

Effect of High Dose Atorvastatin and Ubiquinone on Survival of Balb-c mice with Ehrlich Ascites Tumour (EAT)

M Caner, E Taskin

Citation

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Abstract

Statins are inhibitors of HMG-CoA reductase and are currently used in the treatment of hypercholesterolemia. An antioxidant ubiquinone (Coenzyme Q 10), especially in high doses, is utilized for the prevention of the myopathy secondary to the administration of statins. We injected Ehrlich ascites tumor cells intraperitoneally to forty-five animals and administered atorvastatin 20 mg/kg in Group 1 (n=15), 40 mg/kg in Group 2 (n=15) and saline in the control group (n=15). 4 mg/kg dose of Ubiquinone was added for the prevention of atorvastatin toxicity. The group, which was, administered 20 mg/kg of atorvastatin survived $6,67 \pm 0,97$ days, 40 mg/kg survived $9,27 \pm 0,84$ days while the control group survived $9,14 \pm 0,93$ days. Survival in the 40 mg/kg dose of atorvastatin group was longer than the 20 mg/kg group but there was not different from the control group. However, these differences were not significant. In conclusion, administration of high dose atorvastatin did not have a positive effect on the survival in a tumor model with EAT cells. Higher doses of atorvastatin may be needed to increase survival in this model.

INTRODUCTION

Synthesis of mevalonate from 3-hydroxy-3-methyl-Coenzyme A (HMG-CoA) is the most important step of the cholesterol synthesis. Mevalonate is the precursor of isoprenoid, which enables bonding with the fundamental molecules during the cellular proliferation. HMG-CoA reductase is the catalytic enzyme of HMG-CoA reductase and essential in synthesis of the cholesterol. Statins are used in the treatment of hypercholesterolemia as inhibitors of the HMG-CoA reductase (8). Recent studies on statins have demonstrated that they may inhibit the proliferation of human breast cancer cells (2), and in addition they have an in vitro antitumor activity on melanoma, adenocarcinoma, neuroblastoma and leukemias (3,5,8). Moreover, cytotoxic activity of one of them (Lovastatin) was demonstrated experimentally (8). Statins have proangiogenic effects in low therapeutic concentrations and angiostatic effects in higher concentrations (1). Reportedly, inhibition of HMG-Co A reductase has a dose dependent biphasic effect on angiogenesis. This effect is mentioned to be independent from the antilipidemic effects of the statins. Furthermore, in vivo use of statins is thought to elicit a preventive effect against tumourigenesis. In addition, Phase-1 clinical studies have shown induction of apoptosis in the tumor when statins reach certain plasma concentrations (4,5,6). Ubiquinone

(Coenzyme Q 10), especially in high doses, is utilized for the prevention of the myopathy secondary to the administration of statins. Although ubiquinone considerably reduces the severity of the effects of statins, it does not diminish the incidence of myopathy secondary to the statins (7,8). In our study we gave atorvastatin at high doses with ubiquinone to the mice in a tumor model with Ehrlich ascites tumor to investigate the effect of the treatment on the survival of the experimental animals.

MATERIAL AND METHOD

Balb-c mice [please include strain; supplier or origin of mice; age of mice; gender of mice] with mean weight 20-25 grams were used in the study. Animals were divided into three groups as Experiment 1, Experiment 2 and Control. There were 15 animals in each group. Mice had similar weight and physical characteristics. All groups were injected with 1×10^6 EAT cells intraperitoneally. Immediately after injection of the tumor, atorvastatin diluted with saline was administered by gavage in 20 and 40 mg/kg doses to the Experiment 1 and Experiment 2 groups, respectively. Simultaneously 4 mg/kg of ubiquinone was given to prevent myopathy in these two groups treated with atorvastatin. Control group received saline via gavage in a similar volume given to the experimental animals. Parallel with the development of the tumour, abdominal bulging was

observed approximately on day 10. Dates of demise were noted daily for each group.

RESULTS

Mean survival period was shortest in Group 1 ($6,67 \pm 0,97$), which was treated with atorvastatin 20 mg/kg/day. Group 2, treated with atorvastatin 40 mg/kg/day had the longest survival period ($9,27 \pm 0,84$) (Table 1). Comparison of the mean values with the controls ($9,14 \pm 0,93$) was not statistically significant. Survival period of all groups are given in Figure 1.

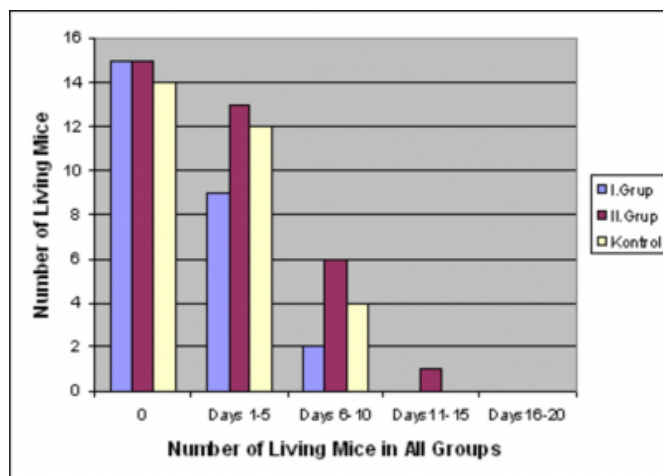
Figure 1

Table 1: Mean periods of survival of the groups are seen below.

	Group 1	Group 2	Controls
Survival (days)	$X \pm SE$	$X \pm SE$	$X \pm SE$
	$6,67 \pm 0,97$	$9,27 \pm 0,84$	$9,14 \pm 0,93$

Figure 2

Figure 1: Survival periods of the groups are seen.



DISCUSSION

Ehrlich Ascites Tumor (EAT) model is a type of a tumour that is frequently used in the studies. It is both used to develop a tumour model and in chemotherapy investigations. Ehrlich tumor is an undifferentiated solid tumour. Following subcutaneous injection of Ehrlich tumour cells, a tumour of 1 cm in diameter is obtained approximately within one week. This highly virulent tumour causes the death of almost 100 % of experimental animals in a very short period (7 to 12 days) ($_{9,10}$). Large-scale virulence, quick development and infiltrative nature of the tumour reflect its high-grade

malignancy.

In our study, we aimed to investigate the effect of high dose atorvastatin (20 and 40 mg/kg) on tumour development in Balb-c mice using the EAT model. According to our findings, in comparison to controls, Group 1 and Group 2, which received high dose atorvastatin, showed no positive effect of atorvastatin on survival of the mice with EAT tumour was observed. Moreover, it appeared to diminish survival. Similar results were also obtained during the use of high dose lovastatin in the patients with advanced gastric adenocarcinoma ($_{11}$). [Please elaborate on how your results and those in patients treated with lovastatin were similar. According to these results, in Ehrlich ascites tumour high doses of atorvastatin was found to have no positive effect and may even lower the survival expectation. These findings vary according to the type of the tumour, dose and duration of atorvastatin.

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Author Information

Metin Caner

Department of General Surgery, Cerrahpasa Medical Faculty

Elif Taskin

Department of Medical Biology, College of Veterinary Medicine, Istanbul University