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ORIGINAL ARTICLE

Psoriasis treatment: faster and long-standing results after bathing in geothermal seawater. A randomized trial of three UVB phototherapy regimens

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balneotherapy; Blue Lagoon; geothermal seawater; histological score; psoriasis; quality of life

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SUMMARY

Background

The combination of seawater baths and narrowband ultraviolet B (NB-UVB) is a known treatment for psoriasis. This study evaluates two treatment regimens that combine bathing in geothermal seawater and NB-UVB therapy in comparison with NB-UVB monotherapy.

Methods

Sixty-eight psoriasis patients were randomly assigned to outpatient bathing in geothermal seawater combined with NB-UVB therapy three times a week, intensive daily treatment involving bathing in geothermal seawater combined with NB-UVB therapy, or NB-UVB therapy alone three times a week; treatment period was 6 weeks. Disease severity [Psoriasis Area Severity Index (PASI) and Lattice System Physician's Global Assessment scores], quality of life (Dermatology Life Quality Index) and histological changes were evaluated before, during and after treatment. The primary end point was the proportion of patients who achieved PASI 75 at 6 weeks.

Results

At 6 weeks, the percentage of patients who achieved PASI 75 and PASI 90 was significantly greater for both regimens, bathing in geothermal seawater three times a week (68.1% and 18.2%, respectively) and intensive treatment with geothermal seawater (73.1% and 42.3%, respectively) than for NB-UVB monotherapy (16.7% and 0%, respectively) ($P < 0.05$ in all comparisons). Clinical improvement was paralleled by improvement in quality of life and histological score and a reduction in NB-UVB doses.

Conclusion

Bathing in geothermal seawater combined with NB-UVB therapy in psoriasis induces faster clinical and histological improvement, produces longer remission time and permits lower NB-UVB doses than UVB therapy alone.

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Water-based therapy involving natural thermal springs, hot springs, mineral water, or seawater is currently used to treat psoriasis patients in treatment centres all over Europe (1). Examples of unique places for water-based therapy are the Dead Sea in Israel, the Kangal hot spring in Turkey and the Blue Lagoon in Iceland. Climatotherapy, such as that received in the Dead Sea area, refers to a combination of sun exposure and bathing in seawater where an important role is attributed to natural UV radiation (2, 3). To simulate climatotherapy as linked to special geographic settings, a combined treatment with seawater baths and artificial UV irradation (balneophototherapy) was established. Both open prospective studies (4–6) and randomized controlled trials involving a large number of psoriasis patients show the superiority of balneophototherapy over UVB monotherapy (7, 8).

The Blue Lagoon in Iceland is a geothermal lagoon containing a mixture of seawater and freshwater that formed when warm saline fluid was discharged onto a lava field after a geothermal power plant was built in the area in 1976 (9). Open prospective studies show that bathing in this geothermal seawater for 3–4 weeks has beneficial effects on psoriasis (10–13), and combination treatment with narrowband ultraviolet B (NB-UVB) therapy further increases the efficacy (14, 15). There are three notable differences in psoriasis treatment at the Blue Lagoon compared with the usual balneotherapy or spa therapy. The chemical composition of the Blue Lagoon is different compared with other spas, with an extremely high concentration of silica (135–140 mg/kg), moderate salinity (2.7%) and no H_2S content (Table 1) (9). To the best of our knowledge, the dominant micro-organisms in the water, *Silicibacter lacuscaerulensis* and cyanobacteria (16, 17), are not found under similar conditions anywhere else in the world. Due to the northerly latitude of Iceland, the natural sun is relatively weak (18). Interestingly, no human pathogenic bacteria or fungi have been shown to thrive in the lagoon (19).

Table 1. Characteristics of the water in the Blue Lagoon

pH	7.70
Temperature (°C)	24
Dissolved solids (mg/kg water)	
SiO_2	137
Na^+	9280
K^+	1560
Ca^{2+}	1450
Mg^{2+}	1.41
CO_2	16.5
SO_4^{2-}	38.6
H_2S	0.0
Cl^-	18 500
F^-	0.14
Total	31 900

No randomized controlled trials have been conducted to assess the efficacy of bathing in geothermal seawater combined with NB-UVB therapy compared with traditional NB-UVB therapy. In addition, the histopathological and psychosocial effects of geothermal seawater baths combined with NB-UVB therapy have never been evaluated before. Here we present the results of a randomized controlled study evaluating the clinical, histopathological and psychosocial efficacy of NB-UVB therapy alone and two different treatment regimens including geothermal seawater baths followed by NB-UVB therapy.

MATERIALS AND METHODS

Study design and patients

This study was a randomized open multi-arm parallel study to evaluate NB-UVB therapy and two treatment regimens including bathing in geothermal seawater combined with NB-UVB therapy in patients with chronic plaque psoriasis. The Icelandic National Bioethics Committee (08-097-S1) and the Icelandic Data Protection Authority approved the study protocol. Patients provided written consent to participate in the study. Eligible patients were recruited to the study from September 2009 to May 2010 and followed up for 2 years. One hundred and nineteen patients were screened. The majority of the patients (80%) were referred by a dermatologist, but some responded to an advertisement in a newspaper. The diagnosis of psoriasis had been confirmed by a dermatologist in all cases. Key inclusion criteria were the following: (a) diagnosis of chronic plaque psoriasis; (b) Psoriasis Area and Severity Index (PASI) score (20) of 7 or higher; and (c) being unresponsive to topical treatment and being a candidate for phototherapy or systemic treatment. Patients with other forms of psoriasis (e.g. guttate, pustular or erythrodermic) or skin diseases that could interfere with study evaluations were excluded. All ongoing psoriasis treatment was stopped at least 4 weeks prior to inclusion in the study.

Of the 119 patients screened, 68 patients fulfilled all criteria and were enrolled in the study. All patients provided informed consent before participating in the study. Of the 51 excluded patients, 27 had a PASI score lower than 7, and 6 had another psoriasis subtype. Ten patients were excluded because of ongoing active treatment for psoriasis or psoriatic arthritis. Data were collected at the Department of Dermatology at the Landspitali University

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Hospital in Reykjavik and the Blue Lagoon Clinic. Blood and histological samples were processed and analysed at the Departments of Immunology and Pathology at the Landspitali University Hospital.

Treatment regimens

For randomisation of the patients, a random number table was used. Patients were randomly assigned, in a 1:1:1 ratio, to three therapeutic arms:

1 *Outpatient bathing in geothermal seawater and NB-UVB treatment (GSW).* The treatment included bathing in geothermal seawater for 1 h and NB-UVB therapy immediately afterwards three times a week for 6 weeks. Patients were advised to rub the silica mud from the lagoon on the skin while bathing and to use moisturizing cream (Blue Lagoon Mineral Intensive Cream), which contains mineral salts from the lagoon and no active ingredients, twice daily.

2 *Intensive treatment in geothermal seawater and NB-UVB therapy (IT-GSW).* This treatment protocol consisted of bathing in geothermal seawater for 1 h two times a day and NB-UVB therapy once daily immediately after the first bath six times/week for 2 weeks. Patients were advised to rub the silica mud from the lagoon on the skin while bathing and to use moisturizing creams twice daily (Blue Lagoon Mineral Intensive Cream). After 2 weeks, patients were treated with a conventional outpatient NB-UVB therapy three times a week for 4 weeks.

3 *Conventional narrowband UVB therapy (NB-UVB).* This group received a regular, monitored NB-UVB radiation therapy three times weekly for 6 weeks. Patients took a shower immediately before the UVB treatment was given and used moisturizing creams containing no active ingredients twice daily (Eucerin Original Healing lotion, Beiersdorf, Hamburg, Germany).

The same NB-UVB treatment protocol was used for all patients based on skin type, with initial doses of 130–400 mJ/cm^2 with subsequent increases of 15–65 mJ/cm^2 after each treatment session. The UVB source was a Waldmann 7001 cabin (Waldmann, Villingen-Schwenningen, Germany) with an NB-UVB lamp (TL01, Philips, Eindhoven, the Netherlands) with peak emission at 311 nm.

Efficacy end points

The primary objective of the study was to assess the efficacy of three different psoriasis regimens: conventional NB-UVB therapy and two different combination treatments involving bathing in geothermal seawater. The primary efficacy variable was the proportion of patients who achieved a reduction in PASI score (20) of at least 75% (PASI 75) after 6 weeks of treatment. Key secondary efficacy end points included (a) the proportion of patients with a reduction in PASI score of at least 90% (PASI 90) at week 6; (b) the proportion of patients with a Lattice System Physician's Global Assessment score (Lattice score) (21) of 'clear of disease' or 'almost clear' at week 6; (c) the change from baseline in Dermatology Life Quality Index (DLQI) (22) at week 10; (d) histological changes from baseline in skin biopsies at week 6; and e) the number of days with clearance or marked improvement of the disease (time to relapse).

The DLQI is a 10-item questionnaire that determines whether psoriasis affects patient-reported quality of life, with overall scores ranging from 0 (not at all) to 30 (very much) (22), and it was assessed at baseline and at 10 weeks. Trozak's histologic grading system for psoriasis (23) was used for histological blinded assessment of the skin biopsies, as it is a more observer-independent assessment tool. The presence of predetermined histopathological characteristics of psoriasis (regular elongation of rete ridges, club-shaped rete ridges, oedema and elongation of dermal papillae, perivascular infiltrate in the upper dermis, absent granular layer, parakeratosis, suprabasal mitosis, Munro's microabscesses and spongiform pustules) was scored in routine sections of biopsies. The individual parameters were scored from 1 to 3, and a cumulative score (0–19) was recorded for each biopsy specimen.

Disease activity was assessed at baseline and 1, 2, 4, 6 and 10 weeks after beginning the treatment. All patients were examined in the following order by the same physician (JHE): clinical examination, photographic documentation, PASI score determination, Lattice score determination and quality-of-life assessment with the DLQI. In addition, after these assessments at baseline, week 2 and week 6, a 4-mm punch biopsy from a target lesion was obtained from seven patients in each treatment group. The thickest lesion on the extremities was selected as the target lesion.

Patients who did not achieve at least a 50% reduction from baseline in PASI score at week 6 were either withdrawn from the study (non-responders) or invited to cross over to receive intensive combination treatment. Patients in all study groups who achieved a 50–75% reduction in PASI score continued NB-UVB therapy three times a week for 4 weeks or until attainment of PASI 75/PASI 90, and patients who achieved PASI 75 were invited to continue NB-UVB therapy until attainment of PASI 90 (maximum 10 weeks/patient).

Finally, to evaluate how long the effect of each treatment lasted, the number of days until relapse was calculated.

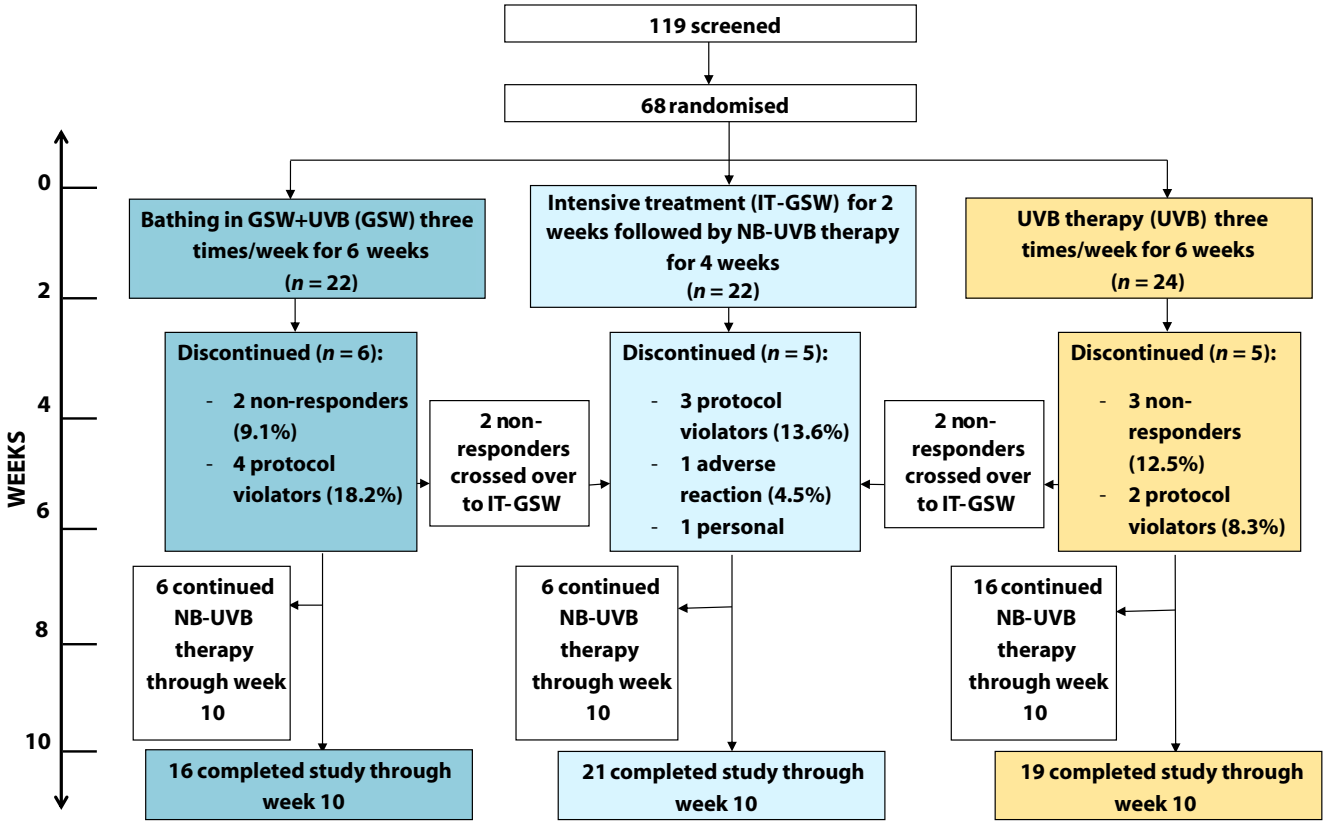

Fig. 1. Disposition of patients and reasons for discontinuation. Sixty-eight psoriasis patients enrolled in the study, but 16 patients discontinued: 5 because of lack of efficacy (Psoriasis Area Severity Index score still below 50 after 6 weeks of treatment), 1 because of an adverse event, 9 because of protocol violation (missing treatment) and 1 because of personal reasons. Two non-responders in the UVB group and 2 non-responders in the GSW group crossed over to the IT-GSW group. GSW, geothermal seawater.

Patients were followed up for 1 year with telephone interviews where they were asked if they had received retreatment with other antipsoriatic therapies (topical treatment, phototherapy or systemic therapy). We defined the number of days to relapse as the number of days from the study treatment until retreatment.

Statistical analysis

The sample size calculation was based on the primary end point of PASI 75 after 6 weeks of treatment. The study was sufficiently powered to detect a difference of 20% between the combination treatment groups and the UVB group. Given these assumptions and taking into account the results of prior studies (10–15), a sample size of 15 patients per treatment group provided more than 99% power to detect at least one pairwise treatment effect in the primary end point at an overall 5% level of significance.

Efficacy data from all randomised patients were analysed on an intention-to-treat basis. Patients who discontinued study treatment due to unsatisfactory therapeutic effect or who did not follow the study treatment protocol were regarded as treatment failures. For analysis in such cases, missing values were replaced with the most recently available values for all efficacy variables (last observation carried forward) (24). Patients who did not achieve more than a 50% reduction in PASI score and crossed over to receive IT-GSW were included in efficacy summaries for IT-GSW (Fig. 1). The proportions of patients responding to treatment were compared using the two-sided Fisher's exact test. Continuous response variables were compared with the use of analysis of variance (ANOVA). Also, we used Spearman's correlation coefficient to show the correlation between different parameters, including all visits. All statistical tests were two-sided and performed at an alpha level of 0.05.

Table 2. Baseline patient characteristics

Characteristics	GSW ($n = 22$)	IT-GSW ($n = 24$)	UVB ($n = 24$)	P value†
Age (years), mean ± SD	41 ± 10.8	42.2 ± 16	37.9 ± 14.4	0.37
Male, *n* (%)	12 (55)	12 (50)	15 (63)	0.82
Body mass index (kg/m^2), mean ± SD	28 ± 5	28.6 ± 5.4)	28.8 ± 7.1	0.96
Duration of psoriasis (years), mean ± SD	20 ± 14	16.4 ± 11	12.3 ± 8.1	0.09
Psoriatic arthritis, *n* (%)	4 (19)	3 (13)	5 (20)	0.71
Nail psoriasis, *n* (%)	10 (43)	12 (50)	9 (38)	0.61
PASI score, mean ± SD‡	12.3 ± 5.2	11.6 ± 6.2	11.1 ± 4.9	0.22
Lattice score§	Moderate to severe	Moderate to severe	Moderate to severe	1.00
DLQI score, mean ± SD¶	7 ± 4.2	11.6 ± 6.2	7.3 ± 5.1	0.017*
Treated previously, *n* (%)				
Blue Lagoon	6 (27)	10 (42)	7 (29)	0.57
Topical agent	21 (95)	23 (100)	21 (88)	1.00
Phototherapy	21 (95)	19 (79)	16 (67)	0.51
Systemic therapy	2 (1)	2 (8)	1 (4)	0.61
Smoking, *n* (%)	6 (27)	8 (33)	4 (17)	0.77
Family history, *n* (%)	18 (82)	12 (50)	14 (58)	0.35

*$P < 0.05$.
†For comparisons across all treatment groups; calculated by means of ANOVA for continuous variables and χ^2-test for categorical variables. ‡Possible scores range from 0 to 72, with higher scores indicating more severe disease.
§Possible scores range from 'clear of disease' to 'severe disease'.
¶Possible scores range from 0 to 30, with higher scores indicating worse health-related quality of life.
GSW, bathing in geothermal seawater combined with UVB treatment; IT-GSW, intensive treatment in geothermal seawater combined with UVB treatment; UVB, UVB treatment alone; PASI, Psoriasis Area Severity Index; Lattice, Lattice System Physician's Global Assessment; DLQI, Dermatology Life Quality Index.

RESULTS

Patients

All treatment groups were well balanced with respect to demographic characteristics (Table 2). The mean baseline PASI score was 12.3 ± 5.2 in the GSW group, 11.6 ± 6.2 in the IT-GSW group and 11.1 ± 4.9 in the UVB therapy group ($P = 0.22$). Of 68 patients, 56 completed the study (82.4%; Fig 1). Five patients were withdrawn as they did not achieve a 50% reduction in PASI score after 6 weeks of treatment (non-responders). Four of them were assigned to the IT-GSW group. One patient entered the cross-over IT-GSW group a few days after withdrawal, two patients 2 weeks after withdrawal and one patient more than 4 weeks after withdrawal. Other reasons for early termination included adverse events (1/68; 1.5%), protocol violations (9/68; 13.2%) and personal reasons (1/68; 1.5%).

Clinical efficacy

After 6 weeks of treatment, 20/26 patients (77.0%) of the patients in the IT-GSW group and 15/22 (68.2%) in the GSW group met the primary end point of a 75% reduction in PASI score, compared with only 4/24 (16.7%) patients treated with NB-UVB therapy alone ($P < 0.001$ for GSW and IT-GSW vs. NB-UVB) (Table 3, Fig. 2a and Fig. 2b). In addition, 11 out of 26 patients (42%) in the IT-GSW group and 4 out of 22 patients (18%) in the GSW group showed a 90% reduction in PASI score compared with no patients in the UVB group (0%; $P < 0.05$ for both comparisons; Table 3 and Fig. 2d).

According to the protocol, all the patients who achieved PASI 90 at week 6 discontinued active treatment, and patients who achieved PASI 75 were invited to continue NB-UVB therapy until attainment of PASI 90 (maximum 10 weeks/patient). Respectively, 6/26 (30.8%) of the patients in the IT-GSW group, 6/22 (31.8%) in the GSW group and 16/24 (66.8%) in the UVB group continued NB-UVB therapy three times a week until week 10 or until attainment of PASI 75/PASI 90 (Fig. 1). The time required for attaining a 75% reduction in PASI score was significantly shorter for both the IT-GSW group (29.1 ± 25.2 days) and the GSW group (35.5 ± 10.4 days) compared with the UVB group (62.3 ± 14.0 days) ($P < 0.001$ for both comparisons; Fig. 2b and Fig. 2c). No statistical difference was found between the combination treatment groups ($P > 0.05$). The number of NB-UVB sessions required for the patient to attain PASI 75 was also significantly less

Table 3. Response to treatment

	GSW ($n = 22$)	IT-GSW ($n = 26$)	UVB ($n = 24$)
PASI 75, *n* (%)			
6 weeks	15 (68.1)***	20 (77.0)***	4 (17.0)
10 weeks	13 (59.0)	17 (65.4)	13 (54.2)
PASI 90, *n* (%)			
6 weeks	4 (18.2)*	11 (42)***	0 (0)
10 weeks	4 (18.2)	6 (23.1)	2 (8.3)
Lattice score of 'clear'/'almost clear', *n* (%)			
6 weeks	14 (63.6)**	17 (65)***	4 (17)
10 weeks	12 (55)*	15 (58)*	4 (17)
DLQI score 0 or 1 at 10 weeks, *n* (%)	9 (40.9)*	12 (46.2)*	3 (12.5)
Treatment intensity needed to attain PASI 75, mean ± SD			
UVB treatment sessions (*n*)	14.7 ± 4.2***	17.9 ± 10.0**	25.0 ± 6.6
Total UVB dose (J/cm^2)	5.8 ± 2.6***	8.3 ± 5.9***	18.6 ± 8.3
Length of treatment (days)	35.5 ± 10.4***	29.1 ± 25.2***	62.3 ± 14.0

*$P < 0.05$.
**$P < 0.01$.
***$P < 0.001$.
GSW, bathing in geothermal seawater combined with UVB treatment; IT-GSW, intensive treatment in geothermal seawater combined with UVB treatment; UVB, UVB treatment alone; PASI, Psoriasis Area Severity Index; Lattice, Lattice System Physician's Global Assessment; DLQI, Dermatology Life Quality Index.

(GSW 14.7 ± 4.2, IT-GSW 17.2 ± 10.0, UVB 25.0 ± 6.6; $P = 0.001$ for GSW and IT-GSW vs. UVB; Table 3). Furthermore, the mean NB-UVB dose for achieving PASI 75 was 5.8 ± 2.6 J/cm^2 for the GSW group and 8.3 ± 5.9 J/cm^2 for the IT-GSW group compared with 18.58 ± 8.25 J/cm^2 for the UVB group ($P < 0.001$ for GSW and IT-GSW vs. UVB; Table 3).

When the Lattice score was examined, higher percentages of patients who received combination treatment (GSW and IT-GSW) had a Lattice score of 'clear of disease' or 'almost clear' compared with patients treated with NB-UVB therapy alone ($P < 0.01$ for GSW and $P < 0.001$ for IT-GSW vs. UVB) (Table 3; Fig 2c). No statistical difference was found between GSW and IT-GSW ($P > 0.05$) except in the percentages of patients with a 90% improvement in the PASI score at week 6 and in the PASI score results ($P < 0.05$). These clinical findings were also reflected by a significant correlation between the PASI score and Lattice score (Spearman's $r = 0.7318$, $P < 0.0001$).

Patients who received combined treatment showed better response in areas poorly exposed to NB-UVB radiation compared with patients treated with NB-UVB therapy alone. This was observed in 10 patients in the GSW group, 13 patients in the IT-GSW group and 12 patients in the UVB group, and these areas were noted to have cleared in 7 patients in the GSW group compared with only 2 patients treated with UVB alone.

Despite the large difference in number of days until relapse of psoriasis between patients in the GSW group and those in the UVB group (246.1 ± 161.0 vs. 140.9 ± 165.3; $P = 0.0796$), the difference did not reach statistical significance. However, the difference in number of days was statistically significant (283.9 ± 137.0 vs. 140.9 ± 165.3; $P < 0.0083$) in favour of the IT-GSW treatment group when this treatment was compared with NB-UVB therapy alone. Nine out of 19 patients (47.4%) who received NB-UVB therapy alone had started another treatment only 1 month after the last treatment session, compared with only one (1/21; 4.8%) of the patients in the IT-GSW group ($P = 0.0028$) and 3 out of 16 patients (18.8%) in the GSW group ($P = 0.15$).

Quality of life

Twelve patients out of 26 (46%) in the IT-GSW group and 9 patients of 22 (40%) in the GSW group achieved a DLQI score of 0 or 1 by week 10 compared with 3 patients out of 24 (12%) who were treated with NB-UVB therapy alone ($P < 0.05$ for both comparisons; Table 3).

Histological response to treatment

At baseline, typical histopathological characteristics of psoriasis were seen in all patients (hyperkeratosis, elongated rete ridges, perivascular mononuclear cell infiltrate

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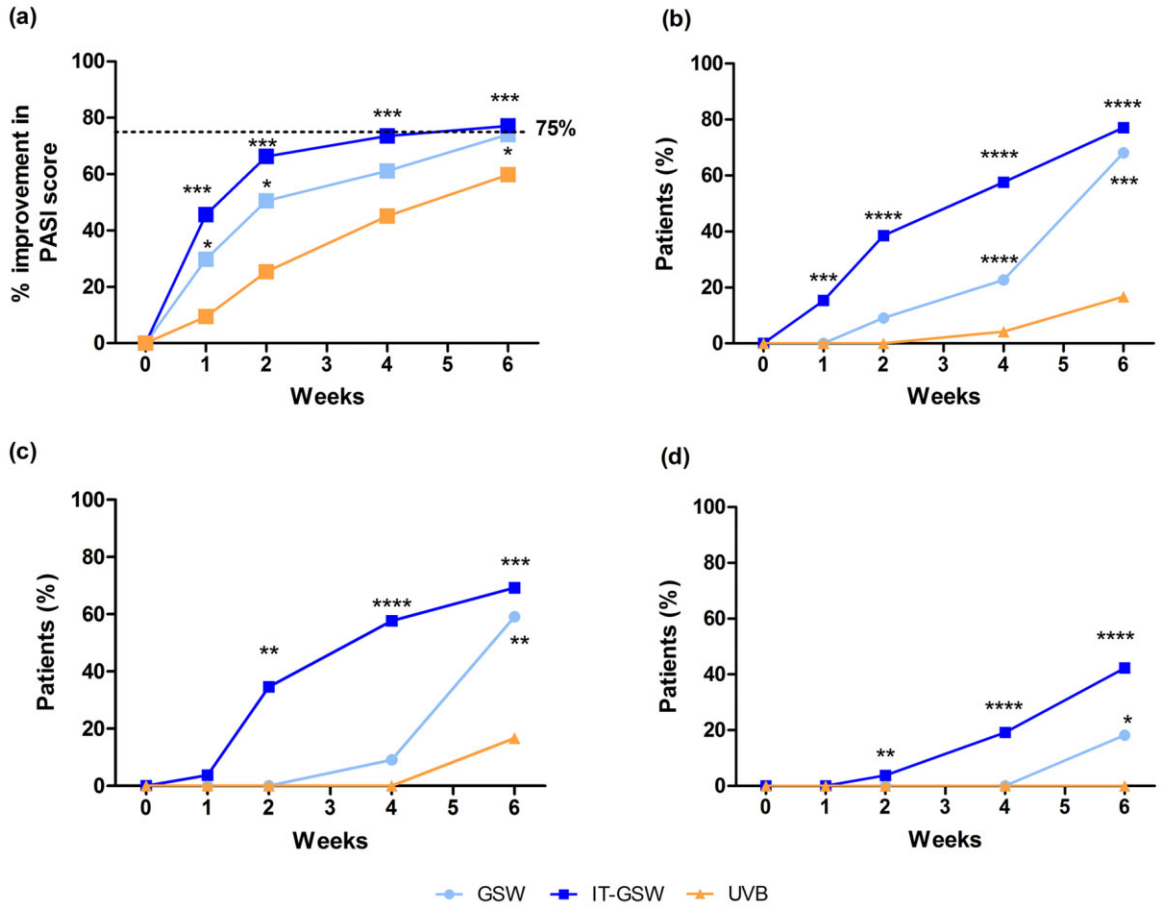

Fig. 2. Intention-to-treat analysis: proportion of patients achieving clinical responses from baseline through week 6 using intention-to treat population. (a) Median percentage reduction of baseline Psoriasis Area Severity Index (PASI) score through week 6. (b) Percentage of patients attaining 75% reduction from baseline PASI score. (c) Percentage of patients attaining Lattice System Physician's Global Assessment score of 'clear' or 'almost clear' (0 or 1). (d) Percentage of patients attaining 90% reduction from baseline PASI score. Last observation carried forward to week 6 for dropouts. GSW, outpatient bathing in geothermal seawater combined with UVB treatment; IT-GSW, intensive bathing in geothermal seawater combined with UVB treatment; UVB, UVB monotherapy. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$, ****$P < 0.0001$.

and Munro abscesses; see Fig 3). Patients in both combination treatment groups showed a significant decrease in psoriatic histological symptoms as measured by the Trozak score after only 2 weeks of treatment: from 10.5 ± 4.7 to 3.29 ± 3.7 ($P < 0.05$) for the GSW group and from 8.1 ± 2.4 to 3.0 ± 2.4 ($P < 0.05$) for the IT-GSW group (Fig 3). The histological symptoms were further reduced in biopsies from patients in the IT-GSW group after 6 weeks of treatment, to 0.5 ± 1.0 ($P < 0.01$, Fig 3). There was no significant difference in Trozak score in the GSW group between 2 and 6 weeks (Fig 3). No significant decrease was observed for patients treated with UVB therapy alone (10.0 ± 2.6 before treatment, 7.7 ± 1.6 after 2 weeks and 4.0 ± 3.7 after 6 weeks of treatment). In addition, no significant difference was observed when all the treatment groups were compared with each other. Trozak histological score was significantly correlated with both PASI score (Spearman's $r = 0.42$, $P < 0.001$) and Lattice score (Spearman's $r = 0.55$, $P < 0.0001$).

Safety

One treatment-related adverse event was reported, where one patient in the IT-GSW group developed an itchy papular eruption confined to the forearm, which was diagnosed as polymorphous light eruption. The patient was treated with topical steroids and excluded from the study. Two patients reported upper respiratory tract infections, one in the GSW group and one in the IT-GSW group. The most commonly reported adverse event was erythema at the biopsy site, which occurred in 4 (18%) patients in the GSW group, 5 (21%) in the IT-GSW group and 4 (17%) in

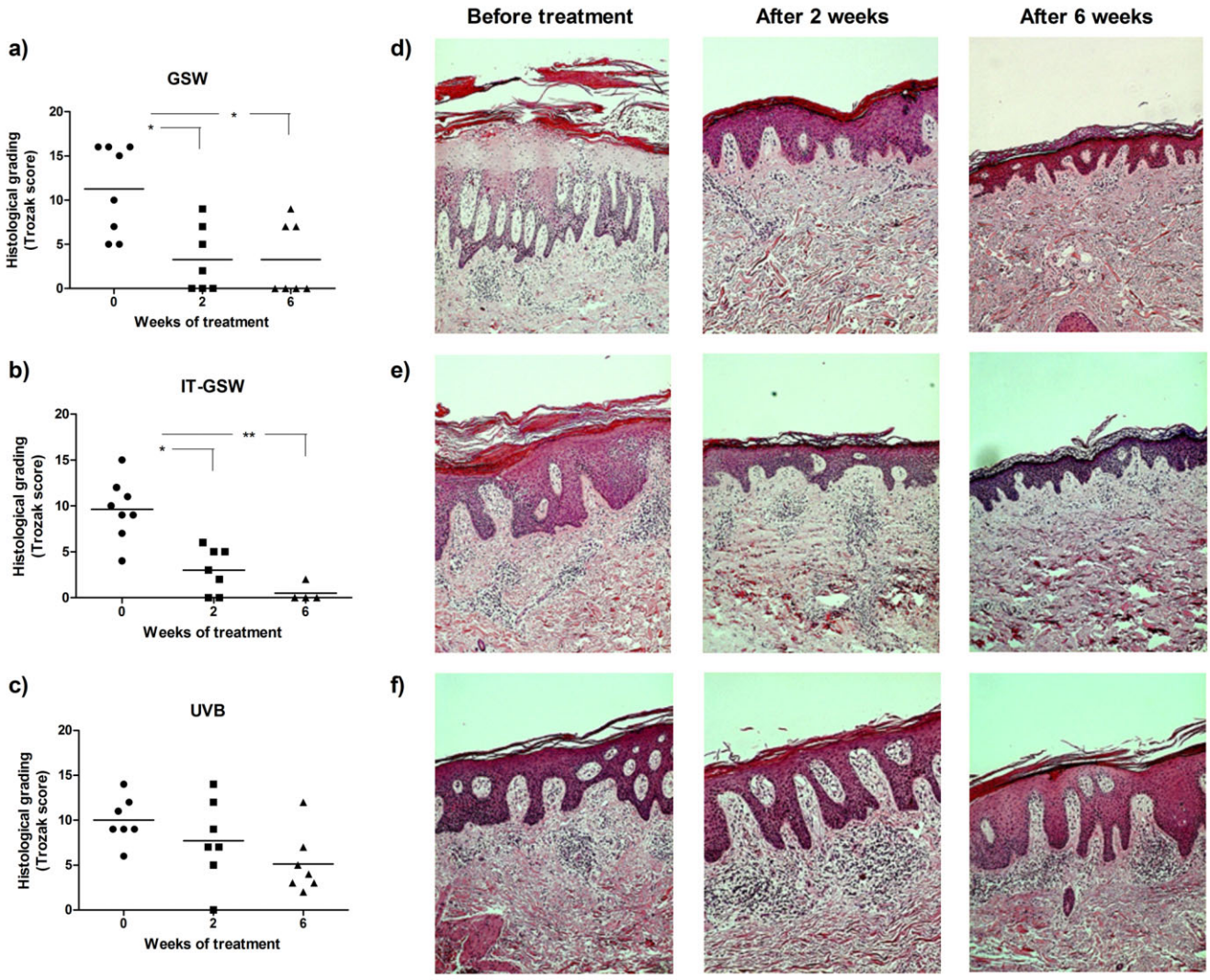

Fig. 3. Histological assessment using Trozak's grading system before and after 2 and 6 weeks of treatment. (a) Patients who underwent outpatient bathing in geothermal water combined with UVB therapy (GSW). (b) Patients who underwent inpatient bathing in geothermal water combined with UVB therapy (IT-GSW). (c) Patients who underwent UVB therapy alone (UVB). (d–f) Representative photographs from one patient each in the GSW group (d), IT-GSW group (e) and UVB group (f). $*P < 0.05$, $**P < 0.01$, $***P < 0.001$, $****P < 0.0001$.

the UVB therapy group. No serious adverse events were reported during the study period.

DISCUSSION

This study confirms previous reports (10–15) that the addition of UVB therapy to bathing in geothermal seawater is an effective treatment for psoriasis. NB-UVB therapy combined with bathing in geothermal seawater, compared with NB-UVB therapy alone, was associated with faster reduction in PASI score, Lattice score and Trozak histological score, as well as quality-of-life (DLQI) score. In addition, the combination treatments resulted in reduced total NB-UVB dose and a longer remission.

The combination of bathing in geothermal seawater and NB-UVB therapy had a rapid onset of action, as evidenced by significant reductions in PASI score occurring as early as week 1 and by the significantly higher percentage of patients achieving PASI 75 or Lattice score of 'clear' or 'almost clear' as early as week 1. Furthermore, 42% of patients who received intensive combination treatment achieved PASI 90 after only 6 weeks of treatment.

After 6 weeks, only 17% of the NB-UVB-treated patients had reached PASI 75. Therefore, most of these patients continued NB-UVB therapy until week 10. However, most of the patients in the combination treatment groups had reached PASI 75 or PASI 90 after 6 weeks and discontinued treatment. The mean total cumulative dose of NB-UVB,

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the number of exposures and the time required to achieve at least PASI 75 were significantly lower in both combination treatment groups compared with the UVB therapy group ($P < 0.001$).

The clinical improvement was paralleled by improvement in quality of life (DLQI score) and Trozak histological score. The blinded histopathological evaluation shows that combination treatment with bathing in geothermal seawater and NB-UVB therapy almost completely eliminated the characteristics of psoriasis as measured by Trozak score after only 2 weeks of treatment. The fact that the PASI evaluation was not blinded is a limitation of the study. However, the histological assessment was blinded, and it demonstrated a significant correlation with the clinical findings. The DLQI assessment was carried out at baseline and at week 10. The 10th-week evaluation point might not be optimal, but it was considered that too-frequent evaluation could lead to bias in the DLQI score.

After 6 months, only 30% of patients in either combination treatment group had relapsed (started another therapy), compared with 56% of patients treated with UVB monotherapy. The scalp and intertriginous areas are poorly exposed during NB-UVB therapy, and this could possibly explain why efficacy was lower in the UVB monotherapy group. It has been shown that the silica mud and the micro-organisms growing in the geothermal seawater are bioactive and can improve the skin barrier of normal skin and prevent premature skin aging (25). It is therefore possible that 'active ingredients' in the geothermal seawater have a healing effect on psoriasis.

Bathing in tap water or hot baths may have a beneficial effect on psoriasis, but to our knowledge, no clinical studies have shown this. One randomized controlled trial (8) demonstrates that bathing in tap water before UVB exposure is slightly better than UVB monotherapy. In the present study, the patients who were treated with UVB therapy alone took a shower immediately before the UVB treatment was given to make the treatment groups as comparable as possible. In addition, it is well documented that hot seawater baths alone have a minor therapeutic effect, usually not exceeding a 30% improvement in PASI score (5, 26).

We do not yet fully understand the biological basis for the efficacy of the geothermal seawater psoriasis treatment. At present, there are several ongoing studies trying to identify and isolate the agents responsible for the beneficial effects of bathing in geothermal seawater.

Treatment options for psoriasis have expanded considerably in recent years. Many new therapeutic agents, such as the biologic drugs, are expensive and can cause serious side effects. Despite the absence of long-term major therapeutic efficacy, UV radiation therapy combined with balneotherapy remains an inexpensive and clinically beneficial therapeutic option for psoriasis patients.

In conclusion, patients bathing in geothermal seawater before NB-UVB treatment need fewer sessions and lower cumulative doses compared with patients treated with NB-UVB monotherapy. In addition, combination treatment induces faster improvement in clinical and histological scores and a longer remission time after treatment as compared with NB-UVB therapy alone.

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Authors' contributions: The first author collected the data, which were maintained in a database at the Landspitali University Hospital of Iceland, and wrote the draft manuscript. BS and JHO participated in the design of the study and critically revised the manuscript. BAA supervised the histological examination and revised the manuscript. BRL revised the manuscript and participated in the design of the study. All authors had full access to the data and final responsibility for the decision to submit for publication.

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