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Original Research Article

## Comparing the effect of statins on hepatic fibrosis induced by carbon tetrachloride in Wistar rats

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### ABSTRACT

**Background:** The clinical studies have shown contrary results regarding hepatoprotective effect of statins. However, antifibrotic properties of statins in *in vitro* and *in vivo* experimental models have been demonstrated. The purpose of this study was to assess and compare the effect of statins on serum liver enzymes and their antifibrotic effects.

**Methods:** Forty two rats were divided into 7 groups (I to VII) (n=6). Liver toxicity was induced by injecting carbon tetrachloride (1 ml/kg). Control groups received corn oil (0.1 ml/100 gm) and carboxy methyl cellulose (0.50%) respectively. Group III to VII received carbon tetrachloride (CCl<sub>4</sub>) for 6 weeks and then groups IV, V, VI and VII received simvastatin (10 mg/kg), atorvastatin (15 mg/kg), rosuvastatin (2 mg/kg) and silymarin (50 mg/kg) for another 8 weeks respectively. Serum aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase (ALP) levels were estimated in all the groups at baseline, 6 weeks and 14 weeks. At 14 weeks, histopathology of liver was done in all groups.

**Results:** At 14 weeks, all the test groups (IV, V and VI) showed a significant decrease in serum ALT, AST and ALP levels as compared to control (p<0.05) and group III (p<0.05). On intergroup comparison, liver enzymes in rats in group VI (rosuvastatin) and group V (atorvastatin) were decreased more in comparison to group IV (simvastatin) but the difference was not statistically significant except for AST levels where the difference was significant between the statins. There was decrease in hepatic fibrosis by statins with rosuvastatin being superior followed by atorvastatin and simvastatin.

**Conclusions:** In the present study statins decreased the serum AST, ALT and ALP levels and histopathological changes were reversed by statins in CCl<sub>4</sub> induced hepatotoxic models.

**Keywords:** Statins, Hepatotoxicity, Carbon tetrachloride, Hepatic fibrosis

### INTRODUCTION

Liver diseases are considered as a public health disease because of underway epidemics of obesity and diabetes. The range of liver diseases varies from simple steatosis, hepatosteatosis, liver fibrosis (non-alcoholic fatty liver disease, liver cirrhosis) and finally hepatic cellular carcinoma.<sup>1</sup> Hepatic fibrosis, a reversible wound healing process, is a result of chronic non resolving inflammation. Carbon tetrachloride (CCl<sub>4</sub>) by altering the permeability of plasma lysosomal and mitochondrial membranes impairs

the functioning of hepatocytes and causes chronic liver injury. Also generation of highly reactive metabolites of free radicals in plasma leads to centrilobular necrosis in hepatocytes.<sup>2</sup>

Statins are specific inhibitors of the 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase which is a rate limiting enzyme in cholesterol biosynthesis, and are primary agents used in the treatment of hyperlipidemia. The number of patients taking statins is increasing world over and American College of Cardiology has extended

the indication of statins for prevention of cardiovascular diseases. Statins have pleiotropic properties such as anti-inflammatory, anti-proliferative, antithrombotic, anticancer and immunomodulatory in vivo and vitro in addition to cholesterol lowering effects. Statins also reduce the triglycerides level in liver and ameliorate severe hepatic steatosis thereby improving the fibrogenesis.<sup>2</sup> A recent systematic review and meta-analysis has concluded that statins attenuate the progression of hepatic fibrosis. Statins have a role in the prevention of hepatic decompensation in patients with cirrhosis and can decrease all-cause mortality in chronic liver disease.<sup>3</sup> The status of statins in patients with hepatic fibrosis is conflicting and researchers are of the opinion that further studies are required to elucidate the effect of statins in patients with hepatic fibrosis.

With this background, the present study aimed at evaluating and comparing the effect of statins on liver enzymes and their antifibrotic properties.

## METHODS

The animal care and experiments conducted in this study were in accordance with committee for the purpose of control and supervision of experiments on animals (CPSCEA) guidelines for handling and care of animals. The study was initiated after obtaining clearance from institutional animal ethics committee (IAEC/KMC/89/2016), Kasturba Medical College, Manipal Academy of Higher Education.

### Drugs/reagents

Corn oil, CCl<sub>4</sub>, silymarin (50 mg/kg), carboxymethyl cellulose (CMC) 0.5%, atorvastatin (15 mg/kg), rosuvastatin (2 mg/kg), simvastatin (10 mg/kg) and fluvastatin (10 mg/kg). Serum aspartate aminotransferase

(AST), alanine aminotransferase (ALT) and alkaline phosphatase (ALP) kits were obtained from Hitech Biomedicals, Mangalore. The animals were divided into 7 groups as shown in Table 1.

Baseline serum AST, ALT and ALP levels were estimated in all the groups (group I to group VII). Then liver fibrosis was then induced by injecting CCl<sub>4</sub> to 30 rats (group III, IV, V, VI and VII) at a dose of 1 ml/kg, 1:1 mixture with corn oil, intraperitoneally twice weekly for 6 weeks.<sup>4</sup> Induction of liver fibrosis was assessed by the biochemical estimation. Biochemical estimation was done at 6 weeks to check for increase in the liver enzymes i.e. serum AST, ALT and ALP. Group I of rats (n=6) were injected intraperitoneally corn oil 0.1 ml/100 gm twice a week for 6 weeks (vehicle) and served as a negative control group. Group II of rats were given orally normal saline daily for 6 weeks and served as control.

After 6 weeks, biochemical estimation (serum AST, ALT and ALP) was done in all groups, followed by administration of the following compounds.

Group I and III were administered saline, group II was administered CMC; group IV was administered simvastatin and CMC; group V was administered atorvastatin and CMC; group VI was administered rosuvastatin and CMC; and group VII was administered silymarin. These drugs were administered for 8 weeks.

At the end of (8+6) 14 weeks the blood samples were collected for estimation of serum AST, ALT and ALP. The blood samples were centrifuged at the rate of 3000 revolutions per minute (rpm) for 15 mins to separate serum, which was used to measure the levels of ALT, AST and ALP by using Semi Auto Analyser and expressed in U/l.

**Table 1: Grouping of animals for the study.**

Groups (n=6)	Drugs	Dose	Duration
<b>Group I</b>	Corn oil	0.1 ml/100 gm <sup>4</sup>	Twice a week for 6 weeks
<b>Group II</b>	CMC	0.50% <sup>5</sup>	8 weeks (after 6 weeks)
<b>Group III</b>	Corn oil + CCl <sub>4</sub>	0.1 ml/100 gm+1 ml/kg <sup>4</sup> [1:1 mixture of CCl <sub>4</sub> and corn oil]	Twice a week for 6 weeks
<b>Group IV</b>	Simvastatin+CMC	10 mg/kg <sup>6</sup>	8 weeks (after 6 weeks)
<b>Group V</b>	Atorvastatin+CMC	15 mg/kg <sup>7</sup>	8 weeks (after 6 weeks)
<b>Group VI</b>	Rosuvastatin+CMC	2 mg/kg <sup>8</sup>	8 weeks (after 6 weeks)
<b>Group VII</b>	Silymarin	50 mg/kg <sup>9</sup>	Thrice a week for 8 weeks (after 6 weeks)

After twenty-four hours of last drug dosing, each animal was weighed and then sacrificed by cervical dislocation. Liver, removed by dissection, was washed with the physiological solution and dried. The tissues were fixed in 10% formalin and embedded in paraffin wax. Sections of the tissues were stained by hematoxylin and eosin (H&E) stain and seen under microscope for histological changes.

### Statistical analysis

Data analysis was performed using statistical package for the social sciences (SPSS) version 17.0 and excel software. For baseline values, descriptive analysis was done. The results were expressed as mean±standard error of mean (SEM). To compare the levels of serum AST, ALT and

ALP between the different groups analysis of variance (ANOVA) followed by post hoc Tuckey’s test was used. For comparing the histological scoring in different groups Pearson’s-Chi square test was used. P value <0.05 was taken as significant.

**RESULTS**

Serum AST, ALT and ALP levels were estimated at baseline, six weeks and 14 weeks.

**AST**

The values of AST in different groups shown in Table 2. A significant increase in AST values is seen in group III as compared to group I (p=0.013) at 6 weeks. Group IV, V, VI and VII also show a significant increase (p<0.05) compared to control group I. At 14 weeks, there is an increase in AST value in group IV as compared to group I (p<0.001), group II (p=0.002). On comparing group IV with group III and group V there is no statistically significant difference (p>0.05).

However a significant increase in AST values is seen in group IV as compared to group VI (p=0.001) and group VII (p<0.001).

**Table 2: The values of AST (U/I) in different groups at baseline, 6 weeks and 14 weeks.**

Groups	Baseline (0 week)	6 weeks	14 weeks
I	74.50±8.26	76.83±6.01	78.50±6.03
II	91.16±2.54	91.16±2.54	91.16±2.54
III	65.66±18.45	144.0±19.01*	144.0±19.01
IV	68.50±11.60	140.67±18.43*	197.5±19.05**a
V	93.66±11.61	163.17±12.62*	129.6±32.65
VI	57.83±6.49	172.66±11.92*	81.83±14.62 <sup>b</sup>
VII	51.66±10.81	187.5±11.23*	59.33±7.73 <sup>b</sup>

The values are mean±SEM; \*p<0.05 as compared to control (group I and group II) at 6 weeks; \*p<0.005 as compared to group II at 14 weeks; <sup>a</sup>p<0.001 as compared to group I at 14 weeks; <sup>b</sup>p<0.001 as compared to group IV at 14 weeks

**ALT**

The values of serum ALT in different groups is shown in Table 3. At 6 weeks, a significant increase in ALT values is seen in Group V as compared to group I and group II (p<0.001). Groups III, IV, VI and VII also show an increase in ALT values but the increase is not statistically significant as compared to control groups. After 14 weeks there was a decrease in serum ALT in group IV, V, VI and VII and the decrease was significant in group IV as compared to group I (p=0.048) and group II (p=0.049). On intergroup comparison of statins and between statins and silymarin, no significant difference (p>0.05) was observed.

**Table 3: The values of ALT (U/I) in different groups at baseline, 6 weeks and 14 weeks.**

Groups	Baseline (0 week)	6 weeks	14 weeks
I	62.66±8.58	97.50±18.9	122.0±26.07
II	71.83±7.65	121.83±25.98	121.83±25.98
III	45.33±11.00	185.0±17.32	101.67±18.55
IV	66.66±12.78	230.0±2.30	43.16±11.38*
V	49.66±11.02	382.0±71.02*	55.83±8.10
VI	31.83±31.83	172.5±7.57	54.66±5.35
VII	43.00±5.05	219.8±19.31	45.16±16.74

The values are mean±SEM; \*p<0.001 as compared to group I and group II at 6 weeks; \*p<0.05 as compared to group I and group II at 14 weeks

**ALP**

The values of serum ALP in different groups shown in Table 4. There is significant difference between group I and group V (p=0.04) and group I and group VI (p<0.001) at 6 weeks. Also a significant difference is seen in group V (p=0.017) and group VI (p<0.001) in comparison to group II. At 14 weeks, there is decrease in ALP levels in group IV, V, VI and VII as compared to group III. However the decrease in non-significant in group IV (p=0.05). On the other hand the decrease at 14 weeks in comparison to group III is significant in group V (p=0.008), group VI (p=0.024), and group VII (p=0.011). Intergroup comparison between statins and silymarin does not show any significant difference (p>0.05).

**Table 4: The values of AST (U/L) in different groups at baseline, 6 weeks and 14 weeks.**

Groups	Baseline (0 week)	6 weeks	14 weeks
I	86.16±21.74	91.66±6.91	70.33±5.10
II	67.50±17.26	67.50±17.26	67.50±17.26
III	46.83±9.68	173.5±6.78	106.83±21.68
IV	41.83±3.24	168.1±6.05	54.00±11.31
V	50.16±11.97	298.0±54.06*	41.50±3.57*
VI	73.00±21.87	392.5±88.46 <sup>a</sup>	48.50±4.89*
VII	75.50±6.71	256.16±58.37	43.33±7.40*

The values are mean±SEM; \*p<0.05 compared to group I and group II at 6 weeks; <sup>a</sup>p<0.001 as compared to group I and group II 6 weeks; \*p<0.05 as compared to group III at 14 weeks

**Histopathological changes**

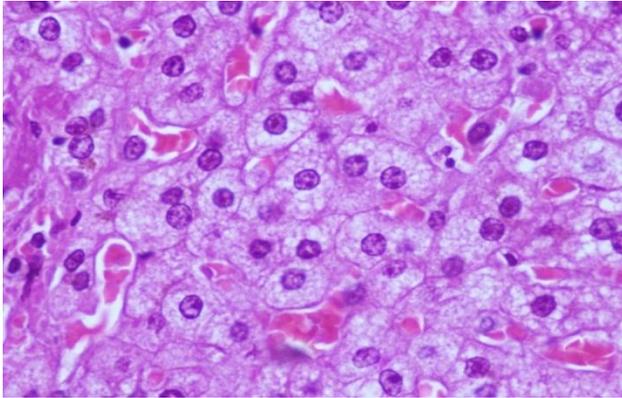
Liver histology was done after the administration of statins/silymarin for 8 weeks. The histological changes were categorized as inflammation, fatty changes, necrosis and fibrosis.

Chi-square test was done to compare the histological changes between the groups.

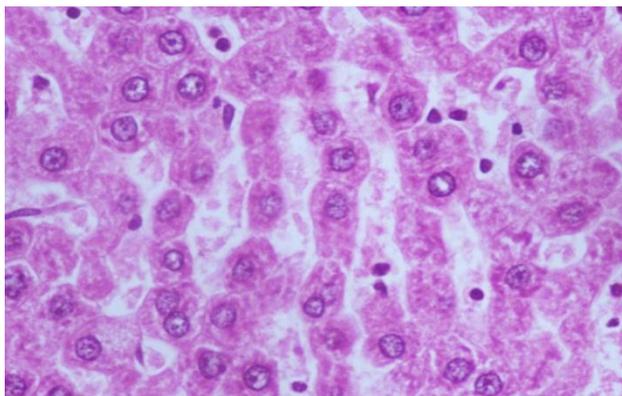
A significant difference (p=0.03) between the groups was seen regarding inflammation. There was no inflammation

in group VI and group VII but in group V the inflammation was seen which was similar to that of group III. Group IV, V, VI and VII did not show any fatty changes.

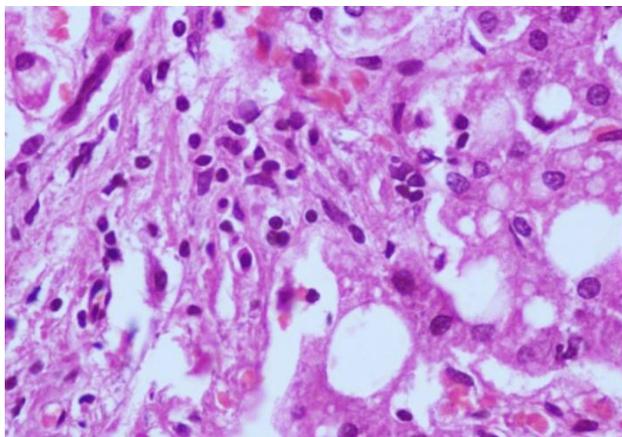
Regarding necrosis a highly significant difference ( $p < 0.001$ ) was seen between the groups. Group IV did not show any necrosis. However group V, VI, VII has shown focal positive necrosis.



**Figure 1: Hepatocytes showing feathery degeneration and early steatosis (H&E; x400).**



**Figure 2: Hepatocytes showing feathery degeneration and granular mitochondrial prominence (H&E; x400).**



**Figure 3: Periportal (zone 1) lymphocytic infiltrates (H&E; x400).**

A highly significant difference ( $p = 0.005$ ) between the groups was seen on comparing fibrosis. Increased fibrosis is seen in group IV, followed by group V and then by group VI. CCl<sub>4</sub> treated group shows changes in histology in the form of feathery degeneration and early steatosis, as shown in Figure 1. Statin treated groups show histological features like periportal lymphocytes and neutrophils infiltration as shown in Figures 2 and 3.

## DISCUSSION

Some studies reveal statins to have protective effect in hepatic fibrosis, while others did not find any such beneficial effect. The present study was undertaken to evaluate the potential impact of statins on liver functions and hepatic fibrosis using Wistar rats. The study was carried out using liver function tests to evaluate the safety of different statins. Liver fibrosis was induced using CCl<sub>4</sub>. At 6 weeks there is a significant increase in serum liver enzymes (AST, ALT, and ALP) in the CCl<sub>4</sub> treated groups as compared to control groups. The halogenated alkanes CCl<sub>4</sub> are used as a hepatotoxic model and produces effects like fatty degeneration, fibrosis and even hepatocellular death.<sup>10</sup> When liver is exposed to CCl<sub>4</sub>, various biological processes are mobilized like peroxisome proliferator-activated receptors (PPAR) signalling pathway, glycerolipid metabolism, arachidonic acid metabolism. This is achieved by regulating targets like ALDH2, and CYP3A4.<sup>11</sup>

At 14 weeks, rosuvastatin and silymarin decreased the AST levels significantly as compared to simvastatin group. Simvastatin treated group showed an increase in the levels of AST. On the contrary, in bile duct ligated mice administration of simvastatin (0.2 mg/kg) decreased ALT by 87% and AST by 83%.<sup>12</sup> Prophylactic administration of simvastatin prevents LPS induced endothelial dysfunction and inflammation. Thus simvastatin has shown to possess hepatoprotective action.<sup>13</sup>

At 14 weeks simvastatin, atorvastatin, rosuvastatin and silymarin treated groups showed a decrease in serum ALT levels but a significant decrease was seen in simvastatin group. However the difference between the ALT levels in different statins and silymarin group was not statistically significant. A systematic review showed that statins may improve serum aminotransferase levels in addition to ultrasound finding.<sup>14</sup> More studies are required before it could be considered as a treatment for the same.<sup>14</sup>

ALP levels at 14 weeks are reduced in simvastatin, atorvastatin, rosuvastatin and silymarin group. Though the decrease is significant in all the groups, there is a non-significant decrease in simvastatin group. Studies show that statin treatment may improve liver enzyme levels as well as hepatic steatosis.<sup>15</sup> Post-marketing studies have shown that atorvastatin is mostly associated with cholestasis liver injury whereas hepatocellular injury is more common with simvastatin.<sup>16</sup> However, in a meta-analysis of randomized, placebo-controlled trials it was

found that statins used for the treatment of hyperlipidemia or for primary or secondary prevention of cardiovascular disease in total of 49,275 patients from 13 trials supported previous observations that pravastatin, lovastatin, and simvastatin, at low-to-moderate doses, are not associated with a significant risk of derangement of liver function test (LFT).<sup>17</sup>

In studies done in obese animals with steatosis or non-alcoholic steatohepatitis, statins have shown to provide hepatic protection (70-90%) against ischemia-reperfusion injury.<sup>18</sup> The histological changes found in the liver of rats treated with CCl<sub>4</sub> include loss of normal hepatocytes, deposition of collagen and formation of fibre segments.<sup>11</sup> The changes in liver hepatocytes was seen after 6 weeks of administration of CCl<sub>4</sub>. In the present study, rats in statin groups have shown less change in liver histology in terms of inflammation, fatty changes, necrosis and fibrosis. The liver histology in CCl<sub>4</sub> group showed changes in the form of feathery degeneration, deposition of hemosiderin pigment, sinusoidal dilation, hepatic steatosis, drop-out necrosis. Focal positive necrosis and feathery degeneration was seen in silymarin treated group. Statin treated groups show histological features like periportal lymphocytes and neutrophils infiltration. Statins have an inhibitory effect on proinflammatory cytokine production, like tumor necrosis factor- $\alpha$ , IFN- $\gamma$ , interleukins like (IL)-1 $\beta$ , and IL-6. By reducing neutrophil influx, they attenuate the events, such as macrophage influx, lymphocyte activation, cytokine release and thus prevent inflammation.<sup>19</sup>

By decreasing inflammatory mediators and increasing the anti-inflammatory mediators, statins attenuate the effect of hepatotoxic agents. The effect of atorvastatin (5 mg/kg) was examined in pathogenic liver effects induced by angiotensin II in male Wistar rats. Angiotensin II produced oxidative stress, hepatic stellate cells (HSC) activation, infiltration of inflammatory cells. Atorvastatin attenuated these effects and thus can have beneficial effects in hepatic inflammation induced by different agents.<sup>20</sup>

Statins can thus have beneficial effects in hepatic dysfunction/fibrosis induced by different hepatotoxic agents. All statins lowered the liver enzymes except simvastatin which increased the AST levels. While comparing the effect of statins on hepatic fibrosis, rosuvastatin seemed to be superior to atorvastatin and simvastatin.

## CONCLUSION

The current study demonstrated that statins normalizes the liver enzyme levels i.e. serum AST, ALT and ALP in CCl<sub>4</sub> induced hepatotoxic model. On comparison between the statins, rosuvastatin and Aatorvastatin are superior to Simvastatin though the difference is not statically significant except for AST levels. Fibrosis is prevented by statins in CCl<sub>4</sub> induced hepatotoxic models with rosuvastatin being superior followed by atorvastatin and then simvastatin.

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