Comparative Study of the Mesenchymal Stem Cell and Simvastatin in the Treatment of Hepatic Fibrosis in Rats Induced by Carbon Tetrachloride

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Abstract

Background: One of the leading causes of death in the United States is hepatic fibrosis. For the treatment of liver disease, bone marrow mesenchymal stem cells have been advocated. Different types of fibrosis may be alleviated by simvastatin. BM-MSCs and BM-MSCs were compared in the research, as well as simvastatin for the treatment of carbon-induced liver fibrosis tetrachloride. Methods: Fifty rats were divided into three groups: CCl4 was administered into rats in groups II and III to induce fibrous liver disease. CCL4 was injected into the rats in Group III. BM-MSCs are given intravenously in group IV, which consists of one dosage. CCL4 was injected into the rats, and they were subsequently administered simvastatin orally once daily for Eight months. Participants in Group V were administered BM-MSC as well as simvastatin. Blood samples were collected at the conclusion of the experiment. collected and liver tissues were processed for biochemical examination histological and immunohistochemical analysis CCL4 was the result.

There was a large increase in liver enzymes and the destruction of normal hepatic structures, as well as a considerable rise in the mean area percentage of collagen fibre deposition and TGF-expression levels. There was an improvement in liver enzymes and histological structure, however the anti-fibrotic impact of BM-MSC was superior than the anti-fibrotic effect of simvastatin. The combination of BM- MSC and simvastatin had a more powerful anti-fibrotic impact and protected liver tissue's histological structure than simvastatin alone.

Conclusion: The combination of BM-MSCs and simvastatin improves liver fibrosis produced by CCl4 therapy

Liver fibrosis, CCL4, BM-MSCs, simvastatin, TGF- are some of the key terms.
**Introduction**

Chronic liver illnesses, such as hepatitis C and B, alcoholic and non-alcoholic fatty liver disease, autoimmune hepatitis, and exposure to toxins or chemicals, such as medications, may lead to liver fibrosis (1). Cell death may occur as a result of excess extracellular matrix deposition in the liver due to the distortion of the vasculature and the inability to exchange oxygen, nutrients, and waste products between hepatocytes and liver sinusoids (2).

Carbon dioxide (CCL4) is an environmentally harmful chemical that has been found to be utilised extensively in fire extinguishers; it is also used to make refrigerants and as an industrial cleaning agent.

People are exposed to CCL4 by inhalation from the atmosphere and through contact with the skin. Because of its harmful effects, its use have been restricted to a few industrial domains (3).

Liver necrosis may occur because CCL4 releases free radicals that form lipid peroxide and change enzyme function; cell membrane damage occurs as a result; and the liver begins to degenerate (4). During liver fibrogenesis, hepatic stellate cells (HSCs) are activated.

Fibrous scarring and the breakdown of the normal hepatic architecture are the results of an elevated inflammatory response and an overabundance of extracellular matrix proteins (ECM). Cirrhosis of the liver develops quickly if untreated (5).

Despite the initial cause, mesenchymal stem cells (MSC) are being investigated as a potential treatment approach for liver fibrosis. Bone marrow, umbilical cord blood, and adipose tissue may all be used to isolate MSCs. MSCs generated from bone marrow (BM-MSCs) are the most straightforward and have received the most research attention (6). Liver fibrosis may be reduced by BM-MSCs' ability to prevent HSC activation, reduce the proliferation of activated HSCs, diminish the inflammatory response, and enhance hepatocyte regeneration via several ways (7).

Three-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor statins are often used to treat liver fibrosis. In addition to lowering cholesterol levels, statins also alleviate endothelial dysfunction and boost nitric oxide bioavailability.

Anti-fibrotic, antioxidant, anti-inflammatory and immunomodulatory activities are also present (8).
Materials and Methods

Animals: Fifty mature male albino rats weighing 200-220 g were used in this investigation. In the Faculty of Medicine, Cairo University, they were kept in the animal house unit. For a period of four months, from April to July 2019, rats were housed in a standard environment with a comfortable temperature. The care of these animals was strictly regulated by the National Research Council’s Experimental Animal Committee.

In order to get MSCs, the tibia and femur of six-week-old male albino rats (other than those in the research groups) were flushed in modified Eagle's medium supplemented with 1% penicillin streptomycin in order to obtain bone marrow for the study. After that, cells were incubated for 12-14 days in a primary culture at 37°C in 5% humidified CO2. EDTA and phosphate buffer saline (PBS) were used to clean the culture. Centrifuged for 20 minutes at 2,400 rpm, then held in place using a lubricant.

In this study, 50 adult male albino rats weighing between 200 and 220 grammes were employed. They were housed at the animal house section of Cairo University's Faculty of Medicine. Four months, from April to July of this year, rats were kept in an environment that was both conventional and pleasant. The Experimental Animal Committee of the National Research Council rigorously controlled the treatment of these animals.

Male albino rats six weeks old were used in the study to flush their tibia and femurs in modified Eagle's medium supplemented with 1% penicillin streptomycin to acquire bone marrow for the study in order to obtain MSCs. After that, cells were cultured for 12-14 days at 37°C in 5% humidified CO2 in a primary culture. EDTA and phosphate buffer saline (PBS) were employed to clean the cell culture. At 2,400 rpm, a lubricant was used to hold the sample in place while it was centrifuged for 20 minutes.
One milligramme per kilogramme of body weight per day of CCl4 diluted in 1 cc of olive oil twice a week for six weeks (10).

Ten rats were administered CCl4 for six weeks in group III (BM-MSCs-treated group). This was followed by intravenous injection of a single dose of BM-MSCs (3x106 cells in 1.5 ml of PBS). After a period of eight weeks, the rats were killed (10).

For six weeks, CCl4 was administered to ten rats in Group IV (the Simvastatin-treated group). Once this was completed, the rats were given daily doses of simvastatin, 10 mg/kg, administered via a gastrostomy tube and dissolving in a 0.5 percent solution of xanthan gum, before being euthanized (10).

As in group II, CCl4 was delivered to ten rats for six weeks in group V (MSC+ Simvastatin-treated group). Group V received the same dosages of MSCs and SIMV as group III and IV.

Diethyl ether was used to kill the rats at the conclusion of the experiment. Direct blood samples from the heart were obtained via a midline abdomeno-thoracic incision. Dissected liver samples were produced for histological testing.

Analytical testing: The serum was separated from the blood samples centrifuged at 3,000 RPM (15 minutes) in order to determine the serum levels of aspartate (AST), alkaline phosphatidase (ALP), and albumin (11).

Examinations of the histopathology
Fixed in buffered formalin at 10%, liver samples from the right lobe were embedded in paraffin. Samples were stained with hematoxylin and eosin (H&E) and Masson's trichrome stains to identify collagen fibre buildup in liver tissue after the samples had been obtained (12).

Detection of TGF-β via immunohistochemistry:
The paraffin-embedded tissues were dewaxed and rehydrated before four serial slices were taken. Sections were then treated with TGF-b polyclonal antibody and a second antibody of biotin-labeled streptavidin anti-biotin horseradish peroxidase, then blocked with 3% hydrogen peroxide and 10% nonimmune animal serum. Dehydrated in xylene after staining with diaminobenzidine and Mayer hematoxylin. The presence of TGF-b in liver tissue
The appearance of brown-deposited granules proved the existence of tissue (13).

MSC markers were detected using CD105 immunostaining in hepatic tissue that had been treated with BM-MSC. Ab27422 is the rabbit polyclonal primary antibody for the CD105 antigen (14). A morphometric analysis:

Image-Pro Plus version 6.0 (Media Cybernetics Inc., Bethesda, Maryland, USA) was used to evaluate collagen fibre accumulation and TGF-immunostaining in 10 photographs from each group.

There was a one-way analysis of variance (ANOVA) with a Post Hoc LSD test used to examine differences and comparisons between all sets of data.

Results:

Examining a person's biochemistry (table 1) AST, ALT, and ALP levels in the serum were all higher in group II as compared to the control group, but albumin levels were lower. AST, ALT, and ALP levels all decreased significantly (p 0.05), but a substantial rise (p 0.05) was seen in Groups III, IV, and V have lower serum albumin levels than Group II. Group V also had higher scores than groups III and IV.

Analyses of the Histopathology

H&E-stained liver slices from the control group exhibited normal polygonal classic hepatic lobules in both subgroups a and b. It seems that hepatocytes were spreading outward from the lobule's central vein, and that they had acidophilic cytoplasm and small vesicles; some of these hepatocytes also have two nuclei, and blood sinusoids are located between the hepatic cords (fig 1A). One of the most common features of a healthy liver is the presence of the portal vein as well as the bile duct. Hepatocytes with acidophilic cytoplasm were seen in the normal portal region, as well as the presence of some hepatocytes that had been binucleated (fig 1B).

Despite this, liver slices from group II exhibited a congested dilated central vein, as well as a large congested sinusoid. Inflammatory cells have infiltrated the cytoplasm of hepatocytes (fig 2A). The cytoplasm of the majority of hepatocytes is vacuolated, whereas some contain a deep pyknotic nucleus (fig 2B). Portal vein was infiltrated with inflammatory cells and was dilated and clogged. The cytoplasm of the majority of hepatocytes is vacuolated, while some contain a deep pyknotic nucleus (fig 2C).
For group III, there was a central vein, multiple hepatocytes with vesicular nuclei, some of which are binucleated, a few with vacuolated cytoplasm, and an open blood sinusoid in the centre of the vessel (fig 3A).

Hepatocytes with vesicular nuclei, some of which are binucleated, are common in the portal region, as are blood sinusoids with vacuolated cytoplasm and blood vessels (fig 3B) hepatocytes in group IV had binucleated, vacuolated cytoplasm, and a congested central vein, as well as a broad sinusoid and hepatocytes with vesicular nuclei (fig 4A). Hepatocytes with vesicular nuclei, other hepatocytes with pyknotic nuclei, and others with vacuolated cytoplasm were seen in the portal region, as were a clogged portal vein, a broad sinusoid, and an inflammatory cell infiltrate (fig 4B).

Sections of the liver from group V, on the other hand, exhibited mostly typical hepatic tissue, with hepatocytes emanating from the central vein, vesicular nuclei, and acidophilic cytoplasm in some of the hepatocytes (fig 5A). Some hepatocytes in the portal region had two nuclei, whereas others had typical blood sinusoids; the portal vein was present (fig 5B)

Sections of liver stained with Masson trichrome in the control group revealed very little deposition of collagen fibres in the portal region (fig 6A).

While in group II, collagen fibres were clearly visible surrounding the portal region (fig 6B). Group III, on the other hand, revealed a modest accumulation of collagen fibres surrounding the portal region (fig 6C). Collagen fibre deposition around the portal region was considerable in group IV (fig. 6D), while collagen fibre deposition around the portal area was minimal in group V (fig. 6E) (fig 6E).

Liver slices stained with TGF-b1 immunostaining from the control group exhibited just a little amount of positive reactivity (fig 7A). There was a considerable level of positive immunostaining in the second group (fig 7B). Group III, on the other hand, had just a minor response (fig 7C). Group IV's response was modest (fig 7D). There was a little amount of immune-positive reactivity in group V, however (fig 7E).

Detection of CD105 positive stem cells by immunohistochemical labelling in liver sections from the control group was negative (fig 8A). CD105 antibody had a positive response only in groups III and V (figures 8B& 8C), showing the existence of stem cells.
Table (1): Serum levels of AST, ALT, ALP and Albumin in groups I, II, III, IV and V

<table>
<thead>
<tr>
<th>Group</th>
<th>AST (U/L)</th>
<th>ALT(U/L)</th>
<th>ALP (U/L)</th>
<th>Albumin (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>100.55±0.44</td>
<td>46.45±1.5</td>
<td>130.68±0.6</td>
<td>3.47±0.08</td>
</tr>
<tr>
<td>II</td>
<td>245.73±0.97a</td>
<td>111.57±2.3a</td>
<td>285.68±0.86a</td>
<td>2.25±0.1a</td>
</tr>
<tr>
<td>III</td>
<td>135.85±0.62ab</td>
<td>74.35±0.84ab</td>
<td>185.55±0.62ab</td>
<td>2.93±0.14ab</td>
</tr>
<tr>
<td>IV</td>
<td>188.28±1.1abc</td>
<td>91.1±0.53abc</td>
<td>218.67±0.93abc</td>
<td>2.58±0.12abc</td>
</tr>
<tr>
<td>V</td>
<td>116.58±0.74abcd</td>
<td>55.85±1.1abcd</td>
<td>148.97±0.71abcd</td>
<td>3.03±0.15abcd</td>
</tr>
</tbody>
</table>

Values are expressed as means ± SD, Value p < 0.05 is significant. a p < 0.05 compared with Group I (control group); b p < 0.05 compared with Group II (CCL4 group); c p < 0.05 compared with Group III (MSCs-treated group); d p < 0.05 compared with Group IV (simvastatin-treated group).

Table (2): The mean area % and SD of collagen fibers deposition in groups I, II, III, IV and V

<table>
<thead>
<tr>
<th></th>
<th>Group I</th>
<th>Group II</th>
<th>Group III</th>
<th>Group IV</th>
<th>Group V</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>0.18%</td>
<td>5.24%</td>
<td>1.77%</td>
<td>2.56%</td>
<td>0.25%</td>
</tr>
<tr>
<td>SD</td>
<td>0.0407</td>
<td>0.8591</td>
<td>0.1328</td>
<td>0.6159</td>
<td>0.0434</td>
</tr>
<tr>
<td>Significance at P &lt; 0.01</td>
<td>Groups 2,3,4</td>
<td>Groups 1,3,4,5</td>
<td>Groups 1,2,3,5</td>
<td>Groups 1,2,3,5</td>
<td>Groups 2,3,4</td>
</tr>
</tbody>
</table>

1=sig. with group I  2=sig. with group II  3=sig. with group III  4=sig. with group IV  5=sig. with group V
Table (3): The mean area % and SD of TGF-β1 immunostaining in groups I, II, III, IV and V

<table>
<thead>
<tr>
<th></th>
<th>Group I</th>
<th>Group II</th>
<th>Group III</th>
<th>Group IV</th>
<th>Group V</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean area %</td>
<td>0.39%</td>
<td>7.12%</td>
<td>1.78%</td>
<td>2.71%</td>
<td>0.53%</td>
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<tr>
<td>SD</td>
<td>0.0455</td>
<td>0.4731</td>
<td>0.1571</td>
<td>0.1792</td>
<td>0.0851</td>
</tr>
<tr>
<td>Significance at P &lt; 0.01</td>
<td>Groups</td>
<td>Groups</td>
<td>Groups</td>
<td>Groups</td>
<td>Groups</td>
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<tr>
<td></td>
<td>2,3,4</td>
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<td>1,2,4,5</td>
<td>1,2,3,5</td>
<td>2,3,4</td>
</tr>
</tbody>
</table>

1=sig. with group I  2=sig. with group II  3=sig. with group III  4=sig. with group IV  5=sig. with group V

Figure (1) photographs of liver sections from the control group showing, A: Normal polygonal classic hepatic lobule, hepatocytes are radiating from the central vein (CV) toward the periphery of the lobule, hepatocytes are with vesicular nuclei and acidophilic cytoplasm (arrows), some hepatocytes are binucleated (head arrows), blood sinusoids are in between hepatocytic cords (wavy arrows). B: Normal portal area contain portal vein (PV) and bile duct (BD), hepatocytes are with vesicular nuclei and acidophilic cytoplasm (arrows), some hepatocytes are binucleated (head arrows), blood sinusoids are in between hepatocytic cords (wavy arrows). (H&E X 400)

Figure (2) photographs of liver sections from CCL4 group showing, A: congested dilated central vein (CV), wide congested sinusoid (wavy arrow), hepatocytes have vacuolated cytoplasm (arrow) and marked inflammatory cell infiltration (I). B: congested central vein (CV), wide congested sinusoid (wavy arrow). Most hepatocytes have vacuolated cytoplasm (arrow), others with deep pyknotic nucleus (head arrow) C: portal area contains dilated congested portal vein (PV), bile duct (BD), with inflammatory cell infiltration (I). Most hepatocytes have vacuolated cytoplasm (arrow) and others with deep pyknotic nucleus (head arrow) (H&E X 400)
**Figure (3)** photographs of liver sections from MSCs - treated group showing, A: central vein (CV), numerous hepatocytes with vesicular nucleus (arrows), some hepatocytes are binucleated (head arrows), few with vacuolated cytoplasm (curved arrow) and dilated blood sinusoid open in central vein (wavy arrows). B: portal area with portal vein (PV), few inflammatory cell infiltration (I), numerous hepatocytes with vesicular nucleus (arrows), some hepatocytes are binucleated (head arrow), few with vacuolated cytoplasm (curved arrows) and blood sinusoids (wavy arrows). (H&E X 400)

**Figure (4)** photographs of liver sections from simvastatin - treated group showing, A: congested central vein (CV), wide sinusoid (wavy arrow), hepatocytes with vesicular nucleus (arrow), other hepatocytes are binucleated (head arrow), some with vacuolated cytoplasm (curved arrow). B: congested portal vein (PV), bile duct (BD), wide sinusoid (wavy arrow), inflammatory cell infiltration (I), hepatocytes with vesicular nucleus (arrow), other hepatocytes with pyknotic nucleus (head arrow), some with vacuolated cytoplasm (curved arrow) (H&E X 400)

**Figure (5)**: photographs of liver sections from MSCs+Simvastatin- treated group showing, A: nearly normal hepatic tissue the hepatocytes are radiating from the central vein (CV), hepatocytes are with vesicular nuclei and acidophilic cytoplasm (arrow), some hepatocytes are binucleated (head arrows), sinusoids are in between hepatocytic cords (wavy arrow). B: portal area with portal vein (PV), hepatocytes with vesicular nucleus (arrows), some hepatocytes are binucleated (head arrow), and normal blood sinusoids (wavy arrows. (H&E X 400)
Figure (6): photographs of liver sections stained by Masson trichrome. A: from the control group showing scanty collagen fibers deposition (arrow) around the portal area. B: from the CCL4 group showing marked collagen fibers deposition (arrow) around the portal area. C: from the MSCs-treated group showing mild collagen fibers deposition (arrow) around the portal area. D: from the simvastatin -treated group showing moderate collagen fibers deposition (arrow) around the portal area. E: from the MSCs+ simvastatin -treated group showing few collagen fibers deposition (arrow) around the portal area. (Masson trichrome X400). F: a histogram showing the mean area percent of collagen fibers deposition in groups I, II, III, IV and V.
Figure (7): photographs of liver sections stained by TGF b immunostain. A: from the control group showing scanty TGF b immune positive reaction. B: from CCL4 group showing high TGF b immune positive reaction (arrow) in between hepatocytes. C: from MSCs - treated group showing mild TGF b immune positive reaction (arrow) around the central vein. D: from simvastatin - treated group showing mild TGF b immune positive reaction (arrow) in between hepatocytes. E: from MSCs+ simvastatin - treated group showing little TGF b immune positive reaction (arrow) in between hepatocytes. (TGF b immunostaining X 400). F: a histogram showing the mean area percent of TGF b immune-positive expression in groups I, II, III, IV and V.

Figure (8): photographs of liver sections stained by CD 105 immunostain. A: from the control group showing negative immune reaction for stem cells. B: from MSCs- treated group showing positive immune reaction for stem cells (arrow). C: from MSCs + simvastatin- treated group showing positive immune reaction for stem cells (arrow). (CD 105 immunostaining X 400)
Discussion

Metabolic equilibrium relies heavily on the liver. Too much collagen and ECM deposition leads to hepatic tissue fibrosis. Lipid peroxidation, the generation of reactive free radical metabolites, and the disruption of calcium homeostasis all contribute to the hepatic damage caused by CCL4 (15).

Preventing liver fibrosis with bone marrow mesenchymal stem cells has been recommended (16). Through the production of numerous bioactive chemicals, BMSCs may promote the repair of injured hepatic cells and prevent inflammation, in addition to indirectly modulating the activation of hepatic satellite cells (17).

The most effective medications for treating portal hypertension and associated consequences are statins. Statins have anti-inflammatory, immunomodulatory, and vasoprotective properties (18). Improvement in phenotype and function of sinusoidal endothelial cells, as well as a favourable role in reduction of hepatic stellate cell activity and proliferation, were achieved by simvastatin (19).

CCL4-induced hepatic fibrosis in rats will be compared to the effects of BM-MSCs, simvastatin, or a combination of both on this research.

With respect to the control group's levels of AST, ALT, ALP and albumin, CCL4 significantly raised these markers of liver failure and significantly decreased albumin levels. It was found that the hepatic tissue architecture had been lost, with congested dilated central vein and portal vein, broad congested sinusoid. There is a lot of inflammation invading hepatocytes' cytoplasm. In addition, the mean area percentage of collagen fibre deposition and TGF β immunopositive expression increased significantly. CCL4 caused severe damage to hepatic structures, increasing the production of anti—smooth muscle actin and caspase 3 in hepatic stellate cells, as discovered by (20). Congestion of portal veins and dilatation of the bile duct was also observed to be produced by CCL4 (21), as well as hepatocytes with vacuolated cytoplasm and a rise in TNF- and PCNA (22).
Reaction that is positive for antibodies. Chronic exposure to CCL4 seems to outpace the liver's capacity to regenerate and revert to its natural structure, according to another study (22).

Several other studies revealed that hepatic fibrosis arises as a result of an unbalanced transformation of HSCs into myofibroblast-like cells and extracellular matrix synthesis, which enhances the expression of TGF-1 (23).

TGF-1 fibrogenic activity is strongly influenced by inflammation, according to (24). HSCs are transformed into myofibroblasts by endoglin and growth factors, which are known as key profibrogenic cytokines (25).

Replacement of damaged cells with new hepatocytes and reduction of ECM accumulation is the most effective therapy for liver injury. Anti-fibrogenic substances released by MSCs aid in the prevention of fibrosis (26).

In comparison to the CCL4 group, MSCs significantly improved the biochemical markers of liver function by lowering AST, ALT, and ALP levels and raising serum albumin levels. The natural appearance of MSCs was partially retained.

There were many hepatocytes with vesicular nucleus, some hepatocytes were binucleated, with a substantial decrease in the mean area percent of collagen fibres deposition and TGF b immunological positive expression compared to group II.

Antifibrotic effects of bone marrow-derived stem cells (BM-MSCs) have been clearly shown in this study, which is consistent with the findings of (27), who reported that BM-MSCs can restore normal histological structure in CCL4-induced liver fibrosis. CCl4 toxicity was reduced by BM-MSCs and improved liver function tests. MSCs have previously been shown to have therapeutic promise in the treatment of rat liver fibrosis, according to previous investigations (10& 28).

MSCs play an important function in preventing fibrogenesis in the liver by preventing HSCs from transitioning from a quiet to an active state (29).

Profibrotic genes were repressed and antifibrotic genes were activated by BM-MSCs, according to another research (30).

The potential of BM-MSCs to release vascular endothelial growth factor (VEGF) that has anti-apoptotic, antifibrotic action and regenerates liver tissue was described in another research (31). Additionally, (32) discovered that MSCs normalise IgA and IgM levels.
mitochondrial glutathione peroxidase activity in fibrotic rats.

In a wide range of liver illnesses, statins have a pleiotropic impact. A drop in 3-hydroxy-3-methyl-glutaryl-coenzyme reductase activity led to a decrease in isoprenoid production, as the ensuing altered GTPase activity plays a vital role in the treatment of most chronic liver illnesses (33).

When compared to the CCL4 group, simvastatin significantly reduced AST, ALT, and ALP levels while also significantly elevating serum albumin levels, all of which were associated with modest improvements in liver function tests.

There was still a congested central vein, a large sinusoid, some cells with vacuolated cytoplasm, and a substantial drop in mean area percent of collagen fibres and TGF β immune positive expression in the liver tissue of those using simvastatin compared to those taking placebo. When compared to group IV, group III had better biochemical and histological results, indicating that MSCs had a more effective antifibrotic impact than simvastatin in the therapy of liver fibrosis.

Simvastatin inhibits endotoxemia produced by chronic liver disease, as indicated by researcher (34) in this study. Simvastatin, on the other hand, has been shown to be both safe and effective for people with cirrhosis. The use of statins for the purpose of decreasing blood cholesterol levels was linked to a reduction in the development of hepatic decompensation and hepatocellular carcinoma in a retrospective investigation of individuals with cirrhosis and pre-cirrhosis.

When simvastatin and MSCs were given together, liver function tests were markedly preserved as AST/ALT/ALP/Serum Albumin levels were practically identical to the control group’s values. Compared to groups II, III, and IV, there was a considerable preservation of normal hepatic tissue structure with a significant decrease in the mean area percentage of collagen fibre deposition and TGF β immune-positive expression. These findings are consistent with those from (10).

Liver fibrosis in 2021: MSCs and statins

As an antifibrotic agent, Simvastatin and MSCs have a function in maintaining a delicate balance between matrix metalloproteinases and their inhibitors, which is critical to fibrogenesis, according to the authors. When combined with MSCs, another research indicated
that simvastatin provided stronger protection against liver fibrosis by inhibiting the growth factors TGF- and Smad3 as well as smooth muscle actin in cirrhotic liver HSCs. As a successful treatment for liver cirrhosis, simvastatin and stem cells may work in conjunction (38). In a recent research, it was shown that statins may help stem cells differentiate into a certain kind of cell. Statins aid angiogenesis, cell homing in transplantation, and protect cells from hypoxia (39).

Conclusion

When it came to treating liver fibrosis, BM-MSCs had a better impact than Simvastatin. Combining both of them was the most effective therapy for CCl4-induced fibrosis of the liver.

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