



Effects of Rusanda Spa balneotherapy combined with calcipotriol on plaque psoriasis

Efekti balneoterapije u Banji Rusanda kombinovane sa kalcipotriolom na plak psorijazu

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Abstract

Background/Aim. Treatment of psoriasis is very complex and there are no still universal, nor unique treatment modalities. Apart from conventional treatment, which includes topical calcipotriol (vitamin D3 analogue), balneotherapy is drawing increased attention worldwide. Being part of climatotherapy, balneotherapy is defined as the use of natural environmental factors in the treatment of health conditions, whereas in the treatment of psoriasis it means the use of mineral baths and peloids. The aim of this study was to examine the therapeutic efficacy of mineral waters and peloids of the Rusanda Spa on plaque psoriasis in patients also treated with calcipotriol. **Methods.** The study included 60 patients divided into two groups. The first group included patients treated with mineral waters, peloids and calcipotriol in the Rusanda Spa, while the second one included those treated only with calcipotriol. The study took 21 days, and each patient was followed up for at least one month after ending the treatment. The treatment efficacy was measured by psoriasis area severity index (PASI) scores on the days 0, 7, 14 and 21 during the treatment and 30 after the end of

the therapy. **Results.** After a 3-week treatment in the Rusanda Spa, the first group showed a decrease in PASI score by 59.45%, whereas in the group of outpatients treated by calcipotriol it was 39.34%. On the day 30 following the treatment, the first group presented with the PASI score reduction of 58.44%, and the second group of 34.78%. The therapeutic efficacy of mineral waters and peloids combined with calcipotriol showed to be significantly higher in regard to monotherapy with calcipotriol ($p < 0.05$). In regard to clinical symptoms, the best results were obtained in the reduction of desquamation ($p < 0.001$). **Conclusion.** The results of our study show that in the treatment of plaque-type psoriasis, topical calcipotriol combined with Spa Rusanda balneotherapy is more effective than topical calcipotriol alone. Randomized controlled trials are needed to confirm the effects of balneotherapy as monotherapy in treatment of this type of psoriasis.

Key words: psoriasis; mud therapy; baths; serbia; vitamin d; administration, topical; treatment outcome.

Apstrakt

Uvod/Cilj. Lečenje psorijaze veoma je složeno i još se traga za univerzalno ili jedinstveno efikasnim terapijskim metodama. Osim konvencionalne terapije, koja kod lokalnog lečenja uključuje i primenu kalcipotriola, analoga vitaminu D3, u svetu se pažnja sve više posvećuje i balneoterapiji. Pod pojmom balneoterapije kao sastavnom delu klimatoterapije, podrazumeva se delovanje prirodnih činilaca spoljašnje sredine na ljudski organizam, a u terapiji psorijaze konkretno se misli na upotrebu mineralne vode i peloida. Cilj rada bio je da se ispita terapijski učinak mineralne vode i peloida Banje Rusande na plakozne promene psorijaze kod obolelih koji su istovremeno lečeni kalcipotriolom. **Metode.** Ispitano je 60 osoba koji su bile razvrstane u

dve grupe. Prva grupa je obuhvatila one koji su lečeni mineralnom vodom, peloidom i kalcipotriolom u Banji Rusandi, a u drugoj grupi su bile osobe lečene kalcipotriolom. Ispitivanje je trajalo 21 dan, a ispitanici su praćeni najmanje mesec dana po obustavi terapije. Za procenu terapijske efikasnosti korišćena je standardna metoda određivanja *psoriasis area severity index* (PASI) skora 0, 7, 14, 21. dana terapije i 30. dana po završetku terapije. **Rezultati.** U prvoj grupi lečenih u Banji Rusandi, nakon trodeljne terapije došlo je do sniženja vrednosti PASI skora za 59,45%, dok je u grupi lečenih kalcipotriolom ovo sniženje iznosilo 39,34%. Tridesetog dana po obustavi terapije procenat poboljšanja PASI skora iznosio je 58,44% u grupi lečenih u Banji Rusandi i 34,78% u grupi lečenih kalcipotriolom. Terapijski učinak mineralne vode i peloida u kombinaciji sa kalcipot-

riolom pokazao se značajno efikasnijim od monoterapijske primene kalcipotriola ($p < 0,05$). Od kliničkih simptoma bolesti najbolji terapijski rezultati postignuti su u smanjivanju deskvamacije ($p < 0,001$). **Zaključak.** Rezultati naše studije pokazali su da je kombinovana primena topijskog kalcipotriola i balneoterapije u Banji Rusandi u lečenju psorijaze tipa plaka efikasnija nego topijska primena kalci-

potriola kao monoterapije. Potrebne su randomizirane kontrolisane studije koje bi potvrdile efekte balneoterapije kao monoterapije u lečenju ovog tipa psorijaze.

Ključne reči:
psorijaza; lečenje blatom; kupke; srbija; vitamin d; lokalna primena; lečenje, ishod.

Introduction

Treatment of psoriasis is still very complex and brings together a large number of experts in various fields to find effective therapeutic methods that provide the required level of safety for patients^{1,2}. The treatment may be topical, systemic or combined. Topical treatment has several advantages over systematic methods: it is easier to apply, provides fast action which is directed only to the skin, as well as a lower degree of risks from adverse reactions. Topical treatment includes emollients, keratolytics, corticosteroids, dithranol, various tar preparations, retinoids (tazarotene), immunomodulators (tacrolimus and pimecrolimus), phototherapy ultraviolet A – long wave and ultraviolet B – short wave rays (UVA, UVB light), climate therapy and D3 analogues (calcipotriol). Effects of calcipotriol (vitamin D analogue) in the treatment of psoriasis have been published over the past 25 years, pointing to a long term scientific interest in this drug³⁻⁵.

Climatic treatment includes balneotherapy and sun exposure⁶. Balneotherapy factors, such as mineral water and/or peloids exert favorable therapeutic effects on plaque psoriasis⁷⁻¹¹. A combination of multiple local and/or systemic medications aims to increase the efficiency of psoriasis treatment (PUVA – psoralen +UVA).

The aim of this study was to determine whether therapeutic use of mineral waters and peloids of Rusanda Spa combined with topical calcipotriol has greater effects on clinical symptoms and the course of vulgar psoriasis (plaque form) compared to monotherapy with calcipotriol.

Methods

The study included 60 consecutively examined patients with the diagnosis of plaque psoriasis examined and treated at the Clinic of Dermatovenereology Diseases of the Clinical Center of Vojvodina in Novi Sad. The subjects were randomized into two groups of 30 patients each.

The study group included the patients treated with mineral water, peloids and calcipotriol in Rusanda Spa. The control group included the outpatients treated only with calcipotriol.

Inclusion and exclusion criteria

Inclusion criteria were: plaque psoriasis affecting the extremities and/or trunk and age over 16 years. Exclusion criteria were as follows: all other forms of psoriasis, age under 16 years, cytostatic therapy in the previous 4 weeks, systemic retinoid therapy in the past 12 months, local corti-

costeroid therapy, topical therapy with retinoids or vitamin D3 analogues in the last three months and liver or kidney diseases. In the group of patients undergoing treatment with mineral water and peloids, exclusion criteria also included contraindications to spa treatment, infectious diseases, cancer, frequent and heavy bleeding, cachexia, pregnancy, severe cardiovascular disorders, as well as uncooperative behavior and reported adverse effects.

The study took 21 days, and each patient was followed-up for at least 1 month after ending the therapy.

The study group was treated in Rusanda Spa and patients were subjected to the following treatment schedule: 20-minute mineral baths twice a day, 20-minute 3 cm thick layers of hot peloid packs with polyethylene pressure (38–42°C) once a day, and calcipotriol ointment twice a day. The control group of patients received only calcipotriol ointment twice a day.

Treatment efficacy assessment

In order to assess the therapeutic efficacy, a standard psoriasis area and severity index (PASI) quantitative rating score was used for measuring localization, extent and severity of psoriatic lesions on days 0, 7, 14 and 21 during the treatment and 30th after the end of therapy. A reduction in PASI score $\leq 20\%$ showed a low response rate, 21–40% a satisfactory response rate, 41–60% a good response rate, 61–80% a very good response rate, and 81–100% showed excellent responsiveness¹²⁻¹⁴.

Statistical analysis

Data analysis included descriptive and inferential statistics. The following numerical homogeneous characteristics were calculated and presented: the size of sample, arithmetic mean, median (Med), mode (Mod), range and standard deviation (SD), while categories were presented as absolute and relative numbers. Comparison of mean values was performed using Student's *t*-test. The differences between the obtained and expected frequencies were calculated using Pearson's χ^2 test of agreement. A statistical significance was set at $p < 0.05$.

Results

The water of Rusanda Spa is alkaline (pH 9.3–9.4) oligomineral, hypothermal mineral waters rich in sodium bicarbonate. Characteristics of Rusanda Spa mineral water are shown in Table 1.

Table 1

The composition of mineral waters and peloids in Rusanda Spa			
Mineral water	mg/L	Peloid	mg/kg
Sodium	1235.0	Silicon dioxide	408.0
Potassium	276.4	Titanium dioxide	3.2
Lithium	0.02	Aluminium oxide	110.0
Ammonium	9.0	Manganate	0.8
Calcium	40.0	Iron oxide	26.0
Magnesium	60.0	Iron (III) oxide	23.4
Strontium	0.1	Calcium oxide	48.0
Manganese	0.05	Magnesium oxide	54.0
Iron	0.6	Sodium oxide	23.4
Aluminum	0.2	Potassium oxide	36.0
Hydrocarbons	2200.0	Phosphorus pentoxide	4.5
Chloride	980.0	Sulfate	9.0
Bromides	7.0	S-sulfides	2.5
Iodides	0.8	Chlorine	22.0
Fluoride	1.2	Carbon dioxide	78.0
Phosphate	0.1	Water	41.0
Sulfate	192.0	Nitrate	3.5
Metasilicic acid	14.3	Ammonium	0.8
Metaboric acid	46.8		

Demographic characteristics of patients

The study group treated in Rusanda Spa with mineral baths, peloids, and calcipotriol, included 18 (60%) female patients, which was not statistically significantly higher incidence than men ($\chi^2 = 1.2$; $p > 0.05$). The patients' age ranged from 24 to 75 years, the mean age 55.46 (SD = ± 12.13) years. In 12 (40%) examinees lesions were located only on the extremities, in 13 (43.3%) on the trunk and extremities, and the remaining 5 (16.7%) presented with lesions only on the trunk.

In the group of patients treated with calcipotriol, there was a predominance of male patients (16 of 30 patients), but it was not statistically significant higher number than females. The age of examinees in this group ranged from 20 to 67 years. The average age was 41.73 (SD = ± 13.33) years. In 13 (43.3%) patients lesions were located only on the extremities, while the remaining 17 (56.7%) patients presented with lesions on the trunk and extremities.

There was a statistically significant difference between the two groups in relation to age ($t = 4.1726$; $p = 0.0001$), and no significant difference in sex distribution ($\chi^2 = 1.071$; $p > 0.05$). Also, no significant differences were found in the distribution of lesions within the analyzed groups ($\chi^2 = 5.573$; $p > 0.05$).

Distribution of psoriasis area severity index scores during the treatment

In the study group treated in Rusanda Spa with mineral baths, peloids, and calcipotriol, the PASI scores on day 0 (baseline PASI score) ranged from 2.40 to 17.40. The average PASI score was 9.89. Seven days after the beginning of the therapy, PASI scores ranged from 1.60 to 13.80. The average score was 8.13. On the day 14 of the treatment, PASI scores ranged from 1.60 to 11.60, while the average score was 5.91. After 21 days from the initiation of the therapy, PASI scores ranged from 0.80 to 10.60, while the average score

was 4.01. Thirty days after the treatment ended, PASI scores ranged from 0.80 to 10.60, with the average score of 4.11.

In the group of patients treated with calcipotriol, baseline PASI scores ranged from 2.40 to 16.40, with the average score of 8.54. On the day 7 of the therapy, PASI scores ranged from 2.40 to 15.60, with the average score of 7.84. After 14 days of the treatment, PASI scores ranged from 2.40 to 12.40, and the average score was 6.48. After 21 days of the treatment, PASI scores ranged from 1.60 to 10.40. The average score was 5.18. Thirty days after the end of the treatment, PASI scores ranged from 2.00 to 12.60, with the average score of 5.57. PASI scores are shown in Table 2.

In the study group treated with mineral baths, peloids and calcipotriol, the mean score for erythema at baseline was 3.25, and 2.11 at the end of therapy; this means that after treatment the mean scores for erythema decreased by 35.1%. Based on these results, therapeutic efficacy for erythema may be regarded as satisfactory. The mean scores for infiltration ranged from 3.49 at baseline to 1.39 at the end of the treatment, with a percentage improvement of 60.4, which is a very good therapeutic response. PASI scores for desquamation at the end of therapy decreased from 3.15 to 0.49, with a percentage improvement of 84.5, that is an excellent therapeutic response.

The PASI score for erythema in the group treated only with calcipotriol was 2.87 at baseline, and 2.13 immediately after cessation of the therapy. These results indicate that the average scores for erythema decreased by 25.8% and the therapeutic efficacy may be regarded as satisfactory.

In regard to infiltration, after treatment, the control group presented with an average PASI score decrease by 42.6% and it is considered as good therapeutic efficiency. At the end of the therapy, in patients treated with calcipotriol the PASI score reduction for desquamation was 49.9%, which was also considered as good therapeutic response. Table 3 shows PASI scores for erythema, desquamation and infiltration.

Comparative analysis of the mean PASI scores between the two groups showed no statistically significant difference du-

Table 2
Psoriasis area severity index (PASI) scores in the patients treated with mineral baths, peloids and calcipotriol in Rusanda Spa (group 1) and in the patients treated with calcipotriol (group 2)

Days	PASI score (Group 1)	PASI score (Group 2)	<i>p</i> *
Day 0	9.89	8.54	
med	9.80	8.40	
mod	9.60	8.40	
SD	3.97	3.66	
Day 7	8.13	7.84	
med	8.00	7.40	
mod	8.00	7.20	
SD	3.56	3.54	
Day 14	5.91	6.48	
med	6.30	6.40	
mod	3.20	2.40	
SD	2.71	2.80	
Day 21	4.01	5.18	0.042
med	4.00	4.80	
mod	3.20	4.80	
SD	2.09	2.28	
Day 30 after treatment	4.11	5.57	0.016
med	4.00	5.15	
mod	3.20	2.40	
SD	2.06	2.47	

**p* – statistically significant (< 0.05).

Table 3
Psoriasis area severity index (PASI) scores for erythema, infiltration and desquamation before and after the treatment in the patients treated with mineral baths, peloids and calcipotriol in Rusanda Spa (group 1) and in the control group treated with calcipotriol (group 2)

Plaque psoriasis changes	PASI score (Group 1)	PASI score (Group 2)	<i>p</i>
Erythema before treatment	3.25	2.87	
Erythema after 21 days of therapy	2.11	2.13	
Infiltration before treatment	3.49	2.78	0.049
Infiltration after 21 days of therapy	1.39	1.60	
Desquamation before treatment	3.15	2.89	
Desquamation after 21 days of therapy	0.49	1.45	< 0.001

**p* – statistically significant (< 0.05).

ring treatment at days 0, 7 and 14. Using Student's *t*-test, a statistically significant difference was determined after 21 days of treatment ($t = -2.080$; $p = 0.042$) and 30 days after ending the therapy ($t = -2.487$, $p = 0.016$) in favor of the group treated with the combination therapy (balneotherapy and calcipotriol).

There was no statistically significant difference between the groups in terms of reduction of erythema and infiltration at the end of the treatment, but there was a statistically significant difference in the reduction of desquamation in favor of the group treated with a combination therapy (Student's *t*-test).

Adverse effects

Slight irritation at the site of calcipotriol application was reported during the first week of the therapy by 3 (10%) patients from the study group and by 2 (6.6%) patients from the control group, but discontinuation of the planned treatment was not necessary. In regard to the observed adverse effects, there were no significant differences between the two groups ($\chi^2 = 0.218$, $p > 0.05$).

Discussion

After a 3-week treatment, the study group treated in Rusanda Spa showed a decrease of PASI scores by 59.45%, while in the control group treated only with calcipotriol a decrease was 39.34%. The therapeutic effects of peloids and mineral baths in combination with calcipotriol proved to be significantly more effective than monotherapy with calcipotriol.

It is well-known that mineral waters and peloids exhibit mechanical, thermal and chemical effects when applied to the skin. They reduce the thickness of the stratum *corneum* and stratum *lucidum* of the epidermis, increase the number of lymphocytes, histiocytes, and eosinophils, increase the permeability of the skin, reduce the activity of inflammatory processes, improve microcirculation and enhance the immune processes^{15, 16}. It was found that mineral waters inhibit mast cell activation *in vitro*, that may explain their beneficial anti-inflammatory effects. It is assumed that inhibition of mast cells is achieved by the effects of mineral waters on nerve endings and the substance P in the skin^{15, 16}.

The immunomodulating effects of sulfur-rich water are expressed through the inhibition of proliferation of T-lymphocytes. Bicarbonate and silicium waters reduce degranulation of basophilic granulocytes and suppress the effect on cytokine production. This effect is attributed to selenium, zinc and copper. Although immunomodulating effects of mineral waters have only been established *in vitro*, they can be compared with the pharmacological effects of local immunomodulators, e.g. with imiquimod⁹.

The knowledge about positive effects of mineral waters and peloids on skin has encouraged investigations on their efficacy in the treatment of many skin diseases such as atopic dermatitis, seborrheic dermatitis, chronic eczema and related conditions.

Psoriasis is also one of the diseases that have been successfully treated with balneotherapy, and the object of numerous studies, particularly when dealing with a combination of balneotherapy with other therapeutic modalities, e.g. phototherapy⁹. A small number of studies have examined the effects of monotherapy with mineral waters and peloids, and the only compatible study of this kind has been conducted in Prolom Spa with satisfactory therapeutic results. The study included 35 patients and after 3 weeks of therapeutic use of mineral waters and peloids a 38.75% PASI score reduction was established¹⁷. Compared with the results of our study, these results indicate a lower therapeutic efficacy of Prolom Spa treatment, which may be explained by the fact that in our study balneotherapy was combined with topical application of calcipotriol. It is possible that the therapeutic efficacy was affected by the composition of mineral water, as well as its alkalinity.

It is well-known that alkaline water makes the skin soft and smooth. In combination with heat, it stimulates the transport of substances through the skin in both directions, which possibly increases the transportation of calcipotriol and efficiency of combined therapy over monotherapy as was in our patients. The best results were achieved in reducing desquamation, followed by reduction of infiltration and erythema. After a 3-week therapy, desquamation was reduced by 84.5% and no significant differences were found in a 30-day follow-up period. This effect was statistically significant compared to calcipotriol monotherapy. In the study of Paravina et al.¹⁷ the reduction of desquamation after three weeks of balneotherapy was only 42.71%. Although the average reduction in induration in the study group treated with balneotherapy and calcipotriol was 60.4%, and it was higher than in the study of Paravina and et al.¹⁷, it was not significantly higher than in the group treated exclusively with calcipotriol. Induration reduction in the group treated only with calcipotriol (42.5%) was similar to the results in the above mentioned study (43.59%), indicating a similar level of efficiency of calcipotriol monotherapy and balneal monotherapy in regard to infiltration.

As a clinical sign of the disease, erythema showed the lowest response rate in both groups of patients: neither type of therapy has proved significantly more effective than the other; similar results were obtained in the study conducted in Prolom Spa¹⁷.

The effectiveness of balneotherapy in the treatment of psoriasis has been reported in many studies conducted in the world. If we take into account that our results regarding effectiveness were assessed as good, it can be said that they are in accordance with the results of other authors. In Argentina, 55 patients with psoriasis were treated with mineral baths, peloids and/or algae in Copahue Thermal Complex. Twice a day mineral baths lasted for 10 days on the average and the patients showed improvements in terms of the reduction of erythema and desquamation, which was confirmed by histopathological analysis¹⁰. Beneficial effects of balneotherapy have been reported in Bulgaria, where they use hypothermal water causing skin vasodilatation¹⁸. In Jagodina Spa, 54 patients with vulgar psoriasis underwent a combination of balneotherapy, topical dithranol and phototherapy (20 minute baths, application of 1.5% to 3% dithranol for 10 to 30 minutes, and exposure to UV rays with wavelengths of 300 – 340 nm from 1 to 20 minutes). Three weeks later, 73.3% of patients showed a significant improvement of skin lesions¹⁷. An investigation in Marikostinovo Spa included 100 patients treated with a combination of mineral water and sulfide peloids. Both procedures lasted 10 to 20 minutes a day for three weeks, and 3% of respondents showed a complete regression of skin lesions, in 5% there was a significant improvement, 83% showed moderate improvement, in 5% the therapy showed no effects, and in 4% of patients the condition got worse¹⁸.

A large number of investigations worldwide studied effects of balneotherapy and heliotherapy on chronic stationary psoriasis. The best results were achieved at the Dead Sea in Israel, which is characterized by a high salinity (about 30%), high concentration of minerals in the air (magnesium, bromide and other minerals) and a high number of sunny days per year. The most comprehensive study at the Dead Sea was conducted in 1995 including 1.448 patients with psoriasis. After four weeks of bathing in sea water and sun exposure, 88% of subjects showed improvement. The degree of improvement varied from 80% to 100% reduction in PASI score¹¹. Another prospective study included 100 patients with psoriasis treated at the Dead Sea for four weeks. In 75% of patients there was a complete regression of skin lesions. In further follow-up, after the end of the therapy, 68% of these patients were in complete remission during the next four months, 43% of patients were in remission after six months, and in 10% of patients complete remission lasted for eight months after treatment. By monitoring the length of remission after treatment, it was observed that after climatic and heliotherapy this period was shorter than after some other forms of therapy, such as with cyclosporine or PUVA. However, contrary to this, a comparative study, although including a small number of patients, showed that the efficacy of heliotherapy during four weeks was higher than with UVB phototherapy¹⁹. Attempted treatment by bathing in the Dead Sea and UVB phototherapy (wavelengths of 311 nm) also gave good results. After 35 treatments (three to five times per week), the PASI score decreased from 17.7 to 5.2. The most common side effect of this therapy was rash, found in 87% of cases, and it was caused by ultraviolet radiation. Af-

ter treatment, 55% of patients had recurrence after six months, and 68% of patients after one year²⁰.

A combination of three favorable factors for psoriasis, sun, sea water and air, is applied in patients with psoriasis at the Black Sea in Bulgaria. In a group of 177 patients, the therapy lasted 20 days and covered sun exposure of 5–6 hours *per* day, and bathing in sea water from 5–15 minutes a day. Complete regression of skin lesions was found in 68.9% of patients, 17.1% presented with a significant improvement, and a moderate improvement was found in 9.5% of patients. Only 4.5% of patients did not respond to the therapy (no processing done in terms of statistical significance)²¹.

Salt water soaks have a significant impact on transforming growth factor beta1 (TGFβ1) which is decreased in psoriatic epidermis models. If the affected skin is exposed to 30% sodium chloride solution, TGF-β1 mRNA expression significantly increases, even without additional skin exposure to UVB rays ($p = 0.0024$), compared to untreated psoriatic epidermis models or epidermis treated with 3% sodium chloride solution. If combined with UVB rays, a significant increase in the expression of TGFβ1 mRNA, apart from using 30% sodium chloride, is evident when using Dead Sea salt water in comparison with 3% sodium chloride ($p = 0.00014$)²². A study conducted in spa resorts in Germany showed that a significant reduction in PASI score occurred in psoriatic patients exposed to UVB rays and various concentrations of sodium chloride, compared to patients only exposed to UVB radiation, after 6 weeks of treatment. The best results were found in patients treated with highly concentrated saline spa water baths, sodium chloride concentration between 25% and 27% ($p < 0.001$)^{23,24}. A German study compared the effectiveness of salt water *versus* tap water. Ten psoriasis patients with chronic plaques on the elbows were included in the study. One elbow was soaked in 24% NaCl solution and the other in tap water. Subsequently, broadband UVB irradiation was administered. Balneophototherapy was performed 4 times weekly with a total of 30 treatments. A highly significant ($p < 0.001$) decrease of the clinical baseline score was observed after 30 treatments; however, there was no significant ($p > 0.5$) difference in clearance of the psoriatic lesions between the sites soaked in salt water and tap water²⁵. If we examine the efficacy of psoralens dissolved in a warm-water bath followed by exposure to UVA irradiation (bath PUVA) or salt water UVB phototherapy compared with tap-water UVB phototherapy or UVB irradiation alone in psoriasis, we come to the conclusion that bath PUVA and salt water UVB phototherapy are comparably effective treatments in psoriasis and superior to UVB and tap-water UVB phototherapy ($p < 0.001$)²⁶.

The question is to what extent pretreatment with salt water soaks alters inflammatory and/or carcinogenic effects of UVB phototherapy. Therefore, the impact of balneophototherapy on cyclooxygenase (COX-2) gene expression and apoptosis in normal and psoriatic skin were investigated. Compared with untreated controls, COX 2 gene expression (COX-2 mRNA) was significantly increased in UVB irradiated normal and psoriatic epidermis models. UVB-exposed and non-exposed 30% NaCl

and 30% Dead Sea water-treated normal and psoriatic epidermis models showed significantly higher COX-2 mRNA, when compared with controls and 3% NaCl. In UVB-exposed 30% NaCl and 30% Dead Sea water-treated normal and psoriatic epidermis surviving mRNA was significantly decreased when compared with controls and 3% NaCl. Although balneophototherapy using high-concentrated salt water solutions is associated with increased epidermal COX-2, mRNA expression, apoptosis of keratinocytes is enhanced possibly due to the down-regulation of surviving mRNA expression²⁷.

The control group of our patients treated only with calcipotriol presented with the PASI score reduction of 8.2% after 7 days of treatment, 24.12% after 14 days of treatment, 39.94% after 21 days of treatment, and 34.78% after thirty days from ending the treatment.

It was found that the effectiveness of therapy is achieved by binding of calcipotriol to the vitamin D receptor (VDR) in keratinocytes, and then interacting with regions of DNA inhibiting cell proliferation. Expression of VDR in keratinocytes is directly proportional to the therapeutic response to calcipotriol. This was determined by immunohistochemical analysis *in vivo*. Calcipotriol therapy statistically significantly increases the expression of VDR, the impact of drugs on the proliferation and differentiation of keratinocytes is higher than the impact on inflammation in dermis⁴. In a study conducted by van Rossum et al.²⁸ a four-week therapy with calcipotriol reduced the proliferation of keratinocytes by 11.7% (no processing done in terms of statistical significance). Given these results, it may be assumed that the results of our research, in both groups, would be even better if the therapy lasted longer.

One of the first multicenter studies on the efficacy of calcipotriol in the treatment of plaque psoriasis was conducted in the US in the mid-nineties²⁹. It included 277 patients aged 19 to 83 years. At the end of the first week of treatment, statistically significantly lower scores ($p < 0.001$) were obtained and they were present at the end of 8 weeks of therapy. None of the patients reported worsening of symptoms²⁹. These results also indicate that the efficacy of calcipotriol depends on the duration of treatment. In Singapore, a research included 30 patients: after six weeks of treatment their PASI score was reduced by about 70%³⁰. A multicenter study conducted in several European countries included 308 patients with psoriasis. They were treated with calcipotriol ointment twice a day. The average age of patients was 46.3 years, and the mean duration of the disease was 18 years. The average reduction in PASI score after the first week of therapy was 28.4%, and 48.8% after three weeks of therapy³¹. Good results in the treatment of psoriasis were also achieved combining calcipotriol and heliotherapy, regardless if it was natural or artificial light^{32,33}.

In a European multicenter study conducted in 2004, including 972 patients, the most frequent side effect was calcipotriol induced pruritus reported by 10.9% of patients³⁴. Two studies also showed side effects of topical calcipotriol in 11.4% and 19.8% of respondents, respectively. They manifested as irritation and itching of the skin^{35,36}. In our study, unwanted skin irritation and itching were observed in 10% of

patients treated with balneotherapy and calcipotriol, and in 6.6% of patients treated only with calcipotriol.

A limitation of our study is that we did not examine the effects of balneotherapy as a monotherapeutic modality in the treatment of plaque-type psoriasis. At the moment, there is a limited number of studies whose results suggest that balneotherapy, as a monotherapy, is superior to conservative therapy.

Conclusion

In conclusion, the results of our study show that in the treatment of plaque-type psoriasis, topical calcipotriol combined with Rusanda Spa balneotherapy is more effective than topical calcipotriol alone. Randomized controlled trials are needed to confirm the effects of balneotherapy as a monotherapy in treatment of this type of psoriasis.

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