bind CACIPLIQ20®. RGTAs are inactivated by agents containing silver ions and, more generally, divalent cations that chelate sulphate and carboxylic groups, as well as iodine-containing solutions. CACIPLIQ20® applications conditions were established from mice chronic ulcer model and a clinical study with a related RGTA adapted for corneal ulcers.[7,9] Optimum frequencies of applications were every three days (practically twice a week) and dosage was best at 100 microg/ml. Ulcers closure did not improve if RGTA was applied for a longer period of time than 5 minutes, in coherence with the its strong binding affinity for heparin binding growth factors such as FGF or TGFb (10nM-30nM).[7,9,12,13] In theory, local application of CACIPLIQ20® might induce local skin type IV delayed hypersensitivity with redness, swelling and rush similar to all heparin-like agents.[14] This was not observed in this study and CACIPLIQ20® was very well tolerated.

The marked pain relief induced by CACIPLIQ20® treatment is intriguing and was observed but not quantified in all patients. Heparin has long been reported to relieve pain and is used to alleviate pain caused by burns.[15] RGTA therapy used for corneal ulcers also induced pain relief, with the VAS pain score decreasing from 72/100 at baseline to 50/100 after one week and 29/100 after 4 weeks ($p<0.001$).[16] The mechanisms of this effect are unknown. Some patients with ischemic leg ulcers experience unbearable pain. Thus, the pain- relieving effect of CACIPLIQ20® is a valuable advantage.

Our study has a number of limitations. First, we enrolled only 12 patients. Second, we had no control group of patients not given CACIPLIQ20® therapy. Third, we did not assess the cost-effectiveness of CACIPLIQ20® therapy. Finally, although no adverse effects of the study treatment were recorded, this finding may be ascribable to the small sample size.

CONCLUSION

This pilot study provides the first evidence that matrix therapy is effective for chronic ischemic lower-extremity ulcers in humans. The study patients had CLI or severe limb ischemia (a condition whose prognosis is grim). The widely accepted $TcPO_2$ cut-off below which healing is considered extremely unlikely is 30 mmHg although this value is as low as 10 mmHg in some studies. In patients with CLI who receive the current standard treatment, about half die or require major amputation within the first year. In highly specialized units, revascularisation is attempted in over 90% of patients with CLI and obviates the need for amputation in 75% of cases. However, revascularisation is either not feasible or fails in 14% to 20% of CLI patients.[17] In our population of 12 patients, one would have expected half of the patients either dead or amputated in the year as a consequence of the ulceration. Interestingly none required amputation and two years later none of the patients was amputated nor died as a consequence of the non healed ulcer. The population is too small to draw a conclusion and moreover one has to be cautious as a major cause of amputation remains the infection of the wound. Since completion of this study, 30 additional patients with similar characteristics have received CACIPLIQ20® treatment, also to good effect. Thus, RGTA-based matrix therapy holds considerable promise for patients with non-healing ischemic lower-extremity ulcers for whom no other treatment options are available. ■

Conflict of interest statement: **Both DB and KK are shareholders and employees of OTR3, DB is patent holder of the technology. PD holds below 1% shares and options in OTR3 as patent inventor but no royalties and other fringe benefits. No other direct or indirect benefits were attributed to the other co-authors.**

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