ADVANCED THERAPIES IN WOUND MANAGEMENT

Prof. Dr. Alberto Piaggesi

Diabetic Foot Section - Department of Medicine
University of Pisa - Italy
DISCLOSURE

- Clox Scientific board
- Collplant Consultant, scientific board
- Urgo Advisory board, co-investigator in a multicenter trial
- Optima Molliter Consultant,
WHY ADVANCED THERAPIES FOR WOUNDS MANAGEMENT

• People age and morbidity
• Chronic wounds
• Their severity and duration
• Recurrences
• Complications
• Costs of management

They all are increasing in developed Countries
WHY ADVANCED THERAPIES FOR WOUNDS MANAGEMENT

The future scenario

• More complex patients
• More difficult-to-treat ulcers
• More recurrences
• More complications
• More costs
The Diabetic Foot Syndrome

Editors
A. Piaggesi
J. Apelqvist
THE DIABETIC FOOT SYNDROME

Chronic Metabolic Disturbance

- Hypertension
- Atherosclerosis
- Visual Impairment
- Retinopathy
- Dyslipidemia

DIABETES

- NEUROPATHY
- TRAUMA
- ARTERIOPATHY

ULCER

INFECTION

AMPUTATION

Progressive Cognitive Disorder

[Piaggesi et al. Front Diabet 2017]
THERAPEUTIC APPROACH

- Off-loading
- Re-vascularization
- Control of infection
- Management of co-morbidities
- Local care
- Follow-up
Effectiveness of interventions to enhance healing of chronic ulcers of the foot in diabetes: a systematic review

Abstract

The outcome of management of diabetic foot ulcers remains a challenge, and there remains continuing uncertainty concerning optimal approaches to management. It is for these reasons that in 2008 and 2012, the International Working Group of the Diabetic Foot (IWGDF) working group on wound healing published systematic reviews of the evidence to inform protocols for routine care and to highlight areas, which should be considered for further study. The same working group has now updated this review by considering papers on the interventions to improve the healing of chronic ulcers published between June 2010 and June 2014. Methodological quality of selected studies was independently assessed by two reviewers using Scottish Intercollegiate Guidelines Network criteria. Selected studies fell into the following ten catego-
When the results of this updated review are taken together with those of the earlier report, they provide limited evidence to justify change in routine clinical practice. There are still no good studies to support the use of topical applications or dressing products, a finding supported by Cochrane reviews [18,139–142].

[Game et al. Diabetes Metab Res Rev, 2016]
ADVANCED THERAPIES IN WOUND MANAGEMENT

CELLS AND TISSUE-BASED THERAPIES, PHYSICAL AND BIO-PHYSICAL THERAPIES, SMART AND IT-BASED TECHNOLOGIES

HEALTH ECONOMICS AND REGULATORY ISSUES

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ADVANCED THERAPIES IN WOUND HEALING

• Materials
• Cellular therapies
• Engineered tissues
• Physical therapies
• Smart technologies
ADVANCED THERAPIES IN WOUND HEALING

• Materials
• Cellular therapies
• Engineered tissues
• Physical therapies
• Smart technologies
Neoarteries grown *in vivo* using a tissue-engineered hyaluronan-based scaffold

Barbara Zavan,* Vincenzo Vindigni,†,† Sandro Lepidi,‡ Ilaria Iacopetti,¶
Giampiero Avruscio,§ Giovanni Abatangelo,* and Roberta Cortivo*

*Department of Histology, Microbiology, and Medical Biotechnologies; †Clinic of Plastic Surgery,
‡Clinic of Vascular Surgery, §Unit of Angiology, and ¶Department of Veterinary Sciences, University
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**ABSTRACT** Vascular tissue engineering has emerged as a promising technology for the design of an ideal, responsive, living conduit with properties similar to that of native tissue. The missing link in tissue-engineered blood vessels is elastin biosynthesis. Several biomaterials are currently used but few support elastin biosynthesis in a 3-D array. In previous studies, we demonstrated that a hyaluronan-based scaffold (HYAFF-11™) grafted in the infrarenal rat aorta successfully guided the complete regeneration of a well-functioning small-diameter (2 mm) neoartery. The aim of the present study was to test the ability of HYAFF-11 biodegradable grafts to develop into neovessels of larger size (4 mm) in a porcine model, focusing on extracellular matrix

**There is a considerable clinical need for alternatives to the autologous vein and artery tissues used for vascular reconstructive surgeries such as coronary bypass, lower limb bypass, arteriovenous shunts, and repair of congenital defects to the pulmonary outflow tract.** Thus far, synthetic materials have not matched the efficacy of native tissues, particularly in small-diameter applications (1). The development of cardiovascular tissue engineering introduced the possibility of a living, biological graft that might mimic the functional elastic properties of native vessels (1, 2). A major structural element of arterial walls is elastic fiber, which endows vessels with the critical property of elastic recoil (2). In arteries, elastin dictates tissue mechanics at low strain before stiffer collagen fibers are engaged. Elas-
In vivo regeneration of small-diameter (2 mm) arteries using a polymer scaffold

Sandro Lepidi, * Giovanni Abatangelo, † Vincenzo Vindigni, † ‡ Giovanni Paolo Deriu, * Barbara Zavan, †Carolin Tonello, † and Roberta Cortivo †

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Bioactive glass in tissue engineering

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Published in final edited form as:

BIO-ACTIVE GLASS

Bioactive Glass Surface Reaction

- Adhesion of Ca²⁺, PO₄⁻ and CO₃⁻ ions to the silica gel surface, forming bone-like HA.
- Bone-forming cells colonize the surface of the HA-coated bioactive glass.
- Crystallization of the bone-like matrix and maturation of bone cells lead to new bone formation.
Letter to the Editor

BIOACTIVE GLASS S53P4: a new opportunity for the treatment in the diabetic foot osteomyelitis

R. De Giglio\textsuperscript{a}, I. Stefani\textsuperscript{a}, T. Mondello\textsuperscript{a}, G. De Filippis\textsuperscript{b}, A. Mazzone\textsuperscript{a,\ast}

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\url{https://doi.org/10.1016/j.ejim.2018.04.015}

Received 17 April 2018; Accepted 19 April 2018

0953-6205/\copyright 2018 Published by Elsevier B.V. on behalf of European Federation of Internal Medicine.
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<th>No.</th>
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<th>Level of evidence (for each indication)</th>
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<td>Hydrocolloids</td>
<td>STSG donor sites</td>
<td>2c</td>
<td>Likely to perform equal to other approaches; great variability among the trials</td>
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<td></td>
<td>(including hydrofibres)</td>
<td>DFUs</td>
<td>2c</td>
<td>Low-quality results; Likely to perform equal to other approaches; great variability among the trials; hydrofibers are less cost-effective than other non-adherent dressings</td>
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<td>VLUs</td>
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<td>Low-quality results; likely to perform equal to other approaches; great variability among the trials</td>
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<td>PUs</td>
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<td>Low-quality results; likely to perform equal to other approaches; great variability among the trials</td>
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<td></td>
<td></td>
<td>Burns</td>
<td>2c</td>
<td>Potential benefits lack systematic analysis; RCT performed used dressing-containing silver</td>
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<tr>
<td>2</td>
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<td>STSG donor sites</td>
<td>1b</td>
<td>Moderate-quality evidence</td>
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<td>VLUs</td>
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<td>Low-quality results; likely to perform equal to other approaches; great variability among the trials</td>
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<td>Hydrogels</td>
<td>Burns</td>
<td>2c</td>
<td>Poor-quality results; heterogeneity of the studies</td>
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<td>DFUs</td>
<td>2c</td>
<td>Moderate-quality level of evidence in relation to traditional gauze dressing; likely to perform equal to other approaches</td>
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<td>VLUs</td>
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<td>Based on RCT results, other alternatives may be equally reasonable; high risk of bias; heterogeneous studies; poor quality of analysis performed</td>
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<td>PUs</td>
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<td>PUs</td>
<td>2c</td>
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<td>6</td>
<td>Acellular Matrices</td>
<td>Burns</td>
<td>2c</td>
<td>Based on RCT results, other alternatives may be equally reasonable; short-term results</td>
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<td>2c</td>
<td>Potential benefits lack systematic analysis; RCT performed under different conditions and different inclusion criteria</td>
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<tr>
<td></td>
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<td>VLUs</td>
<td>2c</td>
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</tbody>
</table>

STSG—split-thickness skin graft; DFU—diabetic foot ulcer; VLU—venous leg ulcer; PU—pressure ulcer
ADVANCED THERAPIES IN WOUND HEALING

- Materials
- Cellular therapies
- Engineered tissues
- Physical therapies
- Smart technologies
PHASES OF TISSUE REPAIR AND REGENERATION

WOUND

LAG
• Haemostasis
• Inflammation
• Cytokine release

PROLIFERATIVE
• Neo-angiogenesis
• Matrix formation
• Re-epithelialization

REMODELLING
• Cellular decrease
• Matrix organization

[3] 5 7

21 Days

[Singer et al. 1999]
CELL THERAPY FOR WOUND HEALING

- Contrast Infection
- Reduce inflammation
- Promote angiogenesis
- Promote fibrogenesis
- Attract progenitor cells
- Speed healing
- Increase quality of healing
CELL THERAPY FOR WOUND HEALING

- **Cells**
  - Platelets
  - Leucocytes
  - Keratinocytes
  - Fibroblasts
  - Adipocytes
  - Stromal cells

- **Source**
  - Peripheral Blood
    - Autologous
    - Eterologous
  - Umbilical Cord
    - Eterologous
  - Skin
    - Autologous
    - Eterologous
  - Sub-cutaneous fat
    - Autologous

- **Application**
  - Direct
  - Spray
  - After manipulation
  - Combined
PLATELETS
Effectiveness of Platelet Releasate for the Treatment of Diabetic Neuropathic Foot Ulcers

David J. Margolis, MD, MScE1,2 Jonathan Kantor, MA2 Jill Santanna, MS2 Brian L. Strom, MD, MPH2 Jesse A. Berlin, ScD2

Objective — The goal of this study was to specifically estimate the effectiveness of platelet releasate, a widely available treatment administered by a proprietary group of wound care centers (WCCs) for the treatment of diabetic neuropathic foot ulceration.

Research Design and Methods — Treatment effectiveness was estimated in a retrospective cohort study controlling for treatment selection bias using logistic regression-derived propensity scores.

Results — Platelet releasate was more effective than standard care. The relative risk for a wound to heal after treatment with platelet releasate compared with standard care at a WCC varied from 1.14 (95% CI 1.03–1.27) to 1.59 (1.49–1.70). The effect was greatest in those with the most severe wounds, i.e., large wounds that affect deeper anatomical structures.

Conclusions — Within the limitations of the ability of propensity score analysis to control for selection bias, platelet releasate is more effective than standard therapy. This effect is more pronounced in more severe wounds. Unfortunately, severe wounds have not been evaluated in randomized clinical trials of new interventions. We encourage the inclusion of these patients in future trials.

Diabetes Care 24:483–488, 2001
Effectiveness of Platelet-Rich Plasma to Enhance Healing of Diabetic Foot Ulcers in Patients With Concomitant Peripheral Arterial Disease and Critical Limb Ischemia

Nikolaos Kontopodis, MD¹, Emmanouhil Tavlas, MD¹, George Papadopoulos, MD¹, Dimitrios Pantidis, MD¹, Alexandros Kafetzakis, MD¹, George Chalkiadakis, MD, PhD¹, and Christos Ioannou, MD, PhD¹

Abstract
We sought to investigate the effect of autologous platelet-rich plasma (PRP) on the healing rate of diabetic foot ulcers in patients with diabetes and concomitant peripheral arterial disease (PAD). Diabetic patients with foot ulceration presenting with PAD who were treated with local growth factors in a single center, during a 24-month period from May 2009 to April 2011, were retrospectively reviewed. Based on the severity of PAD, subjects were divided into groups A (Fontaine classification stages I, IIa, and IIb) and B (Fontaine classification stages III and IV), with those included in the latter being considered to suffer from critical limb ischemia (CLI). End points of the analysis were clinical improvement, limb salvage, and amputation rate. Outcome was compared between groups A and B. Overall, 72 patients were evaluated, 30 with CLI. Ulcer area reduction >50% was observed in 58/72 patients while reduction >90% was achieved in 52/72 patients. There were 14 (19%) major and minor amputations, whereas the limb salvage rate was 89%. This variable was significantly different between groups A and B (100% vs 73%, P < .001), as is rate of reduction in ulcer area >90% (83% vs 56%, P = .02). Reduction of ulcer area >50% was observed in the majority of patients in both groups (group A 86% vs group B 73%, P = .23). In conclusion, PRP could serve as a useful adjunct during management of diabetic foot ulcers even in diabetic patients with unreconstructable arterial disease.

Keywords
growth factors, ulcer healing, limb salvage, amputation rate
# GROWTH FACTORS

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<tr>
<td>Macrophages</td>
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</tr>
<tr>
<td>Fibroblasts</td>
<td>FGF, KGF, PDGF</td>
</tr>
<tr>
<td>Monocytes</td>
<td>EGF, TGF-β</td>
</tr>
<tr>
<td>Condrocytes</td>
<td>FGF</td>
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<tr>
<td>Mastocites</td>
<td>FGF</td>
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<tr>
<td>Myocytes</td>
<td>FGF</td>
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<tr>
<td>Neutrophils</td>
<td>VEGF</td>
</tr>
</tbody>
</table>
Research Article

Antibacterial Effect of Autologous Platelet-Rich Gel Derived from Subjects with Diabetic Dermal Ulcers In Vitro

Lihong Chen,¹ Chun Wang,¹ Hengchuan Liu,² Guanjian Liu,³ and Xingwu Ran¹

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Received 13 December 2012; Accepted 29 January 2013

Academic Editor: Weiping Jia
Research Article

Treatment of Nonhealing Diabetic Lower Extremity Ulcers with Skin Graft and Autologous Platelet Gel: A Case Series

Yuan-Sheng Tzeng,¹ Shou-Cheng Deng,¹ Chih-Hsing Wang,¹ Jui-Che Tsai,² Tim-Mo Chen,¹ and Thierry Burnouf³

¹ Division of Plastic Surgery, Department of Surgery, Tri-Service General Hospital, National Defense Medical Center, 11490 Taipei, Taiwan
² Department of Materials Engineering, Tatung University, 10452 Taipei, Taiwan
³ Human Protein Process Sciences, 59000 Lille, France & Institute of Biomaterials and Tissue Engineering, Taipei Medical University, 11031 Taipei, Taiwan

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Received 20 September 2012; Accepted 24 November 2012

Academic Editor: David G. Armstrong
LEUCOCYTES
Use of an autologous leucocyte and platelet-rich fibrin patch on hard-to-heal DFUs: a pilot study

- **Objective:** Leucopatch is a leucocyte and platelet-rich fibrin patch that provides concentrated blood cells and signal substances to the surface of an ulcer. It is produced by centrifugation of the patient's own venous blood. The aim of this pilot multicentre cohort study was to evaluate effects of the leucocyte patch in patients with hard-to-heal diabetic foot ulcers (DFUs).

- **Method:** Non-ischaemic Wagner grade 1 or 2 DFUs with a duration of more than 6 weeks and a maximal area of 10cm² were included. Patients with >40% ulcer area change during a two-week run-in period were excluded. The treatment was applied once a week for up to 19 treatments or until the foot ulcer was completely epithelialised. The primary endpoint was healing within 20 weeks.

- **Results:** Of the 60 patients who gave consent 16 were excluded during run-in period, 44 patients initiated study treatment and 39 were included in the per-protocol analysis. Complete epithelisation was achieved in 34% (per-protocol analysis 36%) at 12 weeks and 52% (59%) at 20 weeks. In patients with ulcer duration less than 6 months, 73% of ulcers healed within 20 weeks. Patients with healed ulcers had larger ulcer area reduction during the first two treatment weeks compared to non-healers. Adverse events were mild and rare.

- **Conclusion:** The leucocyte patch is well-tolerated, easy to use and has potential in the armamentarium of the DFU treatment, provided this outcome is confirmed in an appropriately powered randomised clinical trial.

- **Declaration of interest:** M.L and L.T have received consultation fees from Reapplix A/S. R.L is co-inventor of the Leucopatch technology. All other authors declare no duality of interest associated with this manuscript. This study was financed by Reapplix A/S. Time to data analysis and manuscript preparations have been financed by Medical Faculty (ALF), Lund University, Lund Sweden.

diabetic foot ulcer, platelet-rich fibrin, healing, autologous cell therapy
HOW 3CP TECHNOLOGY PRODUCES A LEUCOPATCH

3CP™

Centrifugation Coagulation Compaction Process

Centrifugation (to separate cells)  Coagulation (complete fibrin polymerisation)  Compaction (of fibrin to form the patch)

[Courtesy Dr. R. Lundqvist, Reapplix S.A.]
LeucoPatch system for the management of hard-to-heal diabetic foot ulcers in the UK, Denmark, and Sweden: an observer-masked, randomised controlled trial

Frances Gane, William Jeffersot, Lisa Tarnow, Judith J. Jacobson, Diane Whitley, Eleanor F. Harrison, Sharon J. Blender, Deborah Fitzsimmons, Magnus Lindahl, for the LeucoPatch II trial team.

Summary

Background The LeucoPatch device uses bedside centrifugation without additional reagents to generate a disc comprising autologous leukocytes, platelets, and fibrin, which is applied to the surface of the wound. We aimed to test the effectiveness of LeucoPatch on the healing of hard-to-heal foot ulcers in people with diabetes.

Methods This was a multicentre, international, observer-masked, randomised controlled trial of people with diabetes and hard-to-heal foot ulcers done in 32 specialist diabetic foot clinics in three countries (UK, Denmark, and Sweden). After a 4-week run-in period, those with a reduction in ulcer area of less than 50% were randomly allocated (1:1) by computer-generated, web-based randomisation (block sizes of two, four, and six) to either prespecified good standard care alone or care plus weekly application of LeucoPatch. The primary outcome was the proportion of ulcers that healed within 20 weeks assessed in the intention-to-treat population (all participants with post-randomisation data collected), defined as complete epithelialisation (confirmed by an examiner who was masked to randomisation group), and remained healed for 4 weeks. This trial is registered with the ISRCTN registry, number 27665670, and ClinicalTrials.gov, number NCT02224742.

Findings Between Aug 30, 2013, and May 3, 2017, 269 participants were randomly allocated to receive treatment (137 to receive standard care and 132 to receive LeucoPatch). The mean age was 61·9 years (SD 11·6), 217 (82%) were men, and 222 (83%) had type 2 diabetes. In the LeucoPatch group, 45 (34%) of 132 ulcers healed within 20 weeks versus 29 (22%) of 134 ulcers in the standard care group (odds ratio 1·58, 96% CI 1·04–2·40; p=0·0235) by intention-to-treat analysis. Time to healing was shorter in the LeucoPatch group (p=0·0246) than in the standard care group. No difference in adverse events was seen between the groups. The most common serious adverse event (SAE) was diabetic foot infection (24 events in the LeucoPatch group [24% of all SAEs] and 20 in the standard care group [27% of all SAEs]). There were no device-related adverse events.

Interpretation The use of LeucoPatch is associated with significant enhancement of healing of hard-to-heal foot ulcers in people with diabetes.

Funding Reapprx ApS.

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Introduction

Diabetic foot ulcers are common and are a major source of disability, distress, and cost. Healing is often delayed for many months and amputation is common. The incidence of new ulceration after healing is about 40% at 12 months, thus diabetic foot ulcers can be a financial burden for patients, their families, and health-care services.4,5 There is an absence of treatments that have been proven to be effective, which relates to the quality of available research, which is mostly of poor design.6

Trials that seek to document the effectiveness of treatments for this complex clinical problem should conform to defined criteria for trial design and reporting, which has not been done thus far.7 To that end, it is necessary that the evaluation of any treatment should be undertaken in a population that responds poorly to good standard care (ie, hard-to-heal ulcers) and should be based on a comparison of the effect of the treatment being tested with contemporaneous controls in an appropriately blinded randomised trial.

One possible treatment option for non-healing ulcers is the use of platelet-rich plasma or platelet-rich fibrin, which might promote healing of hard-to-heal ulcers in people with diabetes, as assessed by the release of cytokines and growth factors involved in tissue repair, angiogenesis, and inflammation.8-11 Although the use of platelet preparations is not new, evidence of their benefits is inconsistent.12-14 However, the recent development of multi-layered patches comprising autologous leukocytes, platelets, and fibrin, which can be made by the bedside and without adding any reagents (Leucopatch, Reapprx ApS, Birkerød, Denmark; appendix), is a possible new option.15-18 Two pilot studies, of which one included participants with hard-to-heal diabetic foot ulcers only,
HEALING RATE AT 20 WEEKS

Δ 12%; OR 1.58 (95% CI 1.04 – 2.04; p = 0.0237)
TIME TO HEAL

Hazard ratio 1.709
(95% CI 1.071–2.728);
p = 0.0246
FIBROBLASTS & KERATINOCYTES
HYAFF 11-Based Autologous Dermal and Epidermal Grafts in the Treatment of Noninfected Diabetic Plantar and Dorsal Foot Ulcers

A prospective, multicenter, controlled, randomized clinical trial

Carlo Caravaggi, md\(^1\)
Roberto De Giglio, md\(^1\)
Chiara Pirelli, md\(^4\)
Manuela Sommaria, md\(^1\)
Sergio Dalla Noce, md\(^1\)
Ezio Faglia, md\(^2\)
Manuela Mantero, md\(^2\)
Giacomo Clerici, md\(^3\)
Pietro Fratino, md\(^3\)
Luca Dalla Paola, md\(^4\)
Giulio Mariani, md\(^5\)
Roberto Mingardi, md\(^6\)
Alberto Morabito, phd\(^7\)

OBJECTIVE — To evaluate the clinical efficacy and safety of HYAFF 11-based autologous dermal and epidermal grafts in the management of diabetic foot ulcers.

RESEARCH DESIGN AND METHODS — A total of 79 patients with diabetic dorsal (n = 37) or plantar (n = 42) ulcers were randomized to either the control group with non-adherent paraffin gauze (n = 36) or the treatment group with autologous tissue-engineered grafts (n = 43). Weekly assessment, aggressive debridement, wound infection control, and adequate pressure relief (fiberglass off-loading cast for plantar ulcers) were provided in both groups. Complete wound healing was assessed within 11 weeks. Safety was monitored by adverse events.

The current standard treatment for foot ulcers consists of debridement, treatment of infection, pressure relief, and arterial revascularization, if required (1). The risk of infection to the deep tissues and bone structures depends on how long the skin lesion remains unhealed. Pressure off-loading has been demonstrated to be of paramount importance in the healing of plantar neuropathic ulcers in short amounts of time (2,3). There are many reports of high percentage rates of plantar ulcer healing in 6–10 weeks under a total contact cast (2–9). This technique of pressure relief is now widely recognized as the “gold standard” in diabetic foot ulcer care in terms of quality of pressure off-loading and time to healing (10).
Two-Step Autologous Grafting Using HYAFF Scaffolds in Treating Difficult Diabetic Foot Ulcers: Results of A Multicenter, Randomized Controlled Clinical Trial With Long-Term Follow-up

Luigi Uccioli, MD¹, Laura Giurato, MD¹, Valeria Ruotolo, MD¹, Adolfo Ciavarella, MD², Michele S. Grimaldi, MD², Alberto Piaggesi, MD³, Ilaria Teobaldi, MD³, Lucia Ricci, MD⁴, Luciano Scionti, MD⁵, Cristiana Vermigli, MD⁵, Roberto Seguro, MD⁶, Lorena Mancini, MD⁷, and Giovanni Ghirlanda, MD⁷
Spray-applied cell therapy with human allogeneic fibroblasts and keratinocytes for the treatment of chronic venous leg ulcers: a phase 2, multicentre, double-blind, randomised, placebo-controlled trial

Robert S Kessler, William A Marston, Robert J Snyder, Tommy D Lee, Dianne Cargill, Herbert B Slade

Summary

Background Many patients with venous leg ulcers do not heal with standard care. HP802-247 is a novel spray-applied cell therapy containing growth-arrested allogeneic neonatal keratinocytes and fibroblasts. We compared different cell concentrations and dosing frequencies of HP802-247 for benefit and harm when applied to chronic venous leg ulcers.

Methods We enrolled adult outpatients from 28 centres in the USA and Canada with up to three ulcers, venous reflux confirmed by doppler ultrasonography, and adequate arterial flow in this phase 2, double-blind, randomised, placebo-controlled trial if at least one ulcer measured 2–12 cm² in area and had persisted for 6–104 weeks. Patients were randomly assigned by computer-generated block randomisation in a 1:1:1:1 ratio to 5·0×10⁶ cells per mL every 7 days or every 14 days, or 0·5×10⁶ cells per mL every 7 days or every 14 days, or to vehicle alone every 7 days. All five groups received four-layer compression bandages. The trial sponsor, trial monitors, statisticians, investigators, centre personnel, and patients were masked to treatment allocation. The primary endpoint was mean percentage change in wound area at the end of 12 weeks. Analyses were by intention to treat, excluding one patient who died of unrelated causes before first treatment. This trial is registered with ClinicalTrials.gov NCT00852995.

Findings 45 patients were assigned to 5·0×10⁶ cells per mL every 7 days, 44 to 5·0×10⁶ cells per mL every 14 days, 43 to 0·5×10⁶ cells per mL every 7 days, 46 to 0·5×10⁶ cells per mL every 14 days, and 50 to vehicle alone. All required visits were completed by 205 patients. The primary outcome analysis showed significantly greater mean reduction in wound area associated with active treatment compared with vehicle (p=0·0446), with the dose of 0·5×10⁶ cells/mL every 14 days showing the largest improvement compared with vehicle (15·98%, 95% CI 5·56–26·41, p=0·0028). Adverse events were much the same across all groups, with only new skin ulcers and cellulitis occurring in more than 5% of patients.

Interpretation Venous leg ulcers can be healed with a spray formulation of allogeneic neonatal keratinocytes and fibroblasts without the need for tissue engineering, at an optimum dose of 0·5×10⁶ cells per mL every 14 days.

Funding Healthpoint Biotherapeutics.