

Vitamin B₁₂ Cream Containing Avocado Oil in the Therapy of Plaque Psoriasis

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Key Words

Psoriasis · Vitamin B₁₂ cream · Avocado oil · Calcipotriol

Abstract

Background: There are already many effective topical therapies available for use in the treatment of chronic plaque psoriasis. Unfortunately, these treatments are often associated with a rather significant risk of undesirable effects. **Objective and Methods:** In this randomized, prospective clinical trial, the effects of the vitamin D₃ analog calcipotriol were evaluated against those of a recently developed vitamin B₁₂ cream containing avocado oil in an intraindividual right/left-side comparison. The trial population consisted of 13 patients, 10 men and 3 women, with chronic plaque psoriasis. The observation period was 12 weeks; the effects of therapy were assessed on the basis of a PASI score adapted to the right/left-side comparison technique, the subjective evaluations of the investigator and patients and the results of 20-MHz sonography. **Results:** There was a more rapid development of beneficial effects with the use of calcipotriol in the initial 8 weeks, although differences in effects were significant only at the time point of therapy week 8 ($p < 0.05$). After 12 weeks, neither the PASI score nor 20-MHz sonography showed significant differences between the two

treatments. While the efficacy of the calcipotriol preparation reached a maximum in the first 4 weeks and then began to subside, the effects of the vitamin B₁₂ cream containing avocado oil remained at a constant level over the whole observation period. This would indicate that the vitamin B₁₂ preparation containing avocado oil may be suitable for use in long-term therapy, a hypothesis further supported by the fact that the investigator and the patients assessed the tolerability of the vitamin B₁₂ cream containing avocado oil as significantly better in comparison with that of calcipotriol. **Conclusion:** The results of this clinical trial provide evidence that the recently developed vitamin B₁₂ cream containing avocado oil has considerable potential as a well-tolerated, long-term topical therapy of psoriasis.

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Introduction

Many effective preparations for use in the topical therapy of psoriasis are currently available. In addition to the antipsoriatics dithranol, topical retinoids and corticosteroids, which have long been established as the standard therapeutic agents, vitamin D₃ analogs are being increasingly used in the topical therapy of psoriasis. One factor

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that is common to these topical agents is a significant potential for causing irritation [1]. It has been proven possible to reduce the risk of such undesirable effects by combining various topical agents or topical and systemic antipsoriatics and, at the same time, to reduce the costs of treatment [2–4].

An unfavorable benefit/side effect profile will reduce compliance in patients who are already experiencing a marked deterioration of their quality of life as a result of psoriasis. For this reason, it is a recognized need to find topical antipsoriatics with a more positive side effect profile. An exploratory investigation of the effects of an innovative vitamin B₁₂ cream containing avocado oil was conducted in the clinical trial discussed in this article.

Initial reports of therapeutic success after (mainly) parenteral administration of vitamin B₁₂ in the treatment of psoriasis were made some 40 years ago.

Ruedeman and Albany [5] administered 1,100 µg vitamin B₁₂ i.m. daily over a period of 10–20 days to 34 patients with psoriasis vulgaris. There was complete remission in 11 cases, nearly complete remission in a further 11 cases and significant improvement of symptoms in 6 cases. Cohen [6] reported on psoriatic patients who had received 1,000 µg vitamin B₁₂ i.m. daily on 6 days per week over a 3-week period. In at least 50% of this collective, complete or nearly complete healing was achieved.

It can be assumed that the effects of the substance in the skin after systemic administration of vitamin B₁₂ are relatively slight, as up to 90% of a dose is eliminated by the renal pathway within 48 h and is therefore not available to the target organ – the skin [7]. With topical application, the excellent depot characteristics [8] of the skin ensure that a large percentage of the vitamin B₁₂ present in the cream base remains continuously available. The fact that dermal vitamin B₁₂ levels are reduced in psoriatic plaques and in apparently healthy skin in patients with psoriasis [9] is a reason for the use of vitamin B₁₂ in psoriasis.

Any new antipsoriatic agent should exhibit innovative activity and a favorable cost-benefit profile while the recurrence rate should be low after discontinuation of therapy with the agent. The therapeutic efficacy should not be less than that of standard topical antipsoriatics. As the basic efficacy of vitamin B₁₂ in the treatment of psoriasis has already been demonstrated, the aim of the clinical trial discussed here was to investigate whether the therapeutic effects of a new vitamin B₁₂ cream containing avocado oil (Regividerm[®], Regeneratio Pharma AG, Wuppertal, Germany) differ from those of a contempora-

ry vitamin D₃ analog, calcipotriol (Psorcutan[®] ointment, Schering AG, Berlin, Germany). The therapeutic effects were evaluated in a randomized, prospective clinical trial in an intraindividual right/left-side comparison.

Patients and Methods

Patient Collective

Included in the trial were 13 patients with stable psoriasis vulgaris, 10 men and 3 women aged 38–67 years (52.9 ± 12.2 years). The mean duration of the disorder was 20.8 ± 12.7 years. Two patients were excluded from the analysis due to deviations from the trial protocol: 1 female patient who exhibited insufficient compliance by occasionally discontinuing use of the cream and receiving intensive UV irradiation and 1 male patient who applied calcipotriol to the skin sites allocated to vitamin B₁₂ cream containing avocado oil. Exclusion criteria were use of corticosteroids, topical retinoids, diethanol or vitamin D₃ analogs in the 7 days prior to commencement of the trial, modification of systemic therapy in the past 3 months or phototherapy during the past 6 weeks, the presence of pustular or erythrodermic forms of psoriasis or age less than 18 or greater than 70 years. Prior to inclusion, it was established that patients had no known hypersensitivity to calcipotriol or to vitamin B₁₂. Other exclusion criteria were avocado oil allergy and $\geq 60\%$ of body surface area requiring treatment on one side of the body (a contraindication for the use of calcipotriol).

The trial medication vitamin B₁₂ + avocado oil contains only naturally occurring substances in a simplified formulation with few ingredients: these are vitamin B₁₂ in a concentration of 700 mg/kg, methylglycoside stearate (Emulsan[®]), avocado oil and distilled water; avocado oil was added from a cosmetic point of view, because of its physicochemical properties, i.e. it spreads easily on the skin. The avocado oil of our trial preparation contained 82.9 mg/kg vitamin E (α-tocopherol) whereas neither vitamin A nor D₃ were detectable.

Patients received detailed information on the intended trial and gave their written informed consent. The trial had been approved by the Ethics Committee of the Faculty of Medicine of the Ruhr University in Bochum.

Trial Design

During the 12-week observation period of the prospective, randomized trial, two cream preparations containing calcipotriol or vitamin B₁₂ with avocado oil were applied to psoriatic plaques on the contralateral body sides of each patient. The preparations were applied twice daily, once in the morning and once in the evening, by the patients themselves. Effects were monitored in control examinations after 2, 4, 8 and 12 weeks.

The primary target variable was the PASI score. The differences in treatment effects were evaluated on the basis of the severity and extent of psoriasis on the two body sides of each patient at baseline and the subsequent examinations as shown in the form of the modified PASI score. The modification made for the purposes of this trial concerned the area evaluated only; it is usually the whole body that is evaluated using a PASI score. As the method involved comparison of contralateral body sides, the PASI score per body side was given a 50% weighting and the head/neck area was ignored for practical reasons. Secondary variables were the subjective evaluations of efficacy

made by the patients and the investigator. In addition, the effects of each treatment were quantified using 20-MHz sonography (DUB 20, Taberna pro medicum, Lüneburg, Germany) by measuring the width of the echolucent area (which shows the extent of acanthosis and inflammatory infiltration) prior to initiation of therapy and 2, 4, 8 and 12 weeks after commencement of treatment [10]. The echo density of the corium was also measured to provide an indication of cellular infiltration [11].

Statistics

In addition to descriptive methodologies, the t test for paired samples was used. Bowker's symmetry test for connected samples was used to analyze the results of the subjective evaluation of the two tested preparations in the form of 2×2 contingency tables. Results with a significance level of $\alpha \leq 0.05$ were considered to be statistically significant.

Results

Evaluation of Efficacy on the Basis of the PASI Score

The baseline PASI score for the body side to which the vitamin B₁₂ cream containing avocado oil was applied was 9.1 ± 4.8 . After 12 weeks of therapy, the score had fallen to 0.8 ± 0.7 (PASI score range: 0–2.1).

The baseline PASI score for the body side to which calcipotriol was applied was 9.2 ± 5.1 . After 12 weeks of therapy, PASI scores were in the range of 0–1.8 (mean: 0.8, SD: 0.7). The effects of the vitamin D₃ analog were more rapid in the initial 8 weeks, as the reduction in mean scores shows (fig. 1, table 1). However, there was no significant difference in the treatment effect (adjusted for baseline) after 2 weeks ($p = 0.056$) or after 4 weeks ($p = 0.055$). Only after 8 weeks was the reduction of the PASI score significantly more marked for calcipotriol therapy in comparison with vitamin B₁₂ cream containing avocado oil ($p < 0.05$). However, after 12 weeks (the target endpoint of the trial), the difference in treatment effect was only 0.09 (PASI score) in favor of calcipotriol ($p = 0.534$).

If the mean PASI scores at two successive examination time points are compared, the differences between baseline and results after 2 weeks and between 2 weeks and 4 weeks are highly significant for both preparations ($p < 0.0001$ in each case). However, there is no significant difference in the reduction of the PASI score between the examination time points 4 and 8 weeks for the calcipotriol preparation ($p = 0.067$). The effects of this preparation therefore stagnated, while there continued to be a significant improvement in symptoms during therapy with the vitamin B₁₂ preparation containing avocado oil ($p < 0.05$). As a result, the treatment effect approached equivalence after 12 weeks.

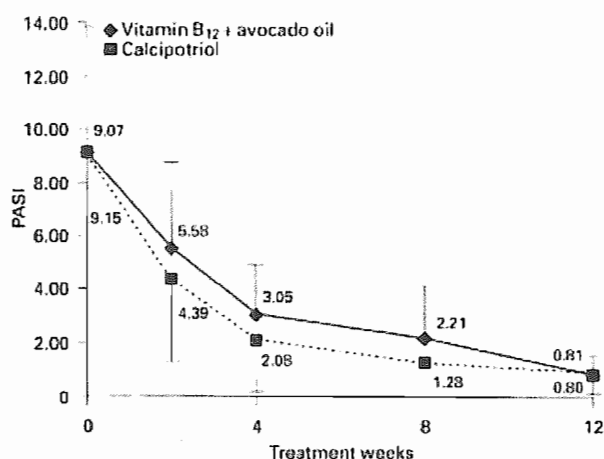


Fig. 1. In the initial 8 weeks, the effects of calcipotriol were more rapidly manifested than those of vitamin B₁₂ with avocado oil. The difference was not significant after 2 weeks ($p = 0.056$) or after 4 weeks ($p = 0.055$) but only after 8 weeks of therapy ($p < 0.05$). After 12 weeks, there were no significant differences in the efficacy of treatment (adjusted for baseline) between the two therapy regimens ($p = 0.534$). Means \pm SD.

Subjective Evaluation of the Two Topical Preparations by Patients and the Investigator

To increase the value of the results of statistical analysis, the originally 4×4 contingency tables were reduced to 2×2 contingency tables, whereby the results 'very good' and 'good' as well as 'moderate' and 'poor' were evaluated in one group.

Due to a random effect, the evaluation of efficacy by the investigator was better for the calcipotriol preparation than for the vitamin B₁₂ cream containing avocado oil ($p = 0.56$). The global evaluation of efficacy by patients was identical with the investigator's evaluation on the basis of the reduced contingency tables (fig. 2a, b).

In the patients' evaluation of the feeling of skin and the effects on clothing, there was a significant superiority of the vitamin B₁₂ cream containing avocado oil over calcipotriol ($p < 0.05$).

The two preparations were identically evaluated for odor, while the color of the calcipotriol preparation (white) was tendentially more acceptable than that of the vitamin B₁₂ preparation containing avocado oil (pink; $p = 0.32$).

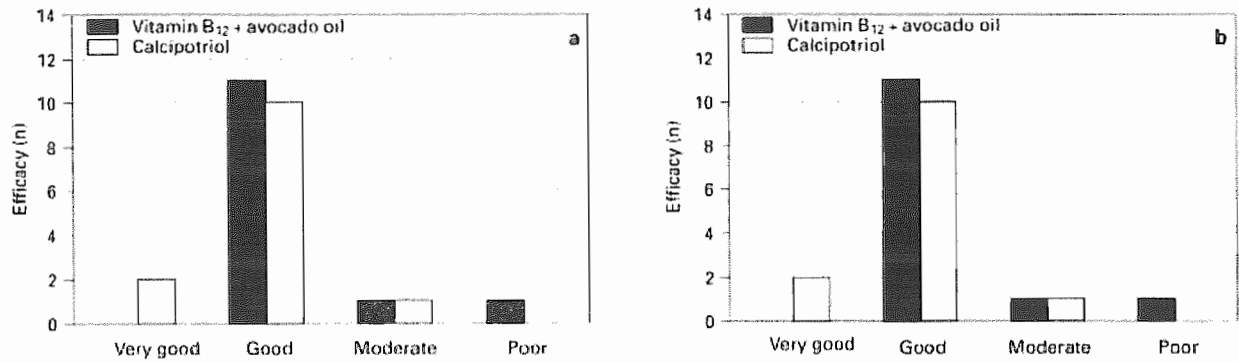


Fig. 2. Evaluation of efficacy by the investigator (a) and by patients (b). In both cases, there is a tendentially better efficacy of the calcipotriol preparation in comparison with the vitamin B₁₂ + avocado oil preparation ($p = 0.56$); investigator and patient evaluations are identical.

Table 1. PASI score evaluation of both treatment groups (vitamin B₁₂ + avocado oil, calcipotriol) for each of the 13 patients at 0, 2, 4, 8 and 12 weeks

Patient No.	Before treatment	After 2 weeks	After 4 weeks	After 8 weeks	After 12 weeks
<i>Vitamin B₁₂ + avocado oil</i>					
1	4.50	3.30	1.90	0.90	0
2	16.20	9.90	4.95	1.65	0.55
3	2.80	1.40	0.80	0.30	0.20
4	4.50	3.30	1.00	1.50	1.20
5	10.80	6.60	4.05	1.70	0.45
6	5.40	2.40	0.60	0.20	0
7	8.85	4.85	4.45	2.55	1.20
8	4.95	2.20	1.10	0.45	0
9	12.00	7.20	6.00	6.00	2.10
10	8.10	5.40	2.70	1.30	0.80
11	12.60	8.40	4.20	4.20	1.40
12	18.70	11.90	5.10	5.10	1.70
13	8.55	5.70	2.85	2.85	0.95
Mean	9.07	5.58	3.05	2.21	0.81
SD	4.8	3.2	1.9	1.9	0.7
<i>Calcipotriol</i>					
1	4.50	3.30	2.60	2.10	0
2	17.85	9.90	6.60	1.65	1.80
3	2.20	1.20	0.80	0.40	0
4	4.50	3.00	0.20	0.20	0.30
5	10.80	6.60	2.10	1.45	0.45
6	5.40	2.40	1.20	0.60	0.90
7	8.85	3.80	1.60	0.65	0.45
8	4.95	1.65	0.55	0.45	0
9	12.00	3.60	1.20	1.20	1.20
10	8.10	1.80	0.90	0.90	0.65
11	12.60	2.00	1.40	1.40	1.40
12	18.70	10.20	3.70	3.40	1.70
13	8.55	7.60	4.75	2.25	1.50
Mean	9.15	4.39	2.08	1.28	0.80
SD	5.1	3.1	1.9	0.9	0.7

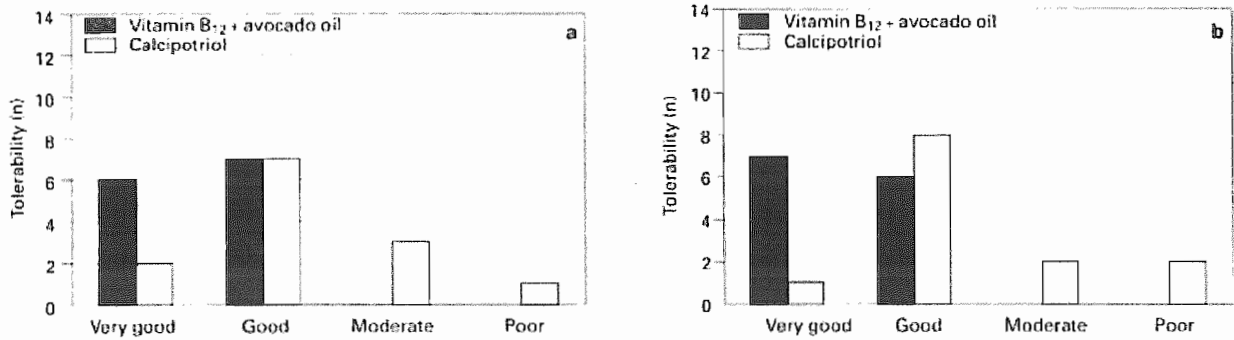


Fig. 3. Evaluation of tolerability by the investigator (a) and the patients (b). In both cases, there is significant superiority of tolerability of the vitamin B₁₂ + avocado oil preparation in comparison with calcipotriol ($p < 0.05$ in each case).

Evaluation of Tolerability by Patients and the Investigator

In the global evaluation of tolerability by the investigator, there was a significant superiority of the vitamin B₁₂ cream containing avocado oil over the calcipotriol preparation ($p < 0.05$). On the basis of the reduced contingency tables, the patient evaluation was identical to that of the investigator ($p < 0.05$; fig. 3a, b). The evaluation of tolerability includes a consideration of undesirable effects (safety collective: $n = 15$ patients). Four patients (26.7%) reported skin irritation during calcipotriol therapy that necessitated a dose reduction. Local pruritus occurred in 1 case (6.7%) during topical therapy with vitamin B₁₂ cream containing avocado oil; the symptoms subsided on continuation of therapy.

Evaluation of Treatment Effects Using 20-MHz Sonography

As in the case of the PASI score, there were significantly more marked decreases in the width of the echolucent area in the initial 4 weeks of therapy during treatment with calcipotriol in comparison with the vitamin B₁₂ preparation containing avocado oil. From therapy week 8, there was only a tendentially more marked decrease in echolucent area ($p = 0.062$) for calcipotriol, while by the end of therapy week 12, there were no significant differences between the therapy regimens for this parameter ($p = 0.389$; fig. 4).

The density of the corium indicates the extent of inflammatory infiltration. If there is a decrease in inflammatory infiltration during therapy, there is a corresponding increase in the density of the corium. There were no

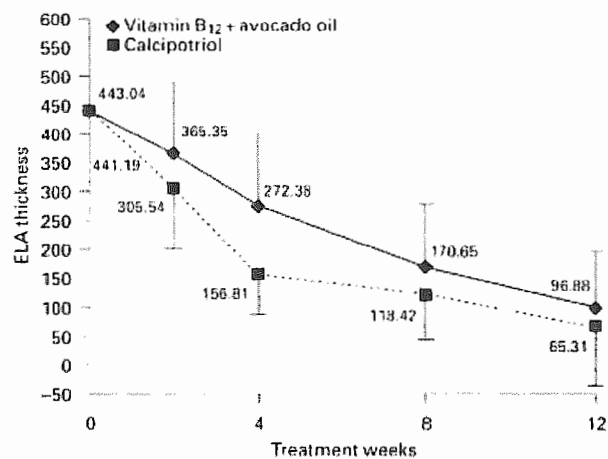


Fig. 4. 20-MHz sonography of a reference plaque: width of the echolucent area (ELA, μm). In the initial 4 weeks of therapy, there was a significantly more marked reduction during therapy with calcipotriol in comparison with vitamin B₁₂ cream containing avocado oil ($p < 0.05$). After 8 weeks ($p = 0.062$) and 12 weeks ($p = 0.389$), there were no significant differences in the thickness of the echolucent area. The figure shows the mean values with the standard deviation before treatment as well as 4, 8 and 12 weeks after the beginning of the treatment.

significant differences between the two treatments in respect of increases in corium density, except at the time point therapy week 4, when there was a significantly greater increase in density during calcipotriol therapy compared with the vitamin B₁₂ preparation containing avocado oil ($p < 0.05$; fig. 5).

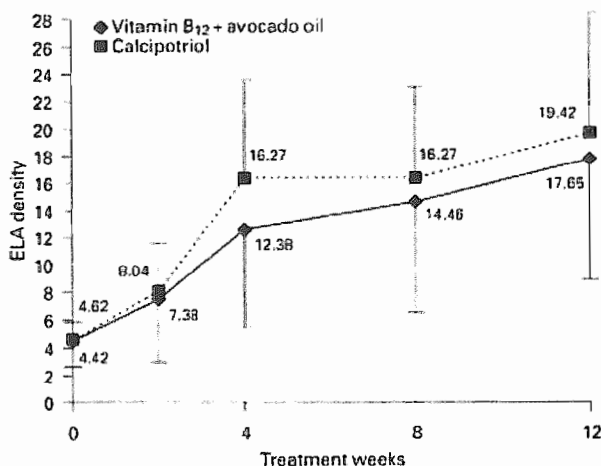


Fig. 5. 20-MHz sonography of a reference plaque: density of the echolucent area (ELA, AU). In week 4, there was a significantly greater density for calcipotriol therapy in comparison with vitamin B₁₂ cream containing avocado oil ($p < 0.05$). At all other measuring time points and on completion of therapy (therapy week 12; $p = 0.106$), there were no significant differences in the density of the echolucent area. The figure shows the mean values and the standard deviation before treatment as well as 4, 8 and 12 weeks after the beginning of the treatment.

Discussion

Psoriasis is one of the most frequently occurring skin diseases, with a prevalence of 1–3%. Although this inflammatory dermatosis seldom becomes life threatening, it is commonly perceived as a major disorder on a level with myocardial infarction and cancer [12]. To date, no causal therapy of psoriasis has been developed. A multi-causal pathomechanism is postulated which principally involves, in addition to hereditary predisposition, a ten-fold increase in epidermopoiesis and inflammatory-immunological factors [13]. The topical and systemic anti-psoriatics interfere with this pathomechanism.

The mechanism of action of calcipotriol is attributable to its antiproliferative effects on keratinocytes [14, 15]. Holland et al. [16] report a reduction of epidermal hyperproliferation and a return to normal keratinocyte turnover rates after a 10-week course of topical therapy with vitamin D₃ analogs. The range of potential undesirable effects associated with this class of medicaments includes skin irritation and inflammation [1] and, in rare cases, hypercalcemia. It is therefore recommended that calcipotriol should not be applied to more than 30% of body surface area and should not be used for longer than 12 months.

In this prospective clinical trial, the efficacy of a recently developed topical vitamin B₁₂ preparation containing avocado oil was compared with that of the topical vitamin D₃ analog (Regividerm vs. Psoreutan ointment). Vitamin B₁₂ modifies nucleic acid synthesis, particularly during hematopoiesis and other cell maturation processes, but cannot be endogenously produced in the human body. At present, generally accepted therapeutic indications for vitamin B₁₂ are restricted to the prevention and treatment of complications arising from vitamin B₁₂ deficiency, such as hyperchromic macrocytic anemia and funicular myelosis [7]. There are individual case reports in which good efficacy in psoriasis is described for systemically administered vitamin B₁₂ preparations [5, 6]. Other research groups have been unable to confirm beneficial effects of systemically administered vitamin B₁₂ in the therapy of psoriasis [17, 18]. It should be borne in mind that due to pharmacokinetic characteristics the bioavailability of systemically administered vitamin B₁₂ is poor. However, the results of our clinical trial demonstrate that topically applied vitamin B₁₂ with avocado oil is effective in the treatment of psoriasis. The data on the amount of vitamin in avocado oil are contradictory. However, it is generally agreed that the main part is vitamin E (α -tocopherol), whereas vitamin A is not found at all or, like vitamin D, only in a very small amount [19–22]. Furthermore, it must be considered that the therapeutic potency of retinoids and vitamin D₃ analogs is considerably higher than that of the vitamins from which they are derived, except for calcipotriol. Since the contents of vitamin A and D were below the provable limit in our trial preparation, the therapeutic effect of avocado oil on psoriasis can be considered as marginal or not demonstrable. Avocado oil was used in some cases for treatment of atopic dermatitis and was seen as less potent than evening primrose oil regarding its efficacy. In the literature, no reference can be found on the use of avocado oil as popular scientific therapy for psoriasis. On the contrary, the use of fish oil as monotherapy for psoriasis was more thoroughly investigated and a low therapeutic effect could be proven, which could be based on an effect on the 5-lipoxygenase metabolism pathway as well as on a reduction of the leucotriene B₄ formation. For avocado oil, these effects have never been discussed or examined, since fatty acids, which are responsible for these action mechanisms, are not found in vegetable oils. The interaction of avocado oil with connective tissue metabolism was described, showing an anti-inflammatory effect by a catabolic activity on collagen [23, 24].

After a 12-week course of therapy, there were no significant differences in treatment effect of calcipotriol and the

vitamin B₁₂ cream containing avocado oil. Neither the clinical evaluation on the basis of the PASI score nor sonographic analysis showed differences in the effects of therapy.

More recent research has demonstrated an immunomodulatory effect of vitamin B₁₂ in vitro. Immunomodulatory effects on T lymphocyte subpopulations have been demonstrated, such as increased induction of T suppressor cells [25]. When this trial was extended to include 27 patients with rheumatoid arthritis, there was a significant reduction in the use of nonsteroidal anti-inflammatory drugs and prednisolone with concomitant oral administration of 1,500 µg vitamin B₁₂ [25]. Another group reports dose-dependent in vitro suppression of interleukin 6 and interferon γ in the presence of vitamin B₁₂ [26]. At present, there are no adequate qualified data on the mode of action and the efficacy of vitamin B₁₂ in vivo.

In our prospective clinical trial, we were able to demonstrate the efficacy of topically applied vitamin B₁₂ with avocado oil in the therapy of psoriasis. There were no sig-

nificant differences in efficacy compared to that of the reference preparation calcipotriol. It is of interest that, after 4 weeks of therapy, there was a marked diminution of the efficacy of calcipotriol while the frequency and severity of skin irritation increased, whereas the efficacy of the vitamin B₁₂ cream containing avocado oil remained largely constant over the whole observation period. It can therefore be proposed that the vitamin B₁₂ cream containing avocado oil may be suitable for use in the long-term therapy of psoriasis. In follow-up trials, we intend to further evaluate the efficacy of vitamin B₁₂ with avocado oil in the treatment of psoriasis as the in vitro results as well as these initial in vivo results proved to be very promising.

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