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Therapeutics

Topical vitamin B_{12}—a new therapeutic approach in atopic dermatitis—evaluation of efficacy and tolerability in a randomized placebo-controlled multicentre clinical trial

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Summary

Background Vitamin B_{12} is an effective scavenger of nitric oxide (NO). As the experimental application of a NO synthase inhibitor, Nω-nitro-L-arginine, led to a clear decrease in pruritus and erythema in atopic dermatitis, it would be reasonable to assume a comparable effect of vitamin B_{12}.

Objectives The efficacy and tolerability of a new vitamin B_{12} cream as a possible alternative to current therapies was examined.

Methods A prospective, randomized and placebo-controlled phase III multicentre trial, involving 49 patients was conducted. For the treatment duration of 8 weeks, each patient applied twice daily (in the morning and evening) the vitamin B_{12}-containing active preparation to the affected skin areas of one side of the body and the placebo preparation to the contralateral side according to the randomization scheme.

Results On the body side treated with the vitamin B_{12} cream, the modified Six Area Six Sign Atopic Dermatitis score dropped to a significantly greater extent than on the placebo-treated body side (for the investigational drug 55·34 ± 5·74 SEM, for placebo 28·87 ± 4·86 SEM, $P < 0{\cdot}001$). At the conclusion of the study, the investigator and patients awarded mostly a 'good' or 'very good' rating to the active drug (58% and 59%, respectively) and a 'moderate' or 'poor' rating to the placebo (89% and 87%, respectively).

Conclusions Topical vitamin B_{12} is a new therapeutic approach in atopic dermatitis. These results document a significant superiority of vitamin B_{12} cream in comparison with placebo with regard to the reduction of the extent and severity of atopic dermatitis. Furthermore, the treatment was very well tolerated and involved only very low safety risks for the patients.

Key words: atopic dermatitis, inducible nitric oxide synthase, nitric oxide, vitamin B_{12}

The inflammatory events of atopic eczema appear to be initiated by activated T lymphocytes present in peripheral blood and in the skin by increasing the production of inflammatory cytokines such as interleukin (IL)-1α, IL-2, IL-6 and interferon (IFN)-γ. Vitamin B_{12} (cyanocobalamin, molecular weight: 1355·4) was able to suppress the cytokine production of T lymphocytes *in vitro* (methyl-cyanocobalamin 80–8000 ng mL^{-1}).[1]

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The formation of IL-6, IFN-γ and IL-1β was induced *in vitro* by various mitogens (phytohaemagglutinin, concanavalin A). For example, methyl-cyanocobalamin inhibited the synthesis of IL-6 induced by phytohaemagglutinin or concanavalin by 60–70%. Methyl-cyanocobalamin could modulate lymphocyte function through augmenting regulatory T-cell activities.[2,3] Methyl-cyanocobalamin (0·1–10 μg mL^{-1}) enhanced cellular proliferation as well as the activity of T-helper (Th) cells for immunoglobulin synthesis of B cells by pokeweed mitogen. Furthermore, the presence

of methyl-cyanocobalamin significantly potentiated the induction of suppressor cells in concanavalin A-activated cultures. The inhibition of cytokine production could explain the therapeutic success of vitamin B_{12} in the treatment of atopic dermatitis.[4]

Inflammatory cytokines stimulate the expression of inducible nitric oxide synthase (iNOS) in keratinocytes and other cell types.[5] High levels of iNOS have been detected in psoriatic lesions and in skin affected by atopic dermatitis,[6,7] and are shown to be associated with a greatly increased release of nitric oxide (NO). An excess of NO production by dermal endothelial cells, infiltrating cells, keratinocytes or Langerhans cells, mainly arises from iNOS activity. Therefore, NO has been found to be implicated in the pathogenesis of atopic eczema and psoriasis.[5,7]

NO is able to modulate cultured keratinocyte proliferation, as incubation of keratinocytes with 0·5 mmol L^{-1} of the sodium nitroprusside (NO donor) resulted in an increase in keratinocyte proliferation by 200%.[8] Therefore, NO stimulates vasodilatation and subsequently erythema and oedema, but is also important in other aspects of the inflammatory and immune responses, such as T-lymphocyte function as well as cell proliferation and differentiation.[6]

A feeling of irritation on the skin causing a desire to scratch (itching or pruritus) is the most constant and most distressing symptom in atopic dermatitis.[9] An explanation for this effect would be the detection of iNOS in skin with atopic dermatitis compared with normal skin where iNOS is absent.[6] Inflammatory cytokines induce iNOS. iNOS activity causes an excess of NO production by dermal endothelial cells or infiltrating cells, arising from iNOS activity, which stimulates vasodilatation and subsequent erythema and oedema, and could also be important in other aspects of the inflammatory and immune responses, such as regulating Th1 cell population expansion and Th1-mediated immune responses.[6]

Atopic dermatitis is associated with an increase in cytokine formation and NO generation due to overexpression of iNOS,[6] leading to provable raised nitrate levels even in the serum.[10] As the experimental application of Nω-nitro-L-arginine, a NO synthase inhibitor, led to a clear decrease in pruritus and erythema in 15 atopic dermatitis patients compared with placebo,[11] it would be reasonable to assume, together with the cited *in vitro* experiments, a comparable effect of vitamin B_{12}. Results from *in vivo* investigations to confirm these assumptions for topical vitamin B_{12} in the therapy of atopic dermatitis and other inflammatory skin disorders are not yet available.

Pure vitamin B_{12} is a crystalline powder, dark red and odourless, used for therapeutic purposes in the form of cyanocobalamin and/or hydroxocobalamin acetate. It is only in the organism that these 'prodrugs' are converted into the active forms of methyl- and 5-adenosylcobalamin. Vitamin B_{12} has a wide therapeutic range, because toxic effects or signs of overdosage, as well as indications of a teratogenic or mutagenic potential, have not been reported. Part of vitamin B_{12} is secreted into the gastrointestinal tract via the bile, and undergoes enterohepatic circulation. Re-absorption will only be possible in the presence of intrinsic factor and healthy ileal mucosa cells. Tissue uptake, storage and utilization depend on the availability of transcobalamin.[12] When vitamin B_{12} is administered in doses that saturate the binding capacity of plasma proteins and the liver, unbound vitamin B_{12} is rapidly eliminated in the urine. Thus, excessive doses will not result in greater retention of the vitamin.[12] For the topical application, it was demonstrated that, despite the size of the molecule, the skin is permeable to vitamin B_{12}.[13]

However, in view of the poor systemic bioavailability of vitamin B_{12} (rapid elimination of up to 90% of a single dose of 1 mg), systemic administration of vitamin B_{12}, e.g. in psoriasis, appears to produce no evidence of a reliable therapeutic effect.[14–16] Therefore in this study, the efficacy of a topically applied vitamin B_{12} cream in atopic dermatitis was investigated compared with the cream base without vitamin B_{12}.

To this end, the efficacy was assessed by the physician and patients, and the tolerability of the preparation was investigated in comparison with the placebo cream base.

Patients and methods

Study design

The study was conducted as a multicentre (Bochum and Potsdam, Germany), placebo-controlled, double-blind, prospective, randomized phase III clinical trial with intraindividual left/right comparison.

Sample size was determined by using unpublished data from earlier studies. A total of 48 patients were to be included in the study at both trial centres, Bochum and Potsdam. In view of the different capacities, the trial centre Bochum was to include 40 patients and the trial centre Potsdam eight patients.

The patients answered, by telephone, an advertisement in a daily paper. If suitability for the study was recognizable on the occasion of this telephone conversation, an appointment was arranged with the patients in the respective trial centre where they were informed about the study, verbally and in writing, by the investigator. If patients agreed to participate in the study and signed the informed consent form after a period of reflection of at least 1 day, they were enrolled in the study following verification of the inclusion and exclusion criteria. The random allocation sequence was generated by the software SASRAND (blocking with four patients) [Version 6·2 of SAS (Statistical Analysis System); SAS Institute, Cary, NC, U.S.A.].

Numbered containers were used to implement the random allocation sequence in each centre.

During the 8-week treatment phase, each patient applied the vitamin B_{12}-containing active preparation twice daily (in the morning and evening) to the affected skin areas of one side of the body and the placebo preparation to the contralateral side, according to the randomization scheme. The time of recruitment was February and March 2001. Patient compliance was estimated by measuring the amount of unused cream returned to the study centres, against the background of the severity and the extent of the individual clinical picture.

Subjects

Subjects included were male and female between 18 and 70 years, suffering from atopic dermatitis for at least 2 years. All patients exhibited at least three of the four major criteria according to Hanifin and Rajka (pruritus, typical morphology and distribution of the changes, chronic recurring course, personal or family history of atopic disease). Exclusion criteria are given in Table 1. All patients had to give written informed consent. All patients exhibited chronic but not acute inflammatory atopic dermatitis without superinfection.

Table 1. Exclusion criteria

Topical treatment with corticosteroids in the last 4 weeks prior to inclusion in the trial superinfection
Systemic treatment with corticosteroids or ciclosporin and photopheresis treatment in the last 4 weeks prior to inclusion in the trial
Ultraviolet irradiation in the last 2 weeks prior to inclusion in the trial
Participation in another drug trial in the last 3 months prior to inclusion in the trial
Known vitamin B_{12} allergy
Known allergy to one of the excipients
Pregnancy or lactation
Strong psychosomatic superimposition
Suspected poor compliance of the patient
Other topical treatment of the test areas (arms/legs), which cannot be dispensed with during the trial period
Atopic dermatitis involvement only outside the test areas
Patient's legal incompetence according to § 104 BGB (Federal Law Gazette)

Assessments

At the beginning and 2, 4, 6 and 8 weeks after the start of the trial the following parameters were determined:

- modified Six Area Six Sign Atopic Dermatitis (SASSAD) score
- investigator's assessment of the efficacy of the trial preparations separately for each body side
- patient's assessment of the efficacy of the trial preparations separately for each body side
- assessment of the tolerability of the trial medication separately for each body side.

For every patient the same physician always did the scoring. The primary efficacy variable was the placebo-corrected treatment effect of the vitamin B_{12}-containing preparation, determined by means of the modified SASSAD score. The following procedure was used to determine this value: the treatment effects for each body side were calculated by subtracting the SASSAD score at the end of treatment from the baseline SASSAD score (adjusting for baseline). To determine the efficacy of the vitamin B_{12} cream, the treatment effect of the placebo, calculated in this way, was subtracted from the treatment effect of the investigational drug; the difference yielded the placebo-corrected effect.

Modified Six Area Six Sign Atopic Dermatitis score

The modified SASSAD Score[9,17] used in this trial records the degree of severity of six different atopic dermatitis signs (dryness/desquamation, itching, erosion, lichenification, erythema, infiltration) using an ordinal scale (0 = not present to 4 = very severe). We added the size of the skin areas affected by these signs (0 = not affected, 1 = < 10%, 2 = 10–25%, 3 = 26–50%, 4 = 51–75%, 5 = 76–100%). A further modification of the original score consists of changing the sign 'exudation' to 'infiltration', because only patients suffering from chronic atopic dermatitis without exudation were included.[18] The degree of severity of the sign multiplied by the respective scale value of the affected skin area yields the individual sign score. When using the SASSAD score, evaluation is carried

out by adding the individual score of each sign to the score of one skin area (arm/leg) and by adding the scores of the skin areas to the total score of one side of the body. The maximum possible range of the modified SASSAD score was 0–240 per body half. All assessments per patient were conducted by the same investigator. The possibility of a small interinvestigator variability was minimized with the aid of investigator training prior to the initiation of the study.

Treatment

The vitamin B_{12}-containing cream, with the concentration of the active substance being 0·07% cyanocobalamin DAB, contained the following excipients: avocado oil DAC, distilled water, methyl glucose sesquistearate INCI, potassium sorbate DAB and citric acid DAB (Regividerm® cream; Regeneratio Pharma AG, Wuppertal, Germany). The placebo cream contained the colouring agent E122 azurubin. The appearance, feel and smell of the active medication was indistinguishable from that of placebo. All study personnel and participants were thus blinded to treatment assignment for the duration of the study.

The specific concentration of 0·07% was used as the results of an earlier dose-finding trial showed that 0·07% was found to be more efficacious than 0·05%, but higher concentrations did not yield additional treatment effects (not published). Avocado oil is used to improve the pharmaceutical properties of the formulation so that the vitamin B_{12} cream can be distributed more easily on the surface of the skin.[19]

All the patients were treated twice daily over a period of 8 weeks, the amount of cream depended on the extent of the affected skin areas and the severity of signs and symptoms. A ribbon of cream of approximately 2 cm in length was recommended for an area of roughly the size of the palm.

Statistics

The statistical evaluation of the primary variables in the sense of a confirmatory proof of efficacy was performed using Wilcoxon's two-sided signed rank test for connected samples.[20,21] The two-sided significance level was set at $\alpha = 0{\cdot}05$. The sample size calculation was premised on a two-sided significance level of $\alpha = 5\%$ and a second type error of $\beta = 10\%$, i.e. a statistical power of 90%. The data of prematurely withdrawn subjects were generated by using repeated values according to the 'carry forward last value' principle.

The overall assessments of efficacy by the investigator and patients (secondary efficacy variables) were analysed using Bowker's symmetry test[21] with the *P*-values having a purely descriptive character. Owing to the low occupancy rate of the cells in the contingency tables, the results were no longer meaningful because of the poor fitting to the χ^2 distribution; for the evaluation the tables were therefore reduced to 2×2 tables by combining 'very good' and 'good' in 'effective' and 'moderate' and 'poor' in 'noneffective'.

The frequencies of the various assessments reported by the investigator and the patients were summarized in Table 2.

Ethical considerations

The study was conducted in accordance with the ICH Guideline for Good Clinical Practice for the clinical testing of drugs (CPMP/ICH/135/95), the Declaration of Helsinki (revised version of Edinburgh 2000) and current German drug law. The study was approved by the Independent Ethics Committees of the Landesärztekammer Brandenburg and of the Ruhr University Bochum.

Results

A total of 49 patients (30 women, 19 men, aged 33·6 ± 14·1 years) were assessed for participation in the study and all patients were randomly assigned to the treatment groups. The initial modified SASSAD score was 99·7 ± 36·6 (vitamin B_{12} cream, range from 10 to 186 on a scale of 0–240) and 95·7 ± 39·2 (placebo, range 8–186). The duration of disease was 21·1 ± 13·2 years (range 3–67 years). All of the 49 randomized patients applied the trial medication at least once. Forty-one patients concluded the trial according to the protocol. Eight patients discontinued the trial prematurely (Table 2).

Primary efficacy variable: Six Area Six Sign Atopic Dermatitis score

On the body side treated with the vitamin B_{12} cream, the modified SASSAD score dropped to a significantly greater extent than on the placebo-treated body side (vitamin B_{12} cream 55·34 with a SEM of 5·74, placebo 28·87 with a SEM of 4·86, $P < 0{\cdot}0002$) (Fig. 1). The treatment effect in the vitamin B_{12}-containing cream group was roughly double that of the placebo group.

Table 2. Summary of withdrawals

Reason	*n*	Details
Noncompliance	3	Two patients did not reappear at the centres One patient used nonpermitted concomitant medication
Deterioration of disease	3	After 2 days, after 7 days and in week 6
Adverse events	2	One patient experienced burning, itching and swelling One patient experienced redness and swelling

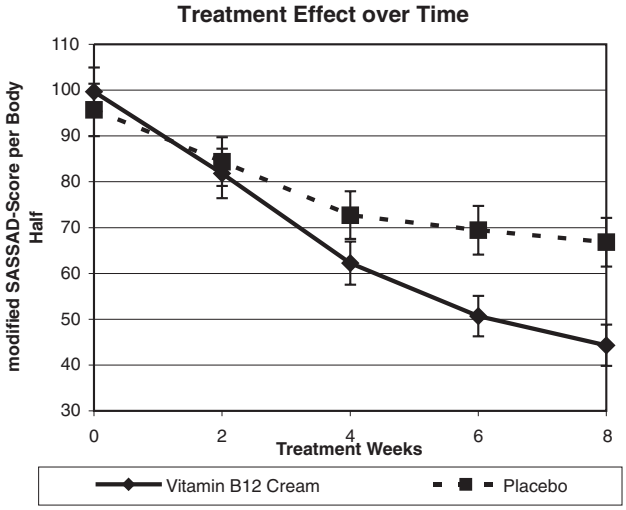

Figure 1. Treatment effect of vitamin B_{12} cream in atopic dermatitis. Significantly stronger drop in the Six Area Six Sign Atopic Dermatitis (SASSAD) value for vitamin B_{12} cream than for placebo (error bars = SEM, *$P < 0{\cdot}05$; week 2, $P < 0{\cdot}12$; week 4, $P < 0{\cdot}003$; week 6, $P < 0{\cdot}0002$; week 8, $P < 0{\cdot}0002$).

Investigator's and patient's assessment of the efficacy

After 8 weeks of treatment two patients (4%) reported a very good efficacy and a further 26 patients (55%) reported a good efficacy of the vitamin B_{12} cream. Fourteen patients (30%) assessed the efficacy as moderate and five patients (11%) as poor (Fig. 2).

The patients rated the efficacy of the placebo as less beneficial. One patient (2%) observed a very good efficacy; only five patients (11%) assessed the efficacy as being good, but 36 patients (76%) assessed the efficacy as being moderate and five patients (11%) as being poor.

The investigator reported a good efficacy for the body side treated with the investigational drug for 27 patients (58%), for 17 patients (36%) a moderate efficacy and for three patients (6%) a poor efficacy.

In the placebo group, the investigator did not observe a very good efficacy in any of the patients (0%). A good efficacy was recorded in five patients only (11%), moderate efficacy in 39 patients (83%) and poor efficacy in three patients (6%).

For the reduced contingency tables with the categories 'effective' and 'noneffective' the overall assessments of the efficacy by the investigators and by the patients show a highly significant superiority of the investigational drug in comparison with placebo ($P < 0{\cdot}005$).

In 26 cases, the patients as well as the investigator rated the treatment with the investigational drug as being superior to the placebo treatment. In five cases

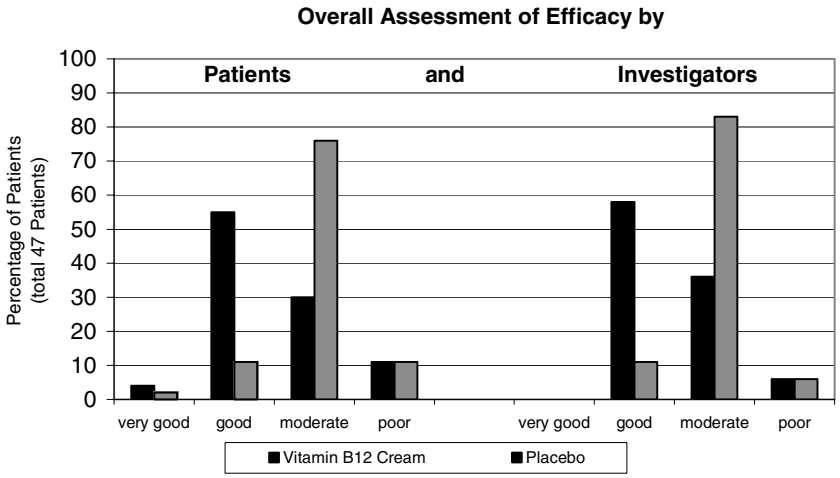

Figure 2. Patients' and investigators' assessments of the efficacy of the investigational drug and the placebo. The efficacy of the investigational drug was rated as 'good' by 55% of the patients and 58% of the investigators. The efficacy of the placebo was rated as 'moderate' by 76% of the patients and 83% of the investigators.

Table 3. Cutaneous adverse events

Adverse event	*n*
Acute phase of atopic dermatitis	8
Local skin irritations (itching, burning and redness)	23
Allergic rhinitis	1
Vesiculation on the wrist	1

only, the placebo treatment was rated as being superior to treatment with the investigational drug.

Adverse events

Altogether 33 cutaneous adverse events were recorded, and none of these was serious (Table 3). A further three noncutaneous adverse events were reported: one ambulatory arthroscopy of the knee, one acute bronchitis and one fracture of the radius. With the exception of one cutaneous adverse event (weeping, itching, limited neck mobility following application of the placebo cream, 'moderate' severity), all were of mild severity. In two cases a 'possible' and in four cases a 'probable' relationship with the trial medication was assumed for the skin irritations occurred only on the body side treated with vitamin B_{12} cream (burning in two patients, itching in two patients, redness in one and hyperthermia and formication in one patient). All adverse events were reversible within several days. No acneiform eruptions were reported.

Discussion

Efficacy

In this double-blind, placebo-controlled clinical trial, a continuously progressive beneficial treatment effect was observed throughout the treatment phase of 8 weeks. Therefore it can be postulated that a continuation of treatment beyond the treatment time of 8 weeks would result in a further alleviation of signs to the point of complete remission.

Vitamin B_{12} and acne

In animal studies it has been demonstrated that vitamin B_{12} is absorbed through healthy skin to a certain extent (approximately 7%).[13] To date there are no human data available on the absorption of topically applied vitamin B_{12}. Vitamin B_{12} taken orally has been reported to cause acneiform eruptions, but all these cases occurred after systemic application of vitamin B_{12} only.[22] Furthermore, it has sometimes been assumed that these acneiform skin changes were due to impurities caused by the production process of vitamin B_{12} and not the vitamin itself. All clinical trials conducted so far on the topical treatment with vitamin B_{12} did not reveal any such adverse events, even after treatment of the face.

Shortcomings of vitamin B_{12} therapy

The red colour of vitamin B_{12} also produces a red-coloured cream. This can at first be a little displeasing for the patient, but it was accepted well by the patients in this study because the cream was rapidly absorbed by the skin.

In the event of discolouring of clothing despite the rapid absorption of the cream, any stains were removed completely by washing at 30 °C.

Definition of fields of application of topical vitamin B_{12}

Based on the available trials, besides the therapy of chronic–stable psoriasis vulgaris,[23] the treatment of atopic dermatitis can be defined as a field of application of vitamin B_{12} cream.

Patients with easily irritable skin represent an important field of application of the well-tolerated, vitamin B_{12}-containing topical preparations. Furthermore, the active ingredient is available in a high-quality, at the same time skin-caring and low-allergenic cream base. This is particularly important in the treatment of atopic dermatitis. Furthermore, the preparation seems to be suitable for use in children. Even problematic skin areas like armpits, popliteal and cubital flexures can be an important field of application for vitamin B_{12} cream due to its nonirritancy.

Following treatment of an acute exacerbating atopic dermatitis with high-potency glucocorticosteroids, vitamin B_{12} cream could be used for follow-up treatment, in order to maintain the therapeutic success and prolong the relapse-free interval. Treatment combinations and comparison with other substances such as tacrolimus or pimecrolimus need further evaluation.

Acknowledgments

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