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Vitamin E Improves the Aminotransferase Status of Patients Suffering from Viral Hepatitis C: A Randomized, Double-Blind, Placebo-Controlled Study

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Vitamin E has been shown to protect against liver damage induced by oxidative stress in animal experiments. Based on our previous findings of diminished vitamin E levels in patients suffering from viral hepatitis, we treated 23 hepatitis C patients refractory to α-interferon therapy with high doses of vitamin E (2 × 400 IU RRR-α-tocopherol/day) for 12 weeks. Study design: pro-spective randomized double-blind cross-over design. Clinical parameters including alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were determined for monitoring the disease state, in parallel vitamin E plasma levels and plasma lipids were determined. The plasma levels of the α-tocopherol were increased about 2-fold in all 23 patients. In 11 of 23 patients the clinical parameters indicative of liver damage were improved during the phase of vitamin E treatment (48% responders). ALT levels in responders were lowered by 46% and AST levels were lowered by 35% after 12 weeks of vitamin E treatment. Cessation of vitamin E treatment was followed by a rapid relapse of ALT and AST elevation, whereas retreatment led to a reproducible ALT decrease by 45% and AST decrease of 37% after a 6 months followup. Since vitamin E is non-toxic even at elevated doses ingested over extended periods, we suggest the treatment of patients refractory to α-interferon therapy suffering from hepatitis C with vitamin E as a supportive therapy.

Keywords: α-tocopherol, oxidative stress, therapy, vitamin E, hepatitis C, liver

INTRODUCTION

Diminished vitamin E plasma levels occur in patients suffering from severe viral hepatitis.[1] Oxidative stress due to increased formation of reactive oxygen species has been identified for several types of viral infection, including hepatitis.[2] Regarding hepatitis C, increased malondialdehyde and protein carbonyls in serum indicated ongoing lipid and protein oxidation, correlated with disease activity.[3] Further, a pronounced rise in oxidative DNA damage was observed in transgenic mice expressing hepatitis B virus.[4] Such oxidative lesions may be respon-

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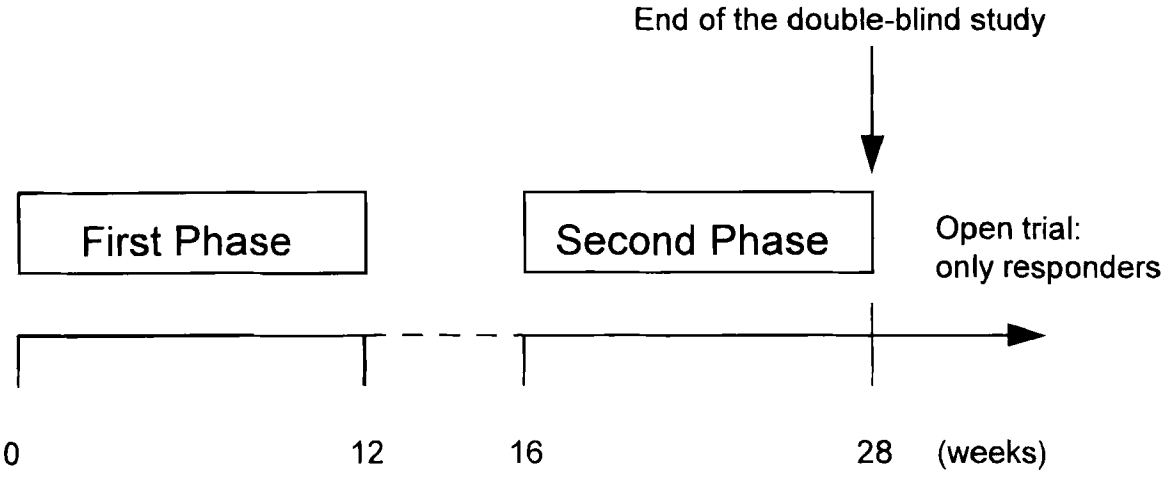
sible for the increased cancer risk associated with chronic active hepatitis. Vitamin E is the most efficient natural, lipid-soluble antioxidant[5–7] and has been shown to protect liver cells from oxidative damage inflicted in animal studies. Consequently, the present study was initiated to evaluate whether treatment with vitamin E improves the aminotransferase status of patients with hepatitis C, who had failed to respond to the classical treatment with α-interferon.

MATERIALS AND METHODS

The effect of vitamin E was studied in a prospective randomized double-blind placebo-controlled study with 26 patients suffering from chronic hepatitis C, as proven by liver biopsy. Twenty-three patients (age 55 ± 11 years; 12 male, 11 female) completed the study; two interrupted for personal reasons, one underwent surgery for hepatocellular carcinoma. Twelve of the remaining patients had liver cirrhosis staged as Child/Pugh A. Eighteen of the patients had been treated previously with α-interferon which had failed in these patients to improve the clinical state of the disease; interferon treatment was contraindicated in two patients, three had refused interferon treatment. Cessation of interferon therapy was at least 4 months before the start of the present study. Inclusion criteria for the study were: replicative chronic hepatitis C (HCV-antibodies and HCV-RNA positive) and elevated ALT above 50 U/L. Antibodies were determined by immunoassay (Abbott, Wiesbaden, Germany); HCV-RNA by a PCR assay (Hoffmann-La Roche AG, Grenzach, Germany). Serum alanine aminotransferase (ALT), aspartate aminotransferase (AST) and lipids were measured using a commercially available assay (Boehringer, Mann-heim, Germany).

The study was performed with a cross-over design (Scheme 1). Eleven patients received vitamin E in the first phase and the placebo in the second phase, the other twelve patients first received the placebo and then vitamin E. Each phase lasted 12 weeks, and between both phases there was an interval of 4 weeks without any treatment (see Scheme 1). Vitamin E dose was 400 IU twice a day (800 IU total/d). ALT, AST, vitamin E, and lipids were determined every 4 weeks.



SCHEME 1 Design of study. The study was carried out in two treatment phases using vitamin E or placebo. In a cross-over design, 11 patients received vitamin E in the first phase, and 12 received placebo in the first phase. The treatment-free interval between the first and the second phase (----) was for at least 4 weeks.

Patients were divided into two groups after termination of the study, based on the changes of ALT levels upon vitamin E treatment. The two groups were designated 'responders' and 'non-responders', respectively. Responders are defined as patients exhibiting a decrease in serum ALT by > 35% below the starting value; 35% is the mean standard deviation of the initial ALT values calculated for all patients (see Table I). Only the responders were included in a group for further treatment with vitamin E (400 IU twice a day) after the end of the study (open trial) and followed for up to 12 months.

Eleven patients received vitamin E during the first phase (responders $n = 5$; non-responders $n = 6$) and twelve during the second phase (responders $n = 6$; non-responders $n = 6$). Written, informed consent was obtained from all patients. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in *a priori* approval by the Human Research Committee at the Heinrich-Heine-University Düsseldorf. Serum levels of vitamin E were determined as described earlier (1). Data are expressed as means ± SD. Differences between means were analyzed for statistical significance by analysis of variance or by Student's t-test. Vitamin E capsules (RRR-α-tocopherol) and an appropriate placebo were kindly provided by Dr. G. Nikoleit, Henkel Co., Düsseldorf, Germany.

RESULTS

During the period of vitamin E treatment mean ALT levels ($n = 23$) decreased by 17%, 23%, and 24% and the AST levels by 12%, 17% and 19% after 4 weeks ($p < 0.05$), 8 weeks ($p < 0.01$), and 12 weeks ($p < 0.01$), respectively (Table I). No statistically significant change in ALT was observed when the patients received placebo. During vitamin E treatment, serum vitamin E and vitamin E/lipids increased approximately 2-fold in all 23 patients; no significant difference of vitamin E levels was observed in the placebo period as compared to basal levels.

Eleven patients showed a partial clinical response as defined by a > 35% decrease in serum ALT which was observed only during vitamin E treatment (responders). The other twelve patients did not show significant fluctuations in ALT levels during the entire study (non-responders). The increase in vitamin E serum levels observed in the period of vitamin E treatment was similar in responders ($n = 11$) (Table II, Fig. 1) and non-responders ($n = 12$) (Table II). The ALT decrease in responders was 31%, 40% and 46% ($p < 0.01$) and the AST decrease in responders was 23%, 32% and 35% ($p < 0.01$) after 4, 8, and 12 weeks of treatment compared to pretreatment values. Cessation of vitamin E treatment was followed by a return to elevated ALT and AST levels in all 11 responders. Retreatment after the end of the study resulted in a renewed decrease in serum ALT (42%) and serum AST (37%) in responders included in the subsequent open trial (n = 10). Among the eleven patients who responded to vitamin E treatment, six patients suffered from liver cirrhosis at the beginning of the study. HCV-RNA remained detectable in all patients, responders and non-responders.

DISCUSSION

The present study shows that almost 50% of the patients suffering from hepatitis C responded favorably to treatment with high-dose vitamin E (800 IU RRR-α-tocopherol/d), as indicated by persistently decreased ALT serum levels. The treatment did not lead to complete normalization of aminotransferases or to elimination of the viral load. Thus, it is suggested that vitamin E supports the endogenous defense against secondary effects associated with viral hepatitis, such as inflammatory events, known to be associated with an increased formation of reactive oxygen species capable of inducing oxidative damage to DNA and cellular membranes.[8] Low

TABLE I Alanine aminotransferase (ALT), aspartate aminotransferase (AST), vitamin E and vitamin E/lipids of all patients with chronic hepatitis C involved in this study ($n = 23$)

	Vitamin E (400 IU twice a day = 800 IU total/d)					Placebo				
	initial	4 weeks	8 weeks	12 weeks	free interval	initial	4 weeks	8 weeks	12 weeks	free interval
ALT (U/L)	90 ± 27	75 ± 34*	69 ± 27**	68 ± 32**	91 ± 31	87 ± 34	80 ± 34	82 ± 36	88 ± 36	90 ± 32
AST (U/L)	59 ± 21	52 ± 23*	49 ± 22**	48 ± 21**	59 ± 20	59 ± 22	52 ± 17	56 ± 19	56 ± 19	57 ± 18
Vitamin E (μmol/L)	25.0 ± 9.3	51.9 ± 14.7**	53.2 ± 15.9**	54.0 ± 13.8**	24.2 ± 7.2	24.8 ± 8.0	24.8 ± 7.3	25.4 ± 8.1	24.5 ± 7.1	26.0 ± 9.5
Vitamin E/lipids (μmol/g)	4.4 ± 1.4	9.3 ± 2.5**	10.0 ± 2.9**	10.1 ± 1.9**	4.6 ± 1.0	4.7 ± 1.1	4.8 ± 0.8	4.6 ± 1.0	4.6 ± 1.0	4.9 ± 1.6

Means ± SD. *significantly different from initial value before treatment with vitamin E or placebo ($p < 0.05$); ** ($p < 0.01$)

TABLE II Alanine aminotransferase (ALT), aspartate aminotransferase (AST), vitamin E and vitamin E/lipids in responders and non-responders

	Vitamin E (400 IU twice a day = 800 IU total/d)					Placebo				
	initial	4 weeks	8 weeks	12 weeks	free interval	initial	4 weeks	8 weeks	12 weeks	free interval
Responders (n = 11)										
ALT (U/L)	93 ± 21	64 ± 24**	56 ± 18**	50 ± 15**	87 ± 30	83 ± 23	82 ± 26	78 ± 21	78 ± 20	89 ± 24
AST (U/L)	57 ± 19	44 ± 19**	39 ± 17**	37 ± 13**	52 ± 18	56 ± 20	49 ± 14	47 ± 11	46 ± 12	56 ± 16
Vitamin E (μmol/L)	26.2 ± 11.3	52.4 ± 15.6**	47.1 ± 16.3**	52.3 ± 11.6**	25.4 ± 8.9	24.4 ± 11.7	24.4 ± 6.7	24.4 ± 8.6	23.0 ± 5.3	24.7 ± 8.1
Vitamin E/lipids (μmol/g)	5.0 ± 1.6	9.3 ± 2.6**	9.3 ± 3.5**	9.9 ± 1.9**	4.9 ± 1.3	4.8 ± 1.4	5.0 ± 0.9	4.7 ± 1.1	4.5 ± 0.9	4.8 ±1.4
Non-responders (n = 12)										
ALT (U/L)	86 ± 30	86 ± 38	81 ± 27	85 ± 32	94 ± 32	91 ± 40	78 ± 39	86 ± 44	97 ± 42	91 ± 38
AST (U/L)	60 ± 22	60 ± 23	58 ± 22	59 ± 21	65 ± 20	63 ± 23	54 ± 19	58 ± 19	65 ± 20	59 ± 20
Vitamin E (μmol/L)	23.9 ± 6.6	51.2 ± 13.8**	58.8 ± 12.5**	55.6 ± 15.3**	24.0 ± 5.0	25.2 ± 5.8	25.2 ± 7.8	26.3 ± 7.5	25.4 ± 7.3	27.2 ± 10.3
Vitamin E/lipids (μmol/g)	4.0 ± 0.9	9.3 ± 2.4**	10.7 ± 2.0**	10.3 ± 1.8**	4.6 ± 0.5	4.6 ± 0.6	4.6 ± 0.7	4.4 ± 0.8	4.7 ± 1.0	5.0 ± 1.7

Responders are defined as patients that show a decrease of ALT > 35% below the starting value upon treatment with vitamin E. Means ± SD. ** significantly different from initial value before treatment with vitamin E or placebo ($p < 0.01$).

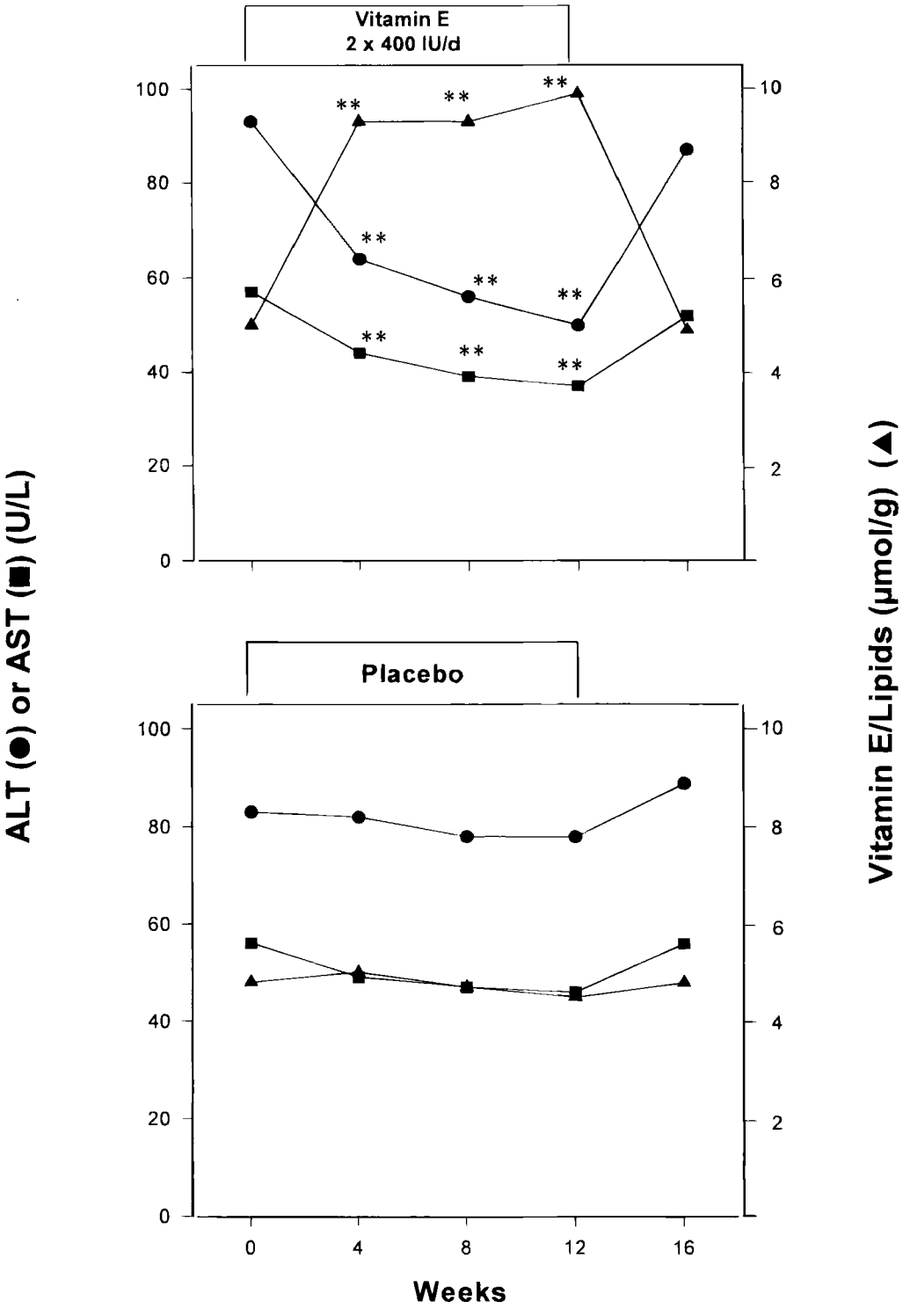


FIGURE 1 Time course of serum alanine aminotransferase (ALT), aspartate aminotransferase (AST) and vitamin E/lipids upon treatment with vitamin E and placebo. Data shown are for responders (see Table II). Treatment was with vitamin E (RRR-α-tocopherol, 2 × 400 IU/d), top, or placebo, bottom, for 12 weeks. ALT (●), AST (■) and vitamin E/lipids (▲). Significantly different from starting value: $^{**}p < 0.01$.

vitamin E levels have been shown in patients suffering from hemochromatosis and Wilson's disease,[9] thought to be due to elevated levels of free iron and copper ions, respectively. Vitamin E is a chain-breaking antioxidant,[5,6] and its effects in the treatment of viral hepatitis might be based on its antioxidant properties. At present, it is unknown why not all of the patients respond to vitamin E; a similar question applies to hepatitis C patients not responding to α-interferon.

The results of this study suggest that vitamin E may be used as supportive treatment of viral hepatitis in patients who do not respond to α-interferon therapy. The benefit of vitamin E treatment in lowering ALT is observed after 4–8 weeks. The ALT level returns to the initial high level upon cessation of treatment with vitamin E, indicating that vitamin E needs to be present over an extended period. Vitamin E has an excellent record of safety,[10] so that no adverse effects are to be expected even in long-term treatment.

Acknowledgments

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