

Superiority of a vitamin B₁₂-containing emollient compared to a standard emollient in the maintenance treatment of mild-to-moderate plaque psoriasis

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Abstract

Psoriasis is a chronic inflammatory skin disease affecting 2%–3% of the population. The wide range of drugs currently available for its treatment could be associated, in the long term, with organ toxicity and adverse events, thus, clinical monitoring throughout treatment is required. This investigator-initiated trial (IIT) evaluated the efficacy and the safety of a vitamin B₁₂-containing ointment in comparison with glycerol-petrolatum-based emollient cream used twice a day to treat mild-to-moderate plaque psoriasis for a period over 12 weeks followed by a wash-out observation period of 4 weeks. This study was conducted as a randomized, controlled, single-blind, intra-patient left- to right-side trial comparing the efficacy and safety of vitamin B₁₂-containing ointment (M-treatment) with a glycerol-petrolatum-based emollient cream (C-treatment). The Psoriasis Area Severity Index (PASI) was determined at baseline (T0), at time points T2 (14 days), T4 (4 weeks), T8 (8 weeks), T12 (12 weeks) and 4 weeks after the end of the wash-out period (F1). In total, 24 patients with plaque psoriasis were randomized to receive left- or right-side treatment with B₁₂ ointment. From time point T2 to time point F1, there was a statistically significant difference in PASI reduction between M-treatment side and C-treatment side. At time point T12, the difference between the mean reductions from baseline PASI scores by 5.92 ± 2.49 (87, 6%) in the M-treatment side versus 1.08 ± 1.02 (23, 1%) C-treatment side was statistically highly significant ($P_{Wex} < 0.001$). On the contemporary panorama in the treatment of psoriasis, we conclude that vitamin B₁₂ ointment will represent a new concrete therapy option and should be considered in the update of therapeutic algorithm for the treatment of psoriasis

Keywords

hydration, psoriasis, vitamin B₁₂

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Introduction

The proinflammatory cytokines involved in psoriasis stimulate the expression of inducible nitric oxide synthase (iNOS) in keratinocytes and other cell types.¹ High levels of iNOS have been detected in psoriatic lesions and in skin affected by atopic dermatitis,^{2,3} and are shown to be associated with a greatly increased release of nitric oxide (NO). NO

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has been found to be implicated in the pathogenesis of atopic eczema and psoriasis.⁴

Nowadays, a huge number of drugs are available to treat psoriasis and topical agents are the first-line therapy for patients with mild psoriasis.⁵ But despite the large number of topical formulations available, patients with psoriasis are often dissatisfied with their treatments.⁶ On this aspect, topical vitamin B₁₂ emollient may represent a safe alternative to the currently available topical therapies. Cobinamide, a cobalamin (vitamin B₁₂) precursor that binds NO with high affinity, showed a potent action as a NO-scavenger in biologic systems.^{7,8} Since it was previously shown that the experimental application of a NO synthase inhibitor lead to a clear decrease in *pruritus* and *erythema* in atopic dermatitis,⁹ it would be reasonable to assume a comparable effect of vitamin B₁₂ and therefore its use as a valid therapy for inflammatory skin diseases.

Systemic administration of vitamin B₁₂ has been reported to decrease the immunological factors responsible for skin inflammation and cell proliferation, producing a significant improvement of symptoms and positive impact on psoriatic patients. Since the important renal excretion (nearly 90%) after parenteral administration, vitamin B₁₂ requires high blood concentrations to reach peripheral targets which can be associated with toxicity.¹⁰ To avoid the possible concentration-related adverse events (AEs), cutaneous application was recently considered the most appropriate way of administration by Stucker et al.¹¹

The aim of this study was to measure the efficacy of a new topical treatment containing vitamin B₁₂ (Mavena® B₁₂ ointment) in patients suffering from plaque psoriasis. In addition, we evaluated the therapeutic responses and the effects of maintenance treatment thereof in a prospective, intra-individual, right versus left clinical trial, comparing topical vitamin B₁₂ ointment with a basic moisturizing emollient cream (Cetaphil®).

Materials and methods

Patient selection

Adult patients of both sexes with a confirmed clinical diagnosis of mild-to-moderate plaque psoriasis based on Psoriasis Area Severity Index (PASI) scores were eligible for the study. The intra-individual

difference between the left and right hemi-body PASI scores had to be not more than 1.0.

Main exclusion criteria were the presence of other forms of psoriasis than psoriasis vulgaris, that is, palmoplantar psoriasis, inverse psoriasis, other form of hyperkeratosis, use of systemic/biological treatment and known hypersensitivity or allergy to any of the study products, any serious current medical condition that could interfere with the evaluation of the study results, patients assessed by the investigator to have poor compliance, enrolled in any other investigational study. Patients, who were pregnant, breastfeeding, or planning to become pregnant during the study time, were also excluded. All subjects gave informed, signed consent to participate in the study.

Study products

The vitamin B₁₂ ointment (Mavena® B₁₂ ointment), containing 0.07% cyanocobalamin in a w/o formulation with 20% avocado oil, polyunsaturated fatty acids and natural moisturizing factors (NMF), is a EU-wide registered topical substance-based medical device (Mavena Health Care Italia srl, Milan, Italy).

The comparative product was the cosmetic formulation Cetaphil®, a glycerol-petrolatum-based hydrating cream (Galderma, La Defence, France).

Study design

The study was conducted as a randomized, controlled, single-blind, intra-patient left-to right comparison. The optimal sample size of this study was determined based on previous publications on this topic/subject/ matter. The enrolled patients neither applied any other topical treatment nor underwent systemic or physical therapies. A total of 24 patients suffering from mild-to-moderate psoriasis patients were planned to be enrolled. Patients were selected based on clinical data and were informed about the study procedure verbally and with written information by the investigator. Patients have been enrolled after consent according to inclusion and exclusion criteria. During the 12-week treatment phase, each patient applied the vitamin B₁₂ ointment (M-treatment) twice daily (in the morning and in the evening) to the affected skin areas of one randomly assigned hemi-body (M-treatment side) and the comparative product (C-treatment) twice daily

(in the morning and in the evening) to the contralateral hemi-body (C-treatment side).

The patients were seen in the outpatient department at the start of treatment (T0), after 2 weeks (T1), 4 weeks (T4), 8 weeks (T8) and 12 weeks (T12). Treatment was discontinued after 12 weeks of treatment, and all patients were referred again after 4 weeks of wash-out phase (F1). PASI was determined at baseline (T0) and at each time point during treatment and after 4 weeks of discontinuation.

At each study visit (baseline, weeks 2, 4, 8, 12 and 4 weeks after the end of the wash-out period), the changes in PASI and patients' satisfaction was assessed. The investigators determined modification of psoriatic plaque extension by direct evaluation of the skin's condition (PASI score) and through subject interview (stinging/burning and pruritus). The subject determined his or her overall preference by direct evaluation of erythema, dryness, scaling, stinging/burning and pruritus. AEs were monitored throughout the study. The local signs and symptoms were qualified as AEs only in cases the investigator judged them as an unexpected, allergic or irritant reaction or the subject had requested discontinuation of the study.

The study was approved by the institutional review board of University of Catanzaro, and the investigation was conducted in accordance with the Declaration of Helsinki (experimentation register no. 48/15 Of 8/10/2015).

Efficacy endpoints

The primary efficacy endpoint of the study was the assessment of improvement in PASI scores occurring in the M-treatment side in comparison with that in the C-treatment side.

Secondary efficacy endpoints were time to relapse, evaluated at the time F1 (first follow-up in the wash-out phase 4 weeks after the end of treatment) and quality of life (QoL). Patient's QoL was assessed at time points T0 to T12 by evaluation of local tolerance of treatment and by reduction of pruritus by means of visual analogue scale (pVAS rating from 0, no; 1–3, mild; 4–6, moderate; and 7–10, severe disorder).

Safety

Safety was assessed by recording occurred AEs at all visits. Relapse was defined as an experience of

a return of disease, requiring an increase in the treated skin areas. The patients were instructed to contact immediately the investigator if any psoriatic lesion relapsed or if any new plaque appeared on the body. The investigator estimated the skin area as a relapse of psoriatic lesions or if it was a new plaque.

Statistical methods

All variables received an explorative examination and were descriptively assessed. The statistical characteristics number, mean, standard deviation, extremes and quartiles were calculated.

The comparisons of score values were performed primarily using non-parametric procedures: Mann–Whitney U-test (for independent samples) and Wilcoxon test (for dependent samples) based on rank sums. Parametric procedures (t-tests) supplemented the analysis based on mean and standard deviation. The analysis of correlation was performed referred to Pearson.

Results

A total of 24 patients between 21 and 75 years, mean (\pm SD) age = 48.2 ± 15.4 years, were enrolled in the study. There were 13 males (54.2%) and 11 females (45.8%). Mean (\pm SD) PASI scores were 6.54 (± 1.98) and 7.27 (± 2.87) for males and females, respectively. There were no statistically significant differences in PASI between male and female patients at T0 ($P_{Uex} = 0.498$).

At baseline (T0), there was no significant difference between the two treatment sides, and the mean PASI score for M-treatment side was 6.88 ± 2.40 and 6.83 ± 2.37 for the C-treatment side ($P_{Uex} = 0.208$) (Table 1).

There was no statistically significant correlation between the baseline value of PASI and age ($P_{pears} = 0.229$). No statistically significant differences in PASI were observed between patients below 50 years and patients older than 50 years (7.58 ± 2.88 and 6.17 ± 1.64 ; $P_{Uex} = 0.208$).

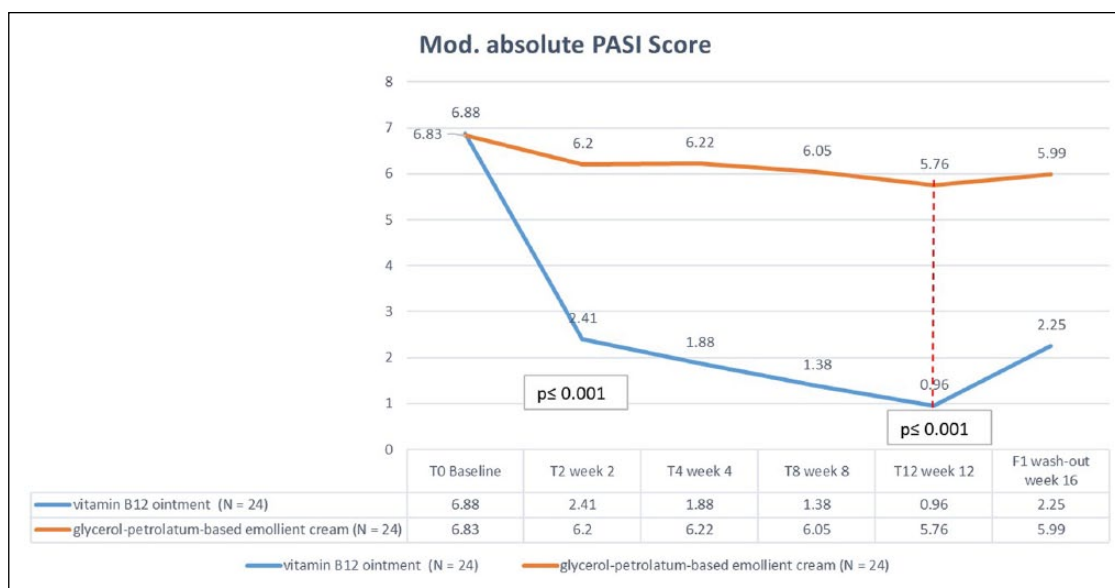
Treatment period

After 14 days of treatment at T2, there was a significant decrease in PASI scores in the M-treated body side, whereas only a small decrease in PASI scores was observed in the C-treated body side.

Table 1. Absolute PASI score based on the M-treatment compared to the C-treatment at respective time of assessment.

Treatment week	M-treatment (N = 24)		C-treatment (N = 24)		Statistical significance $P_{Wex-(pt-)}$ value
	Mean	SD	Mean	SD	
T0, baseline	6.88	2.40	6.83	2.37	0.208
T2, week 2	2.41	1.15	6.20	2.22	<0.001
T4, week 4	1.88	0.97	6.22	2.11	<0.001
T8, week 8	1.38	0.75	6.05	2.13	<0.001
T12, week 12	0.96	0.8	5.76	2.04	<0.001
F1, wash-out week 16	2.25	0.94	5.99	1.94	<0.001

PASI: Psoriasis Area Severity Index; SD: standard deviation.

**Figure 1.** Absolute PASI over the time course of the study (mean/SD).

The mean PASI score decreased by 4.47 ± 2.13 in the M-treated body side and by 0.62 ± 0.77 in the C-treated body side, the difference was statistically highly significant ($P_{Wex} < 0.001$).

Moreover, the decrease in PASI score was observed in all M-treated body side (100%), whereas only 14 C-treated treated body side (58.2%) showed a slight reduction in PASI scores (Figure 1).

At T4, the mean PASI scores of patients were further decreased for both treated body sides; however, all PASI scores in the M-treated body side were still significantly lower than the ones observed in C-treated body side, with mean PASI scores of 1.88 ± 0.97 for M-treated body side compared to 6.22 ± 2.11 with the C-treated body side. The difference was statistically highly significant ($P_{Wex} < 0.001$).

At T8 and T12, all PASI score values of the M-treated body side were still lower than the ones observed in C-treated body side. The mean PASI

scores slightly further decreased for both treated body sides, reaching values at T12 of 0.96 ± 0.86 for the M-treated body side and 5.75 ± 2.03 for the C-treated body side (Figure 1).

Observation after discontinuation

At F1, 4 weeks after discontinuation of treatments, in 23 cases, score values of PASI in the M-treated body side were still lower than the score values observed in C-treated body side. The mean PASI scores of patients increased in both body sides after discontinuation of both treatments with scores of 2.25 ± 0.94 in the M-treated body side and 5.99 ± 1.94 in the C-treated body side. Relapse measured with the mean PASI scores of patients was significantly lower in the M-treated body side compared to the C-treated body side after discontinuation of the treatment (Figure 1).

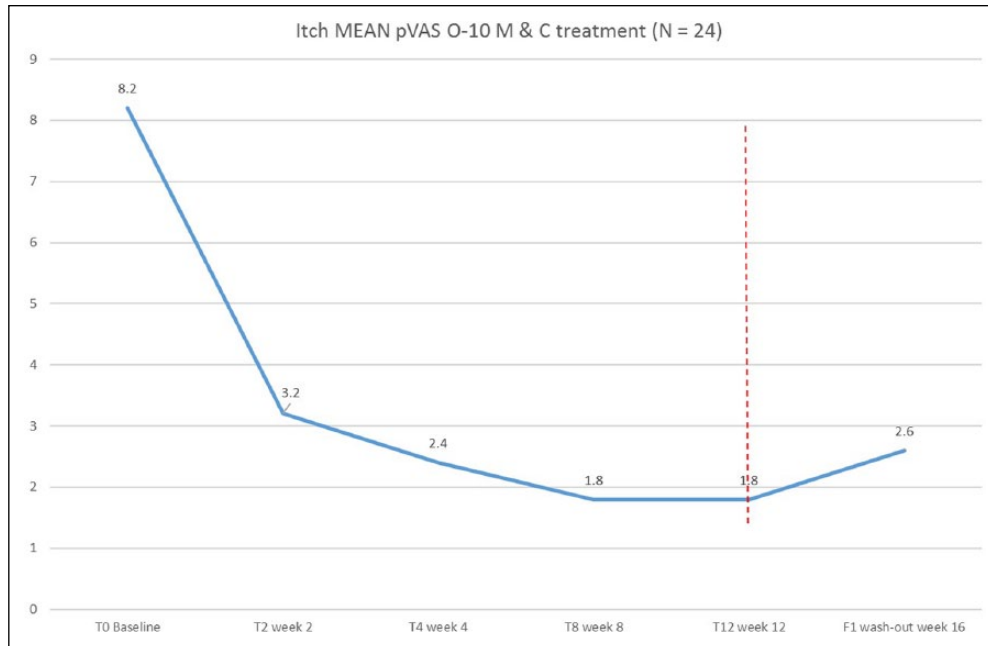


Figure 2. Itch and tolerability variation over the time course of the study.

Secondary endpoints: itch and tolerability

Reduction of itching and high level of tolerability were used to assess the QoL improvement in patient's daily life. Data showed a highly significant reduction in itching and erythema in the M- and C- treated body sides, with a high tolerability. Itch was measured through the pVAS and was evaluated without differentiation within the treatment sides for each time-point of the study (from T0 to F1). Tolerability was measured from T2 to F1 and was evaluated without differentiation within the treatment sides (Figure 2).

Discussion

Our findings show the efficacy of B₁₂ in reducing total PASI score and significant superiority compared to glycerol and petrolatum-based emollient cream in the treatment of mild-to-moderate plaque psoriasis over 16 weeks. The comparison of M- and C-treatments over the time course of the study shows that there were statistically significant differences in PASI between the M-treatment and the C-treatment sides at all time-points from T2 to F1 (each with $P_{Wex} < 0.001$). The mean score of PASI on the M-treated body side decreased by 15% (mean) and 8% (median), while no score value was below 50% on the C-treatment.

Reduction of itching and high level of tolerability were achieved in the M- and C-treated body

sides and a great benefit was shown in erythema, pruritus and tolerability (Figure 2). No differentiation on itching as symptom and general tolerability was done within the intra-patient left- to right-side treatment area. Itching and general tolerability were measured for all patients together. Previous studies with topical emollients solely showed a slight improvement of some symptoms as pruritus and improvement on the skin barrier in psoriasis. B₁₂-based ointment seems to reduce rapidly the PASI score having also an anti-inflammatory effect on psoriatic patients.

In this study, the PASI score to assess the efficacy and tolerability of a B₁₂-based ointment was used. A significant improvement was observed after already 2 weeks of treatment using vitamin B₁₂ topical applications two times a day, while only a maintenance of PASI levels was achieved in the patient treated body side with a glycerol-petrolatum-based emollient cream. All patients referred an improvement in clinical symptoms and decrease in itching; these data have been measured through pVAS. Our results confirm the already demonstrated positive effect of vitamin B₁₂,^{12,13} demonstrating furthermore the reduction in extension and severity of psoriasis and atopic dermatitis with the B₁₂ topical treatment. In addition to the immunomodulatory effect, vitamin B₁₂ ointment reestablish the needed level on psoriatic skin, thus, patients affected from psoriatic are frequently affected by

vitamin B₁₂ deficiency. In conclusion, vitamin B₁₂ ointment can be considered as a valid therapeutic option to anti-inflammatory topical agents available for psoriasis treatments and can be used in the treatment of mild-to-moderate psoriasis. The application of vitamin B₁₂ ointment can be especially considered for sensitive and problematic skin areas (i.e. popliteal area, cubital flexures and armpits). On the contemporary panorama in the treatment of psoriasis, we conclude that vitamin B₁₂ ointment will represent a new concrete therapy option and should be considered in the update of therapeutic algorithm for the treatment of psoriasis.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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References

1. Bowcock AM and Kreuger JG (2005) Getting under the skin: The immunogenetics of psoriasis. *Nature Reviews Immunology* 5: 699–711.
2. Yamashiki M, Nishimura A and Kosaka Y (1992) Effects of methyl-B12 on in vitro cytokine production of peripheral blood mononuclear cells. *Journal of Clinical & Laboratory Immunology* 37: 173–182.
3. Sirsjö A, Karlsson M, Gidlöf A, et al. (1996) Increased expression of inducible nitric oxide synthase in psoriatic skin and cytokine-stimulated cultured keratinocytes. *British Journal of Dermatology* 134: 643–648.
4. Rowe A, Farrel AM and Bunker CB (1997) Constitutive endothelial and inducible nitric oxide synthase in inflammatory dermatoses. *British Journal of Dermatology* 136: 18–23.
5. Linden KG and Weinstein GD (1999) Psoriasis: Current perspectives with an emphasis on treatment. *American Journal of Medicine* 107: 595–605.
6. Korman N, Zhao Y, Lu J, et al. (2015) Psoriasis disease severity affects patient satisfaction with treatment. *Dermatology Online Journal* July 15; 21(7): pii:13030/qt69h903m6.
7. Ormerod AD, Weller R, Copeland P, et al. (1998) Detection of nitric oxide and nitric oxide synthase in psoriasis. *Archives of Dermatological Research* 290: 3–8.
8. Baker H and Comaish JS (1962) Is vitamin B12 of value in psoriasis? *BMJ* 2: 1729–1730.
9. Stücker M, Pieck C, Stoerb C, et al. (2004) Topical vitamin B12, a new therapeutic approach in atopic dermatitis-evaluation of efficacy and tolerability in a randomized placebo-controlled multicentre clinical trial. *British Journal of Dermatology* 150: 977–983.
10. Stankler L (1969) The vitamin B12 level in psoriatic skin and serum. *British Journal of Dermatology* 81: 911–918.
11. Stucker M, Memmel U, Hoffmann M, et al. (2001) Vitamin B12 cream containing avocado oil in the therapy of plaque psoriasis. *Dermatology* 203: 141–147.
12. Ruedemann R Jr (1954) Treatment of psoriasis with large doses of vitamin B12 1,100 micrograms per cubic centimeter; preliminary clinical report. *AMA Archives of Dermatology and Syphilology* 69: 738–739.
13. Cohen EL (1958) Some new treatments for psoriasis. *Practitioner* 181: 618–620.