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5		Family Name	Vairetti
6		Particle	
7		Given Name	Mariapia
8	Corresponding Author	Suffix	
9		Organization	University of Pavia
10		Division	Department Internal Medicine and Therapeutics
11		Address	Via Ferrata, 9a, Pavia 27100, Italy
12		e-mail	mariapia.vairetti@unipv.it
13		Family Name	Melandri
14		Particle	
15		Given Name	Davide
16		Suffix	
17	Author	Organization	Buřalini Hospital
18		Division	Dermatology Units and Burn Center Ausl Romagna
19		Address	Viale Ghirotti, 286,, Cesena 47521, Italy
20		e-mail	davide.melandri@auslromagna.it
21		Family Name	Albano
22		Particle	
23		Given Name	Vincenzo Maria
24		Suffix	
25	Author	Organization	Infermi Hospital
26		Division	Dermatology Unit Ausl Romagna
27		Address	Viale Stradone, 9, Faenza 48018, Italy
28		e-mail	hodermo.ra@auslromagna.it
29		Family Name	Venturi
30	Author	Particle	
31		Given Name	Michela

32		Suffix	
33		Organization	Buřalini Hospital
34		Division	Dermatology Units and Burn Center Ausl Romagna
35		Address	Viale Ghirotti, 286,, Cesena 47521, Italy
36		e-mail	michela.venturi@auslromagna.it
37		Family Name	Flamigni
38		Particle	
39		Given Name	Andrea
40	Author	Suffix	
41		Organization	Riolo Terme
42		Division	
43		Address	Via Firenze, 15, Riolo T 48025, RA, Italy
44		e-mail	ndreaflamigni@inwind.it
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48	Abstract	<p>This study assessed the effects of liman peloid, followed by bath and heliotherapy in psoriatic patients at Cervia, Emilia, Italy. The psoriatic patients were randomized into two groups: group 1 with 56 patients, treated with liman applications, bath, and heliotherapy, and group 2 with 35 subjects, treated with mud-bath therapy using a clay peloid mixed with tap water and heliotherapy. Data was collected for the following: psoriasis area and severity index (PASI); delta-PASI (difference between post- and pre-treatment PASI); delta-PASI3 and delta-PASI6, 3 and 6 months after the end of treatment, respectively; psoriasis recurrences; and the use of both topical and systemic drugs. Although not significant, a decrease in PASI was recorded in group 1 at the end of treatment and after 3 and 6 months. Compared with group 2, there was a significant change in delta-PASI, delta-PASI3, and psoriasis recurrences in group 1 as well as a significant reduction in the topical use of drugs, both cortisone and nonsteroid drugs. This is the first and preliminary study which documented the efficacy of a specific protocol of liman bath heliotherapy in psoriatic patients as documented by a reduction in delta-PASI and delta-PASI3, a decrease in psoriasis recurrences, and use of topical drugs.</p>	
49	Keywords separated by ' - '	Psoriasis - Balneotherapy - Liman peloids - Heliotherapy	
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Efficacy of combined liman peloid baths and heliotherapy in the treatment of psoriasis at Cervia spa, Emilia, Italy

Davide Melandri¹ · Vincenzo Maria Albano² · Michela Venturi¹ · Andrea Flamigni³ · Mariapia Vairetti⁴

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Abstract

This study assessed the effects of liman peloid, followed by bath and heliotherapy in psoriatic patients at Cervia, Emilia, Italy. The psoriatic patients were randomized into two groups: group 1 with 56 patients, treated with liman applications, bath, and heliotherapy, and group 2 with 35 subjects, treated with mud-bath therapy using a clay peloid mixed with tap water and heliotherapy. Data was collected for the following: psoriasis area and severity index (PASI); delta-PASI (difference between post- and pre-treatment PASI); delta-PASI3 and delta-PASI6, 3 and 6 months after the end of treatment, respectively; psoriasis recurrences; and the use of both topical and systemic drugs. Although not significant, a decrease in PASI was recorded in group 1 at the end of treatment and after 3 and 6 months. Compared with group 2, there was a significant change in delta-PASI, delta-PASI3, and psoriasis recurrences in group 1 as well as a significant reduction in the topical use of drugs, both cortisone and nonsteroid drugs. This is the first and preliminary study which documented the efficacy of a specific protocol of liman bath heliotherapy in psoriatic patients as documented by a reduction in delta-PASI and delta-PASI3, a decrease in psoriasis recurrences, and use of topical drugs.

Keywords Psoriasis · Balneotherapy · Liman peloids · Heliotherapy

Introduction

Balneotherapy has been recently defined as a set of methods and practices (bathing, drinking, and inhalation) which use natural

mineral waters, natural peloids, and natural sources of different gases (CO₂, H₂S, and Rn) for medical purposes such as prevention, treatment, and rehabilitation (Gutenbrunner et al. 2010). Balneotherapy is widely used in the treatment of dermatological ailments such as dermatitis, psoriasis, atopic dermatitis, vitiligo, ichthyosis linearis circumflexa, acne vulgaris, contact dermatitis, seborrheic dermatitis, chronic wounds, radiation dermatitis, mycosis fungoides, and epidermolysis bullosa (Huang et al. 2018). The treatment for skin diseases comprises the use of heliotherapy (controlled exposure to the sun) associated with balneotherapy in the presence or absence of medical peloid (Boreham et al. 1995).

In particular, psoriasis is a common chronic immune-mediated skin disease affecting approximately 7.4 million people in the USA and approximately 125 million people worldwide (Rachakonda et al. 2014). Traditional drugs for the treatment of psoriasis have well-known clinical limitations and various side effects. Equally, recent biological therapies that have been approved have potential serious adverse effects so that, even where the benefits outweigh the risks, the long-term safety of these therapies necessarily requires constant pharmacovigilance (Kaushik and Lebwohl 2018).

Balneotherapy emerged as an important treatment modality in the 1800s, and several studies have since reported its use as a safe and effective treatment for psoriasis (Even-Paz and Shani, n.d.).

✉ Mariapia Vairetti
mariapia.vairetti@unipv.it

Davide Melandri
davide.melandri@auslromagna.it

Vincenzo Maria Albano
hodermo.ra@auslromagna.it

Michela Venturi
michela.venturi@auslromagna.it

Andrea Flamigni
ndreaflamigni@inwind.it

¹ Dermatology Units and Burn Center Ausl Romagna, Bufalini Hospital, Viale Ghirotti, 286., 47521 Cesena, Italy

² Dermatology Unit Ausl Romagna, Infermi Hospital, Viale Stradone, 9, 48018 Faenza, Italy

³ Riolo Terme, Via Firenze, 15, 48025 Riolo T, RA, Italy

⁴ Department Internal Medicine and Therapeutics, University of Pavia, Via Ferrata, 9a, 27100 Pavia, Italy

51 Both prospective and retrospective studies have demonstrated the
52 successful treatment of psoriasis using balneotherapy in the Dead
53 Sea (Katz et al. 2012; Talbott and Duffy 2015). The water of the
54 Dead Sea is extremely high in salinity and contains sulfides,
55 microorganisms, algae, and other bioactive materials that may
56 contribute to their therapeutic effects. Bathing in this hypertonic
57 salt solution, 320 g/L, allows Dead Sea minerals to penetrate
58 human skin (Huang et al. 2018). Previous results have demon-
59 strated the use of balneotherapy for psoriasis in Italy too. Several
60 studies performed at the Comano spa in the Trentino region have
61 demonstrated the efficacy of balneotherapy for chronic plaque
62 psoriasis; the use of photobalneotherapy has recently been shown
63 to be better than balneotherapy alone (Peroni et al. 2008). A
64 randomized placebo-controlled study performed using
65 arsenical-ferruginous water from Levico and Vetriolo, in the
66 Trentino region, produced a statistically significant decrease in
67 mild to moderate psoriatic lesions in 34 patients (Borroni et al.
68 2013).

69 The aim of this prospective, randomized clinical study was
70 to evaluate the short-term and long-term efficacy and safety of
71 a liman peloid application followed by bath and heliotherapy
72 versus control group (using a clay peloid mixed with tap water
73 and heliotherapy) in psoriatic patients at Cervia, Emilia, Italy.
74 The balneotherapy was repeated once a day for 18 days.
75 Recurrence of psoriasis as well as the topical and systemic
76 use of (steroid and nonsteroid) drugs were evaluated.

77 Patients and methods

78 This was a prospective, randomized open clinical trial.
79 Protocol authorization 3733/2015 I.5/103 (June 11, 2015).
80 This is a comparative study in which patients were random-
81 ized divided in two groups: group 1 (experimental group) or
82 group 2 (control group).

83 The primary endpoint was to compare the short-term and
84 long-term efficacy of liman peloid therapy, followed by bath
85 and heliotherapy, with the control group. The effects of
86 balneotherapy were assessed by analyzing the psoriasis area
87 and severity index (PASI), delta-PASI (PASI difference between
88 post- and pre-treatment, after an 18-day course of treatment),
89 delta-PASI3 (PASI difference between PASI-3 months and pre-
90 treatment), and delta-PASI6 (PASI difference between PASI-
91 6 months and pre-treatment) (Ring et al. 2015). In addition, the
92 time interval between the end of combined liman peloid bath and
93 heliotherapy and psoriasis recurrence was evaluated.

94 The secondary endpoint included reduction in drug use:
95 The number of patients using both topical and systemic drugs
96 was quantified. In addition, all the patients – using cortisone
97 or/and nonsteroid drugs (calcipotriol, moisturizing creams or
98 with urea, hyaluronic acid, sweet almond oil or cosmetics,
99 retinoids, cyclosporine, methotrexate) – were evaluated at
100 the end of this combined therapy.

Experimental design

101 Written informed consent was obtained from each patient ($n =$ 102
103 91); they were randomized and assigned to group 1 ($n = 56$) or
104 group 2 ($n = 35$). In detail, the experimental design included a
105 group of patients (group 1) who were given a thin layer of
106 liman peloid (total body), followed by bath therapy in water
107 containing sodium chloride, bromide, and iodide (“Acqua
108 Madre”) in the presence of ozone. The therapeutic effects of
109 liman peloids are enhanced by lying on the sun terrace be-
110 tween 10 a.m. and 3 p.m., thereby combining the healing
111 properties of liman peloid therapy with the beneficial effects
112 of heliotherapy. The thermal therapy consisted of one treat-
113 ment for 18 days: a 40-min liman peloid application (40 °C); a
114 bath with total immersion in an individual bath tub lasting
115 20 min (38 °C); and heliotherapy with daily increments of
116 10 min to reach 1 h after 6 days, 2 h after 12 days, and a
117 maximum of 3 h after 18 days. The sun exposure occurred
118 during June–July–August (Krzyścin et al. 2012). Using the
119 same schedule, the control group of patients (group 2) was
120 submitted to mud-bath therapy using a clay peloid mixed with
121 tap water in the presence of ozone followed by the same
122 heliotherapy period.

123 This treatment is authorized by the Italian protocol (Aut.
124 Min. 400.9.20900.9.64.9/120245/748, April 20, 1961).

125 The patients were enrolled in collaboration with the
126 Department of Dermatology of the USL Romagna. Inclusion
127 criteria for study participation were age above 18 years with a
128 clinical or histopathological diagnosis of psoriasis, whether
129 chronic plaque psoriasis, guttate, inverse, palmoplantar, or
130 arthropathic psoriasis (quiescent or active). Patients with scalp
131 and nail psoriasis were also enrolled, as there were no limita-
132 tions linked to the psoriasis site. The severity of psoriasis was
133 not an exclusion criterion either, as subjects with mild, mod-
134 erate, or severe psoriasis, measured on the PASI scale, were
135 admitted, as well as patients able to understand the aim and
136 purpose of the study; patients who signed the informed con-
137 sent form participated in the trial.

138 Exclusion criteria: Patients with pustular psoriasis because
139 of infective risks; patients with decompensated chronic insuf-
140 ficiency of the main organs or systems; patients with severe
141 neuropsychiatric disorders; epileptic patients; patients with
142 severe hematological abnormalities; patients with systemic
143 lupus erythematosus or other diseases exacerbated by sun ex-
144 posure; patients with acute skin infections (viral and bacteri-
145 al); pregnant patients; patients with malignant neoplasms or
146 recent surgical outcomes; decompensated cardiopathic pa-
147 tients; patients in therapy with drugs that could alter the re-
148 sponse to the combined therapy.

149 On the day of admission (day 0), demographic data and
150 patient medical history (comorbidities) and previous treat-
151 ments for psoriasis were collected. The severity of psoriasis
152 was measured by a dermatologist using PASI; patients were

153 asked to fill in a questionnaire about the use of drugs (corti- 191
 154 sone and nonsteroid drugs). At the end of the 18-day treat- 192
 155 ment, patients were evaluated by the same physician for PASI 193
 156 test and adverse events. Three and 6 months after the end of 194
 157 the treatment, the patients were evaluated again by the same 195
 158 physician for PASI test, adverse events, and psoriasis relapses. 196
 159 Psoriasis recurrence represents the period between the end of 197
 160 thermal treatment and the onset of a relapse, this last defined 198
 161 as a return of psoriasis to 50% of baseline identified by the 199
 162 dermatologist visiting the patients in the follow-up. 200

163 Liman peloid and water analysis

164 Liman peloid analysis was performed after filtration by UNI 201
 165 EN 14346:2007, method A. 202

166 Water analysis was performed using inductive coupled 203
 167 plasma-mass spectrometry (ICP-MS) method. Analysis of 204
 168 Cervia thermal water (“Acqua Madre”) demonstrated that this 205
 169 is a mineral-rich salt water. The major components present in 206
 170 this water were Mg, Na⁺, K⁺, Br, Zn, Ca²⁺, I, and bicarbon- 207
 171 ates. The content of some elements such as Na, K, and Mg 208
 172 was approximately of the same order of magnitude both in 209
 173 “Acqua Madre” and Dead Sea water as reported in Table 1, 210
 174 panel A (Nissenbaum 1977). 211

175 Liman peloid analysis is reported in Table 1, panel B: The 212
 176 content of several components is comparable with that found 213
 177 in Dead Sea black mud as reported by Abdel-Fattah and 214
 178 Pingitore (Abdel-Fattah and Pingitore 2009). Levels of Al 215
 179 and K were lower in liman peloids when compared with those 216
 180 found in Dead Sea black mud; the content of other elements, 217
 181 Ca, Ni, Cu, Zn, Cd, and Pb, was the same both in liman 218
 182 peloids and Dead Sea black mud. In addition, using the data 219
 183 previously published by Khlaifat et al. (Khlaifat, Abdelaziz; 220
 184 Al-Khashman, Omar; Qutob 2010), also the content in SiO₂ 221
 185 was comparable in liman peloid and Dead Sea black mud 222
 186 (Table 1, panel B). 223

187 Statistical analysis

188 The differences between the groups with regard to anamnestic 224
 189 features and outcomes were tested by Student’s independent 225
 190 group *t* test and the Pearson chi-square test. The differences 226

between pre- and posttreatment were assessed by the 191
 Wilcoxon test for paired data; the delta variables, used to 192
 assess the improvement between the groups, were assessed 193
 by the Kruskal-Wallis test. 194

The timing of onset of relapse was studied using sur- 195
 vival analysis techniques: Kaplan-Meier curve and log- 196
 rank test. 197

The relationship between the onset of recurrence and the 198
 characteristics of the patients was investigated using the *t* test 199
 for the independent groups and the chi-square test. The tests 200
 were all two-tailed, and the significance threshold used was 201
 0.05. The analysis was performed with the STATA 14.2 for 202
 Windows software. 203

204 Results

205 Patients

206 A total of 91 patients were enrolled and randomized: in 207
 207 group 1 (experimental group), 56 patients were assigned 208
 208 to liman peloid application followed by bath therapy, and 209
 209 in group 2 (control group), 35 patients were assigned to 210
 210 mud-bath therapy using a clay peloid mixed with tap 211
 211 water. Eighty-one (89%) patients completed the study, 212
 212 and 79 (87%) patients returned the completed question- 213
 213 naire after 6 months. 214

214 Table 1 reported the characteristics of patients, the percent- 215
 215 age of topical and systemic treatments with cortisone and/or 216
 216 nonsteroid drugs at the beginning of bath-helioterapia and the 217
 217 most relevant comorbidities in the two groups. The quantifi- 218
 218 cation of patients under topical and systemic treatment with 219
 219 cortisone and nonsteroid drugs was similarly distributed in 220
 220 groups 1 and 2 (Table 2). The most common comorbidity 221
 221 documented in this study was systemic hypertension as previ- 222
 222 ously reported in psoriatic patients (Dauden et al. 2018). 223

223 There was no difference in skin phenotype between the two 224
 224 groups (data not shown). 225

225 Although not significant, a decrease in PASI score was 226
 226 measured in group 1 at the end of treatment and after 3 and 227
 227 6 months as shown in Fig. 1 and Table 3. A greater delta-PASI 228
 228 ($p = 0.0068$) and delta-PASI3 ($p = 0.0055$) were obtained in 229

t1.1 **Table 1** Comparison between
 t1.2 Cervia versus Dead Sea water
 (mg/l) (panel A) and Liman versus
 t1.3 Dead Sea mud (%) (panel B)

Panel A										
Water	HCO ₃	Br	Ca	I	K	Mg	Na	Zn		
Cervia	280	431	580	1.5	2600	10,000	49,000	26		
Dead Sea	93	4750	15,720	0.1	6700	39,400	38,680	0.6		
Panel B										
Peloid	SiO ₂	Al	Ca	Cd	Cu	Ni	Pb	K	Zn	
Liman	27.4	0.71	3.2	<0.0005	0.0006	0.0017	0.0007	0.28	0.0023	
Dead Sea mud	29.6	1.8	3.0	0.0004	0.0007	0.0015	0.0005	0.9	0.0022	

t2.1 **Table 2** Characteristics,
t2.2 treatments, and comorbidities of
psoriatic patients

		Experimental group (group 1, n = 56)	Control group (group 2, n = 35)
t2.3	Age (years)	52.3 ± 14	57.9 ± 11
t2.4	Sex (male/female)	32/24	25/10
t2.5	<i>Previous treatment</i>		
t2.6	No topical treatment (cortisone)	16 (28.6%)	10 (28.6%)
t2.7	No topical treatment (not steroid)	24(42.8%)	9 (25.7%)
t2.8	Topical cortisone treatment	35 (62.5%)	25 (71.4%)
t2.9	Topical not steroid treatment	27 (48.2%)	26 (74.3%)
t2.10	No systemic treatment (cortisone)	45 (80.3%)	33 (94.3%)
t2.11	No systemic treatment (not steroid)	29 (52.8%)	25 (71.4%)
t2.12	Systemic cortisone treatment	6 (10.7%)	2 (5.7%)
t2.13	Systemic not cortisone treatment	22 (39.3%)	10 (28.6%)
t2.14	<i>Comorbidities</i>		
t2.15	Hypertension	5 (8.9%)	9 (25.7%)
t2.16	Hypertriglyceridemia	0	1 (2.8%)
t2.17	Diabetes mellitus	0	3 (8.6%)
t2.18	Cefalea	0	1 (2.8%)
t2.19	Glaucoma	0	1 (2.8%)
Q3 t2.20	Epilexia	1 (1.8%)	0
t2.21	Discopathy	2 (3.6%)	1 (2.8%)
t2.22	Previous melanoma	1 (1.8%)	2 (5.7%)
t2.23	Fibromyalgia	2 (3.6%)	1 (2.8%)
t2.24	Benign prostatic hyperplasia	1 (1.8%)	1 (2.8%)
t2.25	Psoriatic arthropathy	3 (5.4%)	0
t2.26	Hashimoto syndrome	1 (1.8%)	0

229 group 1 as compared with group 2 (control group) as reported
230 in Fig. 1 b and d, respectively.

231 An example of lesions in a patient with psoriasis was re-
232 ported: Fig. 2 shows the lesions before treatment (Fig. 2a),
233 posttreatment (Fig. 2b), 3 months after treatment (Fig. 2c),
234 and 6 months after treatment (Fig. 2d).

235 The analysis of psoriasis recurrences in the following 3 and
236 6 months demonstrated a significant decrease in group 1 as
237 compared with group 2, $p < 0.0384$ using log-rank test
238 (Fig. 3). No significant relation between recurrences and the
239 considered variables was found.

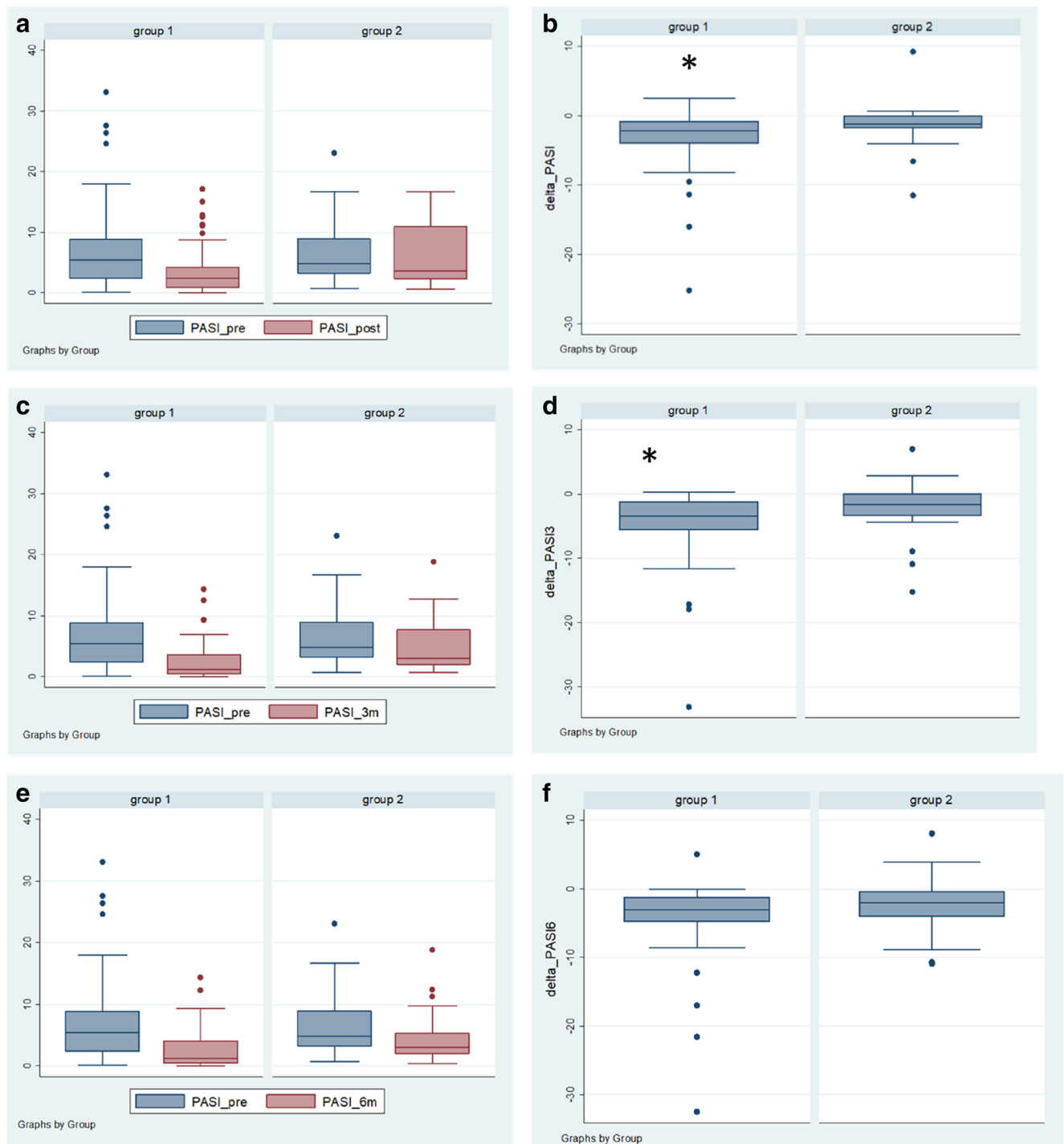
240 The quantification of topical and systemic treatments
241 showed a significant reduction in the topical use of drugs
242 during liman peloid bath heliotherapy. A smaller number
243 of patients in the experimental group as compared with
244 the control group used topical cortisone (10.4% versus
245 64.5%, $p < 0.0001$, respectively) and nonsteroid drugs
246 (59.2% versus 83.9%, $p < 0.027$, respectively). No signif-
247 icant decrease in the systemic use of drugs, both corti-
248 sone and not steroid drugs, was obtained.

249 No side effects were reported in the patients enrolled in the
250 present study.

Discussion

251 This prospective, randomized clinical study demonstrated the
252 efficacy of combined liman peloid bath and heliotherapy in
253 psoriatic patients versus control group at Cervia spa, Italy. The
254 main findings were (1) a greater delta-PASI, seen also clini-
255 cally in terms of erythema, infiltration and desquamation, and
256 delta-PASI3; (2) a decrease in psoriasis recurrences; and (3)
257 the reduced use of topical drugs. 258

259 Balneotherapy and peloid therapy have emerged in the last
260 two decades, as an opportunity to pursue natural treatments
261 against psoriasis. There is a large amount of evidence from
262 controlled trials showing that the combination of complemen-
263 tary medicine with traditional therapies for psoriasis is more
264 efficacious than traditional therapies alone (Talbot and Duffy
265 2015). Although the opportunity to use balneotherapy for pso-
266 riasis exists in more than one thermal center in Italy (Peroni
267 et al. 2008) (Borroni et al. 2013), overwhelming evidence
268 supports the effectiveness of Dead Sea balneotherapy in the
269 treatment of psoriatic patients (Huang et al. 2018) (Kopel et al.
270 2013) (Adler-Cohen et al. 2012). In this study, we compare the
271 characteristics of liman peloid with those of Dead Sea black



Q4 **Fig. 1** PASI and delta-PASI evaluated in psoriatic patients. Group 1, experimental group of patients treated with liman application, bath, and heliotherapy; group 2, control group of patients treated with mud-bath therapy using a clay peloid mixed with tap water. The effects of thermal therapy were assessed by the analysis of PASI and delta-PASI after treatment (**a** and **b**, respectively) and with a follow-up of 3 months (c

and **d**, respectively) and 6 months (**e** and **f**, respectively). A greater delta-PASI ($p = 0.0068$) and delta-PASI3 ($p = 0.0055$) were obtained in group 1 as compared with group 2 (control group). PASI-pre, PASI pre-treatment; PASI-post, PASI posttreatment; PASI_3m, PASI 3 months after treatment; PASI_6m, PASI 6 months after treatment

272 mud; a comparable composition in several components was
 273 found and in particular as regards the levels of toxic elements
 274 such as Pb and Cd. Comparing liman peloid and Dead Sea

black mud, the elemental composition is similar, and Dead 275
 Sea black mud was reported as a safe mud for the consumer 276
 with additional antibacterial properties probably due to 277

t3.1 **Table 3** The mean changes in PASI scores at each time point

t3.2		Experimental group (group 1, n = 56)	Control group (group 2, n = 35)
t3.3	Pre-treatment PASI	7.4 ± 7	6.5 ± 5
t3.4	Posttreatment PASI	3.8 ± 4	5.7 ± 4
t3.5	PASI 3 months	2.6 ± 3	4.9 ± 4
t3.6	PASI 6 months	2.8 ± 3	4.6 ± 4

Results are expressed as percentage of mean ± SD

278 chemical and/or physical phenomena (Abdel-Fattah and
279 Pingitore 2009) (Ma’or et al. 2006). The composition of ther-
280 mal water used in this study presents similarities with the
281 Dead Sea water, probably because both thermal waters are
282 concentrated and used after a sun evaporation. These similar-
283 ities support the data obtained in the present study on the
284 effects in psoriatic patients: a reduced delta-PASI, decreased
285 recurrences, and good quality of life maintenance.

286 We also demonstrate that in the patients treated with liman
287 peloid, a reduction in the use of topical drug occurred, and the
288 positive results of this study were obtained without the use of
289 phototherapy with an artificial source of ultraviolet light but with
290 the beneficial effects of heliotherapy. Also heliotherapy alone,
291 inducing an immune modulation, plays an important role in
292 mediating the clinical improvement of psoriasis (Søyland et al.
293 2011) as does balneotherapy, which is shown to improve PASI
294 score and reduce inflammation in psoriatic patients (Péter et al.
295 2017). Furthermore, comparing the results of balneotherapy vs
296 standard treatment or vs a combination treatment (standard

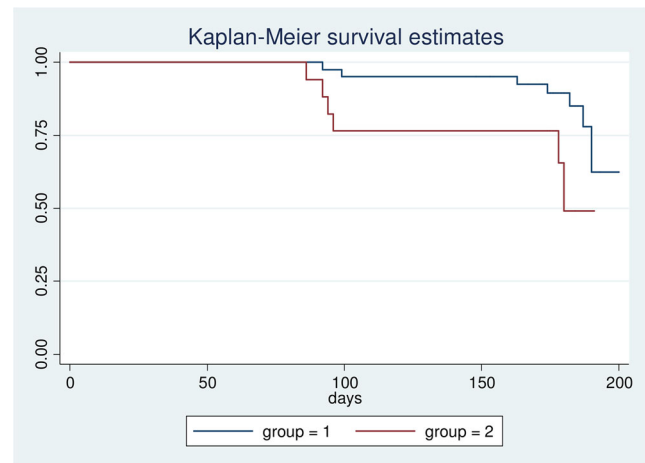
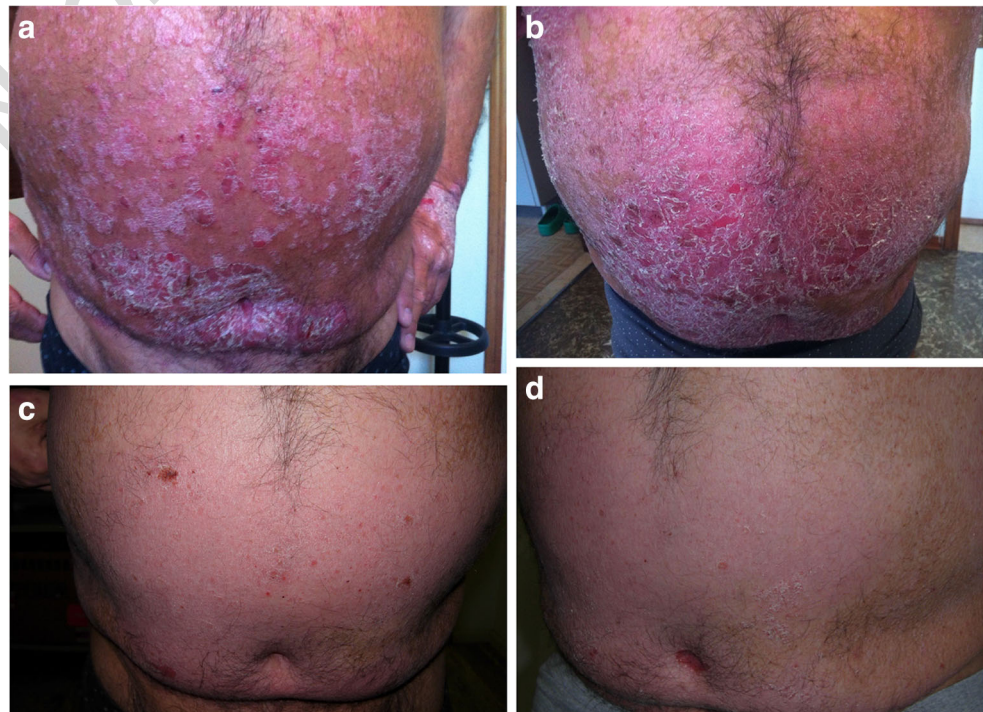


Fig. 3 Kaplan-Meier survival curve of psoriasis recurrences in group 1 (patients, treated with liman application, bath, and heliotherapy) and group 2 (patients treated with mud-bath therapy using a clay peloid mixed with tap water). A significant decrease in group 1 as compared with group 2, $p < 0.0384$ using log-rank test, was found

therapeutic modalities plus balneotherapy), Baros et al. (2014) 297
298 achieved the best short-term and long-term results with combi-
299 nation therapy. In our study, liman peloid bath heliotherapy is a
300 further step in combining treatments, because it adds UV irradiation
301 to the beneficial properties of balneotherapy and merges
302 them with the systemic or topical agents used by patients.

303 Our good results with greater delta-PASI and delta-PASI3 lead
304 us to suggest that this could be a valid and effective short-term
305 option for patients who would like a temporary discontinuation
306 of pharmacological therapy. Moreover, the reduction of the use
307 of topical but not of systemic drugs during liman peloid bath

Fig. 2 Lesions of a patient with psoriasis before and after treatment with liman application, bath, and heliotherapy. **a** Before treatment; **b** posttreatment; **c** 3 months after treatment, and **d** 6 months after treatment



308 heliotherapy suggests that this could be an alternative therapy for
309 patients with mild to moderate psoriasis, while it could be an
310 adjuvant treatment for those with severe forms of psoriasis.

311 A definitive therapy for psoriasis treatment is absent, and
312 the drugs available are only able to control this disease.
313 Unfortunately, also innovation in psoriasis treatment that in-
314 cludes short-term results using biological drugs has demon-
315 strated a variety of effects, side effects, drug-drug interactions,
316 and costs (Kaushik and Lebwohl 2018) (Ferrándiz et al.
317 2010). Of note, the use of balneotherapy and peloid therapy
318 as an effective and “off label” treatment for psoriatic patients
319 is further supported in the present study. These treatment op-
320 tions have virtually no side effects and involve no drug-drug
321 interactions or hospitalization.

322 Limitation of the study

323 The limitation of this study is the absence of a double-blind
324 study which is difficult to perform during balneotherapy. In
325 addition, this is the first study in which liman peloid was used
326 for the treatment of psoriasis, and the number of patients
327 should be increased in future evaluations.

328 Conclusion

329 Although the application of liman peloid bath sun therapy
330 cannot be considered a substitute for systemic therapy, it ap-
331 pears to be an important adjuvant or additional therapy in the
332 treatment of psoriatic patients.

333 **Acknowledgments** We thank Prof. Anthony Baldry for revising the
334 English.

336 Compliance with ethical standards

337 **Conflict of interest** The authors declare that they have no conflicts of
338 interest.

339 **Ethical approval** All procedures performed in studies involving human
340 participants were in accordance with the ethical standards of the
341 Institutional Research Ethics Committee and with the 1964 Helsinki
342 Declaration and its later amendments or comparable ethical standards.

343 **Informed consent** Informed consent was obtained from all participants
344 prior to being included in the study.

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