 doi:10.20944/preprints202211.0133.v1

Article

New Therapeutic Applications of Ozenoxacin in Superficial Skin Infections in Geriatric Patients: A Case Series

Jordi Esquirol Caussa[1,2,3,4], Josep Sánchez Aldeguer[1,5,6,7], Elisabeth Herrero Vila[2], Iñaki Antón Gorostidi[8], Miquel Colomer Giner[9], Anna Olivé Torralba[10], Josep Mª Abella Grau[11], Sònia Jiménez Herreros[7] and Carlos Llobregat Delgado[7]

1 Escoles Universitàries Gimbernat (adscrites a la UAB, Sant Cugat del Vallès)
2 ISADMU / Centro Médico Teknon (Barcelona)
3 Residència Sant Salvador (Sant Cugat V., Barcelona)
4 Llar Mirasol (Sant Cugat V., Barcelona)
5 Facultat de Medicina (Universitat Autònoma de Barcelona)
6 Residència Sant Quirze (Sant Quirze del Vallès)
7 Residència Santa Rosalia (Sabadell)
8 Residència Gravi (Polinyà)
9 Resdidència El Álamo (Caldes de Montbui)
10 Residència Desalup-Horta (Barcelona)
11 Residència Allegra (Sabadell)
12 Residència Sant Salvador (Sant Cugat del Vallès)
* Correspondence: jordi.esquirol@eug.es

Abstract

INTRODUCTION: Superficial cutaneous bacterial infections have a high incidence in geriatric patients. The most implicated pathogens are gram-positive cocci (Staphylococcus aureus, Streptococcus pyogenes) while gram-negative germs are also implicated. Resistances to common topical antibiotics (mupirocin, fusidic acid) require alternatives to gram-positive and gram-negative microorganisms.

Ozenoxacin cream for topical use (non-fluorinated bactericidal quinolone), in other countries and with other galenics, is indicated in children older than 6 months and in adults as a treatment of superficial bacterial infections, such as acne. In Spain, ozenoxacin cream is indicated only for non-bullous impetigo; scientific evidence show effectiveness also in other superficial skin bacterial infections.

A cases series of clinical use of ozenoxacin in bacterial superficial skin infections in geriatric patients (institutionalized or community dwelling) is presented.

METHODS: Multicenter case series (March-August 2022) of bacterial superficial skin infections treated with ozenoxacin cream (10mg/g every 12h, 5days); data from medical records (controls: 1-3-5 days), after obtaining informed consent (use of data and images).

RESULTS: Series of 28 patients (mean age: 84,79) from nine nursing homes and one outpatient geriatric service, including acute and subacute/chronic cases.

In all cases treatment was ozenoxacin 10mg/g topical cream applied every 12 hours for 5 days according to medical prescription (except for one case in which 3 days were enough for complete healing and another case treated for 10 days).

Results showed complete healing in all 20 acute cases and significant clinical improvement in all subacute/chronic cases (with complete healing in one of them). Professionals scored the effectiveness in acute cases as a mean 4.5 points (maximum score: 5, p<.0001) and in subacute/chronic cases as 3.8 points (p=.010).

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There was no skin irritation or other adverse effects in anyone of the patients, and clinical improvement of pain, itching and other symptoms was observed, suggesting an anti-inflammatory effect.

DISCUSSION AND CONCLUSIONS: Our results seem to demonstrate the effectiveness and tolerability of ozenozacin cream in bacterial infections other than non-bullous impetigo. Ozenoxacin cream is indicated only for the treatment of non-bullous impetigo; however, it is also shown to be effective, both in the scientific evidence and in our case series, for other superficial bacterial skin infections, both acute and subacute/chronic, suggesting the opportunity for clinical studies with an experimental design to evaluate the findings of clinical practice and to be able to have a therapeutic alternative to compensate for the complications of the appearance of resistance.

Keywords: skin infection; antibiotics; quinolone; S. aureus; geriatrics

INTRODUCTION

Ozenoxacin is a quinolone family antibiotic, approved for topical administration in humans. It is the first non-fluorinated quinolone for topical use, bactericidal as it penetrates the bacterial cytoplasm in the first minute of exposure. It is indicated as a treatment for non-bullous impetigo from 6 months of age in Europe, from 2 months of age in the United States and Canada and for the treatment of superficial skin infections of bacterial origin and for acne in Japan as a 2% lotion.[i,ii]

Its spectrum of action includes gram-positive bacteria such as Staphylococci (aureus, epidermidis, capitis, haemolyticus, hominis) and beta-hemolytic Streptococci (agalactiae, pyogenes, pneumoniae) and Enterococci faecalis. Its spectrum of Staphylococci action includes those resistant to other antibiotics (Meticillin Resistant Staphilococcus Aureus, MRSA) in addition to those sensitive to other antibiotics (Meticillin Sensitive Staphilococcus Aureus, MSSA).[iii] Regarding Gram-negative bacteria, ozenoxacin has shown efficacy against Enterobacteria such as different species of Escherichia (including E. coli), Citrobacter, Kebsiella (including K. pneumoniae), Enterobacter, Morganella, Serratia, Salmonella or Shigella and other Gram-negatives such as Hemophilus (including H. influenza), Moraxella or Neisseria (including Neisseria gonorrhoeae).[i] Ozenoxacin has not shown activity against Pseudomonas, anaerobic bacteria or fungi.

The most prevalent bacteria in skin and soft tissue infections (SSTI) are showing antibiotic resistance (especially MRSA but also other bacteria involved) in a considerable percentage to topical antibiotics commonly used against bacterial skin infections, such as mupirocin or fusidic acid. Ozenoxacin does not present any resistance against these bacteria so far,[iv] having shown microbiological efficacy with 100% clinical cure and greater than 90% eradication rates in MSSA, MRSA and Streptococcus pyogenes skin infections, being more effective compared to other topical antibiotics.[v] The antibiotics indicated for impetigo are usually ozenoxacin, mupirocin, fusidic acid and retapamulin.[vi] In cases of impetigo, mupirocin has been shown to be effective against methicillin-resistant Staphylococcus aureus (MRSA), but culture and antibiotic susceptibility testing is recommended in these cases. Retapamulin is indicated in cases of colonization by germs sensitive to methicillin and Streptococcus pyogenes, but not in cases of MRSA. Fusidic acid is not indicated in the United States of America for impetigo due to the increasing appearance of resistance; ozenoxacin is shown as an effective alternative to impetigo caused by both MRSA germs and other germs.[vii,viii,ix] The use of topical ozenoxacin could help eradicate impetigo while minimizing antimicrobial resistances.[x,xi]

In patients with impetigo, scientific evidence shows that systemic absorption after topical administration of ozenoxacin on intact or eroded skin is negligible, both children and adults, and is therefore not contraindicated in pregnancy. Its cutaneous application does not cause phototoxicity or photosensitization and has a rate of less than 1% of local irritation,

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being considered a well-tolerated and safe drug in its cutaneous application in children over 2 months of age, adolescents, and adults.[xii]

In Spain, ozenoxacin is marketed as a topical cream in a 10mg/g concentration, indicated for the short-term treatment of non-bullous impetigo in adults, adolescents, children and infants (over 6 months of age).[xiii,xiv] There is evidence for the off label use of ozenoxacin in SSTI in children other than the non-bullous impetigo indication.[xv]

Intertrigo is a SSTI with prevalence of between 11% and 21% in geriatric centers that affects the submammary fold, inguinal region, armpits or abdominal area. With respect to other indications for superficial skin infection, there is scientific evidence for the use of ozenoxacin in submammary intertrigo in elderly people living in geriatric centers, with good results and no unwanted effects.[xvi] The most isolated organisms in the intertrigo are bacteria such as MSSA, MRSA, Streptococcus pyogenes, Proteus, Pseudomona, Corynebacterium and fungi such as candida or others and their treatment is based on empirical topical antibiotics or antifungals in addition to the reduction of moisture and friction and the use of clothing made of natural materials.

In the same sense, some of the most frequent pyodermitis in people with diabetes are produced by the same germs and, more specifically for the diabetic foot, the most isolated pathogens are usually ozenoxacin-sensitive bacteria such as gram-positive (Staphilococcus, Streptococcus, Enterococcus), gram-negative (Escherichia Coli, Proteus, Enterobacter, Klebsiella), apart from Pseudomona aeruginosa or fungi such as Candida albicans.[xvii]

Other skin infections in which the most common germs (Staphilococcus Aureus and Streptococcus pyogenes) are involved in addition to impetigo can be, for Staphilococcus Aureus: cellulitis, lymphangitis, folliculitis, furuncle, hidradenitis suppurativa, abscess, acne,[xviii] bite or puncture wounds, pyoderma, dactylitis ampullosa or botryomycosis. Streptococcus pyogenes is also commonly involved, in addition to impetigo, in cellulitis, lymphangitis, erysipelas, perianal dermatitis, ecthyma, pyoderma and dactylitis ampullosa.

The main objective of the study was to analyze the clinical effectiveness of ozenoxacin in superficial bacterial skin infections in adults, as well as treatment's safety and tolerability.

MATERIAL AND METHODS

A prospective, uncontrolled, intervention longitudinal research project (case series) was proposed, including institutionalized and community dwelling men and women with bacterial skin infections.

Candidates were chosen from people living in the community or institutionalized in nursing homes, who met the inclusion criteria and who had shown their free willingness (or of their legal representatives) to participate in the study based on the information provided by the medical and nursing staff. Other people could also be included in the study, as long as they met the inclusion criteria and did not meet any of the exclusion criteria.

The participant candidates or their legal guardians (in case of judicial incapacity) were given the participant information and data protection sheet (ARSOPOL) and the informed consent was requested. Subsequently, the initial data collection file was filled out with the inclusion and exclusion criteria and the measurements of the specified variables were taken. Participants were assigned a code to maintain confidentiality.

A 5-day intervention of applying ozenoxacin cream every 12 hours on the infected skin lesion was proposed. Serial photographs of the lesion were taken before starting the treatment, at 3 days and at 5 days and the final data collection questionnaire was filled out.

Inclusion criteria: Men and women over 50 years of age, community dwelling or institutionalized, with localized bacterial superficial skin infection, with or without solution of skin continuity (mainly impetigo, ecthyma, intertrigo, dermatitis, folliculitis, boil or furuncle, hidradenitis suppurativa, acne, pyoderma, dactylitis ampullosa, wounds, ulcers or other skin infections localized superficial with clinical suspicion of bacterial infection).

 doi:10.20944/preprints202211.0133.v1

Exclusion criteria: Extent greater than 36 cm2, fever, lymphadenopathy extended to more than one territory, suspicion of skin infection by fungi or pseudomonas, immunity alteration or immunosuppressive treatment.

Withdrawal criteria: lack of follow-up visits, appearance of fever, extension of lymphadenopathy in more than one territory, adverse effect (irritation, itching or pain) located around ointment's administration area.

Study variables: Age, gender, area of residence, location of injuries; clinical diagnosis of injuries; extension of the lesions at the beginning of the treatment, on the 3rd day and on the 5th day; qualitative analysis of the lesion's appearance at the beginning of the treatment, on the 3rd day and on the 5th day; Color of the background, color of the environment, presence of exudate; Appearance of symptomatic adverse effects (irritation, itching, pain).

Intervention: Topical administration of ozenoxacin cream (10mg/g) every 12 hours, for 5 days.

Data collection: Day 1: at the first diagnosis of an acute lesion suggestive of being treated with ozenoxacin, compliance with the inclusion criteria and non-compliance with the exclusion criteria were assessed. If the appropriate criteria are met, participation in the study was offered by presenting the information sheets to the participant and informed consent. If agreement to participate in the study, digital images of the lesions were taken and topical treatment with ozenoxacin cream (10mg/g) every 12 hours was started. The possible appearance of adverse events will be always monitored. All images were taken digitally, with good lighting, recommending to always take images of each patient in the same settings (treatment room) for comparison and analysis of evolution purposes. Day 3: the evolution of the injuries was observed, and a digital image of the injuries was taken. Day 5: the evolution of the lesions was documented with digital images and the treatment was considered completed after the 10th application (every 12 hours, 5 days). Five days after the end of the treatment, an assessment was made to detect the possibility of relapses.

The clinical response was based on the clinical assessment by the investigator at the follow-up visit following a predefined scale with the following categories: 5: Clinical success, 4: Clinical improvement, 3: slightly improvement, 2: therapeutic failure, and 1: worsening. Clinical success was considered the total absence of the lesion or very significant improvement.

Statistical analysis: As this is a proof-of-concept study, no sample size was calculated, and no statistical analysis was previewed beside descriptive statistics of the variables. Quantitative data collected in the study were statistically analyzed to answer the objectives of the study. Qualitative data were analyzed to document the evolution of the injuries. The calculation of the statistical significance of the professional assessment of the effectiveness of the treatment was carried out by taking the value of the population average in 3 points and with a 95% confidence level.

RESULTS

This prospective observational pilot study was conducted from March to August 2022 in 9 nursing homes near Barcelona (Spain). Adult patients who had superficial skin infections other than nonbullous impetigo in which oral antibiotics, due to severity or extension of the lesions were not needed, were considered for this study. Patients with a history of hypersensitivity to ozenoxacin were excluded. At the baseline visit, all the patients or their legal representants were informed and the informed consent was obtained, reflected in their clinical history.

During the study period, a total of 29 patients were recruited of which 28 completed the full program, 22 females and 6 males (patient number 20 did not complete follow-up visits and was eliminated). Mean age was 84,79 (max=99, min=53, Standard Deviation SD=10.14). Fifteen of the patients (53.7%) had cognitive impairment. Twenty (71.4%) of the patients (15 females and 5 males) had local acute infections and eight (28.5%) had subacute or chronic lesions (7 females, 1

 doi:10.20944/preprints202211.0133.v1

man). All patients received treatment with 2 daily applications of ozenoxacin 10mg/g for 5 days (except one that healed in 3 days, and another one that was treated for 10 days). Images were obtained before starting the treatment and at days 3 and 5. Patient's individual data is shown in Table 1.

In the Acute Infections Group (AIG, n=20), all of the patients included except one had Cognitive Impairment; three of them had Congestive Heart Failure, two of them had Type 2 Diabetes, two had Chronic Kidney Disease (CKD), one had Chronic Obstructive Pulmonary Disease (COPD) and one of them was under oral anticoagulant treatment. Five of the AIG patients (25%) were diagnosed of intertrigo (4 submammary, 1 inguinal), three (15%) were diagnosed of cellulitis (nipple, leg and after byte origin), two were been diagnosed of furuncle (one on the ear and another one on the leg), two with scratch injuries, two with infected scalp lesions, two with wounds (posthematoma and traumatic) and one sebaceous cyst, one pyodermitis, one dorsal impetigo and one paronychia. All patients were treated with topical ozenoxacin for 5 days, except for one submammary intertrigo that healed completely in three days (Figure 1). All patients showed good evolution, having completely healed in the applied treatment time; clinical response was assessed by professionals, that showed satisfaction with the treatment with an average score of 4.5 out of a maximum of 5 points (max=5 min=3, SD=.75, p<.00001, Confidence Interval CI=[4.149, 4.851]). None of the patients included presented discomfort or adverse effects to the treatment. None of the patients included presented a recurrence or worsening of the lesions after 5 days of discontinuing treatment.

In the Chronic Infections Group (CIG, n=8), only one patient had Cognitive Impairment, four had Venous Chronic Insufficiency, two had CKD, one had Peripheral Vasculopathy, and one had Obesity. Four of them had chronic venous ulcers, three had pressure ulcers and one with ischemic infected lesions. All patients were treated with topical ozenoxacin for 5 days, except one venous ulcer that was treated for 10 days (Figure 2). All patients showed good evolution, having improved their chronic wounds in that period; the venous ulcer that was treated for 10 days healed completely in that period. Clinical response was assessed by professionals, that showed satisfaction with the treatment with an average score of 3.8 out of a maximum of 5 points (max=5 min=3, SD=.83, p=.010, Confidence Interval: CI=[3.106, 4.494]). None of the patients included presented discomfort or adverse effects to treatment. None of the patients included presented a recurrence or worsening of the lesions after 5 days of discontinuing treatment.

Pictures of lesions were taken meanly at baseline and at days 3 and 5 (end of therapy). No samples were taken for microbiological determination, except for patient number 29 that was diagnosed by Staphilococcus pyogenes infection.

After the topical administration of ozenoxacin 10 mg/g every 12 h for 5 days, all 28 patients achieved clinical success. The mean global score of the qualitative results was 4.3 (SD=.79, p<.00001, CI=[3.994, 4.606]) from a total maximum of 5 points. In none of the cases was it necessary to apply oral treatment added to the topical one and in any case was required additional medication for pain or other symptoms.

The details of each included patient are shown in Table 1. In the Supplementary appendix all pictures from the initial lesions and follow up of the evolution can be found showing the evolution after twice a day treatment with ozenoxacin 10mg/g cream.

In all cases, the tolerability of the drug was total; no signs of local irritation or any other local or systemic alterations were reported.

DISCUSSION

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For years, the most indicated antibiotics for SSTI have been fusidic acid and mupirocin (marketed in Europe in the 1960s and 1991, respectively); Retapamulin was marketed in Europe until 2019, although it is not available now.

Both mupirocin and fusidic acid are indicated for all types of bacteria originated SSTI, both primary infections (impetigo, folliculitis) and secondary infections (impetiginization, infected eczematous lesions, wounds, and lacerations).[xix, xx] Excessive or inappropriate use of these topical antibiotics has led to a large increase in antibiotic resistance to both antibiotics in many countries.[iv]

Since the treatment of these pathologies is usually empirical, it is often difficult to find published scientific evidence that reflects the real updated status of resistance rates against these antibiotics. Studies in pediatric patients show resistance to mupirocin in up to 31% of patients. Likewise, Staphylococcus aureus resistance rate to fusidic acid increased from 17% in 1999 to 29% in 2013; restricting free dispensing of mupirocin reduced resistance rates from 28% to 11% in just 11 years in New Zealand.[xxi]

There are no studies available from Spain in adult patients, and only one study in pediatric patients shows data on resistance of Staphylococcus aureus of 2% and MRSA of 5.6% to fusidic acid and to mupirocin of 7% and 4%, respectively.[xxii]

Ozenoxacin is a non-fluorinated quinolone for topical use, indicated in Spain only for non-bullous impetigo, while in other countries such as North America and Japan (as a lotion) it is indicated for other bacterial SSTI such as acne.[ii] In vitro studies show ozenoxacin activity against a wide spectrum of gram-positive and gram-negative germs, except for Pseudomonas.[i] Ozenoxacin has a bactericidal effect, more active than mupirocin or fusidic acid and other quinolones against Gram-positive SSTI and, due to its chemical configuration, it seems difficult for germs to develop resistance.[vi] In recent years, evidence has been published on the use of ozenoxacin in indications other than impetigo, both in pediatric patients[xv] and in adults.

In our series of cases, the results show a high effectiveness of ozenoxacin in the patients included, especially in patients with acute pathologies. In the case of chronic pathologies, a good evolution of the lesions was also observed in the five days of application, while complete healing was not expected because they were pathologies with slower evolution.

The rapid disappearance of the symptoms associated with the infection (such as pain, erythema, itching or sensation of irritation) seem to indicate a kind of anti-inflammatory effect of this antibiotic, as had already been reported in previous studies.[xxiii]

Although ozenoxacin is only indicated for patients with non-ampullous impetigo, the results of our series show that its use could be extended to many other pathologies that include bacterial SSTI. This could entail benefits for patients, both due to the reduction of bacterial resistance antibiotics and due to its effectiveness against multi-resistant germs as MRSA.[i]

Our series of cases is relatively short, and the design was not controlled, but the variety of pathologies included allows us to observe the usefulness of this drug beyond the initially authorized pathologies. To our knowledge, this is one of the first studies of topical ozenoxacin 10mg/g cream carried out in geriatric patients, while a previous study in a similar pediatric population has been reported.[xxii]

Ozenoxacin is a bactericidal quinolone that is easy to apply topically (every 12 hours) and that does not present side or annoying effects. Its use is generally indicated for 5 days, although its more continuous application has not produced any adverse effect.

 doi:10.20944/preprints202211.0133.v1

CONCLUSSION

Given the in vitro sensitivity profile and the in vivo effectiveness shown by ozenoxacin cream 10mg/g in pathologies other than non-bullous impetigo in our series of adult patients, also showing great adherence to treatment due to the convenience of the dosage, and without the appearance of adverse effects or discomfort, this drug could be considered for its use to manage bacterial SSTI caused by susceptible microorganisms and not restrict its use only to impetigo.

Authors contributions: All authors making substantial contributions to conception and design, or analysis and interpretation of data; and to writing and revising the present manuscript. All authors have approved the final version.

Conflict of interest statement: The authors declare no conflict of interest.

Funding source: None

Consent statement: Informed consent was obtained from all patients to publish their personal data and images.

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TABLES

Patient	Type	Diagnosis	Other pathologies	Age (years)	Gender (M/F)	Treatment Days	Results
1	Acute	Submammary intertrigo	CI	85	D	5	5
2	Acute	Scratch injuries	CI	86	D	5	5
3	Acute	Paronychia	CKD, COPD	95	D	5	5
4	Acute	Submammary intertrigo	CI	99	D	3	5
5	Subacute/Chronic	Infected ischemic lesions, toes	CKD, PV	93	D	5	3
6	Subacute/Chronic	Venous ulcer, lower limb	CVI	76	D	10	5
7	Subacute/Chronic	Venous ulcer, lower limb	CVI	92	D	5	3
8	Subacute/Chronic	Pressure ulcer, malleolus	CI	84	D	5	4
9	Acute	Traumatic wound	CI	89	D	5	3
10	Acute	Impetigo, back	CI	76	H	5	5
11	Acute	Cellulitis, nipple	CI	89	D	5	5
12	Acute	Ulcer posthematoma	CI, OA	84	D	5	3
13	Acute	Scalp, lower limb	CI, CKD, CHF	80	D	5	5
14	Acute	Scalp, lower limb	CI	79	H	5	5
15	Subacute/Chronic	Pressure ulcer, malleolus	CKD, COPD	95	D	5	5
16	Acute	Cellulitis, lower limb	CI, CHF	90	H	5	5
17	Acute	Sebaceous cyst	CI	90	H	5	4
18	Acute	Scratch injuries		85	D	5	4
19	Acute	Pyoderma		93	D	5	4
21	Acute	Furuncle	CI	92	D	5	5
22	Subacute/Chronic	Venous ulcer, lower limb	CVI	58	H	5	3
23	Subacute/Chronic	Venous ulcer, lower limb	CVI	82	D	5	4
24	Acute	Submammary intertrigo	CI	87	H	5	5
25	Acute	Submammary intertrigo	CHF	85	D	5	3
26	Acute	Post-bite cellulitis	DM	83	D	5	5
27	Acute	Inguinal intertrigo	CI	88	D	5	5
28	Subacute/Chronic	Pressure ulcer, toe	Ob	87	d	5	4
29	Acute	Furuncle (Staph. pyogenes)		52	d	7	4

Table 1: Cases included (CI: Cognitive Impairment/Dementia; CKD: Chronic Kidney Disease; COPD: Chronic Obstructive Pulmonar Disease; PV: Peripheral Vasculopathy; CVI: Chronic Venous Insufficiency; OA: Oral Anticoagulants; DM: Diabetes Mellitus; CHF: Congestive Heart Failure; Ob: Overweight/Obesity).

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FIGURES

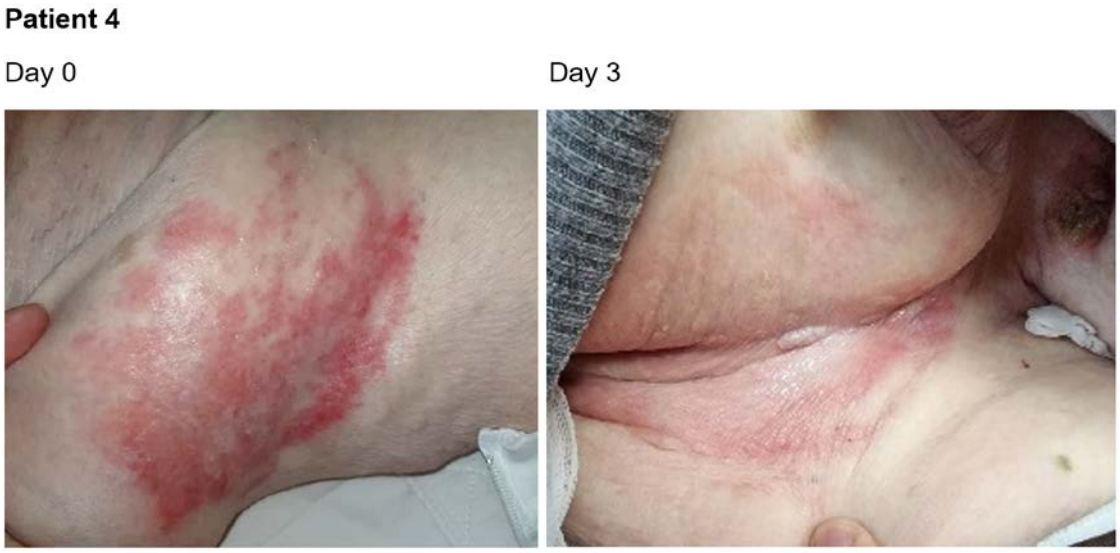

Figure 1: Acute case healed in three days (submammary intertrigo, case number 4).

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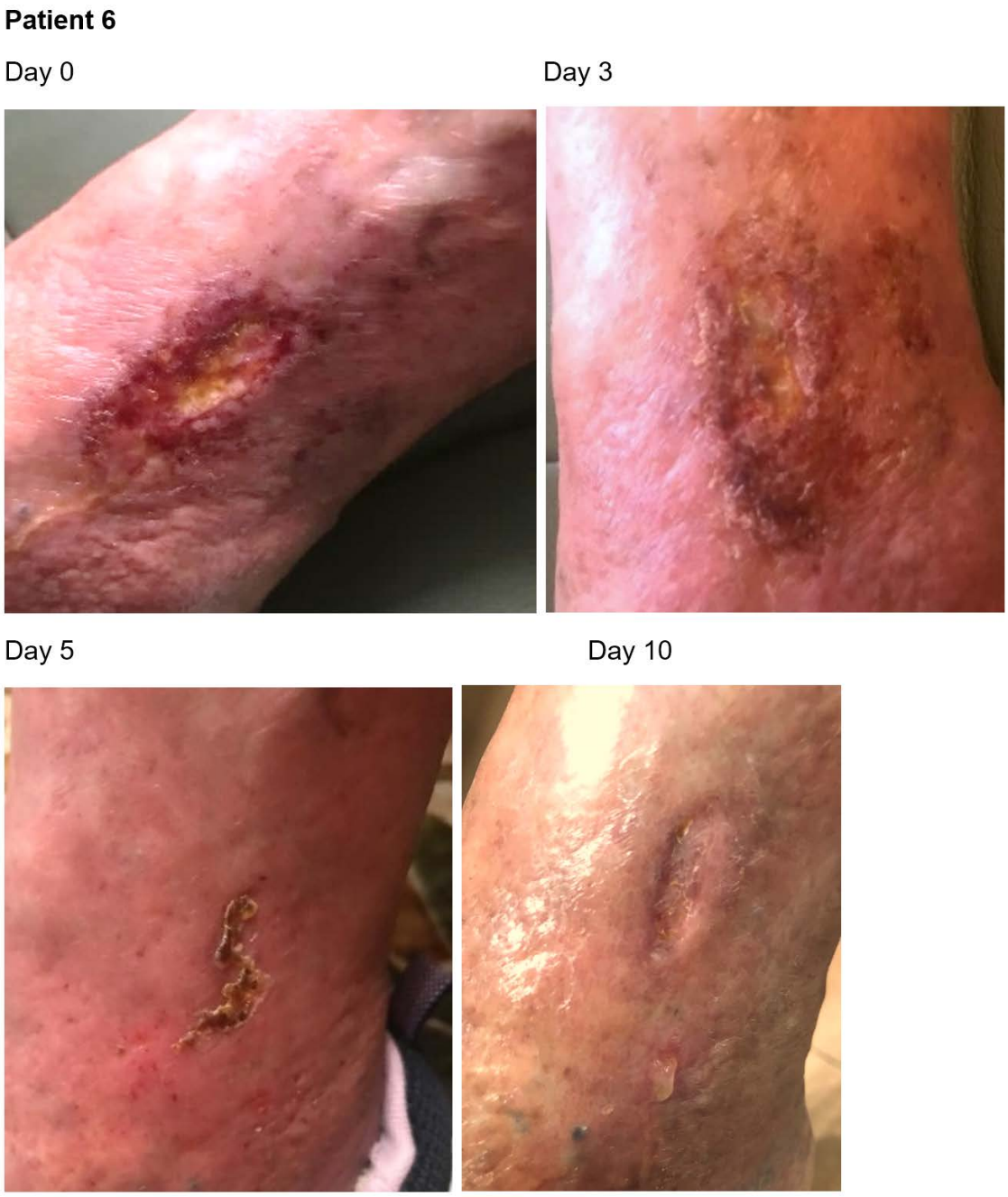

Figure 2: Subacute/chronic case healed in 10 das (chronic leg venous ulcer, case number 6).

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