

Management of Guttate and Generalized Psoriasis Vulgaris: Prospective Randomized Study

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Aim. To assess the efficacy of betamethasone dipropionate 0.05% cream plus ultraviolet B (UVB) radiation with and without additional penicillin therapy in the treatment of guttate psoriasis, and to compare the efficacies of oral psoralen plus ultraviolet A (PUVA) therapy and systemic retinoids therapy for treatment of generalized psoriasis.

Methods. Sixty patients with guttate ($n = 20$) and generalized psoriasis vulgaris ($n = 40$) of various intensity and duration treated at the Department of Dermatology, Medical School in Skopje, from February 2000 to January 2002, were included in this prospective, open-label, randomized, parallel group study. The clinical features of the patients were quantified according to the mean psoriasis area and severity index (PASI) values. Student's t-test for paired samples and two independent samples were used in statistical analysis.

Results. The final PASI values were not significantly different for the patients receiving different treatments of guttate psoriasis or generalized psoriasis. The initial PASI values for guttate psoriasis patients treated with betamethasone dipropionate plus UVB with and without penicillin treatment (5.7 ± 2.1 and 5.9 ± 2.5 , respectively) declined to 0.5 ± 0.8 and 1.0 ± 0.9 , respectively, after the therapy. The initial PASI values in generalized psoriasis patients receiving PUVA dropped from 24.1 ± 3.6 to 1.7 ± 1.5 by the end of the therapy. Finally, pre-treatment PASI values in patients with generalized psoriasis receiving retinoids decreased from 24.6 ± 3.5 to 0.9 ± 1.1 after treatment. However, patients receiving systemic retinoids for generalized psoriasis had statistically higher incidence of side effects than patients receiving PUVA therapy ($t = 6.458$, $df = 38$, $p < 0.001$).

Conclusion. Penicillin should be applied in addition to local corticosteroids with UVB in the treatment of guttate psoriasis, since the disease may be triggered by a streptococcal infection. In cases of generalized psoriasis vulgaris, PUVA therapy caused fewer side effects than did systemic retinoids.

Key words: betamethasone; psoriasis; PUVA therapy; retinoids; ultraviolet therapy

Psoriasis is a chronic inflammatory cell-mediated autoimmune dermatosis (1), clinically characterized by scaly erythematous lesions due to an increased epidermal turnover and the proliferation of keratinocytes (2). The size of a single lesion varies from a pinpoint to plaques covering large areas of the skin. The three key events in psoriasis are epidermal keratinocyte hyperproliferation without accompanying differentiation, vascular proliferation, and associated inflammation (3). The role of T cells in psoriasis was demonstrated by the remission of severe psoriasis after treatment with a drug consisting of diphtheria toxin and the receptor-binding domain of IL-2, which are toxic for activated T cells (4). Similarly, targeting monocytes and T cells with IL-10 treatment causes a considerable reduction of psoriatic areas and decreases severity index (5,6).

Psoriatic keratinocytes are characterized by the production of defensins, antimicrobial peptides of the skin (7). Patients with acute guttate psoriasis have

flares of psoriasis following streptococcal infections and increased antibody titers to streptococcal antigens (8,9). Streptococcal toxins are pyrogenic toxin superantigens (10), which activate large fractions of the T cell population with restricted T cell receptor repertoire. Such T cells (11,12) secrete massive amounts of cytokines believed to cause the histological features of psoriasis (11-14). Research done so far points to the involvement of a superantigen in the etiology of psoriasis (15-18).

Although there is no cure for psoriasis, a variety of treatments are available for control or inhibition of the epidermal hyperproliferation, promotion of maturation of skin cells, and prevention of the inflammation. Treatment with ultraviolet B (UVB) radiation or psoralen plus ultraviolet A radiation (PUVA) greatly reduces the number of activated T cells in the epidermis and dermis of psoriatic skin by inducing T cell apoptosis, often resulting in long-standing remissions (19-21). Systemic treatments with retinoids have been

successfully used in the treatment of severe cases of psoriasis (22), but their mechanism of action is not well understood (23). On the other hand, treatment with topical corticosteroids or cyclosporine inhibits the production of cytokines by intralesional T cells. This suppressive therapy, however, rarely reduces the number of lesional T cells by more than 50% (24) and, as a result, psoriasis often recurs after the cessation of the suppressive therapy. Therefore, psoriasis treatment includes a long-term drug therapy and close follow-up of the patients for possible undesirable side effects.

The aim of our study was to evaluate and compare the therapeutic efficiency and tolerability of betamethasone dipropionate 0.05% cream plus UVB with and without penicillin in guttate psoriasis, and the efficiency of oral psoralen plus UVA (PUVA) vs systemic retinoids in the management of generalized psoriasis. Guttate and generalized form of psoriasis were chosen for the comparative study of two types of treatment because these psoriasis types affect the quality of life and work activities of patients, as compared with a stable, limited chronic plaque disease form.

Patients and Methods

Study Design

In a prospective, open-label, randomized, controlled, parallel-group trial conducted at Department of Dermatology, Skopje University Hospital, we compared the efficiency of betamethasone dipropionate 0.05% cream (Beloderm, Belupo, Koprivnica, Croatia) plus phototherapy (UVB) with the same therapy plus penicillin in the treatment of guttate psoriasis. In a parallel trial, conventional psoralen (8-methoxypsoralen) (Melaoline, UniPharma SA, Kifissia, Greece) and UVA (PUVA) therapy was compared with systemic retinoids (acitretin) (Neotigason, Roche, F. Hoffmann-La Roche Ltd, Basle, Switzerland) in the treatment of generalized psoriasis. All patients signed an informed consent to participate in study.

Eligibility Criteria

Patients were included in the study if they fulfilled the following criteria: 1) age ≥ 18 years; 2) histologically confirmed psoriasis form; and 3) normal results of physical and biochemical tests (serum albumin, lipids, total calcium, albumin-adjusted total calcium, urea, phosphate, alkaline phosphatase, and creatinine). Therapy was introduced with patient's inclusion in the study.

Exclusion criteria were the following: 1) use of phototoxic or immunosuppressive drugs; 2) presence of other skin lesions (actinic keratoses or lentigo) or photodamaged skin; 3) use of systemic or intralesional therapy or photo(chemo)therapy for psoriasis in the previous two months; 4) use of topical treatments during the study period; 5) conditions or medications that might interfere with or sensitize patients to any of the treatments; 6) concomitant bacterial, fungal, or viral skin infections; 7) significant worsening of the clinical state during the therapy, and/or development of serious side effects; and 8) nonadherence to the treatment.

None of the patients had a history of renal, hepatobiliary, or malignant disease, hypertension or recurrent acute infection. All patients completed the study.

Patients

The study included 60 patients with guttate ($n=20$) and generalized psoriasis vulgaris ($n=40$) of various intensity and duration, treated at the Department of Dermatology, Medical School in Skopje, from February 2000 to January 2002. There were no significant differences in the demographic data, including skin types, between the two groups of patients.

Treatment Regimens

Patients with guttate psoriasis were randomly allocated by ClinStat software (<http://www.sghms.ac.uk/depts/phs/staff/jmb/jmbsoft.htm>) into two groups, one receiving topical therapy with betamethasone dipropionate 0.05% cream and phototherapy (UVB) and the other undergoing the same treatment plus penicillin. The assignment of a patient to a particular treatment was concealed until interventions were assigned. The UVB therapy was performed four times per week over six weeks, and the topical therapy was performed once daily after the phototherapy. Penicillin (1.6 MU IM once a day) was given for the first two weeks of treatment.

Patients with generalized psoriasis were also randomly allocated to two groups, one receiving conventional PUVA therapy and the other systemic retinoids (acitretin). PUVA therapy was performed four times per week for six weeks, and two additional weeks twice a week. Systemic retinoids were given according to the manufacturer's recommendations (30 mg as an initial daily dose).

Clinical and Histologic Assessment

The change in clinical condition (extensity and intensity of lesions) of the patients in comparison with baseline (week 0) was the primary criterion for treatment efficacy. Psoriasis area and severity index (PASI) (25) was assessed after 2, 4, 6, and 8 weeks of treatment. At the end of the study, we estimated the different therapy outcomes using the following scale: 0=worse; 1=no change; 2=moderate improvement (partial reduction in scaling and/or erythema and/or infiltration); 3=considerable improvement (significant reduction in all three variables); and 4=clearing (almost no skin changes left, except residual erythema as in macular psoriasis) (26). Psoriatic skin samples were histologically examined as well.

Statistical Analysis

The data were evaluated by descriptive and analytical statistical methods, and then correlated with the clinical observations. To determine the statistical significance of our conclusions and test the null hypothesis, we used Student's t-test for paired samples and t-test for two independent large samples and ANOVA. The level of significance was $p < 0.01$ for the effectiveness of the therapy on clinical improvement, and $p < 0.05$ for comparison of the efficacy of applied therapies.

Results

Patients with Guttate Psoriasis Vulgaris

The group of 20 patients with guttate psoriasis was divided in two subgroups, each with equal number of patients (Fig. 1).

The first subgroup (I-a) included 6 women and 4 men. Median age of the patients was 25 years (range 17-37) and median duration of the disease 22 days (range 15-35). Two patients had antistreptolysin titer (AST) concentrations > 200 U/L and 2 had chronic tonsillitis. Cultures from nose and throat swabs were negative for all patients. The patients were treated with betamethasone dipropionate 0.05% cream and UVB for 6 weeks. After six weeks of therapy, moderate improvement was observed in 5 patients, considerable improvement in 2, and complete clearing of the lesions in 3. The mean PASI value for this group of patients decreased from 5.9 ± 2.5 before treatment to 1.0 ± 0.9 after treatment (Table 1).

The second subgroup (I-b) included 5 women and 5 men. Median age of the patients was 22 (range 16-32) years and median duration of the disease 25 (range 19-45) days. Four patients had AST > 200 U/L, all had negative cultures of nose and throat swabs and 3 had chronic tonsillitis. The patients were treated with betamethasone dipropionate 0.05% cream,

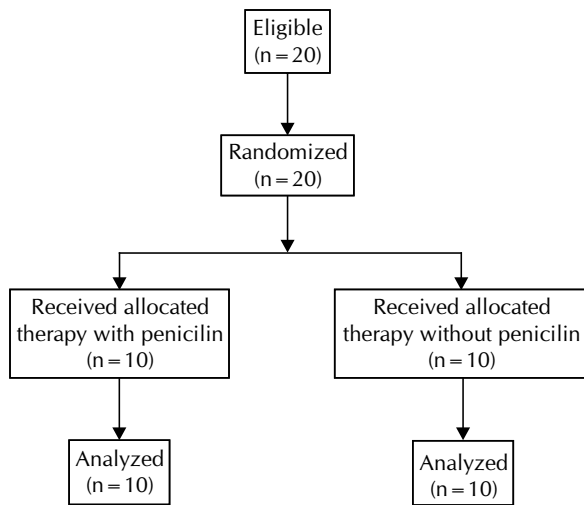


Figure 1. Flow chart of 20 patients with guttate psoriasis, randomly assigned to one of two subgroups with 10 patients each. One subgroup received betamethasone dipropionate 0.05% cream in combination with ultraviolet B (UVB) therapy and penicillin, whereas the other received the same therapy but without penicillin.

UVB therapy, and penicillin for 6 weeks. After six-week therapy, 2 patients showed moderate improvement, another 2 showed significant improvement, and 6 patients had complete disappearance of the lesions. The mean PASI value decreased from 5.7 ± 2.1 before treatment to 0.5 ± 0.8 after treatment (Table 1).

The greatest reduction in the mean PASI value was observed between the fourth and sixth week of treatment. At the end of the sixth week, both groups demonstrated pronounced reduction in mean PASI values (Table 1). There was no significant difference between the average PASI values for the two subgroups during the course and at the end of treatments (Table 1). Global assessment of the efficacy of the two treatments showed no significant difference in the effectiveness of two therapies (ANOVA; $F_x = 1.402$, $df = 5$, $p > 0.05$).

The patients in both subgroups did not report systemic or local side effects from the therapy. Whereas the AST values during the fourth week of therapy did not change in the two patients with increased AST concentrations and treated with betamethasone dipropionate 0.05% cream and UVB therapy, AST concentrations for all patients treated with betamethasone dipropionate 0.05% cream, UVB therapy, and penicillin remained or were reduced to normal. However, this difference was not statistically significant (Table 1).

The routine laboratory results were normal for all patients in both subgroups (data not shown).

In our study, the anamnesis seemed commonly positive for upper-respiratory infection. For instance, 35% of our patients reported a previous respiratory infection. Clinical signs of focal infection (chronic tonsillitis) were noticed in 25% of the patients. We did not isolate β -hemolytic streptococcus from the nose and/or throat of any of our patients, which, how-

ever, does not completely exclude the possibility of infection in the tonsillar core and/or other structures. Several-fold increase in the AST titer was found in six patients. AST values did not exclude a streptococcal infection either.

Patients with Generalized Psoriasis Vulgaris

The group of 40 patients with generalized psoriasis and extensive body surface involvement ($> 30\%$) was likewise divided in two subgroups with equal number of patients (Fig. 2). The clinical diagnosis of psoriasis was histologically verified in all patients.

The first subgroup (II-a), receiving PUVA therapy, included 14 women and 6 men. Their median age was 39 years (range 27-63) and median duration of the disease was 5 years (range 2-12). Psoriatic lesions were found on the scalp, trunk, and extremities. The mean PASI value before treatment was 24.1 ± 3.6 (Table 2). Out of 20 patients with generalized psoriasis treated with PUVA, 3 showed moderate improvement, 10 showed considerable improvement, and 7 complete clearance of lesions. At the end of the eight-week therapy, the mean PASI value decreased to 1.7 ± 1.5 (Table 2).

The second subgroup (II-b), receiving systemic retinoids, included 2 women and 18 men. Median age was 42 years (range 37-65) and median duration of the disease was 5 years (range 3-15). Psoriatic lesions were distributed over the scalp, trunk, and extremities. The mean PASI value before treatment was 24.6 ± 3.5 (Table 2). Moderate improvement was noticed in 2 patients, considerable improvement in 8, whereas 10 patients showed complete clearance of lesions. At the end of the eight-week therapy, the mean PASI value decreased to 0.9 ± 1.1 (Table 2).

There was a successive, highly significant decrease in mean PASI values in both subgroups (Table 2). To determine the difference in the effect between PUVA therapy and systemic retinoids, we carried out Student's t-test for two independent samples. Signifi-

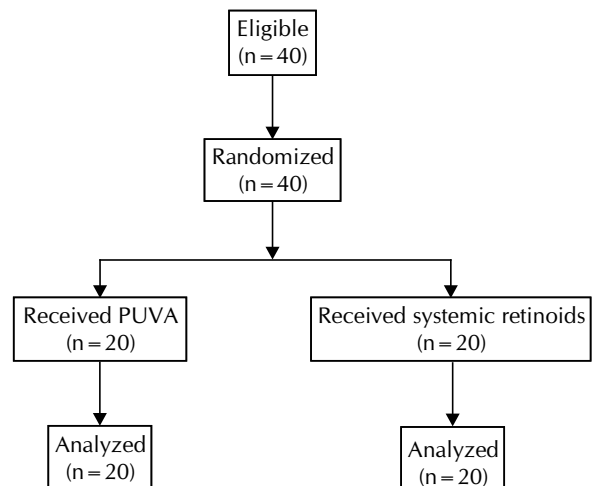


Figure 2. Flow chart for the randomized trial for 40 patients with generalized psoriasis. The patients were randomly assigned to one of two subgroups, each with 20 patients. One group received psoralen with ultraviolet A radiation (PUVA) therapy and the other received systemic retinoids.

Table 1. Mean PASI (psoriasis area and severity index) values for guttate psoriasis patients on betamethasone dipropionate 0.05% cream (B) plus ultraviolet B (UVB) therapy either without or with penicillin (P)

Treatment	Mean PASI value at week					p ^b
	0	2	4	6		
B + UVB	5.87 ± 2.47	4.63 ± 2.40	2.68 ± 1.73	0.96 ± 0.90		< 0.001 (t = 8.859, df = 9)
p ^a	0.841	0.407	0.241	0.222		
B + UV + P	5.66 ± 2.12	3.84 ± 1.70	1.86 ± 1.24	0.48 ± 0.79		< 0.001 (t = 9.088, df = 9)

^aStudent's t-test for independent samples.

^bStudent's t-test for paired samples before and after treatment.

Table 2. Mean PASI (psoriasis area and severity index) values for patients with generalized psoriasis receiving either psoralen with ultraviolet A radiation (PUVA) therapy or systemic retinoids

Treatment	Mean PASI value at week					p ^b
	0	2	4	6	8	
PUVA	24.06 ± 3.62	19.40 ± 3.08	14.58 ± 2.21	9.38 ± 3.02	1.69 ± 1.55	< 0.001 (t = 32.941, df = 19)
p ^a	0.657	0.019	0.788	0.005	0.069	
Retinoids	24.56 ± 3.50	21.95 ± 3.5	14.36 ± 2.78	6.91 ± 2.11	0.9 ± 1.07	< 0.001 (t = 31.577, df = 19)

^aStudent's t-test for independent samples.

^bStudent's t-test for paired samples before and after treatment.

cant difference was found between the average PASI values after the second and sixth week of therapy ($p < 0.05$, Table 2). On the other hand, the difference between the average PASI values after the fourth week and at the end of therapy was not significant in either of the subgroups (Table 2). Global assessment of the efficacy of the two treatments demonstrated no significant difference in the effectiveness of the two therapies (ANOVA; $F_x = 1.002$, $df = 5$, $p > 0.05$).

The decrease in PASI values for both subgroups was greatest between the sixth and eighth week of therapy (Table 2).

The difference in systemic and local side effects between the two subgroups of patients with generalized psoriasis was statistically significant ($p < 0.001$, Table 3). Among the patients treated with PUVA, one developed nausea at the beginning of the therapy, which disappeared when the patient started taking psoralen after breakfast. After the second PUVA exposition, two patients developed phototoxic erythema, which ceased within four days of the exposure. One patient reported light pruritus at the end of the therapy, which subsided after daily application of an indifferent emollient. Activation of latent herpes simplex was seen in one patient, who was then treated with local virostatic and later required facial photoprotection.

In the second subgroup of patients treated with systemic retinoids, 14 patients developed cheilitis and one complained of generalized pruritus, which subsided after the therapy with an indifferent emollient and disappeared completely when the daily dose of systemic retinoids was reduced.

Increased concentrations of serum lipids were noted in 3 patients and increased serum hepatic enzymes in one patient (data not shown). These effects subsided once the daily doses of systemic retinoids were reduced and an appropriate diet introduced. The routine laboratory results were within the normal ranges for all other patients in both subgroups (data not shown).

The difference in systemic and local side effects between the two generalized psoriasis subgroups was statistically significant.

Table 3. Difference in systemic and local side effects between psoralen with ultraviolet A radiation (PUVA) and systemic retinoids administered in the group of patients with generalized psoriasis

Treatment	No. of patients			p ^a
	with side-effects	without side-effects	total	
PUVA	5	15	20	< 0.001
Retinoids	19	1	20	

^aStudent's t-test for proportion (t = 6.458, df = 38).

Discussion

Treatments of patients with guttate psoriasis with betamethasone dipropionate 0.05% cream and UVB therapy with or without penicillin gave similar results. Previous research showed that additional local application of corticosteroids synergizes with the therapeutic effect of UVB therapy, with therapy success between 50-80% over a period of five weeks (27,28). In parallel, treatment of guttate psoriasis with corticosteroids, UVB, and penicillin gave higher success rate, between 60-90% (27,28).

We compared PUVA therapy and systemic retinoids as two treatment modalities in the group of patients with generalized psoriasis vulgaris. Although we observed significantly different success rates of the two treatment types at the second and sixth week of therapy, there was no significant difference between PUVA and retinoids at the end of the treatment (eighth week). Moreover, the final results demonstrated that both therapies showed highly significant reduction of the mean PASI values over the course of treatment. However, we observed significant difference in side effects, which were more common in patients receiving systemic retinoids.

Moseley and Ferguson (29) recommend PUVA four times a week, which gave significant or complete clearance of the lesions in 88% of the treated patients after 20 exposures (about six weeks of therapy). Our results were similar: 85% of the patients receiving PUVA four times per week experienced significant or complete clearance of the lesions at the end of the sixth week. Due to the higher occurrence of side effects when larger doses of UVA were used at lower

frequency of PUVA treatment (30), we chose to follow the aforementioned protocol. Overall, the acute side effects, usually nausea, and burning and itching of the skin (incidence of 20%) were mild enough not to interrupt the treatment.

When applying PUVA therapy one must take into consideration, later chronic side effects of high UVA doses. Fortunately, photoageing of the skin and actinic keratoses, which may become squamous cell carcinoma (31) or lentigo, were not registered in our study group. Furthermore, the latest epidemiological studies showed that PUVA therapy was independently carcinogenic only in high cumulative doses above 1,000 J/cm² (32). Concurrent immunosuppressive and phototoxic therapies must be avoided if PUVA is applied.

In extensive plaque-type psoriasis the acitretin produces significant improvement in 50-60% of the patients between the second and third week of treatment (33), which is in concordance with our results.

The clinical shortcomings of the oral retinoids include delayed therapeutical effect and numerous adverse effects, which can cause reluctance in patients to continue with the therapy. Cheilitis and dry lips were observed in 90-100% of treated patients in another study (34); we observed them in 70% of our patients. Increased concentrations of serum lipids in 3 patients (15%) reverted to the normal levels after reduction in the drug dose. The mutagenic and teratogenic effects of retinoids, however, are the main reason for their limited use in most severe cases (35).

The limitations of this study stem from biases associated with determining the PASI values, and from the fact that the dermatologist who assessed the PASI values knew what treatment was administered to each patient. However, it is not likely that this affected the results because the criteria for establishing the PASI values are well defined and all PASI values were determined by the same dermatologist. This is further confirmed by the fact that guttate psoriasis patients treated with penicillin in addition to betamethasone dipropionate 0.05% cream plus UVB showed similar reductions in the PASI values because patients receiving the same treatment without additional penicillin treatment, a finding that we did not expect. Matching on age, sex, and skin color also limited the risk of bias from confounding factors.

In conclusion, although we did not observe significant difference in the final outcome of the therapies for guttate psoriasis, ie, treatment with betamethasone dipropionate 0.05% cream and UVB therapy with or without penicillin, we still favor the therapeutical approach that includes penicillin, because there is a causal relationship between psoriasis guttata and infection with β -hemolytic streptococcus, which acts as a superantigen (8-10).

The group of patients with generalized psoriasis vulgaris showed no significant difference in the final effect of the therapies they received, ie, PUVA and systemic retinoids. However, we observed significant difference in side effects, which were more common in patients treated with systemic retinoids. Therefore, we believe that PUVA therapy rather than systemic

retinoids should be applied in cases of generalized psoriasis vulgaris.

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