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Evaluation of Efficacy and Safety of "Test Drug" in Liver Disorder Subjects with Abnormal Liver Function Test (LFT) - An Open Labeled, Multicenter, Non-Comparative, Interventional, Prospective Clinical Study

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Abstract: ***Background: Test drug is a polyherbal formulation developed by Sava Healthcare Ltd, for the management of various liver disorders. Aim: The main aim was to evaluate efficacy and safety of Test drug in liver disorder subjects with abnormal liver function test (LFT). Materials and Methods: An open labeled, multicenter, non-comparative, interventional, prospective clinical study was conducted.Subjects were advised to consume 2 tablets of Test drug twice daily orally after meals with water for 2 months or till complete normalization of LFT whichever was earlier. The efficacy endpointswere change in AST, ALT, serum total bilirubin, adverse events, vital parameters and safety laboratory parameters. Efficacy endpoints were analyzed using student paired t test. P values were reported based on two-sided tests and interpreted at 5% level of significance. Results: 53 subjects completed the study. Test drug was safe and significantly effective in normalizing elevated liver enzymes. Normalization of elevated liver enzymes happened in 15 days in few subjects. At the end of the treatment, liver functions were within normal limits in all the subjects. Test drug was also effective in reducing inflammation and fatty liver changes as observed in USG findings. Mild to moderate adverse events reported which were not related to the study drug. No significant change in any of the safety laboratory parameters and vitals was observed. Conclusion: Test drug is safe and effective medicine for the treatment of Liver Disorder Patients with Abnormal Liver Function Test.***

Keywords: Alcoholic hepatitis, Alcoholic fatty liver disease, Abnormal Liver Function Test, Liver Disorder

1. Introduction

Alcohol, drugs, xenobiotics, viruses, and metabolites can damage liver cells and release aspartate aminotransferase (AST) and alanine aminotransferase (ALT) into blood circulation. The diagnostic indicators of liver diseases and injury include increase in serum AST and ALT, jaundice, increase in clotting times, edema, and hepatic encephalopathy. Liver diseases impair liver metabolic functions and progress to fatty liver disease, hepatic fibrosis and cirrhosis[1-2].

Therapies developed for various liver diseases are often limited in efficacy, carry risk of adverse effects and are often too costly, especially for the developing world. Therefore treating liver diseases with plant-derived compounds which are accessible and do not require laborious pharmaceutical synthesis seems highly attractive. Furthermore, in spite of the advances in conventional medicine in the last decades, professionals and the lay public of developed countries pay increasing attention to phytomedicine [3-11].

"Test drug" is developed by Sava Healthcare Ltd for SavestaLifesciences INC, an Ayurvedic Proprietary Medicine. Test drug is approved by State FDA as LIVO Tablet [Table 1]. Almost all ingredients possess heaptoprotective activity against various heapatotoxins such as alcohol, drugs, viruses and chemicals. Ingredients help to normalize elevated liver enzymes, increases bile secretion (Cholerectic property) from liver and improves overall liver function. Looking at the activities of the ingredients of the Test drug, a hypothesis was postulated that Test drug could be useful in the management of various liver disorders. Hence to test the hypothesis a clinical study was planned.

2. Materials and Methods

This was an open labeled, multicenter, non-comparative, interventional, prospective clinical study. The primary objective was to assess efficacy of test drug by assessing AST and ALT from baseline visit to each visit and end of therapy.Secondary objectives were to assess efficacy and safety of test drug by assessingserum total bilirubin, adverse events, vital parameters and safety laboratory parameters. Males or females subjects of age18-65 years, with diagnosis of hepatic disorder with abnormal LFT (Serum total bilirubin level ≥ 2 mg/dl, or AST or ALT >2 times ULN) with or without signs and symptoms such as dark-colored urine, light-colored stools, pruritus, pruritic red hives, fever, nausea, vomiting, anorexia, and right upper abdominal discomfort, pain or feeling of pressure and with or without fatty liver changes observed in ultrasonography of abdomen

were enrolled in the study. Subjects were excluded if: (1) duration of clinically apparent jaundice >3 months (2) other causes of liver disease including evidence of chronic viral hepatitis (Hepatitis B or C) and Biliary obstruction (3) previous entry into the study, or use of either prednisolone within 6 weeks of admission (4) AST >500 U/L or ALT >300 U/L (5) suspected hypersensitivity to contents of study drug (6) suffering from advanced liver disease, uncontrolled diabetes, multisystem failure, HIV, cancer, severe renal insufficiency, serious cardiovascular disease and patients with history of gastritis, peptic ulcer, bleeding ulcer, renal failure (7) pregnant or lactating

On screening visit, a written informed consent was obtained from subject. Subject's medical and surgical history was taken and investigations [CBC, ESR, Hb%, BSL-F, Liver function tests, Renal function tests, Lipid profile, urine examinations, HIV test, screening of hepatitis B and C and UPT (only for fertile females)] were done. Subject's chest x-ray PA view (to rule out tuberculosis), ECG (to rule out arrhythmia and recent ischemia) and USG of abdomen (to rule out cirrhosis and to confirm fatty liver and hepatitis) were done. Subjects were advised to refrain from any conventional treatment for liver disorder. Subject was called for baseline visit assessment (day 0).

On baseline visit, subjects were recruited if he/she met all the inclusion criteria. Subjects underwent general and systemic examinations. On baseline visit and every follow up visit, Clinical signs and symptoms (if any) were evaluated on subjective assessment scale, where 0 represented absence of sign and symptom, 1= mild, 2=moderate and 3= severe sign and symptom. Subjects were advised not to consume alcohol during the study period. Subjects were given study medication packed in HDPE bottle (each containing 80 tablets). Subjects were advised to take study medication in a dose of 2 tablets twice daily orally after meals with water for next 60 days or till complete normalization of liver functions whichever was earlier. Subjects who continuously missed dosing for >3 consecutive days or total missed dose >6 days during the study period were treated as dropouts. Subjects were called for follow up on day 15, day 30, day 45 and day 60 or till complete normalization of liver functions whichever was earlier. Subjects were allowed to come for follow up either 5 days prior or after the scheduled follow up visit, provided subject continued the given treatment. Subject's Liver functions test was done on every follow up visit. If subject's liver function tests were within normal limit, then subject was treated as completers. Subject's global evaluation and Investigator's global evaluation for overall improvement were done on last follow up. Tolerability of the Test drug was assessed by the investigator and subject on last follow up. Subjects were advised to do safety laboratory tests, USG upper abdomen and ECG. Subjects were closely monitored for any adverse events from baseline visit till the end of the study.

The study was initiated only after a written approval was obtained from Independent/ Institutional Ethics Committee (IEC) and subsequent registration of the study on CTRI website The CTRI number of the study is CTRI/2018/04/013034 Registered on: 04/04/2018. The study was conducted as per approved protocol and as per Good Clinical Practices guidelines given by AYUSH in March 2013.

3. Statistical Analysis

Based on the assumptions that reduction in SGOT after treatment would be 96.0% (with mean change in SGOT is 743.8) with desired precision of 5%, a total of 50 completed cases were needed to assess the study objective at 80% power and 5% level of significance. The efficacy variables were analyzed using student paired t test, student t test, chi square test. Adverse events were summarized counting both the number of separate events and the number. Laboratory investigations and vital signs were analyzed using student t test.All P values were reported based on two-sided tests and these statistical tests were interpreted at 5% level of significance.

Table 1: Composition of the Test drug

Sr. No.	*Ingredient*	*Botanical name*	*Part Used*	*Quantity*
1.	Punarnava Extract	*Boerhaaviadiffusa*	Whole Plant	110 mg
2.	Bhumyamalaki Extract	*Phyllanthusniruri*	Whole Plant	100 mg
3.	Guduchi Extract	*Tinosporacordifolia*	Stem	70 mg
4.	Daruharidra Extract	*Berberisaristata*	Root	50 mg
5.	Kalmegha Extract	*Andrographispanicu lata*	Whole Plant	50 mg
6.	Himsra Extract	*Capparisspinosa*	Root	50 mg
7.	Kutaki Extract	*Picrorhizakurroa*	Root	50 mg
8.	Musta Extract	*Cyperusrotundus*	Rhizome	50 mg
9.	Pippali Extract	*Piper longum*	Fruit	5 mg

4. Results

Sixty one subjects were screened, 5 did not meet inclusion and exclusion criteria hence were not recruited in the study. Three subjects dropped out due to lost to follow ups. Fifty three subjects were available for analysis [Table 2].

Table 2: Diagnosis of Subjects

Alcoholic Fatty Liver	Only ALD without Fatty Liver	Fatty Liver without Alcohol History	Infective Hepatitis	Drug Induced Hepatitis
23 (43.40%)	20(37.74%)	02 (3.77%)	03 (5.66%)	05 (9.43%)

There were 47 (88.7%) males and 06 (11.3%) females. The mean age of the subjects was 35.79 ± 09.26 years. The mean AST level at the beginning of the study was 86.37 ± 69.68, that reduced significantly to 65.61 ± 44.87 (24.03%), 49.00 ± 39.70 (43.26%), 39.73 ± 37.25 (54%) and 37.67 ± 35.47 (56.38%) on day 15, day 30 day 45 and day 60 respectively [Figure 1].

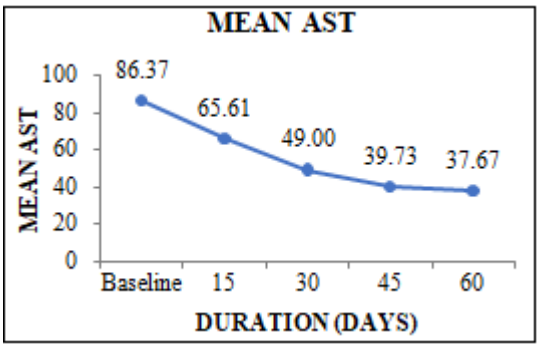

Figure 1: Change in Aspartate aminotransferase (AST)

At baseline visit, the mean ALT level was 66.68 ± 36.91 that reduced significantly to 53.98 ± 27.97 (19.05%), 40.77 ± 21.56 (38.86%), 33.52 ± 17.27 (49.73%) and 31.87 ± 12.40 (52.20%) on day 15, day 30, day 45 and day 60respectively [Figure 2].

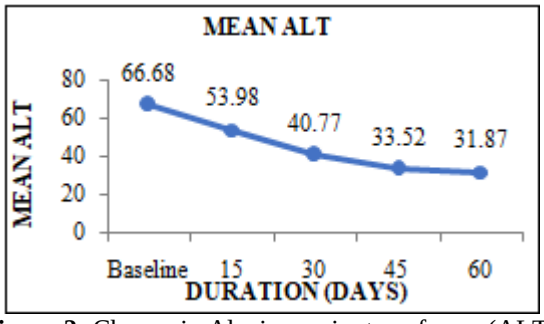

Figure 2: Change in Alanine aminotransferase (ALT)

The mean serum total bilirubin at the beginning of the study was 02.10 ± 00.86, which reduced significantly to 01.55 ± 00.73 (26.19%), 01.15 ± 00.46 (45.24%), 00.97 ± 00.21 (53.81%) and 00.95 ± 00.18 (54.76%) on day 15, day 30, day 45 and day 60 respectively [Figure3].

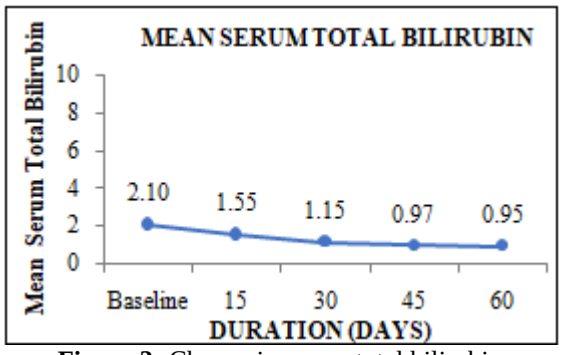

Figure 3: Change in serum total bilirubin

At baseline visit, the mean serum direct bilirubin was 00.77 ± 00.45, which reduced significantly to 00.26 ± 00.12 (66.23%) on day 60.The mean serum indirect bilirubin at baseline visit was 01.35 ± 00.55, which reduced significantly to 00.70 ± 00.20 (48.15%) on day 60. At baseline visit, the mean serum alkaline phosphatase was 122.61 ± 41.49, which reduced insignificantly to 118.63 ± 32.09 on day 60. At baseline visit, the mean GGTP level was 80.47 ± 120.53 that reduced significantly to 53.93 ± 055.15 on day 60. The mean total protein at baseline visit was 07.38 ± 00.61 that reduced insignificantly to 07.25 ± 00.56 on day 60. At baseline visit, the mean serum albumin was 04.20 ± 00.49, which reduced insignificantly to 04.15 ± 00.42 on day 60.

Liver functions became normal in 2 (3.77%) subjects, 19 (35.85%) subjects 18 (33.96%) subjects and 14 (26.42%) subjects on day 15, 30, 45 and 60 respectively. At screening visit, 15 subjects hadhepatomegaly with grade I fatty liver and on last visit 7 subjects had hepatomegaly with grade I fatty liver. Seven subjects had grade II fatty liver at screening visit, on last visit only 2 subjects had grade II fatty liver. At screening visit, 3 subjects had hepatomegaly with grade II fatty liver and none of the subject reported to have hepatomegaly with grade II fatty liver on last visit. At screening visit, 4 subjects had hepatomegaly, after treatment there were 2 subjects with hepatomegaly. Initially 24 subjects had no significant abnormality in liver, after treatment there were 42 subjects with no significant abnormality in liver.

Significant improvement in jaundice (from day 30 onwards), nausea and vomiting (from day 15 onwards), was observed and no subjects reported jaundice, nausea and vomiting on last visit. Significant improvement in abdominal pain was observed from day 15 onwards and on last visit 50 (94.3%) subjects reported no abdominal pain and 03 (5.7%) subjects reported mild abdominal pain. Significant improvement in abdominal tenderness was observed from day 15 onwards and on last visit 52 (98.1%) subjects reported no abdominal tenderness and 01 (1.9%) subject reported mild abdominal tenderness. Significant improvement in anorexia was observed from day 30 onwards and on last visit 2 (3.8%) subjects reported mild anorexia and 51 (96.2%) subjects reported no anorexia. Significant improvement in pruritus was observed from day 30 onwards and on last visit 01 (1.9%) subject reported mild pruritus and 52 (98.1%) subjects reported no pruritus.

As per global evaluation of overall improvement assessed by physician, very much improvement was observed in 47 (90.4%) subjects and much improvement was observed in 05 (9.6%) subjects. As per global evaluation of overall improvement assessed by subjects, very much improvement was observed in 47 (90.4%) subjects and much improvement was observed in 05 (9.6%) subjects.

As per physician and subjects' assessment, 98.1% subjects reported excellent tolerability and 1.9% subjects reported good tolerability to Test drug. 18.9% subjects had adverse events during study period. Most common was body pain followed by fever, cold, throat irritation, vomiting, acidity and menstrual pain. Severity of events was mild among all the subjects except throat irritation was moderate in nature. These adverse events were resolved completely after rescue medication was given. Study treatment was not stopped during these adverse events, hence were not related to study drug.

All the parameters of hemogram, lipid profile, and renal profile were within normal limits at baseline visit. After completion of the treatment, no significant change in any of these laboratory investigations was observed. All the vitals such as pulse rate, blood pressure, body temperature,

respiratory rate and ECG were within normal limits at baseline visit and on last visit.

5. Discussion

Majority of the subjects included in the study were suffering from fatty liver disease (23 subjects with Alcoholic Fatty Liver Disease and 2 subjects with fatty liver without alcohol history) followed by Alcoholic liver disease without fatty liver (20 subjects), drug induced hepatitis (5 subjects) and infective hepatitis other than hepatitis B and C (2 subjects).
The Test drug was significantly effective in normalizing liver functions from day 15 onwards as evidenced by complete normalization of liver function tests in 2 subjects. There was significant reduction in elevated liver enzyme such as ALT, AST and GGT suggestive liver protective effect of treatment.Liver functions were within normal limits in all the subjects on last visit. The Test drug was equally effective in all types of liver disorders as evidenced by significant improvement observed in liver function tests and USG findings. Also the test drug was significantly effective in improving symptoms of liver disorders such as abdominal pain, abdominal tenderness, nausea, vomiting and fatigue from day 15 onwards and continued till the end of the study. A significant improvement in symptoms such as anorexia, pruritus, jaundice and bowel movement was observed from day 30 onwards and continued till the end of the study. Majority of the subjects reported very much overall improvement at the end of the study as assessed by physician and subjects.

Alcohol abuse, obesity, type II diabetes, dyslipidemia, insulin resistance, viral infection, drug toxicity leads to liver damage. Accumulation of fat globules in hepatocytes due to variety of causes leads to fatty liver disease. Release of cytokines due to varied etiologies and failure of antioxidant defense mechanism result in inflammation of liver (hepatitis). Continuous hepatic insult leads to fibrosis and ultimately results in cirrhosis of liver which is an irreversible condition [12-15]. Ingredients of Test drug such as *Phyllanthusniruri*, *Boerhaaviadiffusa*, *Cyperusrotundus* and *Andrographispanniculata* reduce visceral adiposity, improve liver enzymes abnormalities, decrease hepatic lipid peroxidation, inhibit liver X receptor mediated activation of sterol regulatory element binding protein-1c and fat accumulation in liver cells in fatty liver disease [16-19].

Piper longum, *Boerhaaviadiffusa*, *Picrorhizakurroa*, *Tinosporacordifolia*, and *Andrographispaniculata*are useful in alcoholic hepatitis. These ingredients provide hepato-protection by preventing the leakage of biochemical marker enzymes from the cells into the blood [20-23]. *Phyllanthusniruri*, *Berberisaristata*, *And rographispanniculata*, *Cyperusrotundus*, and *Boerhaaviadiffusa* help inhibit viral entry, inhibit cellular DNA polymerase activity, provide anti-oxidant support, bring down elevated liver enzymes and provide overall protection to liver in viral hepatitis [24-28]. *Andrographispanniculata*, *Cyperusrotundus*, *Piper longum*, *Boerhaaviadiffusa* and *Capparisspinosa*areuseful in normalizing reactive oxygen species levels, inhibiting cellular proliferation, and inducing apoptosis in HepG2 cell, normalize elevated liver enzymes in drug induced hepatotoxicity [29-32]

Almost all the ingredients of Test drugpossess heaptoprotective activity against various heapatotoxins such as alcohol, drugs, viruses and chemicals. Ingredients help to normalize elevated liver enzymes, increases bile secretion (Cholerectic property) from liver and improves overall liver function. By the virtue of synergistic activity of the ingredients, the Test Drugis effective in liver disorder subjects with abnormal liver function tests.

The reported adverse events were mild in nature except throat irritation which was moderate in nature. These adverse events resolved completely after rescue medication was given. Study treatment was not stopped during these adverse events, hence were not related to the Test drug. Excellent drug tolerability was reported by subjects and physician at the end of the study. No significant post treatment change in any of the lab investigations and vitals were observed, suggesting safety of test drug. Taken together test drug is safe and effective in liver disorder subjects with abnormal liver functions.

6. Conclusion

Test drug is safe and significantly effective in normalizing elevated liver enzymes. The effect of the Test drug in terms of normalization of elevated liver enzymes can be seen after 15 days of treatment. The Test drug is significantly effective in improving symptoms of liver disorders such as abdominal pain, abdominal tenderness, nausea, vomiting, fatigue, jaundice, anorexia and pruritus. Test drug is also effective in reducing inflammation and fatty changes in liver as observed in USG findings. Thus the Test Drug is safe and effective in subjects suffering from non-alcoholic fatty liver disease, alcoholic fatty liver disease, alcoholic hepatitis, drug induced hepatitis and viral hepatitis (other than B and C).

7. Financial support and sponsorship

The study was supported by Sava Healthcare Ltd, Research and development center, MIDC Chinchwad, 411019

8. Conflicts of interest

Dr. V. V. Kuber is an employee of Sava Healthcare Ltd, Research and development center. Others have no conflicts of interest.

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