An open label non-comparative case series on the efficacy of an enzyme alginogel

• **Objective:** To evaluate the efficacy of an enzyme alginogel in outpatients with chronic or acute wounds left to heal by secondary intention.
• **Method:** This evaluation was a single-centre, single-arm, case series involving 23 patients with wounds of diverse aetiologies treated with the enzyme alginogel (Flaminal; Flen Pharma). The product was applied in accordance with the manufacturer's instructions and wounds were covered with secondary dressings. Treatment was based on a scheduled protocol and patients were assessed at days 14, 30 and 60.
• **Results:** Median baseline dimensions for the wounds were surface area 2.6cm^2 and volume 2.8cm^3. Median wound duration before application of the enzyme alginogel was 292 days, with 16 chronic wounds (78%). Three wounds were clinically infected at baseline; two were negative by day 14 and the third by day 30. After 2 months, wound surface area and volume had decreased, as could be expected. Two adverse events were reported: an allergic reaction in the skin surrounding the wound and transient maceration.
• **Conclusion:** The enzyme alginogel facilitated healing in chronic and acute wounds of diverse aetiologies. Additional research is warranted to confirm the clinical utility of the dressings in the management of chronic or acute wounds left to heal by secondary intention.
• **Declaration of interest:** The author has no conflict of interest to declare. There were no external sources of funding for this evaluation.

enzyme alginogel; acute wound; chronic wound

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Acute wounds follow a well-defined healing process involving four overlapping stages: coagulation, inflammation, cell proliferation and repair of the matrix, epithelialisation and remodelling of the scar tissue.[1] Chronic wounds, by comparison, become 'stuck' in either the inflammatory or the proliferative stage of healing and do not progress to complete healing.[2] As such, the molecular environment of the acute wound differs significantly from a chronic wound.[3]

A basic model of wound healing is described by the TIME framework, comprising the four components that underpin wound bed preparation — tissue management, inflammation and infection control, moisture balance, and epithelial (edge) advancement.[4] This framework allows health professionals to assess what is happening in the wound bed and to present a systematic, scientific approach to wound assessment.[5] When the TIME framework was introduced it focused solely on chronic wounds, however, over time, it has become an invaluable tool for treatment of acute wounds as well.[4]

One of the newest class of wound care products is the enzyme alginogels. Flaminal (Flen Pharma NV) is the first wound care product available in this class and, depending on the formulation, is indicated for either the management of moderate to heavily exuding wounds (Flaminal Forte) or for lightly to moderately exuding wounds (Flaminal Hydro). It is composed of hydrated alginate polymers in a polyethylene glycol (PEG) matrix embedded with a patented antimicrobial enzymatic complex (glucose oxidase, combined with lactoperoxidase, stabilised by guaiacol [GLG]).[6] These two enzymes form free radicals, which destroy the cell walls of absorbed bacteria in a manner similar to our own natural white cell defences.[7]

As an alginate dressing, enzyme alginogels are highly absorbent and suitable for use on exuding wounds, and for the promotion of autolytic debridement of debris in very moist wounds. However, enzyme alginogels also manage the bacterial bioburden of a wound. They do this in three ways: the enzyme complex kills bacteria, while the alginate component removes bacteria from the wound bed by debridement, creating a moist wound environment, which stimulates the host's immune system.[8,9] Only absorbed bacterial cell walls are destroyed by the enzyme complex and not the cell walls of human cells within the wound bed, such as keratinocytes and fibroblasts; therefore, enzyme alginogels may be indicated for long-term use in exuding wounds irrespective of the wound bacterial bioburden.[8,9]

This patented enzyme system has a proven broad-spectrum antibacterial activity, including multiresistant strains of bacteria.[8,9] No resistance to the enzyme system has been reported to date.

The antibacterial activity and toxicity of enzyme alginogels has been compared with common wound care products in laboratory studies. *In vitro* cytotoxicity assays, conducted on human keratinocytes in culture, showed enzyme alginogels to be essentially non-toxic, while an approximate 70% decrease in activity was recorded for 10% povidone- iodine.[8] The antimicrobial activity of enzyme alginogels was similar to silver sulphadiazine, and significantly greater than that of a hydrocolloid dressing (DuoDERM; ConvaTec), which demonstrated no activity against a range of clinically significant microorganisms *in vitro*.[8] Compared with a hydrocolloid gel, enzyme alginogels have also been shown to reduce healing time in venous leg ulcers.[6] The efficacy of enzyme alginogels in a range of wounds, including pressure ulcers (PUs), venous leg ulcers and burn wounds, has been demonstrated.[6]

The aim of this evaluation was to assess the efficacy of the enzyme alginogel in patients with chronic or acute wounds left to heal by secondary intention. Efficacy was determined by evidence of healing, as noted by full epithelialisation of the wound.

Method

This single-centre, single-arm evaluation was conducted in the outpatient clinic of the Army Military Hospital, Rome from October 2007 until December 2009. The hospital has a small target population. Potential participants were identified from among mixed outpatients of varying ages from the civilian world and from humanitarian missions.

Participants

All patients attending the clinic were assessed for inclusion in the evaluation. Each patient was provided with a full explanation of the evaluation protocol and written informed consent was obtained from all participants prior to the start of the evaluation. Patients were considered eligible for inclusion if they were over 18 years of age with an acute or chronic wound of any duration and aetiology. An additional inclusion criteria was the availability of a community nursing team, so wound treatment could be continued in the home setting.

Patients were excluded if they had a known sensitivity or allergy to any of the wound care product materials, or the suspected presence of systemic infection, as determined by symptoms of fever, aches, chills, nausea, vomiting and/or weakness.

Ethics committee approval was not sought as the CE-marked wound-care product was used in accordance with its approved indications and not as part of a comparative trial.

Interventions

Flaminal is available in two formulations, which differ according to their alginate content. Flaminal Forte (5.5% alginate content) is suited for moderate-to-heavily exuding wounds and Flaminal Hydro (3% alginate content) is suited for low-to-moderate exuding wounds. The attending physician selected the formulation, Flaminal Hydro or Flaminal Forte, according to exudate levels. Wounds with severe exudate levels were dressed with Flaminal Forte and foam, moderately exuding wounds were dressed with Flaminal Hydro and foam, while lightly exuding wounds were dressed with Flaminal Hydro and gauze. Neither the patient nor the researcher was blinded to the dressing type.

Dressing changes and wound assessments were performed in the wound care unit by specialist nurses, under the care of a supervisor. The enzyme alginogel was applied in accordance with the manufacturer's instructions. Following cleansing with polyhexanide solution, a 3–5mm layer of the enzyme alginogel was applied to the wound and secured by secondary bandages (polyurethane foam or non-adherent dressing [NAD] gauze, depending on exudate level). The enzyme alginogel was left on the wound for 1–4 days, as long as the gel remained intact, and depending on the wound type and the amount of exudate produced. Dressing change frequency depended on the wound bed. On necrotic and sloughy wounds, dressings were changed daily; on granulating wounds, dressings were changed every 2–4 days. According to the manufacturer's instructions, Flaminal can remain in place as long as the viscous alginogel structure has not liquefied or disappeared. Wounds also received standard complementary treatment of care, such as off-loading shoes for diabetic foot ulcers (DFUs), pressure-redistributing mattresses for PUs and compression bandaging for mixed aetiology leg ulcers.

Patients were assessed at baseline, 14 days, 30 days and 60 days. The dressing protocol was terminated at 60 days, or once full healing was achieved, whichever occurred first. For the purpose of wound healing, wounds are categorised as either acute or chronic, with chronic wounds being of more than 12 weeks' duration.

Exudate levels were monitored throughout the evaluation for moderately and heavily exuding wounds by measuring the weight of the foam dressing. As the weight decreased, and thus the exudate levels decreased, the dressing regimen would be revised accordingly.

Outcomes

The wound duration and wound aetiology were recorded on entry. Wound assessments were recorded on the evaluation form at baseline and follow-up, which included wound size, tissue appearance, signs of local infection (defined by heat, pain, redness and swelling), exudate level, condition of wound edges and surrounding skin, and pain levels.

A rating for each of these parameters was provided at the final assessment.

The Visitrak measurement device (Smith & Nephew) was used to determine the wound surface and depth. Exudate level was determined by the weight of the secondary dressing (foam). Swab samples were taken from wounds demonstrating clinical signs of infection. The swabs were put in transport medium and were sent to the laboratory, where they were processed immediately. Standard methods for isolation and identification of aerobic and anaerobic bacteria were used. Pain levels were measured using a visual analogue scale (VAS) scale.

Statistical analysis

Data were analysed descriptively. Categorical data are presented by their number and percentage, and numerical variables by their mean±SD, median and range. When comparison between baseline and follow-up values were performed, a non-parametric Wilcoxon signed-rank test was used. A p value <0.05 was considered as indicative of statistical significance. Data analysis was conducted using SPSS software (v14.0; IBM).

Results

A total of 23 patients with wounds of diverse aetiology were treated with the enzyme alginogel. Patient ages ranged from 20 to 91 years, with a median age of 62 years (mean 54±23 years). Fifty-seven per cent were male (n=13) and 43% female (n=10). The number and types of wound, as well as the median wound duration prior to inclusion in the trial, are given in Table 1.

The most frequently encountered wounds in the outpatient's clinic were PUs, followed by DFUs. Nine PUs (category II/III) were included in the evaluation, all of which were chronic wounds (>12 weeks' duration). Of the seven DFUs evaluated, three were acute and four were chronic. All patients received standard care in addition to the enzyme alginogel.

In total, seven wounds were classed as acute (30%). The acute wounds comprised three DFUs, two traumatic wounds, one surgical excision and one dermatological lesion ('other'). Sixteen wounds were classed as chronic (70%), comprising nine PUs (category II/III), four DFUs, one non-healing traumatic wound, one superficial open laparocele, and one arterial ulcer.

Thirteen patients received Flaminal Forte and 10 received Flaminal Hydro; however, as exudate levels decreased, patients receiving Flaminal Forte had their dressing changed to Flaminal Hydro, as per the manufacturer's instructions.

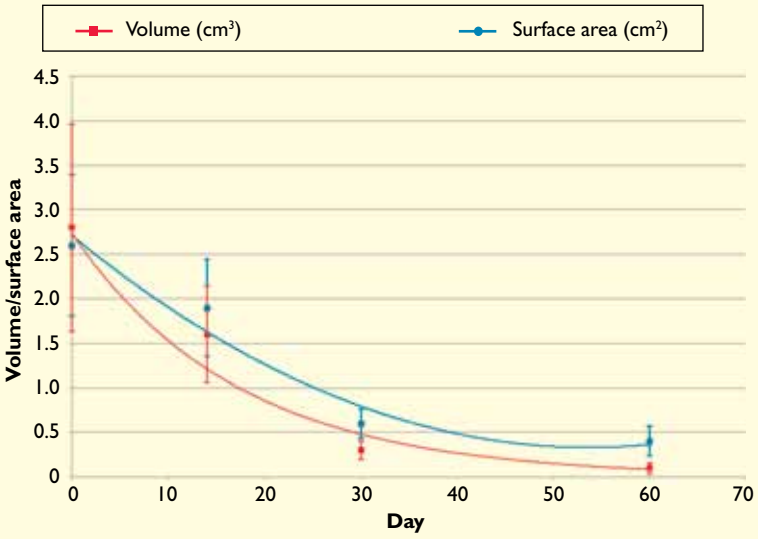
The underlying pathologies in patients with chronic wounds comprised cerebrovascular disease (one PU), venous insufficiency (one PU), chronic renal insufficiency (one DFU), fracture (one DFU, two PUs), spastic tetraparesis and immobility (one PU), diabetes, arterial insufficiency, pacemaker (one DFU), pyoderma gangrenosum, dermatomyositis (one arterial ulcer), arteriopathy, osteoporosis (one DFU).

All chronic wounds included in the evaluation were recalcitrant and had been treated unsuccessfully with different wound care products. These included Betadine gel (povidone-iodine 10%) (Meda Pharma SpA), Citrizan gel (equine catalase 8000 IU/g, gentamycin 0.1%; IDI Farmaceutici SpA), Fitostimoline cream (aqueous extract of Triticum vulgare 15%, fenoxyethanol 1%; Farmaceutici Damor SpA), Integra bilayer matrix wound dressing (Integra LifeSciences), Iodosorb (cadexomer iodine with 0.9% iodine; Smith & Nephew), Iruxol iontment (collagenase clostridiopeptidase A 1.2IU/g, proteases 0.24IE/g; Smith & Nephew).

Table 1. Wound aetiology, chronicity and duration at inclusion

Wound type	n (%)	Acute	Chronic	Median duration (days)(range)
Pressure ulcer	9 (39%)	0	9	335 (128–7128)
Diabetic ulcer	7 (30%)	3	4	246 (22–1593)
Traumatic wounds	3 (13%)	2	1	77 (0–397)
Arterial ulcer	1 (4.3%)	0	1	1195
Other	3 (13%)	2	1	0 (0–731)
Total	**23 (100%)**	**7**	**16**	**—**

Fig 1. Evolution of mean wound size during evaluation period



Error bars represent the standard error of the mean (SEM)

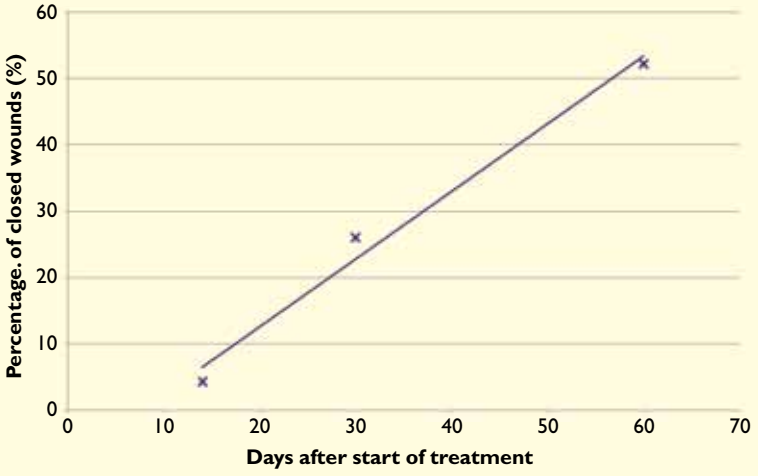
Fig 2. Evolution in healing of a pressure ulcer 1214 days' duration at start of treatment (a), and treated with enzyme alginogel for 14 days (b) and 30 days (c)

Table 2. Wound evolution at baseline and follow-up (n=23)

Parameter*	Day 0 (n=23)	Day 14 (n=22)	Day 30 (n=21)	Day 60 (n=13)
Surface area (cm^2)	2.6±3.8 (1.3)	1.9±2.6 (1.3)	0.6±0.8 (0.2)	0.4±0.8 (0.0)
Volume (cm^3)	2.8±5.6 (1.1)	1.6±2.6 (0.7)	0.3±0.5 (0.1)	0.1±0.3 (0.0)
Neo-epithelial tissue (%)	5.0±15.0 (0.0)	14.0±26.0 (0.0)	41.0±46.0 (30.0)	55.0±48.0 (90.0)
Granulation (%)	32.0±29.0 (40.0)	53.0±29.0 (50.0)	30.0±31.0 (30.0)	28.0±37.0 (10.0)
Fibrin (%)	59.0±31.0 (60.0)	34.0±30.0 (30.0)	19.0±26.0 (0.0)	8.0±17.0 (0.0)
Necrosis (%)	4.0±12.0 (0.0)	0.0±0.0 (0.0)	0.0±0.0 (0.0)	0.0±0.0 (0.0)

*Results expressed as mean±SD (median);
The decrease in the number of patients assessed over the evaluation period is due to wound either achieving healing or being withdrawn

Fig 3. Cumulative number of closed wounds over 60-day evaluation period



Wound size

After 60 days, a significant decrease in wound surface area and wound volume was noted in all wounds ($p<0.001$; Fig 1).

In spite of the fact that these chronic wounds had not responded to previous treatment, a decrease was noted in wound surface area and volume for the PUs, with the final mean values being 0.2±0.3cm^2 and 0.1±0.2cm^3, respectively, compared with 2.4±3.5cm^2 and 2.2±4.4cm^3 at day 0. Complete healing was achieved in two of the PUs (22%) by day 30 and four (44%) by day 30. Evolution of wound healing in a PU is shown in Fig 2.

The DFUs also showed a decrease in wound size; by day 30 the mean wound surface area had decreased to 0.4±0.6cm^2 and wound volume was 0.1±0.2cm^3, compared with 2.1±3.1cm^2 and 0.8±1.6cm^3 at day 0. Complete healing was seen in one DFU (14%) by day 14, two (29%) by day 30 and four (57%) by day 60.

With the sole exception of one traumatic wound, which increased in size from baseline to day 14 and then decreased, all of the wounds decreased in size over time.

The others wounds in the evaluation were included in such small numbers that it is not possible to draw any significant conclusions. Of the three traumatic wounds, one acute wound healed during the evaluation period, the other acute wound healed after the evaluation and the chronic wound was surgically closed, as the enzyme alginogel had successfully

Table 3. Evolution of pain, as measured by VAS pain score, before, during and after application of the enzyme alginogel

	Day 0 (n=23)			Day 14 (n=22)			Day 30 (n=21)			Day 60 (n=13)		
	Before	During	After	Before	During	After	Before	During	After	Before	During	After
PU	2.0	0.2	0.6	1.6	0.7	0.9	0.8	0.0	0.4	0.0	0.0	0.0
DFU	3.0	0.7	1.4	2.3	0.7	1.3	1.5	0.8	1.2	0.5	0.0	0.5
Traumatic	5.0	2.3	0.7	4.0	3.5	1.0	1.7	2.3	0.7	0.7	1.3	0.0
Arterial	8.0	5.0	5.0	3.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Other	1.7	1.7	0.3	0.7	0.7	0.3	0.0	0.0	0.0	0.0	0.0	0.0
Total*	2.9±3.2 0.0–8.0	1.0±1.9 0.0–5.0	1.0±1.9 0.0–5.0	2.0±2.5 0.0–8.0	0.9±1.9 0.0–6.0	0.9±1.7 0.0–5.0	1.0±1.6 0.0–5.0	0.6±1.5 0.0–5.0	0.6±1.2 0.0–4.0	0.3±0.8 0.0–2.0	0.3±1.1 0.0–4.0	0.2±0.6 0.0–2.0

*Total is given as mean±SD and range;
PU=pressure ulcer; DFU=diabetic foot ulcer

prepared the wound bed for skin grafting. The arterial ulcer healed by day 30, while the dermatological lesion did not heal within the evaluation period, but subsequently healed with the same care regimen. The laparocele healed by day 60 and the surgical excision by day 30.

Complete healing was seen in one acute wound by day 14, a further six wounds (two acute and four chronic) by day 30 and five more (all chronic) by day 60 (Fig 3). In one wound, a PU, treatment was stopped at day 30, due to an allergic reaction, and two wounds were surgically closed before the final assessment, as the enzyme alginogel was used to prepare the wound bed for skin grafting. Wounds that had not healed by day 60 were deemed to be progressing towards healing and the investigator continued treating them with the enzyme alginogel until healing was achieved (data not presented).

Wound bed characteristics

The percentage of wounds covered by necrosis and fibrin decreased during the 60-day evaluation period, whereas percentage of wound area covered by granulation and epithelial tissue increased (Table 2). This trend appeared independent of wound aetiology.

Exudate levels diminished during the evaluation period, as is normal and was to be expected. Maceration was most common in the PU group; however, in all groups, maceration decreased with time. Three wounds were locally infected with pathogens; one PU with osteomyelitis with *Staphylococcus aureus* and *Pseudomonas aeruginosa*, one DFU with MRSA and one PU with *Serratia* spp. By day 14, only the DFU remained infected (with MRSA), with all wounds cleared by day 30. There were no other incidence of infections.

Table 4. Overall evaluation of enzyme alginogel performance on wounds that achieved complete healing (n=20)

	Excellent	Good	Poor
Wound evolution	12 (60%)	8 (40%)	0 (0.0%)
Wound edges evolution	10 (50%)	9 (45%)	1 (5.0%)
Surrounding skin evolution	9 (45%)	10 (50%)	1 (5.0%)
Ease of application	20 (100%)	0 (0.0%)	0 (0.0%)
Ease of removal	20 (100%)	0 (0.0%)	0 (0.0%)
Exudate management	4 (20%)	16 (80%)	0 (0.0%)
User friendly	20 (100%)	0 (0.0%)	0 (0.0%)
Overall opinion	12 (60%)	8 (40%)	0 (0.0%)

Pain levels

A reduction in pain before, during and after wound care product change was noted over the course of the evaluation (Table 3). As expected, pain levels were greatest with the arterial ulcer (n=1) at inclusion, followed by traumatic wounds (n=3). Of the seven patients with DFUs, five (71%) experienced no dressing-related pain, which could be expected in this group as it is likely that these patients suffered sensory neuropathy. In each group, VAS pain scores decreased over time (Table 3).

Overall evaluation of the wound care product

The enzyme alginogel was rated as either good or excellent by the wound care team in all 20 cases

that completed the evaluation, recorded for wound evolution, ease of application, ease of removal, exudate management, user friendly and overall opinion, (Table 4). For wound edges evolution and surrounding skin evolution the enzyme alginogel was rated as either good or excellent in 19 cases (95%). Two adverse events were reported: an allergic reaction seen in surrounding skin and transient maceration. No serious adverse events were reported.

Discussion

This evaluation presents a mix of acute and chronic wounds, with typical wound aetiologies for a mixed population in a hospital outpatient setting. In all wounds, the amount of necrosis and fibrin decreased over time as the percentage of epithelial and granulation tissue increased, indicating that, by addressing each of the parameters of the TIME paradigm, the wounds were able to progress towards healing.

The results show that the enzyme alginogel reduced the bacterial bioburden in the three wounds with local infections, and no wounds developed an infection during the evaluation period. It should be noted that wounds were cleansed with polyhexanide, an antimicrobial, which could have had an initial effect on the wound bioburden. As there were no withdrawals as a result of tolerability or other safety considerations, the enzyme alginogel was considered safe for use for all the wound types evaluated.

The chronic wounds in this evaluation were recalcitrant and, prior to the evaluation, had not responded to several other wound care products. In addition to the change of product, management of the wound was placed under an expert practitioner, which may have contributed to the positive effect seen with enzyme alginogel. In some wounds, healing can be a slow process. In this case series eight wounds (two acute and six chronic) healed after the evaluation period had ended. Improved clinical outcomes are not only beneficial to the patient and their multidisciplinary team, but are also more cost-effective, benefiting the health service provider.[10]

Cost effectiveness remains a key consideration in product selection. While this evaluation did not set out to determine the cost-effectiveness of enzyme alginogels, some cost benefits were observed. As the tubes are self-sterilising, due to the antimicrobial properties, they are suited for multiuse on the same wound, thus minimising wastage. Furthermore, the enzyme alginogel is able to restore the bacterial balance of a wound, determined by the lack or reduction in signs of local infection, and, unlike traditional antimicrobials, it is not cytotoxic[8] and can be used for longer time periods.

Future research should include a larger comparative investigation to confirm and expand on these preliminary results. It would also need to assess the cost-effectiveness of these products.

Limitations

As this was an uncontrolled evaluation, it is prone to different types of bias, including regression of the mean, temporal changes and, possibly, selection bias. Given the small sample size and case series study design, the evidence that can be drawn from this evaluation comprises level 4.[11] Thus, this evaluation cannot demonstrate causality. Wounds, especially acute ones, are expected to heal over time. Therefore, it would be expected that many of the wounds would heal within 2 months. However, as some of the chronic wounds included in the evaluation were considered 'difficult-to-heal', the results could be considered clinically significant.

Conclusion

The enzyme alginogel facilitated healing in both acute and chronic wounds. Of interest, healing was achieved even in difficult-to-heal wounds, including a PU of 19 years' duration. The findings of this case series suggest that the enzyme alginogel improves several parameters, including a reduction in wound size, when used in the treatment of acute and recalcitrant wounds in an outpatient clinic. Additional studies are, however, warranted to confirm the clinical utility and cost-effectiveness of this wound care product in the management of chronic or acute wounds left to heal by secondary intention. ■

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