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CLINICAL REPORT

A Three-Year Randomized Trial in Patients with Dysplastic Naevi Treated with Oral Beta-carotene

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Ultraviolet irradiation provokes the development of new melanocytic naevi, or changes in existing naevi, leading to repeated surgery of atypical naevi and becoming a continual burden for individuals with many of these lesions. To determine the influence of long-term medication with the radical scavenger β-carotene on newly developing atypical naevi, a single-centre, randomized, placebo-controlled study, prospective over 3 years, was started double-blind in 62 patients with numerous clinically atypical naevi. Beta-carotene (25 mg) was given twice daily for 36 months in the treatment group ($n = 30$) and saccharose capsules as placebo in the control group ($n = 32$). The total number of newly developed naevi in the β-carotene group ($n = 18$) was 68 versus 88 in the placebo group ($n = 21$) (not significant). Of 12 different locations on the human body evaluated separately, only in two, the lower arm ($p = 0.03$) and the feet ($p = 0.03$), was there a difference for the β-carotene group in the quantification of naevi. Overall, it is concluded that β-carotene does not reduce the development of new naevi in patients with numerous atypical naevi. ***Key words: clinical trial; melanocytic naevi; ultraviolet.***

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The term ''dypslastic naevus syndrome'' for numerous melanocytic atypical naevi, hereditary or non-hereditary, is characterized by an increased number of clinically and histologically atypical naevi starting in puberty. Patients with dysplastic naevus syndrome have an increased risk of contracting melanoma during their lifetime (1, 2). Atypical naevi are characterized by an asymmetrical, bizarre configuration with polycyclical or blurred borders. They vary in colour from pink to brown to black, with an eccentric palpable nodule and a reddish border, and have an average size of more than 5 mm (1, 2). Previous research suggests that there is a relationship between exposure to sunlight, the total number of melanocytic naevi and the regional distribution of naevi on the human body (3, 4). A high count of acquired melanocytic naevi is one of the major risk factors for melanoma (5, 6).

Free radical oxidative stress has been implicated in the pathogenesis of a variety of human diseases, including ultraviolet-induced skin cancer (5–7). Natural antioxidant defence mechanisms have been found to be defective in these patients (5, 8). Disease progression seems to be retarded by supplementation of the natural antioxidant defences. Potential antioxidant therapies include natural antioxidant enzymes and vitamins or synthetic agents with antioxidant activity (7).

Beta-carotene is derived from yellow and green vegetables and exhibits provitamin A (retinol) activity. It can delay the onset of erythema in solar urticaria and is effective in light-sensitive skin diseases such as polymorphic light eruption, especially in erythropoetic protoporphyria, a disease sensitive to light between 380 nm and 560 nm (9, 10). The protective function of β-carotene is its quenching of singlet oxygen and free radical reactions (8). There is a controversy about tumour formation by chemicals and UV irradiation by betacarotene. Some authors argue that beta-carotene is protective, others that beta-carotene increases tumour formation (for review see 7, 8, 10, 11). Additionally, since the 1980s β-carotene has been proposed as a possible dietary preventive agent against cancer (7, 10, 11). In epidemiological studies and clinical trials with β-carotene as a dietary antioxidant, however, no consistent proof has been obtained that it protects humans against skin cancer (12, 13).

This study was performed to gain insight into the efficacy and safety of β-carotene and its effects on the number of naevi after long-term medication.

PATIENTS AND METHODS

After approval had been obtained from the ethics committee, a prospective, randomized, placebo-controlled study was performed in a single centre over 3 years in patients with numerous clinically atypical naevi. Clinical criteria were: 1) asymmetrical, polycyclic, bizarre configuration, 2) blurred borders, 3) varying red, brown or black colour, 4) eccentric palpable nodule, reddish border, and 5) average size of more than 5 mm. With more than three criteria fulfilled, the naevus was called atypic. Sixty-two healthy patients aged between 18

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and 60 years and with numerous atypical naevi were recruited from our dermatological outpatient clinic. Randomization was done according to G. Marsaglia & T. A. Bray (seed numbers randomized by reaction time of programme user) (14). The study was blinded for the patient and the investigators at the start of the study.

Carotaben tablets® (25 mg β-carotene, Fa. Hermal, Hamburg, Germany) were taken twice daily by the treatment group and placebo tablets (saccharose capsules) twice daily by the control group for the 36 months planned.

The main outcome criterion for efficacy was the increase in number and size of benign and atypical naevi during the study, differentiated for the body areas face, throat, abdomen, chest, back, lower arm, upper arm, hands, buttocks, upper leg, lower leg and feet. Moreover, UV-exposed body sites (extremities) were compared to non-exposed areas (trunk). All these data were evaluated by the same specially trained doctor every 3 months. Safe use and tolerability of the medication were judged by the patients and by the doctor for all 3-month periods until month 36, including questions concerning yellowish skin colour (not present, some, middle severe, very heavy).

The significance level for all *p*-values was chosen to be $\alpha < 0.05$; normal distribution with the one-sided *t*-test, or non-normal distribution with the Kruskal-Wallis test and the chi-square approximation.

RESULTS

Of 62 patients, 30 were randomized to the treatment group and 32 to the placebo group (Fig. 1). Thirty-nine patients (18 in the β-carotene group, 21 in the placebo group) finished the study after 36 months, whereas 23 patients (12 in the β-carotene group, 11 in the placebo group) did not finish the study. The baseline analysis revealed similar age, sex and body weight distributions in the two groups who completed the study (Table I). The frequency of atypical naevi was also similar but the distribution of skin types was slightly different. Concomitant medication was taken in 8 (44%) patients in the β-carotene group (19% anti-allergic drugs, 13% contraceptives, 6% others) and in 11 (52%) in the

Table I. *Clinical characteristics of the patients who completed the whole study*

	Therapy group	
	β-carotene $n=18$	Placebo $n=21$
Age, years (mean (range))	32.6 (21–51)	38.7 (19–54)
Sex, % (male/female)	61/39	48/52
Body weight, kg (range)	72 (55–110)	67 (52–86)
Atypical naevi, % (mean)	11	9
Tanning, %		
Never	22	33
Occasionally, tan less than average	22	28
Always tan about average	50	33
Always tan more than average	6	5

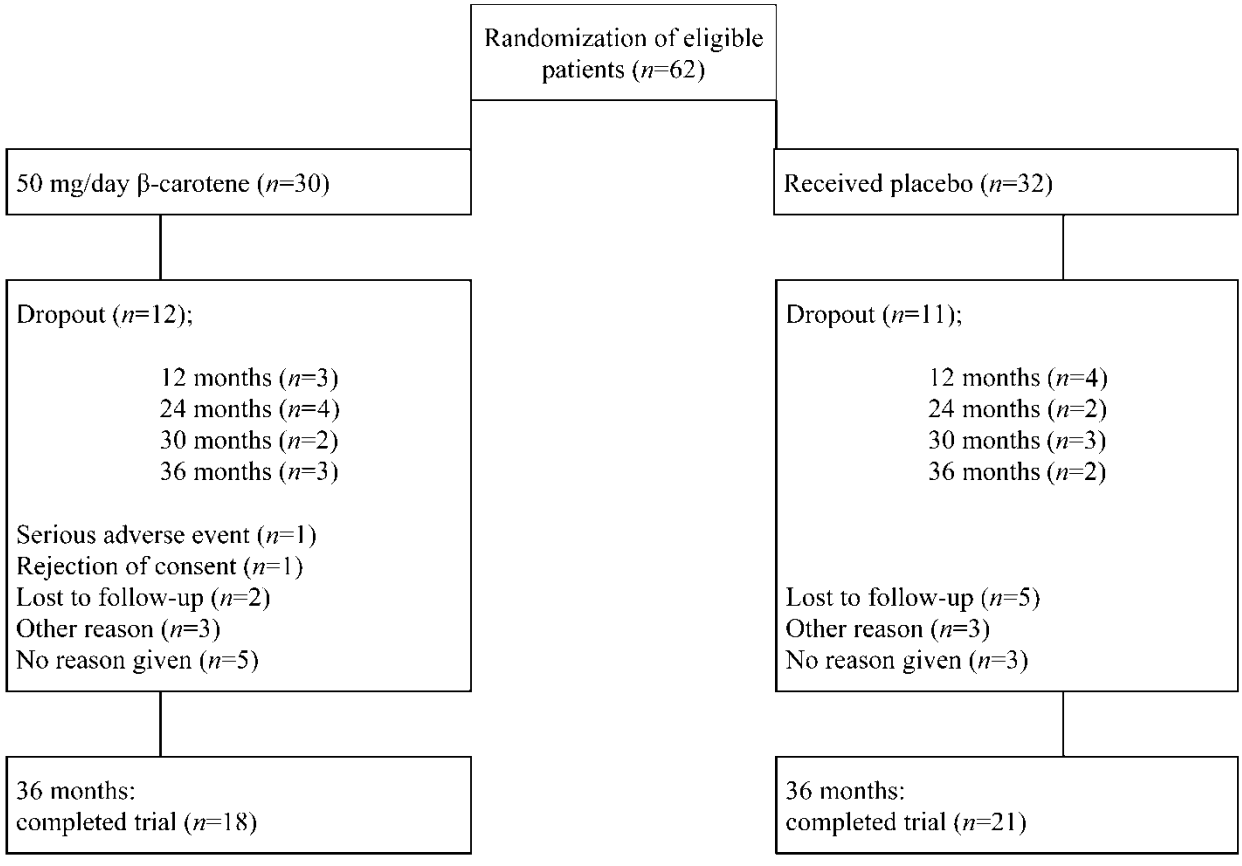

Fig. 1. Patient distribution profile.

Table II. *Sum of melanocytic naevi over 36 months of the study*

Naevi in all locations	β-carotene ($n=18$) Mean ± SD min – max	Placebo ($n=21$) Mean ± SD min – max
Screening	262 ± 121	315 ± 200
	62 – 507	65 – 778
3 months	274 ± 118	338 ± 218
	71 – 508	73 – 868
6 months	279 ± 115	344 ± 218
	72 – 508	76 – 868
9 months	284 ± 116	349 ± 221
	73 – 514	321 – 884
12 months	293 ± 115	355 ± 227
	74 – 516	77 – 942
15 months	297 ± 115	365 ± 225
	75 – 516	77 – 954
18 months	299 ± 115	368 ± 226
	75 – 519	81 – 962
21 months	302 ± 117	373 ± 228
	80 – 532	81 – 966
24 months	307 ± 119	378 ± 230
	80 – 554	82 – 977
27 months	313 ± 124	381 ± 233
	80 – 563	81 – 981
30 months	318 ± 126	385 ± 233
	305 – 583	83 – 986
33 months	324 ± 130	391 ± 236
	309 – 591	88 – 1011
36 months	330 ± 133	403 ± 248
	84 – 594	90 – 1028

SD = standard deviation; min = minimum, lowest naevus cell count; max = maximum, highest naevus cell count; according Kruskal-Wallis test $p=0.5170$ (= no statistical significance)

placebo group (cardiac and antihypertension drugs 20%, contraceptives 16%, vitamins 12%, others 10%).

At the start of the study, a mean of 262 naevi per patient was counted on all body sites in the β-carotene group and 315 in the control group (Table II). At the end of the study, the mean (± SD) increase in newly developed naevi during the study was 68 ± 33 in the β-carotene group and 88 ± 65 in the placebo group. The mean difference in the total number of new naevi in the two groups was not statistically significant. At the end of the study, however, the β-carotene treatment was superior to placebo for naevi on the lower arms ($p=0.03$) and feet ($p=0.03$), showing fewer newly developed naevi (benign and atypical).

All patients in the β-carotene group developed yellowish discoloration of the skin. This was the reason for three patients dropping out. During the 3 monthly examinations, however, between 11% and 30% of patients in the β-carotene group temporarily showed no discoloration of the skin. On the other hand, 12% of patients in the placebo group had yellowish skin diagnosed at some time during the trial.

Adverse events were reported by 16 (53%) in the β-carotene group and by 5 (16%) in the placebo group. The β-carotene group complained of yellowish discoloration of the skin periorally and on the hands and feet ($n=8$), different gastrointestinal discomfort ($n=6$) and on irregularities of menses ($n=2$); in one case, pruritus, scaling of the hands, pityriasis rosea, effluvium and psychical impairment. Five patients (16%) in the placebo group complained of dizziness, pruritus, folliculitis, flue-like symptoms and leucocytosis. Nine of the 12 dropouts in the β-carotene group complained of discomfort when they finished the study, and 3 of 11 in the control group. In the β-carotene group, one male patient of 49 years (serious adverse event) died of metastases of his known melanoma 6 months after the start of the study. Eighteen years previously he had developed a superficial spreading melanoma, Level 4, Breslow 2.4 mm in the right axilla, lymph node metastases in the same year, lung metastases 1 year previously, cerebral metastases and multiple skeletal metastases 6 months before the start of the study. Beta-carotene medication was not judged as causal for this serious adverse event.

DISCUSSION

The analysis of new naevi on all body sites revealed gradually increased counts in both groups; a mean increase of 20 more new naevi in the placebo group is not statistically significant in relation to the overall number of naevi. Among all 12 body locations studied (the sun-exposed and the non-sun-exposed), β-carotene influenced the development of new melanocytic naevi in only one highly UV-exposed body site (lower arm) and in only one seasonally UV-exposed body site (feet) in patients with numerous atypical naevi. Naevi on the abdomen, back, buttocks, chest, upper arms, upper legs, lower legs, face, throat and hands were not influenced.

In the baseline analysis, all criteria except age distribution were homogenous between the groups, with a higher age in the control group (mean age 38.7 years versus 32.6 in the β-carotene group). The number of naevi might decrease with age over 60 years (15, 16). The maximum of 54 years in the placebo group thus does not affect the study outcome. Confounders might be the imbalances in skin types. Skin types III and IV were seen more often in patients in the β-carotene group, a trait that might influence the development of naevi. Moreover, the fact that vitamin tablets had been taken by some patients in the β-carotene group might have influenced the study outcome.

UV irradiation influences the outcome of the naevus cell count and the classification as benign or atypical, because UV irradiation leads to activation of naevi (3, 4, 17). Therefore a randomized protocol was chosen to "minimize" the effects of different UV exposure habits as days in the sun per year, holidays in the sun, number of sunburns or work outside or sun reaction skin type,

while unfortunately the latter came out to show a better tanning in the group that received β-carotene (Table I). Moreover, UV-light can significantly decrease both the circulating plasma carotenoids and the levels of antioxidants in the skin (10). The clinical manifestations of solar damage, skin cancer, certain photodermatoses and photoaging, are attributable in part to free radical production (8, 10). β-carotene dietary supplementation blocked the UV-induced depression of the overall immune response shown for UV suppression of contact dermatitis and for tests for recall antigens (18, 19) and moderately reduced UV erythema in some studies (10) but had no effect in others (20). This is important because sun-induced immune suppression promotes the occurrence of naevi (20, 21).

Vitamin A and its analogues have long been known for their anticancer properties in squamous cell carcinoma (23), basal cell carcinoma (24) and metastatic melanoma (25). Carotenoids may effect carcinogenesis either directly by their antioxidant activity or indirectly via conversion to retinoids which alter cellular differentiation and proliferation (22). Topical 0.05% tretinoin lotion on atypical naevi has shown a definite biological effect, fading or eliminating some atypical naevi (26). In contrast, in a similar follow-up study in 11 patients treated with oral isotretinoin, no clinical or histological changes in atypical naevi were found (27), and according to our results with no influence in naevus cell count with oral β-carotene.

Recent randomized controlled epidemiologic studies show no benefit of antioxidant vitamins (7, 28). Moreover, the relative risk of dying from lung cancer or cardiovascular disease was increased in some of these studies (β-carotene and retinol efficacy trial; CARET) (29) and in the α-tocopherol/β-carotene cancer prevention study (30). The methodology of these studies was later criticized because of the inclusion of high-risk patients such as smokers and others exposed to asbestos (31). A third study (Physicians' Health Study) included 22,071 healthy male US physicians aged from 40 to 84 who received 50 mg of β-carotene on alternate days. No differences in cardiovascular diseases, malignant neoplasms or the overall mortality could be determined (32). This is important for our study outcome, because one of the melanoma patients of the β-carotene group showed progression during the study. In the light of these studies, β-carotene is not a risk factor for progression of melanoma. In contrast, epidemiological studies with dietary supplementation of β-carotene, the CARET and α-tocopherol/β-carotene studies, showed that this long-term supplementation with β-carotene is an additional risk factor for smokers (7, 33). For further study, we recommend evaluation of the rate of smokers.

This study was started double-blind at the time of randomization and distribution of the drug, but as it progressed the yellowish discoloration of the skin could have made the randomization "open" for some patients and for the physician. While on the one hand there might be some bias as a result of this, on the other hand 11–30% of the patients in the β-carotene group temporarily showed no yellowish discoloration of the skin and additionally the doctor diagnosed yellow skin in 12% of the patients in the control group. In relation to all 28 adverse events, the complaint about slight gastrointestinal discomfort was described in 21% of adverse events in the β-carotene group and ceased after the end of the study. No measurements of dermal carotenoids (34) or blood levels were performed, but the safety of the drug could be shown clinically.

Beta-carotene is indicated in erythropoetic protoporphyria and other photosensitivity diseases or might be used to reduce the negative effects of phototoxic drugs (9). Beta-carotene (30 mg) can be recommended for short holiday periods with high UV exposure, preferably in combination with α-tocopherol and ascorbic acid (19). No beneficial or harmful effect on basal cell or squamous cell carcinoma was found as a result of a β-carotene supplementation of 30 mg per day for 4.5 years (35). In addition to physical and chemical sun protection, alternative methods of UV protection with textiles should be discussed with patients with dysplastic naevus syndrome.

In our study in patients with numerous atypical naevi, higher doses of β-carotene per day (50 mg) and a long treatment period of 36 months did not retard the increase in number of atypical naevi. No effect of β-carotene on newly developing or existing naevi could be proven with possible confounding factors in this population, such as baseline differences in vitamin intake, skin type and the lack of having evaluated for smoking.

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