Wound Bed Preparation With a Dermal Substitute (Hyalomatrix® PA) Facilitates Re-epithelialization and Healing: Results of a Multicenter, Prospective, Observational Study on Complex Chronic Ulcers (The FAST Study)

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Abstract: The FAST study evaluated the performance and safety of Hyalomatrix® PA (a dermal substitute) in the treatment of chronic wounds of different etiology. **Methods.** This was a multicenter, prospective, observational study involving 70 Italian centers and 262 elderly patients. Patients were observed from the start of treatment with a dermal substitute (Hyalomatrix® PA [HPA]) until healthy dermal tissue suitable for a thin autograft was visible or until the growth of new epithelium from the wound edge was reported. Tracking the wound edge advancement was used to assess the dermal substitute’s performance. The main endpoint was the reduction in threshold area (≥ 10%) of the ulcer. Treated ulcers were characterized as follows: 46% vascular, 25% diabetic foot, 12% traumatic wounds, 2% pressure ulcers and 15% other. **Results.** Re-epithelization (≥ 10%) was achieved in 83% of ulcers in a median time of 16 days. Twenty-six percent (26%) of wounds achieved 75% re-epithelization within the 60-day follow-up period using only HPA treatment. A follow-up showed that 84% of ulcers achieved complete re-epithelialization by secondary intention. **Conclusion.** These findings indicate that HPA is a safe and effective dermal substitute. The results show that re-epithelialization process following HPA treatment is independent upon etiology, area, and depth of the ulcer, and treatment is more effective on acute ulcer formation.

The aim of treating any type of wound is to create an environment that promotes normal and timely healing. A chronic wound is a wound that is delayed in one of the wound-healing stages (usually the inflammatory stage) and cannot progress any further. A chronic wound leaves the patient at risk of infection, hospitalization and potential amputation of the infected limbs.¹

These types of wounds are highly prevalent and expensive and their costs are predicted to increase annually.²,³ Unfortunately, the healing process is extremely slow, thus underlining the importance of investigating...
novel candidate treatment regimes specifically aimed at accelerating the healing process.

Current standard treatment for a chronic ulcer consists of surgical debridement, treatment of infection, and surgical or medical correction of any deficit to arterial blood supply. More recently, the concept of a clean moist environment has been widely accepted in the treatment of ulcers. Moreover, the moisture-retentive dressings provide a moist environment that stimulates capillary growth, facilitates autolytic debridement, and accelerates ulcer healing. However, in some cases, standard care therapies including compression therapy in venous ulcers, off-loading in diabetic neuropathic ulcers, wound cleansing, debridement, infection management, are insufficient.

Over the past 10 years, in order to stimulate the healing process in non-healing chronic wounds, different types of advanced dressings, acellular dermal-epidermal matrices, and bioengineered skin substitutes have been applied with varying success.

Hyaluronic acid (HA) is a skin polymer used in tissue engineering to facilitate healing. In slow-healing wounds such as chronic wounds where there is little granulation tissue, there is often a deficiency of hyaluronic acid. Such a deficit leads to insufficient regeneration of connective tissue and poor formation of new blood vessels, as HA appears to be a rate-limiting substrate in wound healing. Exogenous hyaluronic acid applied to a debrided wound keeps it moist and ensures a high concentration at the site of action. It is widely recognized that hyaluronic acid plays a multifaceted role in each stage of wound healing (inflammation, granulation tissue formation, re-epithelialization, and remodeling) stimulating angiogenesis, fibroblast migration, and the orderly deposition of essential components of the extracellular matrix.

Hyalomatrix PA® (HPA, Anika Therapeutics S.r.l., Abano Terme, Italy) is a non-woven pad composed of HYAFF® 11, which is an esterified derivative of hyaluronic acid coupled with a layer of medical grade silicone. The silicone layer controls water vapor loss avoiding an excessive loss of fluids and acts as a semi-permeable barrier to the external agents.

The matrix of HYAFF 11 is a biodegradable (transforms to gel) and bioabsorbable material, which following degradation, releases a high concentration of hyaluronic acid at the wound site.

HPA, an acellular dermal substitute, was conceived and designed to act as a dermal substitute to prepare the wound bed for subsequent grafting on extensive, deep skin burns, and to treat post-traumatic or post-surgical wounds where there is partial or total loss of dermal tissue. It is specifically designed to replace the dermis and provides a 3-dimensional matrix facilitating cellular invasion and capillary growth. Promising results obtained in the treatment of these acute wounds have prompted an evaluation of its application to chronic wounds.

Recent clinical experience on the use of HPA led to the development of a protocol for this system regarding treatment of chronic wounds (diabetic foot, vascular, and post-surgical ulcers), which defines the indications, timing of application, and overall ulcer management.

In slow-healing wounds, the high local concentration of hyaluronic acid released on the site following degradation of HYAFF matrix kick starts the healing process recreating an acute wound that can progress through the normal stages of healing.

Clinically, it is possible to see a chronic wound turned in acute wound assessing the presence of the good quality granulation tissue and of the re-epithelialization process. The evidence of edge stimulation at the wound margin is recognized as a useful indicator of the healing process. Therefore, to objectively evaluate the performance of HPA, the analysis of the data as based on the principle of the epithelial (edg e) advancement. The “wound edge effect” was assessed by measuring advancement of the wound edge, and a threshold area reduction of the ulcer (epithelial advancement) of ≥ 10% was considered as an endpoint measure.

**Key Points**

- In slow-healing wounds, such as chronic wounds where there is little granulation tissue, a deficiency of hyaluronic acid often exists. Such a deficit leads to insufficient regeneration of connective tissue and poor formation of new blood vessels, as HA appears to be a rate-limiting substrate in wound healing.

**Patients and Methods**

This is a national, multicenter, observational, prospective study to evaluate the clinical outcome of HPA in the treatment of chronic wounds of different etiologies. The main endpoint of this study was the reduction in threshold area (≥ 10%). This study complies with the ethical standards as specified in the 1975 Declaration of Helsinki. Patients provided informed written consent for every surgical procedure. Italian clinical specialists in diabetology, plastic surgery, vascular surgery, and dermatology completed a case report form for each consecutive patient affected by a chronic ulcer that was treated with HPA.
Data related to the baseline visit, each individual follow-up visit, and the final visit were recorded on separate forms. Returned case report forms were submitted to a data cleaning process and were checked for missing or incongruent data by author FG.

All patients had chronic ulcers and had undergone conventional treatments for at least 2 months previously that proved ineffective. Patients who presented with signs of infection were excluded from the study. Patients using medications known to interfere with healing (e.g., corticosteroids, immunosuppressive, or cytotoxic agents) were not excluded since concomitant therapy is considered an essential part of wound treatment in ulcers with immunological etiology. The follow-up lasted until the clinician considered the wound treated with HPA had turned into an acute wound and had progressed further. Therefore, patients were observed from the start of treatment with HPA until healthy dermal tissue suitable for a thin autograft (skin graft) was visible or until the growth of new epithelium from the wound edge was evident that would enable wound healing by secondary intention.

**Ulcer evaluation.** At baseline visit, the etiology of each ulcer was classified into one of the following categories: vascular ulcer (sub-classified as venous, arterial, and mixed); diabetic foot ulcer (sub-classified as neuropathic, neuroischemic, and ischemic); pressure ulcer; post-traumatic ulcer; and "other," which included all ulcers not otherwise classified (vasculitic ulcers and iatrogenic ulcers). Demographic characteristics of the patients, time of ulcer onset, the presence of comorbidities, concomitant treatments, wound locations, and wound bed characteristics were also recorded. Ulcer severity was assessed in terms of size (square centimeters by multiplying the maximum length and width) and depth according to the type of tissue exposed at baseline and follow-up visits. Physicians classified each ulcer in one of the following three categories: 1) ulcers without tendon or joint exposed; 2) ulcers with tendon and/or joint exposed; 3) ulcers with bone tissue exposed or involved. At the final visit, a clinical judgment on the use of HPA was reported (e.g., performance, tolerability, handling, exudate management). Adverse events were also reported throughout the study.

**Pain assessment.** Pain relief during treatment with HPA was also evaluated. The Visual Analogue Scale (VAS) was used to assess pain intensity. Patients without impaired sensitivity completed the test at each follow-up visit prior to treatment. For this analysis, only patients with a VAS score of > 0 at baseline and at least another VAS evaluation within 1 month were considered.

**Application of HPA.** Standard wound bed preparation was recommended prior to application of HPA, which included appropriate wound bed preparation with debridement of necrotic, non-vital tissue and hemostasis. Before or during treatment, it was recommended that patients suffering from peripheral vascular disease undergo revascularization procedures in accordance with the criteria established by the Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASD II). Offloading was recommended for patients with neuropathic plantar foot ulcers.

At baseline visit, HPA was applied directly to the clean, uninfected ulcers under sterile conditions. A non-adherent dressing was then placed in contact with HPA as a secondary dressing. HPA and the non-adherent dressing were left undisturbed for at least 1 week, provided no complications occurred (e.g., pain and/or clinical signs of infection of the lower limb). The secondary non-adherent dressing was changed weekly or earlier if the wound was exuding heavily. The HYAFF was completely absorbed by the 15th day and the wound bed was visible through the transparent elastomer film in most of the ulcers. At that point, a suitable dermal layer had been restored and a thin autograft could be applied, or for smaller wounds, healing could be reached spontaneously (for secondary intention) with the help of common dressings.

**Statistical Analysis**

Returned questionnaires were submitted for data analysis and checked for missing or incongruent data. Quantitative variables were described as mean with range or in instances of skewed distributions with median, and first (Q1) and third (Q3) quartiles. Categorical variables were expressed as frequency distributions. The product-limit (Kaplan-Meier) method for one or more groups of right-censored data with reversed Y-axis was used to estimate the percentage of patients achieving at least 10% of re-epithelialization in relation to the number of days after the treatment. If the event did not occur before a patient was submitted for autologous skin graft or was af-
Table 1. Characteristics of treated ulcers at baseline.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Venous n (%)</th>
<th>Arterial/Venous n (%)</th>
<th>Diabetic foot n (%)</th>
<th>Other origin n (%)</th>
<th>Total n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Main location</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ankle</td>
<td>18 (30)</td>
<td>20 (33)</td>
<td>6 (9)</td>
<td>5 (7)</td>
<td>49 (19)</td>
</tr>
<tr>
<td>Foot</td>
<td>0 (0)</td>
<td>3 (5)</td>
<td>56 (85)</td>
<td>7 (10)</td>
<td>66 (25)</td>
</tr>
<tr>
<td>Leg</td>
<td>39 (64)</td>
<td>33 (55)</td>
<td>0 (0)</td>
<td>39 (53)</td>
<td>111 (43)</td>
</tr>
<tr>
<td>Other</td>
<td>4 (6)</td>
<td>4 (7)</td>
<td>4 (6)</td>
<td>22 (30)</td>
<td>34 (13)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>61 (100)</td>
<td>60 (100)</td>
<td>66 (100)</td>
<td>73 (100)</td>
<td>260 (100)</td>
</tr>
<tr>
<td><strong>Size of ulcer</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 15 cm²</td>
<td>14 (23)</td>
<td>29 (33)</td>
<td>22 (33)</td>
<td>26 (35)</td>
<td>82 (31)</td>
</tr>
<tr>
<td>15 – 50 cm²</td>
<td>30 (50)</td>
<td>24 (40)</td>
<td>34 (51)</td>
<td>26 (35)</td>
<td>114 (44)</td>
</tr>
<tr>
<td>&gt; 50 cm²</td>
<td>17 (28)</td>
<td>16 (27)</td>
<td>10 (15)</td>
<td>22 (30)</td>
<td>65 (25)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>61 (100)</td>
<td>60 (100)</td>
<td>66 (100)</td>
<td>74 (100)</td>
<td>261 (100)</td>
</tr>
<tr>
<td><strong>Depth</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Partial-thickness of ulcers not involving tendons or joints</td>
<td>60 (98)</td>
<td>44 (74)</td>
<td>18 (28)</td>
<td>43 (58)</td>
<td>165 (64)</td>
</tr>
<tr>
<td>Full-thickness ulcer involving tendons and joints</td>
<td>1 (2)</td>
<td>14 (23)</td>
<td>27 (41)</td>
<td>21 (28)</td>
<td>63 (24)</td>
</tr>
<tr>
<td>Full-thickness ulcer involving bones and joints</td>
<td>0 (0)</td>
<td>2 (3)</td>
<td>20 (31)</td>
<td>10 (14)</td>
<td>32 (12)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>61 (100)</td>
<td>60 (100)</td>
<td>65 (100)</td>
<td>74 (100)</td>
<td>260 (100)</td>
</tr>
<tr>
<td><strong>Duration of ulcer</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 6 months</td>
<td>11 (18)</td>
<td>17 (28)</td>
<td>45 (68)</td>
<td>44 (59)</td>
<td>117 (45)</td>
</tr>
<tr>
<td>6 months to 1 year</td>
<td>12 (20)</td>
<td>14 (23)</td>
<td>11 (17)</td>
<td>13 (17)</td>
<td>50 (19)</td>
</tr>
<tr>
<td>&gt; 1 year</td>
<td>38 (62)</td>
<td>29 (49)</td>
<td>10 (15)</td>
<td>18 (24)</td>
<td>95 (36)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>61 (100)</td>
<td>60 (100)</td>
<td>66 (100)</td>
<td>75 (100)</td>
<td>262 (100)</td>
</tr>
</tbody>
</table>
fected by an infection, the observation was considered as censored. The log-rank test was applied for among-group comparisons. Significance was set at $\alpha = 0.05$. Statistical analysis was performed using JMP software (version 4.0; SAS Institute Inc., Cary, NC).

**Results**

Between March 2006 and December 2007, a total of 262 patients were enrolled into the study from 70 participating Italian centers. The mean age was 70 years (range 33–103) and 53% of the subjects were women. Six patients affected by two ulcers were considered, where analysis was only performed on the widest ulcer, therefore ensuring that the number of treated ulcers was equal to the number of subjects. The median number of times that HPA was applied to the ulcer was 2 and median in situ residence was 8 days (Q1–Q3: 6–14).

**Ulcer characteristics.** The 262 ulcers were characterized as follows: 121 (46%) vascular (of which 50% were venous, 15% arterial, and 35% arterial/venous); 66 (25%) diabetic foot (of which 56% were neuroischemic, 27% ischemic, 17% neuropathic); 31 (12%) traumatic wounds; 5 (2%) pressure ulcers; and 39 (15%) other (eg, vasculitis, iatrogenic ulcers). Table 1 summarizes the baseline ulcer characteristics according to etiology.

As expected, given that 121 (46%) of the ulcers were vascular, 111 (43%) were located on the leg. The median area was 21.5 cm² (Q1–Q3: 12–50) and 34 (13%) of the ulcers were wider than 100 cm². Thirty-six percent (n = 95) of ulcer s had tendon, joint, or bone exposure of which 46 (49%) were diabetic foot ulcers. Ulcer onset was greater than 12 months in 95 (36%) of the ulcers of which 67 (71%) were vascular.

**Re-epithelialization.** Figure 1 shows the percentage of patients achieving at least 10% re-epithelialization in relation to the number of days following HPA treatment. Re-epithelialization of $\geq 10\%$ was achieved in 217 (83%) of the ulcers in a median time of 16 days (Q1–Q3: 10–29).

Figure 2 shows the rate of re-epithelialization related to etiology (a) in addition to parameters indicative of wound severity: size (b), depth (c), and time of onset (d). When ulcer etiology was considered, venous ulcers reached the endpoint before arterial and mixed ulcers or the diabetic foot ulcers even if log-rank analysis did not reveal any statistically significant difference. As expected, ulcers that were smaller, superficial, or partial-thickness showed a higher rate achieving at least 10% re-epithelialization than ulcers that presented with more severe conditions; however, these differences were not statistically significant. Interestingly, time of onset was noted to be a statistically significant variable achieving 10% of re-epithelialization. In particular, the endpoint of at least 10% of re-epithelialization within 60 days of follow-up was observed in 88% of patients affected by ulcers with onset $\geq 1$ year, while the same endpoint was achieved by 73% of patients affected by ulcers with onset $> 1$ year ($P < 0.05$).

Sixty-eight (26%) wounds achieved at least 75% re-epithelialization within 60 days of the follow-up period after treatment with HPA only. Although this was not the primary objective of this investigation, it is worth noting that a later follow-up analysis revealed that 220 (84%) of ulcers achieved complete re-epithelialization by secondary intention. These results suggest that treatment with HPA for the healing of ulcers can be achieved by secondary intention, thus avoiding autograft morbidity.

**Pain.** Changes in pain intensity were measured by mean VAS. Among the observed 262 patients, 16 reported no pain at baseline (VAS = 0) and 17 did not report any pain evaluation after baseline. VAS distributions at baseline and within 30 days from the initial treatment were compared for the remaining 229 patients (Figure 3). The VAS median value at baseline was 50 (Q1–Q3: 18–74), while the VAS median within 30 days was 15 (Q1–Q3: 3–40). The VAS median trend shows rapid pain relief after HPA application. Pain intensity was reduced almost 3-fold within 30 days after the initial treatment with HPA.

**Adverse events.** Thirty-five adverse events (AEs) were reported from 262 patients (13.5%). The most frequent AEs were infection (13 events, 5%) and increased pain...
(6 events, 2.3%), some of which (4 infections and 5 pain increases) were possibly related to the treatment. Other AEs that may have been related to HPA included one case of microbleeding, two cases of maceration of the perilesional skin, one case of skin erythema, and flush of the perilesion skin. However, all AEs were resolved within a short time with no further consequences. One patient died due to concomitant disease (congestive heart failure) that was unrelated to HPA treatment.

**Clinical assessment.** At the final visit, a qualitative test was given to the clinicians in order to better understand some defined properties of HPA, such as handling, ease of use, compatibility with secondary dressings, ease of silicone film removal, safety, tolerability, and performance. These modalities were all scored as “very good/optimal.”

**Discussion**

These results indicate that the use of HPA on a chronic wound bed after surgical debridement provides a stimulus for the renewal of the stagnant wound healing process, allowing the formation of a dermal-like neo-tissue on which keratinocytes can proliferate.

Despite adequate wound bed preparation and standard-care management, some wounds fail to heal or heal slowly. This may be a consequence of a dysfunctional healing response resulting from inappropriate production of cytokines, growth factors, proteases, and reactive oxygen species by cells within the granulation tissue, which leads to ongoing inflammation, poor angiogenesis, extracellular matrix (ECM) degradation, and lack of epithelial cell migration from the wound margin. Treatment tailored toward reversing these events initiates the heal-
This large, prospective, observational study provides indication on the use of HPA in hard-to-heal ulcers of various origins. The purpose of this study was to generate data on the clinical outcome of this novel treatment on the chronic wound population. Despite the limitation that this was not randomized or controlled, the present study has the advantage of considering leg ulcers with a wide spectrum of clinical characteristics without being restricted by more rigorous inclusion and exclusion criteria.

The results obtained show that the re-epithelialization process seems not to be dependent on the etiology, area and depth of the total ulcers treated, and that the treatment is more successful when the ulcers exist for a shorter period (< 1 year).

There is a general consensus in the scientific literature indicating that wound duration, size and depth of ulcer are the most important factors for predicting outcome.

Diabetic foot ulcers that are larger than 2 cm², more than 2 months’ duration, and full-thickness, and venous ulcers that are larger than 10 cm² and more than 6 months’ duration, are considered chronic ulcers. Furthermore, the longer a wound is open, the greater the risk of complication (e.g., infection). The present study shows that HPA is capable of acting as a bioinductive, hyaluronan-based dermal substitute that stimulated the healing process in 217 (83%) of the treated ulcers. Considering international wound care guidelines, all ulcers treated in the present study can be considered “hard-to-heal” ulcers, and the results indicate that the use of HPA can modify the healing process even in these complex ulcers. The present results show that in ulcers with an onset > 1 year, 191 (73%) reached at least 10% of re-epithelialization within 60 days of the observed period. It is likely that a more advanced approach aimed at stimulating the tissue repair process would have been necessary to achieve closure with regard to the remaining 71 (27%) ulcers that did not reach the epithelialization rate.

**Conclusion**

Chronic wounds have a significant adverse effect on patients’ quality of life. Therefore, achieving pain relief is an important goal in wound management that significantly increases patients’ quality of life and reduces costs associated with pain therapy. A rapid and progressive reduction in pain intensity was observed using the VAS just a few days after HPA administration.

The present study suggests that HPA is a useful adjuvant treatment in chronic skin ulcers of various etiologies. It is considered a safe, easy to use, biocompatible, and effective dermal substitute that can be an integral part of a standard-of-care approach, particularly for treating severe ulcers. The efficacy and the tolerability of the product should be further confirmed in randomized, prospective, clinical trials.

**Acknowledgement**

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**References**


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