Liv.52 DS Tablets

Evaluation of Efficacy and Safety in Alcoholic Liver Cirrhosis

ABSTRACT

The present study was planned to evaluate the clinical efficacy and safety of Liv.52 DS tablet in alcoholic liver cirrhosis. Alcoholic liver disease is a major cause of morbidity and mortality worldwide. Alcohol can cause liver damage in the form of steatosis or fatty liver, hepatitis, fibrosis, and liver cirrhosis.

The present study was an open clinical trial, conducted as per the ethical guidelines of Declaration of Helsinki. All patients suffering from early alcoholic cirrhosis were included in the study, while patients having evidence of esophageal varices, hepatic encephalopathy and malignant jaundice, and pregnant women were excluded from the study. A thorough history, symptomatic evaluation and clinical examination was done for all patients before treatment and during follow-up visits every month till the end of treatment after 6 months along with recording the occurrence of any adverse event/s. Liver function tests, hemogram and other biochemical tests were done at baseline and at the end of the study after 6 months. The predefined primary endpoints were rapid relief from clinical symptoms and physical signs along with improvement of efficacy biochemical parameters. The predefined secondary endpoints were short- and long-term safety, and overall compliance to the drug treatment.

A total of 50 patients were enrolled into the trial and all patients completed the study. The study observed a significant reduction in the clinical symptom scores of asthenia, easy fatigability, tiredness, nausea, anorexia, abdominal discomfort, abdominal pain, stool frequency and muscle cramps; physical sign scores of muscle wasting, jaundice, anemia, edema, ascites, and hepatomegaly; and liver function test parameters of alanine transaminase, aspartate transaminase, total bilirubin, alkaline phosphatase, albumin, and prothrombin time at the end of the 6-month therapy with Liv.52 DS tablet. There were no clinically significant adverse events, either reported or observed, during the entire study period. Therefore, it may be concluded that Liv.52 DS tablet is clinically safe and effective in the management of alcoholic liver cirrhosis.

INTRODUCTION

Alcoholic liver disease is a major cause of morbidity and mortality worldwide. In Western countries, up to 50% of end-stage liver disease has alcohol as the main etiologic factor. The mortality from alcoholic cirrhosis is higher than nonalcoholic cirrhosis, and survival at 5 and 10 years is only 23% and 7% in some studies, with 25% of patients dying within 1 year. Alcohol can cause liver damage in the form of steatosis or fatty liver, hepatitis, fibrosis, and liver cirrhosis. In general, the amount and duration of alcohol abuse...
correlate with the presence and severity of liver damage, at least with respect to the initial stage of fatty liver. Combinations of herbal medicines are commonly prescribed for liver disease with anecdotal reports of good results. Liv.52 DS tablet is a combination of such medicines that are often prescribed for their use in alcoholic liver disease. The current treatment is directed at the management of the complications of cirrhosis and prevention of further liver damage.

Liv.52 DS tablet is a polyherbal formulation that consists of powders of Capparis spinosa, Cichorium intybus, Solanum nigrum, Cassia occidentalis, Terminalia arjuna, Achillea millefolium, Tamarix gallica and Mandur bhasma. It is a hepatotonic and has been used traditionally in the treatment of various liver disorders. This study was planned to evaluate the clinical efficacy and safety of Liv.52 DS tablet in the management of alcoholic liver cirrhosis.
**PATIENTS AND METHODS**

**Inclusion criteria**
All patients aged between 28 to 71 years, and suffering from early alcoholic cirrhosis were included in the study.

**Exclusion criteria**
Patients having evidence of esophageal varices, hepatic encephalopathy and malignant jaundice, and pregnant women were excluded from the study.

**Study procedure**
The study was an open, non-randomized and non-comparative, prospective clinical trial, conducted at the Department of Gastroenterology, Jagjivanram Western Railway Hospital, Mumbai Central, Mumbai, India, as per the ethical guidelines of Declaration of Helsinki. The study protocol, case report forms (CRFs), regulatory clearance documents, product-related information, and informed consent forms (in English, Hindi and Marathi) were submitted to the institutional ethics committee and were approved by the same.

The patients who attended the OPD general surgical unit of Department of Gastroenterology, Jagjivanram Western Railway Hospital, Mumbai Central, Mumbai, India were informed about the study drug, its effects, duration of the trial, and overall plan of the study. The patients were included in the clinical study only after written informed consent was obtained from each of them, and a witness, independent of the clinical trial, signed the informed consent form.

The history was noted by interviewing the patient. Thorough clinical examination and symptomatic evaluation was carried out and the details were noted down in the CRF. Patients were advised to take Liv.52 DS tablet at a dose of 1 tablet twice a day, for 6 months.

All patients were reviewed every month till the end of treatment, and symptomatic evaluation and clinical examination was done, along with recording the occurrence of any adverse event/s (either reported or observed).

Liver function tests, hemogram and other biochemical tests were done at baseline and at the end of the study after 6 months.

**Primary and secondary endpoints**
The predefined primary endpoints were rapid relief from clinical symptoms and physical signs along with improvement of biochemical parameters. The predefined secondary endpoints were short- and long-term safety as assessed by no change in the safety biochemical parameters, and overall compliance to the drug treatment.

**Adverse events**
All adverse events, either reported or observed, were recorded in the CRF with information about severity, onset, duration, and action taken regarding the study drug. Relation of adverse events to the study medication was predefined as "unrelated" (a reaction that does not...
follow a reasonable temporal sequence from the time of administration of the drug), “possible” (follows a known response pattern to the suspected drug, but could have been produced by the patient’s clinical state or other modes of therapy administered to the patient), and “probable” (follows a known response pattern to the suspected drug that could not be reasonably explained by the known characteristics of the patient’s clinical state).

Patients were allowed to voluntarily withdraw from the study, if they experienced serious discomfort during the study or sustained serious clinical events requiring specific treatment. For patients withdrawing from the study, efforts were made to ascertain the reason for dropout. Non-compliance (defined as failure to take less than 80% of the medication) was not regarded as treatment failure, and reasons for non-compliance were noted.

**Statistical analysis**

Statistical analysis was done according to intention-to-treat principles. The changes in various parameters from pre-treatment values to post-treatment values were carried out using Fisher’s exact test for all parameters, except hepatomegaly. Analysis for hepatomegaly was carried out using Friedman’s test followed by Dunnett’s multiple comparison Posthoc test. Statistical analysis for biochemical parameters was carried out using Student’s paired t-test. The minimum level of significance was fixed at 95% confidence limit and a 2 sided p value of <0.05 was considered significant.

**RESULTS**

A total of 50 patients with alcoholic cirrhosis were included in the clinical trial and 40 patients completed the trial. A significant reduction (p<0.005 to p<0.0001) was observed with the clinical symptom scores of asthenia, easy fatigability, tiredness, nausea, anorexia (Figure 1), abdominal discomfort, abdominal pain, stool frequency, and muscle cramps (Figure 2) after 6 months of treatment with Liv.52 DS tablet. Improvement in the clinical symptoms started appearing in the 1st month of the treatment itself.

A significant reduction (p<0.023 to p<0.001) in physical sign scores was observed with muscle wasting, jaundice, anemia, edema, ascites, and hepatomegaly (Figure 3) at the end of the 6-month treatment with Liv.52 DS tablet. Significant improvement in the
Table 2. Efficacy of Liv.52 DS tablet in physical signs of alcoholic liver cirrhosis patients

<table>
<thead>
<tr>
<th>Sl. No.</th>
<th>Physical signs</th>
<th>Pre-treatment</th>
<th>1st month</th>
<th>2nd month</th>
<th>3rd month</th>
<th>4th month</th>
<th>5th month</th>
<th>6th month</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Muscle wasting</td>
<td>20</td>
<td>18 (NS)</td>
<td>12 (NS)</td>
<td>12 (NS)</td>
<td>9 (p&lt;0.019)</td>
<td>9 (p&lt;0.019)</td>
<td>7 (p&lt;0.004)</td>
</tr>
<tr>
<td>2.</td>
<td>Jaundice</td>
<td>21</td>
<td>17 (NS)</td>
<td>17 (NS)</td>
<td>11 (p&lt;0.039)</td>
<td>8 (p&lt;0.005)</td>
<td>8 (p&lt;0.005)</td>
<td>9 (p&lt;0.01)</td>
</tr>
<tr>
<td>3.</td>
<td>Anemia</td>
<td>20</td>
<td>17 (NS)</td>
<td>14 (NS)</td>
<td>11 (NS)</td>
<td>8 (p&lt;0.009)</td>
<td>8 (p&lt;0.009)</td>
<td>8 (p&lt;0.009)</td>
</tr>
<tr>
<td>4.</td>
<td>Edema</td>
<td>15</td>
<td>16 (NS)</td>
<td>11 (NS)</td>
<td>7 (NS)</td>
<td>5 (p&lt;0.018)</td>
<td>5 (p&lt;0.018)</td>
<td>5 (p&lt;0.018)</td>
</tr>
<tr>
<td>5.</td>
<td>Ascites</td>
<td>16</td>
<td>12 (NS)</td>
<td>11 (NS)</td>
<td>8 (NS)</td>
<td>6 (p&lt;0.023)</td>
<td>6 (p&lt;0.023)</td>
<td>6 (p&lt;0.023)</td>
</tr>
<tr>
<td>6.</td>
<td>Hepatomegaly</td>
<td>1.80 ± 0.88</td>
<td>1.18 ± 0.50 (NS)</td>
<td>1.13 ± 0.46 (p&lt;0.05)</td>
<td>1.08 ± 0.47 (p&lt;0.05)</td>
<td>0.95 ± 0.44 (p&lt;0.001)</td>
<td>0.88 ± 0.40 (p&lt;0.001)</td>
<td>0.85 ± 0.43 (p&lt;0.001)</td>
</tr>
</tbody>
</table>

Statistical analysis was carried out using Fisher’s exact test for all parameters, except hepatomegaly. Analysis for hepatomegaly was carried out using Friedman’s test followed by Dunnett’s multiple comparison Posthoc test.

physical signs started from 4th month of the therapy. A significant reduction (p<0.03 to p<0.0001) in liver function test parameters of alanine transaminase, aspartate transaminase, total bilirubin, alkaline phosphatase, albumin, and prothrombin time (Figure 4) were observed at the end of the 6-month therapy, as compared to pre-treatment values. There was no alteration in hematological and other biochemical safety parameters as compared to before and after the treatment. There were no clinically significant adverse events, either reported or observed, during the entire study period.

DISCUSSION

Cirrhosis is a chronic disease due to liver cell damage and proliferation of fibrous tissue. The damage eventually becomes extensive and normal structure of the liver is distorted and its function becomes impaired. This abnormality affects almost every physiologic process including digestion, endocrine, circulatory, and other metabolic functions. These changes themselves slowly aggravate liver damage. The aim of treatment in cirrhotic patients is to prevent metabolic abnormalities and progression of liver cell damage. The traditional healers’ approach to management of chronic liver disease is to regulate and strengthen the liver, gastrointestinal and immune system. Regulation of gastrointestinal system may improve the general well being of patients, while improvement of constipation may prevent absorption of harmful substances and indirectly decrease ascites.

The protection of liver cells against toxic materials including drugs, lipid peroxidation and free radical injury may decrease inflammation, improve liver blood flow and ultimately help in reduction of ascites and blood pressure. Immune dysfunction is a component of liver disease and thus, immunomodulation by herbal therapy prevents oxidative stress, inflammation and strengthens the detoxifying power of liver cells.

All these effects strengthen liver, regulate body metabolism and ultimately inhibit further liver cell damage by favoring regeneration.

The present clinical study observed a significant reduction in the clinical symptom scores of asthenia, easy fatigability, tiredness, nausea, anorexia, abdominal discomfort, abdominal pain, stool frequency, and muscle cramps after 6 months of treatment with Liv.52 DS tablet. A significant reduction in physical sign scores was observed with muscle wasting, jaundice, anemia, edema, ascites, and hepatomegaly at the end of the 6-month treatment with Liv.52 DS tablet. A significant reduction in liver function test parameters of alanine transaminase, aspartate transaminase, total bilirubin, alkaline phosphatase, albumin, and prothrombin time were observed at the end of the 6-month therapy, as compared to pre-treatment values. There were no clinically significant adverse events, either reported or observed, during the entire study period.

Although the exact mechanism of Liv.52 DS tablet on liver function as well as body metabolism is not yet clearly known, it can be stated that the medicinal herbs of Liv.52 DS tablet, alone or in combination, can influence cellular functions and body metabolism.

The diuretic effect of Terminalia arjuna and anti-inflammatory and anti-immunotoxicity effect of Cichorium intybus have been shown in
Figure 3. Efficacy of Liv.52 DS tablet in physical signs of muscle wasting, jaundice, anemia, edema, ascites, and hepatomegaly in alcoholic liver cirrhosis patients

**Muscle wasting**

*\( p<0.019 \) and *\( p<0.004 \) as compared to pre-treatment value

**Jaundice**

*\( p=0.039 \), *\( p=0.005 \) and *\( p=0.01 \) as compared to pre-treatment value

**Anemia**

*\( p<0.009 \) as compared to pre-treatment value

**Edema**

*\( p=0.018 \) as compared to pre-treatment value

**Ascites**

*\( p<0.023 \) as compared to pre-treatment value

**Hepatomegaly**

*\( p<0.05 \) and *\( p<0.001 \) as compared to pre-treatment value

clinical and experimental studies.\(^{11-13}\)

The anti-oxidative and anti-hepatotoxic property of esculetin and p-methoxybenzoic acid, the main constituents of *Cichorium intybus* and *Capparis spinosa*, respectively, have been reported in chemically-induced hepatotoxicity in experimental animals.\(^{14-16}\) *Achillea millefolium*, another component of Liv.52 DS tablet, contains several bioactive constituents including flavonoids and terpenoids with anti-oxidative and anti-inflammatory properties.\(^{17-19}\)

The curative and hepatoprotective effect of Mandur bhasma and *Cassia occidentalis*, the other two components of Liv.52 DS tablet, were observed against chemically-induced liver damage in experimental animals.\(^{20,21}\) Furthermore, the anti-oxidative property of flavonoid content of
**CONCLUSION**

Liver cirrhosis is a commonly encountered syndrome in medical practice. However, there is no clinically effective and safe medication that can be recommended in the management of alcoholic liver cirrhosis. This study was conducted to evaluate the clinical efficacy and safety of Liv.52 DS tablet in alcoholic liver cirrhosis.

This study observed a significant relief from the clinical symptoms and physical signs, and a reduction in liver function test parameters at the end of the 6-month therapy, as compared to pre-treatment values. There were no clinically significant adverse events, either reported or observed, during the entire study period. Thus Liv.52 DS tablet, directly or indirectly, influences the cellular...
and body metabolism and plays favorable and protective role in maintaining liver integrity and restoring its function. Hence, Liv.52 DS tablet is beneficial in the treatment of cirrhotic patients. Therefore, it may be concluded that Liv.52 DS tablet is clinically safe and effective in the management of alcoholic liver cirrhosis.

REFERENCES


