

Efficacy and Tolerability of Hyaluronan (ialuset®) in the Treatment of Pressure Ulcers

A Multicentre, Non-Randomised, Pilot Study

Brigitte Barrois,¹ Muriel Carles,² Michel Rumeau,² Laurence Tell,³ Jean-François Toussaint,⁴ Marc Bonnefoy⁵ and Florent de Vathaire⁶

- 1 Service de Médecine Physique et Réadaptation, Centre Hospitalier de Gonesse, Gonesse, France
- 2 Hôpital de la Grave, Service de Gériatrie, Toulouse, France
- 3 Hôpital H. Gabrielle Service de Rééducation Fonctionnelle, Saint Genis Laval, France
- 4 Clinique du Cabirol, Service de Rééducation Fonctionnelle, Colomiers, France
- 5 Centre Hospitalier Lyon Sud, Service de Médecine Gériatrique, Pierre-Bénite, France
- 6 Unité INSERM 605, Villejuif, France

Abstract

Background: Pressure ulcers are complex chronic wounds and a frequent cause of morbidity in elderly subjects in hospitals and nursing homes. Local treatment is based on the use of dressings that protect the wound and provide a favourable environment for healing to occur. ialuset®, a treatment based on hyaluronan (hyaluronic acid), is already available on the market and known to be an effective treatment for venous leg ulcers. However, no clinical trials of hyaluronan as a treatment option for pressure ulcers have been reported as yet.

Methods: The purpose of this review was to investigate the efficacy and tolerability of ialuset® in the treatment of pressure ulcers. To this end, this article reports data from 21 predominantly elderly patients with National Pressure Ulcer Advisory Panel grade II, III or IV pressure ulcers treated with ialuset® cream or gauze pads over a 3-week period in ten hospitals in France.

Results: A significant median decrease of 4cm² in the surface area of treated wounds was observed after 3 weeks of ialuset® use ($p < 0.05$ vs baseline). A $\geq 50\%$ reduction in pressure ulcer surface area was seen in 65.0% of patients (95% CI 44.8, 84.3). Nine patients (45%) showed a $\geq 50\%$ increase in epithelial surface compared with the initial lesion. Patient-reported pain appeared to decrease during the 3-week treatment period, although this decrease did not quite reach statistical significance ($p = 0.07$). Additionally, a significant decrease in the mean percentage of fibrous tissue in the wound was observed ($p = 0.02$), as was a non-significant increase in granulation tissue ($p = 0.1$). General efficacy was considered as good or very good for nearly all patients on review of the data (19/20 patients as assessed by clinicians). Overall tolerability was also considered good or very good in 12/15 assessments by patients at day 21.

Conclusion: These preliminary findings suggest that ialuset® is a promising option in the treatment of pressure ulcers; however, further investigation in the form of large, randomised clinical trials is required before firm conclusions can be drawn regarding the efficacy and tolerability of this treatment in this context.

Introduction

Pressure ulcers, also known as skin ulcers, decubitus ulcers and bedsores, are complex chronic wounds. They are a frequent cause of morbidity in elderly subjects in hospitals and nursing homes, and require costly and time-consuming treatments.^[1-5]

The healing process of chronic wounds such as pressure ulcers is less straightforward than that of acute wounds, leading to difficulties in treatment management. Chronic wounds may not heal at all if left untreated.^[6] Local treatment of pressure ulcers is based on use of dressings that protect the wound and provide a favourable environment for healing to occur. The benefits of creating a moist healing environment with occlusive dressings were first identified in the 1960s when it was shown that such an environment could increase the rate of epithelialisation, and therefore of overall healing, of superficial wounds.^[7-9] Since that time, several trials have investigated the use of a range of gels for the treatment of chronic wounds.^[10,11]

Hyaluronan, also known as hyaluronic acid, is a component of the extracellular matrix, and plays a natural role in the healing process.^[12] It maintains a moist environment, thus favouring tissue regeneration. ialuset® (Laboratoires Génévrier, Antibes, France),¹ a treatment that is based on hyaluronan, is already available on the market and has been demonstrated to be effective in the treatment of venous leg ulcers.^[13,14] However, no clinical trials of hyaluronan as a treatment option for pressure ulcers have yet been published. The aim of this report was to review the available data from patients treated with ialuset® cream or gauze pads to determine whether hyaluronan is a viable option in the treatment of pressure ulcers.

Methods

Male and female patients aged ≥ 18 years were included in the analysis if they had grade II, III or IV pressure ulcers (according to the National Pressure Ulcer Advisory Panel [NPUAP] system of classification) located anywhere on the body.^[15]

Two types of hyaluronan-based treatment were used in the patient group analysed: ialuset® cream or ialuset® gauze pads. Treatment type was determined by physicians for each patient according to the depth of the pressure ulcer; generally, ialuset® cream was used for deeper wounds. Treatment success was defined as a reduction in pressure ulcer surface area of at least 95% during the treatment period. Improvement was defined as a $\geq 50\%$ increase in the epithelial surface compared with the initial area. Pain was evaluated on a 100mm visual analogue scale (VAS) in a total of 15 patients.

The main efficacy criteria were the reduction of the surface area of the pressure ulcer during the study, and the percentage of re-epithelisation of the wound in relation to the original surface area. Tracings were used to determine the surface area of the wound. The success rate was defined as a reduction in surface area of at least 95% during the study. Secondary efficacy criteria were: pain, measured on a VAS; the nature and quantity of analgesics taken for the pressure ulcer; changes to the characteristics of the wound base, i.e. percentage of necrotic, fibrous and granulation tissue; level of exudate, assessed on a 4-point verbal scale; and overall efficacy, as judged by the patient and the investigator on a 4-point verbal scale. Tolerability criteria included overall tolerability, as judged by the patient and the investigator on a 4-point verbal scale, and changes to the characteristics of surrounding skin in terms of inflammation, oedema, purpura, erythema and ooz-

¹ The use of trade names is for product identification purposes only and does not imply endorsement.

ing. Parameters were assessed on days 1, 7, 14 and 21 (± 1 day) of treatment. Treatment compliance and occurrence of adverse events were noted in the case report form. The treatment chosen was gauze pads or cream, according to the estimated depth of the pressure ulcer. The depth of the pressure ulcers treated with the gauze pads ranged from 0.1 to 1.3cm, with the majority being between 0.3 and 0.5cm. All but one of the pressure ulcers treated with the cream measured between 1 and 1.3cm in depth. The Braden scale is a clinically validated tool that allows healthcare providers to reliably score a patient's level of risk for developing pressure ulcers. It is a summated rating scale made up of six subscales scored from 1 to 3 or 4, for total scores that range from 6 to 23. The subscales measure functional capabilities of the patient that contribute to either higher intensity and duration of pressure or lower tissue tolerance for pressure. A lower Braden scale score indicates lower levels of functioning and, therefore, higher levels of risk for pressure ulcer development.

Data from patients receiving antibacterials or any treatments that would delay the healing of the wound (corticosteroids, cytostatics, immunosuppressants) were not included in this review; all other concomitant medications, including analgesics, were permitted.

Statistical Analysis

The Wilcoxon signed rank-sum test for matched pairs was used to test for differences in variables measured at the beginning and end of the treatment period. Analysis of the variance (ANOVA) of the values and of the ranks of the values was used to identify potential prognostic factors playing a role in treatment efficacy. All analyses were performed using the SAS® statistical software package. Success rate estimation and 95% confidence intervals (CIs) were determined using the actuarial method.^[16]

Results

Data collected between April 2003 and November 2005 from a total of 21 patients from ten centres were included in the analysis. The general character-

istics of the relatively elderly study population, who were affected by a variety of associated pathologies, are shown in table I. All patients had NPUAP grade II, III or IV pressure ulcers, with the majority being located on either the heel or the sacrum (table II). Prior to treatment with ialuset®, the patients' pressure ulcers were at proliferation/granulation or re-epithelialisation stage, unresponsive to 5–7 days of treatment with two types of dressing, had undergone $\geq 75\%$ debridement, consisted of $\leq 25\%$ fibrous or necrotic tissue, had surface areas of 4–100cm² and were ≤ 1.5 cm deep. Fifteen patients were treated with ialuset® gauze pads, and six patients with ia-

Table I. Patient characteristics at inclusion (n = 21)

Characteristic	Value
Age (y) [mean \pm SD]	77 \pm 16
Females [n (%)]	12 (57)
Weight (kg) [mean \pm SD]	
males	74 \pm 17
females	51 \pm 12
Height (cm) [mean \pm SD]	
males	170 \pm 4
females	161 \pm 4
BMI (kg/m ²) [mean \pm SD]	
males	25 \pm 6
females	20 \pm 4
Arterial systolic BP (mm Hg) [mean \pm SD]	133 \pm 20
Arterial diastolic BP (mm Hg) [mean \pm SD]	75 \pm 9
Serum albumin (g/L) [mean \pm SD]	32 \pm 6
Nutritional status (no.)	
good	11
correct	7
bad	2
Braden score (risk of pressure ulcer) [mean \pm SD]	16 \pm 4
Associated pathologies (no.)	
respiratory system disorder	3
cardiovascular system disorder	11
cancer	1
fracture resulting from accident	7
haematological disorder	2
infectious disease	1
diabetes mellitus	1
neurological disorder	1
smoker	1
urological disorder	2
digestive system disorder	4

BMI = body mass index.

Table II. Baseline pressure ulcer characteristics for study patients (n = 21)

Pressure ulcer characteristic	Value
Grade [n (%)]	
II	7 (33)
III	13 (62)
IV	1 (5)
Duration [n (%)]	
<1 month	3 (14)
1–2 months	9 (43)
2–5 months	5 (24)
5–24 months	4 (19)
Previous history of pressure ulcers [n (%)]	2 (10)
Location [n (%)]	
Heel	10 (47)
Sacrum	6 (28)
Tibia	1 (5)
Malleolus	1 (5)
Thigh	1 (5)
Buttock	1 (5)
Hip	1 (5)
Necrotic tissue (%) [mean ± SE]	2.9 ± 5.6
Fibrous tissue (%) [mean ± SE]	10.5 ± 9.7
Granulation tissue (%) [mean ± SE]	86.7 ± 11.7
Unresponsive pressure ulcer [n (%)]	20 (95)
Estimated surface area (cm²) [median (range)]	14 (4–90)
Estimated depth (cm) [median (range)]	0.50 (0–1.30)
Appearance of surrounding skin [n (%)]	
Inflammation	
nil	6 (28.5)
slight	6 (28.5)
moderate	8 (38)
significant	1 (5)
Oedema	
nil	13 (62)
slight	3 (14)
moderate	3 (14)
significant	2 (10)
Purpura	
nil	21 (100)
Erythema	
nil	8 (38)
slight	7 (33)
moderate	6 (29)
Oozing	

Continued

Table II. Contd

Pressure ulcer characteristic	Value
nil	13 (61)
slight	5 (24)
moderate	2 (10)
significant	1 (5)
Pain (100mm VAS) [mean ± SE]^a	37.3 ± 30.5 ^b
a Six missing values.	
b Estimated value.	
SE = standard error; VAS = visual analogue scale.	

luset[®] cream. However, measurement of the area of the wound (primary criterion) was not available for one patient treated with ialuset[®] cream. Hence, there were 20 evaluable patients: 15 treated with ialuset[®] gauze and five treated with ialuset[®] cream.

Patients were permitted to switch between treatments. Gauze pads were used by 16 patients altogether, and cream by eight patients. Two patients used both types of treatment simultaneously during the first week, and two patients using the ialuset[®] cream applied treatment only on every second day during the first week. The depth of the pressure ulcers treated with the gauze pads ranged from 0.1 to 1.3cm, with the majority being between 0.3 and 0.5cm. All but one of the pressure ulcers treated with ialuset[®] cream measured between 1 and 1.3cm in depth.

Overall, the median surface area of the pressure ulcers reduced from 10.4cm² (range 1.9–50.9) by real measure of the wound to 3.5cm² (0.0–52.0) [table III]. The median change in surface area was –4.0cm² (range –21.9 to +14.8) and was found to be significantly different from baseline (Wilcoxon signed rank-sum test, $p < 0.05$) [figure 1]. ANOVA showed that the decrease in surface area from day 1 was significant ($p < 0.001$). No difference was found between the two types of treatment, and no interaction was found between type of treatment and time. Similar results were obtained with an equivalent non-parametric test.

Treatment success was defined as a reduction in pressure ulcer surface area of at least 95% during the treatment period. Only one success (100% reduction) was detected; however, cumulative rates of success at 21 days showed an 80% reduction in

Table III. Actual pressure ulcer surface area (cm²) at days 1, 7, 14 and 21 in evaluable patients during treatment with hyaluronan (hyaluronic acid) cream or gauze pads (ialuset®)^a

Day	Total group (n = 20)	Gauze pad treatment group (n = 15)	Cream treatment group (n = 5)
1	10.4 (1.9–50.9)	9.4 (4.5–50.9)	11.4 (1.9–32.1)
7	6.5 (0.5–47.1)	5.3 (0.5–47.1)	7.5 (3.0–46.8)
14	4.3 (0.6–52.7)	4.2 (0.6–52.7)	5.5 (0.7–14.4)
21	3.5 (0.0–52.0)	4.0 (0.0–52.0)	2.5 (0.5–11.2)

a Values are given as median (range).

surface area in 21.8% of patients (95% CI 8.8, 48.2), and a 50% reduction in 65% of patients (95% CI 44.8, 84.3).

Multivariate analyses were used to search for potential prognostic factors for surface area reduction, whilst adjusting for other potential factors. Sex ($p = 0.0001$), initial depth ($p = 0.01$) and type of treatment (gauze pad vs cream) [$p < 0.001$] were all found to have individual significant effects. Similar results were obtained using equivalent non-parametric tests. The decrease in pressure ulcer median surface area appeared to be greater in female pa-

tients, in pressure ulcers initially ≤ 0.5 mm in depth, and in patients treated with ialuset® gauze pads rather than cream.

At day 21, nine patients (45%) were considered to have improved.

The overall mean (standard error [SE]) of the observed values for the VAS for pain decreased from 37.3mm (7.9) at day 1 to 20.6mm (5.2) at day 21. The overall mean (SE) variation in the VAS for pain over the period day 1 to day 21 was -11.8 (5.6) [$p = 0.07$]. A total of four patients received standard analgesics, which consisted of paracetamol (acetaminophen) in three cases, at some point during treatment; an additional two patients received morphine.

The overall mean (SE) percentages of necrotic, fibrous and granulation tissues were 2.9% (2.1), 10.5% (2.1) and 86.7% (2.5) at day 1, respectively, and 3.6% (2.9), 6.2% (1.9) and 90.2% (3.3), respectively, at day 21. The mean decrease in the percentage of fibrous tissue was found to be statistically significant ($p = 0.02$), while the increase in granulation tissue was close to being statistically significant ($p = 0.1$). The level of exudate was considered to be zero for six patients (29%) on day 1, and for 12 patients (57%) on day 21. The exudate level was considered to be significant on day 1 for four patients (19%) and for three patients (14%) on day 21.

At day 21, 17 patients had no inflammation in this area. The decrease in inflammation was significant from day 14 onwards ($p < 0.01$ vs baseline at day 14 and $p = 0.001$ vs baseline at day 21). Oedema was rated as slight, moderate or significant for eight patients on day 1. On day 21, oedema was graded as non-existent for 17 patients; however, this improvement did not reach statistical significance ($p = 0.1$).

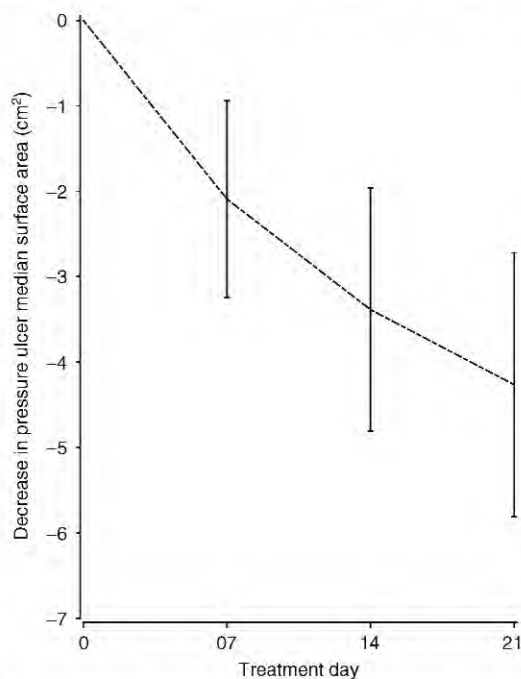


Fig. 1. Decrease in median pressure ulcer surface area (cm²) during 3 weeks of treatment with hyaluronan (hyaluronic acid) cream or gauze pads (ialuset®).

Purpura did not vary significantly between days 1 and 21, and very few patients had a rating above zero. Erythema was present in about half of the patients throughout the treatment period (generally graded as slight or moderate), and there was no significant change in this parameter at day 21. Oozing was present for approximately one-third to one-half of patients at some point during the period under review, but there was no significant change by day 21.

Overall efficacy was rated as good or very good by 19/20 patients as assessed by clinicians, and by 12/14 patients as assessed by the patients themselves.

A total of three adverse events were reported during the treatment period. Two (hyperkalaemia and cancer of the digestive tract) were considered non-related to treatment, while a peripheral erythema reported in the third week by a patient treated with an ialuset[®] gauze pad was considered to be probably related to treatment. Overall tolerability was considered as good or very good at day 21 by 12/15 patients and by 20/21 investigators.

Discussion

In the current analysis, data from 21 predominantly elderly patients with stage II, III or IV pressure ulcers treated with ialuset[®] (cream or gauze pads) over a 3-week period were collated and analysed. A significant decrease (median 4cm²) in the surface area of the treated wounds was observed during the period under review. Over 3 weeks, only 1/20 patients achieved complete wound healing; however, this finding is consistent with clinical studies that have shown that stage II pressure ulcers take between 15 and 64 days to heal with phenytoin,^[17] and grade IV pressure ulcers require between 6 and 12 weeks to heal with collagenase.^[18] As such, longer treatment and follow-up periods are required to assess the full potential of ialuset[®] in the treatment of pressure ulcers.

ialuset[®] was also associated with a significant decrease in the mean percentage of fibrous tissue in the wound in the current study, in addition to a near-significant increase in granulation tissue. General

efficacy was also considered as good or very good for nearly all patients, as was overall tolerability for patients who assessed this variable.

A multivariate analysis was conducted to identify potential prognostic factors for pressure ulcer surface area reduction. Results indicated effects of sex, initial pressure ulcer depth and type of treatment (cream vs gauze pads). However, caution must be exercised when interpreting these results, especially when evaluating differences between the two treatment types, because only a small population was used for the analysis; indeed, only six patients were treated with ialuset[®] cream throughout the period under review. As the cream was generally used for deeper wounds, it might be expected that initial wound depth could significantly confound the suggested effect of treatment type on surface area reduction.

Conclusion

Overall, the results obtained in this analysis suggest that ialuset[®] cream and gauze pads appear to be an effective method for treating pressure ulcers among patients with wounds unresponsive to other types of dressings. However, large-scale randomised studies with a longer follow-up period are required to provide more conclusive evidence and to enable these findings to be generalised to the wider population. Such studies are also required to establish optimal treatment guidelines and standard indications for the two currently available forms of ialuset[®]. Furthermore, comparisons with other available treatments are needed to demonstrate the relative efficacy and tolerability of ialuset[®] in the treatment of pressure ulcers.

Acknowledgements

Funding for this study was provided by the Genévrier Foundation. The authors received honoraria for their contributions to the study. The authors have no other potential conflicts of interest that are directly relevant to the content of this study.

References

1. Allman RM. Pressure ulcer prevalence, incidence, risk factors and impact. *Clin Geriatr Med* 1997; 13: 421-36

2. Barrois B, Allaert FA, Colin D. A survey of pressure sore prevalence in hospitals in the greater Paris region. *J Wound Care* 1995 May; 4 (5): 234-6
3. Smith DM. Pressure ulcers in the nursing home. *Ann Intern Med* 1995; 123: 433-42
4. Thoroddsen A. Pressure sore prevalence: a national survey. *J Clin Nurs* 1999; 8: 170-9
5. Whittington K, Patrick M, Roberts JL. A national study of pressure ulcer prevalence and incidence in acute care hospitals. *J Wound Ostomy Continence Nurs* 2000; 27 (4): 209-15
6. Lazarus GS, Cooper DM, Knighton DR, et al. Definitions and guidelines for assessment of wounds and evaluation of healing. *Arch Dermatol* 1994; 130 (4): 489-93
7. Hinman CD, Maibach H. Effect of air exposure and occlusion on experimental human skin wounds. *Nature* 1963; 200 (4904): 377-8
8. Winter GD. Formation of the scab and the rate of epithelization of superficial wounds in the skin of the young domestic pig. *Nature* 1962; 193: 293-4
9. Winter GD. Effect of air exposure and occlusion on experimental human skin wounds. *Nature* 1963; 200: 378-9
10. Harding KG, Morris HL, Patel GK. Science, medicine, and the future: healing chronic wounds. *BMJ* 2002; 324: 160-3
11. Hollisaz MT, Khedmat H, Yari F. A randomized clinical trial comparing hydrocolloid, phenytoin and simple dressings for the treatment of pressure ulcers [ISRCTN33429693]. *BMC Dermatol* 2004; 4 (1): 18
12. Chen WY, Abatangelo G. Functions of hyaluronan in wound repair. *Wound Repair Regen* 1999; 7 (2): 79-89
13. Humbert P. City/hospital networks for leg ulcers and treatment with ialusct. *Ann Dermatol Venercol* 2002; 129 (10 Pt 2): 1231-4
14. Ortonne JP. A controlled study of the activity of hyaluronic acid in the treatment of venous leg ulcers. *J Dermatol Treat* 1996; 7: 75-81
15. National Pressure Ulcer Advisory Panel (NPUAP). Pressure ulcers prevalence, cost and risk assessment: consensus development conference statement. *Decubitus* 1989; 2 (2): 24-8
16. Breslow N, Day N. Statistical methods in cancer research: II. The design and analysis of cohort studies. *IARC Sci Pub* 1987; 82: 1-406
17. Rhodes RS, Heyneman CA, Culbertson VL, et al. Topical phenytoin treatment of stage II decubitus ulcers in the elderly. *Ann Pharmacother* 2001; 35: 675-81
18. Müller E, van Leen MWF, Bergemann R. Economic evaluation of collagenase-containing ointment and hydrocolloid dressing in the treatment of pressure ulcers. *Pharmacoeconomics* 2001; 19 (12): 1209-16

Correspondence: Dr *Brigitte Barrois*, Service de Médecine Physique et Réadaptation, Centre Hospitalier de Gonesse, 25 rue Pierre de Theilley, BP 71, 95503 Gonesse Cedex, France.

E-mail: Brigitte.barrois@ch-gonesse.fr