NOTES

Effect of Oral β-Carotene Supplementation on Plasma Human Immunodeficiency Virus (HIV) RNA Levels and CD4$^+$ Cell Counts in HIV-Infected Patients

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We conducted a pilot, open-label study to assess the effect of short-term β-carotene administration (180 mg/d with meals for 4 weeks) on the plasma human immunodeficiency virus (HIV) RNA levels and CD4$^+$ lymphocyte counts in 21 HIV-infected patients. We found that plasma HIV RNA levels and CD4$^+$ lymphocyte counts did not change following this short course of β-carotene supplementation. Patients with lower serum concentrations of β-carotene before supplementation were no more likely to have an increase in their CD4$^+$ lymphocyte count or plasma HIV RNA copy number than were those with higher concentrations. No correlation was found between pre- or postsupplementation β-carotene or vitamin A concentrations and pre- or postsupplementation CD4$^+$ lymphocyte counts or plasma HIV RNA titers. This study provides no support for β-carotene supplementation for HIV-infected subjects with normal baseline serum levels of β-carotene and vitamin A.

Whereas low concentrations of serum vitamin A and β-carotene (a precursor of vitamin A) in HIV-infected patients have been associated with decreased CD4$^+$ lymphocyte counts and increased mortality [1], HIV-infected persons who ingest moderately increased amounts of dietary β-carotene have a decreased risk of developing AIDS or dying [2, 3]. Although three previous studies have shown increased lymphocyte counts in HIV-infected patients given supplemental β-carotene [4–6], three other trials found no such benefit [7–9], and none of these previous studies examined the plasma copy number of RNA from HIV. In this pilot study, we assessed the effect of short-term β-carotene administration on the plasma HIV RNA titer and CD4$^+$ lymphocyte counts.

Methods

Subjects were eligible for the study if they were HIV-infected, had 100–300 CD4$^+$ lymphocytes/μL, had been receiving a stable antiretroviral regimen for ⩾8 weeks, and were willing to stop taking any vitamin supplements. Exclusion criteria included hepatic dysfunction, renal insufficiency, anemia, active infection, psychosis, and either blood transfusion or vaccination during the 2 months before enrollment in the study.

At weeks 0, 4, 10, and 16, CD4$^+$ lymphocyte counts, plasma HIV RNA levels, complete blood cell counts, serum creatinine levels, and serum transaminase levels were determined, and clinical evaluations were performed. Nonfasting serum vitamin A and β-carotene levels were measured at weeks 4, 10, and 16. Patients were alternately assigned to early supplementation during weeks 4 to 8 with 60 mg of β-carotene (Roche Pharmaceuticals, Montclair, NJ) three times a day with meals (group A) or to delayed supplementation during weeks 10 to 14 with 60 mg of β-carotene three times a day with meals (group B). This was an open-label study.

Plasma HIV RNA levels were measured by the Amplicor HIV-1 monitor assay (Roche Molecular Diagnostic Systems, Branchburg, NJ) at the Retrovirology Research Laboratory, West Los Angeles Veterans Affairs Medical Center. Vitamin A and β-carotene levels were measured at Western Human Nutrition Research Center in San Francisco. All other blood tests were performed by the clinical laboratory at the West Los Angeles Veterans Affairs Medical Center.

Statistical analyses were performed by use of the χ^2 test (categorical data) or the Student's t test (continuous data). All P values are two tailed. Log_{10} (HIV RNA copy number) was used in all analyses.

Of the 21 subjects enrolled in the study, five (one in group A and four in group B) had been taking one standard-dose

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Informed consent was obtained from all patients, and the guidelines for human experimentation of the U.S. Department of Health and Human Services and of the West Los Angeles Veterans Affairs Medical Center were followed in the conduct of this study.

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Table 1. Serial β-carotene and vitamin A levels, $CD4^+$ lymphocyte counts, and plasma HIV RNA levels in HIV-infected patients.

	Group A				Group B			
Week	β-Carotene level (μmol/L)	Vitamin A level (μmol/L)	HIV RNA copy no. ($\log_{10}$)	$CD4^+$ cell count (/μL)	β-Carotene level (μmol/L)	Vitamin A level (μmol/L)	HIV RNA copy no. ($\log_{10}$)	$CD4^+$ cell count (/μL)
0	. . .	. . .	4.74 ± 0.44 (9)	181 ± 88 (9)	. . .	. . .	4.85 ± 0.66 (12)	183 ± 54 (12)
4	0.55 ± 0.84 (9)	2.07 ± 0.56 (9)	4.87 ± 0.55 (9)	195 ± 115 (9)	0.48 ± 0.36 (12)	1.96 ± 0.60 (12)	4.83 ± 0.76 (12)	189 ± 69 (12)
10	4.69 ± 3.97 (9)*	1.90 ± 0.49 (9)	5.09 ± 0.55 (9)†	167 ± 100 (9)*	0.43 ± 0.26 (12)	2.07 ± 0.60 (12)	4.88 ± 0.71 (12)	187 ± 62 (12)
16	1.69 ± 1.79 (5)	1.83 ± 0.66 (5)	4.81 ± 0.34 (5)	215 ± 86 (5)	4.69 ± 3.35 (11)‡	2.14 ± 0.63 (11)	4.69 ± 0.76 (12)	198 ± 92 (11)

NOTE. β-Carotene was given between weeks 0 and 4 in group A and between weeks 6 and 10 in group B. All values are mean ± SD (no. of patients for whom data were available). · · · = data not evaluated.

* $P < .01$, compared with value determined immediately preceding β-carotene supplementation.

† $P < .05$, compared with value determined immediately preceding β-carotene supplementation.

‡ $P < .001$, compared with value determined immediately preceding β-carotene supplementation.

multivitamin pill per day before study entry. Four subjects (all in group A) completed β-carotene therapy and returned for laboratory and toxicity evaluation 2 weeks after completing therapy, but did not take part in the posttherapy observation phase of the study because of changes in antiretroviral therapy (two) or loss to follow-up (two). Incomplete laboratory data were available for one other patient (in group B). Sixteen subjects (seven in group A and nine in group B) had been receiving stable monotherapy with a nucleoside antiretroviral agent for >6 months at the time of enrollment. The other subjects either declined or could not tolerate antiretroviral therapy. Combination nucleoside therapy and protease inhibitors were not available at our center during the time of the study.

Baseline and pretreatment laboratory values did not differ significantly between the groups. Only one subject was hyporetinemic at baseline (serum vitamin A level, 0.67 μmol/L; normal level, >1.05 μmol/L [10]). No patient had a serum β-carotene level within the lowest 5% for the population [11]. In group A, HIV RNA levels increased significantly, whereas $CD4^+$ cell counts decreased significantly after β-carotene supplementation (table 1). However, no significant changes were seen in group B or in analyses of pooled pre- and postsupplementation results. Following supplementation, one subject had a ⩾25% increase and three subjects had a ⩾25% decrease in the number of $CD4^+$ lymphocytes, whereas two patients had ⩾0.5 $\log_{10}$ decreases and three had ⩾0.5 $\log_{10}$ increases in the plasma HIV RNA copy number.

The baseline β-carotene or vitamin A concentrations or incremental postsupplementation changes in these concentrations did not correlate with the corresponding $CD4^+$ lymphocyte counts or plasma HIV RNA titers ($r < .25$ and $P > .25$ for all determinations). Patients with lower presupplementation β-carotene serum concentrations were no more likely to have an increase in their $CD4^+$ lymphocyte count or plasma HIV RNA copy number following β-carotene supplementation than were those with higher concentrations. Results of analyses of percentage of $CD4^+$ lymphocytes were indistinguishable from those of the number of $CD4^+$ lymphocytes. No adverse clinical or laboratory events or opportunistic infections were observed during the study.

Discussion

In this study, a 4-week course of β-carotene supplementation was not associated with any significant change in the plasma HIV RNA titer or the number or percentage of $CD4^+$ lymphocytes. Limitations of our study include the small patient sample and the low prevalence of hyporetinemia or β-carotene deficiency. Nevertheless, there were no trends favoring β-carotene supplementation. Instead, more patients had decreases in $CD4^+$ lymphocyte counts and increases in the plasma HIV RNA copy number during β-carotene supplementation, and there was no tendency for a greater benefit of therapy for patients with lower baseline β-carotene levels. On the basis of enrollment of 21 patients, the study had an 80% probability (one-tailed) of being able to exclude with 95% confidence (two-tailed) that β-carotene supplementation resulted in ⩾40% of patients having either a 25% increase in the $CD4^+$ cell count or a 0.5 $\log_{10}$ decrease in the plasma HIV RNA copy number.

Three previous studies of HIV-infected patients demonstrated increased numbers of natural killer cells and activated lymphocytes, percentages of $CD4^+$ cells, and $CD4^+$ to $CD8^+$ cell ratios after supplementation with 60 to 180 mg of β-carotene/d for 1–4 months [4–6]. Three other similarly designed studies demonstrated either no increases or decreases in the number of $CD4^+$, $CD8^+$, or natural killer lymphocytes [7–9]. In one of the two previous studies that measured serum β-carotene concentrations, the preintervention serum β-carotene concentration in all subjects was between the 5th and 50th percentile for the general population; vitamin A levels were not measured [7]. In the other study, the mean preintervention β-carotene concentration was below the 5th percentile for the general population, but the mean vitamin A level was well within the normal range [9].

In summary, we were unable to demonstrate any change in the absolute CD4 cell count, the percentage of CD4 cells, or

the plasma HIV RNA concentration following the administration of β-carotene to HIV-infected subjects with normal baseline serum levels of β-carotene and vitamin A. However, the benefit, or lack thereof, of β-carotene supplementation in malnourished HIV-infected subjects who lack access to potent antiretroviral therapy, as is true in developing countries, remains to be critically examined.

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