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Research Article

The Result of Clinical Trial for the New Lonal Drug for Hepatoprotective Effect in Patient with Fatty Liver Disease with Chronic Hepatitis c: Randomized Placebo-Controlled Double Blind Clinical Trail

Ariunaa Z[1]* and Sarnai Ts[2]

[1]*Treatment, Research and Production Company of The Mong-Em, Ulaanbaatar City, Mongolia*

[2]*Professor's Team of Hepatology, Faculty of Internal Medicine, School of Medical Science, MNUMS*

***Corresponding Author:** Ariunaa Z, Treatment, Research and Production Company of The Mong-Em, Ulaanbaatar City, Mongolia.

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Abstract

Introduction: Following researchers determined the Chronic hepatitis C virus infection which was 8,2% (Davaalkham J., *et al*. 2003), 9,6% (Takahashi. M., *et al*, 2004), 9,8% (Tsatsralt-Od., *et al*. 2006), 11,8% (Dagvadorj.Ya., *et al*. 2005) in Mongolia. As researchers noted that hepatitis C genotype 1 and 3 enable to be triglyceride accumulation for liver because it often occurs simultaneously fatty liver disease. Although many types of traditional medicine have been used for for hundreds years, their effectiveness of the therapy is relatively small with inadequate use of poorly understood in practice. These types of medicine's storage, form, flavor are to improve which are prepared based on scientific studying, is to make the clinical trial of drug acts as easily use, emerged as one of the need for market. Therefore, our research team has made the clinical trial based on the chemical and pharmacological study of hepatoprotective effect for lonicera Altaica Pall fruit, an established clinical studies and producing new drugs.

Aim: The aim of our clinical trial was to determine hepatoprotective effect of the new lonal drug in patient with fatty liver disease with chronic hepatitis C.

Material and Method: The research was considered such as clinical trial guideline for new drug issued by the WHO's "Good Clinical Practice". Based on permission given by Biomedical Ethical Community of the Health Ministry of Mongolia approved diagnosis patient with fatty liver disease associated with Chronic Hepatitis C. Research design is Randomized Placebo-Controlled, Double Blind Clinical Trial. We studied 3 groups of participants that was given the following treatment for 21 days: (I) Treatment group: Lonal drug 1.4 gr ×3 times, (II) Control group: Silymarin drug 67.5 mg ×3 times, (III) Placebo group: Placebo drug 1.4 gr ×3 times. We used on histo-morphometric analysis of liver biopsy DISKUS ver 4.80, Olympus BX microscopy.

Results: Lonal drug decreases activation of syndrome hepatic cell cytolysis ALT (p=0.023), AST (p=0.037). Also decreases criteria of cholestasic syndrome such as indirect bilirubin (p=0.611), ALP (p=0.04), GGT (p=0.445). The Lonal medicine was taken for 21 days and comparing the results of lipid metabolism exchange before and after treatment, reduces TG (p=0,402), increases HDL (p=0.047). The participants have taken the Fibroscan analysis and liver biopsy. That was compared to determine before and after treatment such as steatosis and fibrosis degree. Before treatment degree of steatosis was S2: 278.4 ± 75.3 dB/m and after treatment it was dropped from S1: 238.6 ± 70.4 dB/m ($p < 0.05$). And before treatment, such as fibrosis degree F2-3: 8.84 ± 2.2 kPa, after treatment it was decreased in F1-2: 7.18 ± 3.87 ($p<0.01$). In liver histology, comparing before and after treatment the results of liver cell inflammation-fibrosis area was reduced by 1,75 times and decreases hepatic steatosis degree (Strong fatty change was improved Mild fatty change).

Conclusion: New lonal medicine is reducing activation syndrome hepatic cell cytolysis, cholestatic and some criteria of the metabolic syndrome in patient with fatty liver disease associated with chronic hepatitis C. Also new lonal medicine reduces the degree of liver steatosis and fibrosis by the analysis of Fibroscan and liver biopsy.

Keywords: Fibroscan; Liver Biopsy; Lonicera Altaica Pall; Lonal

Introduction

Following researchers determined the Chronic hepatitis C virus infection which was 8,2% [1], 9,6% (Takahashi M., *et al*, 2004), 9,8% (Tsatsralt-Od B., *et al*. 2006), 11,8% (Dagvadorj.Ya., *et al*. 2005) in Mongolia [1]. As researchers noted that hepatitis C genotype 1 and 3 enable to be triglyceride accumulation for liver because it often occurs simultaneously fatty liver disease [2]. Highly appreciated the importance of herbal products have been used for it wide

range of policies to promote proper and use safety in the World Health Organization and many counties. Although many types of traditional medicine have been used for for hundreds years, their effectiveness of the therapy is relatively small with inadequate use of poorly understood in practice. These types of medicine's storage, form, flavor are to improve which are prepared based on scientific studying, is to make the clinical trial of drug acts as easily use, emerged as one of the need for market. A brand new drug called Lonal which was extracted from widely used in traditional medicine fruit Lonicera Altaica Pall with its liver protection effect studied by chemical, general pharmacology and special pharmacology of hepatoprotective effect.

Our studying the new Lonal's most important medical herb is Lonicera altaica Pall that has been using as traditional medicine, in order to treat the liver disease, cholecystitis, edema, heart disease, hypertension, anemia. Also it has been used in order to improve the dysfunction of stomach and intestine, to support the important organs of life and pursue dairy drink appetite.

The frame work of producing the hepatoprotective medicine from that plant's extracts Ariunaa.Z., *et al*. has made the chemical study who has determined it contained anti-inflammatory, choleretic, antioxidant, repair lipid metabolism, such as biological active substance are conducting no danger for human body. Also general and hepatoprotective effect's pharmacological experiments on experimental animals studies have been found to be with liver protection effect.

As a result of new Lonal drug's pharmacological experiments shows that liver function's biochemical and liver histological analysis was conducted different liver tissue reproduction of for the control group and liver fatty change. In liver injury, to support liver cell mitochondria and cytoplasmic enzymes synthesize, increased protein synthesis, to prevent decompensation change and to suppress oxydant in the cell membrane which was determined its effects.

Therefore, our research team has made the clinical trial based on Lonicera Altaica Pall fruit's chemical and pharmacological study of hepatoprotective effect, an established clinical studies and producing new drugs.

AIM:

The aim of our clinical trial was to determine hepatoprotective effect of the new lonal drug in patient with fatty liver disease with chronic hepatitis C.

Research objective

1. To determine the effect of the new drug Lonal during the hepatocellular injury in patient with fatty liver desease associated with chronic hepatitis C.
2. To determine the effect of the new drug Lonal during the cholestatic injury in patient with fatty liver desease associated with chronic hepatitis C.
3. To determine the effect of the new drug Lonal during the metabolic syndrome in patient with fatty liver desease associated with chronic hepatitis C.
4. To determine the impact of new drug Lonal some complication in patient with fatty liver desease associated with chronic hepatitis C.
5. To evaluate the effect of the new drug lonal by Fibroscan (liver stetosis degree and fibrosis degree) and liver biopsy in patient with fatty liver desease associated with chronic hepatitis C.

Research Method and Materials

Ethical issue: Based on permission (Date: 2013.03.07, Protocol number 01) given by Biomedical Ethical Community of the Ministry of Health approved diagnosis patient with fatty liver disease. To be eligible, patients had to meet the following criteria: age >18 years, diagnosis of NAFLD, and ability to understand the objective and contents of the study, and to report the information required. Eligible patients had to sign an informed consent form, after receiving information, on the aim of the study, the type of data and the method of data collection.

Place of clinical trial:

- Professor's team of the Hepatology, Faculty of the Internal Medicine, Medical Science School, Mongolian National University of Medical Science, Mongolia
- Faculty of the Pathology, Pharmacology - Biomedical School, Mongolian National University of Medical Science, Mongolia
- Department of the Gastroenterology, 3rd State Hospital named by Shastin, Mongolia

Clinical trial design

Lonal should be considered such as a new drug clinical research guidelines issued by the World Health Organization "Drug Clinical Research" (Good Clinical Practice) and conducted many guidance documents, "drug clinical trial issued by the Mongolian State Ministry of Health". It was performed in double-blind methods to divide in to 3 groups of participatants where we were using treatment, control and placebo groups in clinical trial I, II stages with randomly they are allocated. Rapidly tests denied that excess alcohol use. Non-Alcoholic fatty liver disease which was diagnosed questionnaire for assessing alcohol consumption (National Institute on Alcoholism and Alcohol Abuse. Assessing Alcohol denied that problems A Guide for Clinicians and Researchers Second Edition).

Used drugs for clinical trial

We studied 3 groups of participants that was given the following treatment for 21 days: (I) Treatment group: Lonal drug 1.4 gr

×3 times, (II) Control group: Silymarin drug 67.5 mg ×3 times, (III) Placebo group: Placebo drug 1.4 gr ×3 times per days.

Lonal drug

Lonal drug:'s raw material Lonicera Altaica Pall fruit was collected to prepare on the Bulnain Mountains in Zavkhan province in September and which was tested in the Central laboratory of the State Specialized Inspection Agency. It was certified "Drug raw materials qualifying". Lonal pills (0.35 mg) were produced in the Traditional Medical Science and Technology Corporation's traditional pharmaceutical industry that was used for just studying.

Figure 1: The new drug Lonal (0.35 mg granule).

Silymarin drug

Accordance with the principle of drug clinical trial research guidelines "The standard treatment group's (control group), drugs were used for similar action, similar components pilot treatment group, past results are medicines was registered international and Mongolian national drug lists " Accordance with above principle Silymarin drug which was manufactured in pharmaceutical industry of Sopharm (Silymarin) was made comparative study for it from approved selling pharmaceuticalin Mongolia.

Placebo drug

In the order to Placebo testing study, we used the drugs that was raw materials of pharmaceutical was used Blueberry its visibility was the same as Lonal drug which was produced in at the research and production "Mong-Em" pharmaceuticy.

Before and after treatment made tests in participants of study

1. Blood analysis
2. Urine analysis
3. Biochemical analysis
4. Coagulation analysis
5. Hepatic virus marker
6. Ultrasonography
7. Fibroscan (Fibroscan Touch 502)
8. Electrocardiography
9. Liver biopsy (DISKUS ver 4.80, Olympus BX microscopy)

Sample size

- In first stage - 10 healthy participants
- In second stage - 65 participants (patient with non-alcoholic fatty liver disease with chronic hepatitis C).
- In order to improve above case studying survey results, those people divided into 3 groups whom we made Fibroscan liver analysis for 15 people, liver biolsy analysis for each additional 5 people.

Research Results

The result of the new lonal drug's effect during the hepatocellular injury in patient with fatty liver desease associated with chronic hepatitis C: When we made clinical trial for patient with fatty liver desease associated with chronic hepatitis C during the hepatocellular injury before treatment average of AST was 77,49 ± 38,22 U/L after treatment it was 53,72 ± 23,21 U/L (p = 0.037), average of ALT before treatment was 94,98 ± 53,62 U/L after treatment it was 63,71 ± 31,5 U/L (p = 0.023). However, control group's 10 participants with hepatocellular injury Silymarin drug was used who shows before treatment it was indicated average of ALT 82,88 ± 45.52 U/L after treatment it was 67,04 ± 33,52 U/l (p=0.048) and average of AST before treatment 78,35 ± 28,52U/L, after treatment it was 65,45 ± 19,25 U/l (p = 0.035).

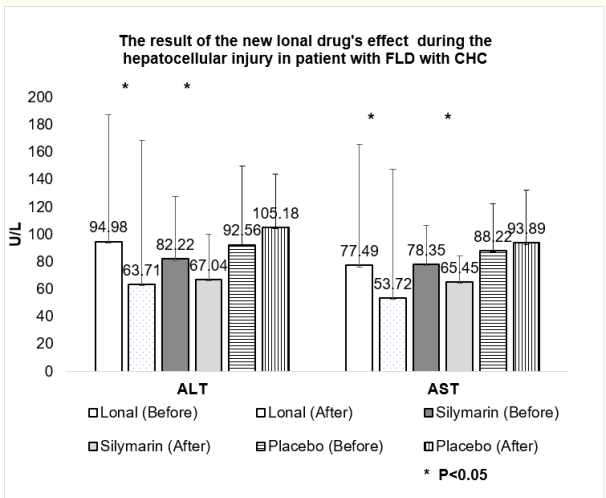

Figure 2: The result of the new lonal drug's effect during the hepatocellular injury in patient with FLD with CHC.

The result of the new lonal drug's effect during the cholestatic injury in patient with fatty liver desease associated with chronic hepatitis C: Drug Lonal was used for cholestatic injury in patient with fatty liver desease associated with chronic hepatitis C before treatment average of total bilirubin was 14,77 ± 7,22 umol/L, after treatment it was 14,38 ± 5,48 umol/l (p = 0.77), average of indirect bilirubin before treatment was 9,82 ± 8,86 umol/L, after treatment its was 8,49 ± 4,2 umol/l (p = 0.611). And the average of direct bilirubin was 6,21 ± 4,04 umol/l in before treatment, after treatment it was 6,41 ± 4,25 umol/l (p = 0.301). Control group's participants were used Silymarin drug average of total bilirubin was 18,32 ± 1.65 umol/l before treatment, after treatment it was increased 17,55 ± 2,50 umol/l (p = 0.427). Before treatment, direct bilirubin average was 6,24 ± 1,42 umol/l, after treatment it was 6,13 ± 1,81 umol/l (p=0.842). And before treatment, indirect bilirubin average was 7,7 ± 2,53 umol/l, after treatment it was 8,16 ± 3,21 umol/l (p = 0.840).

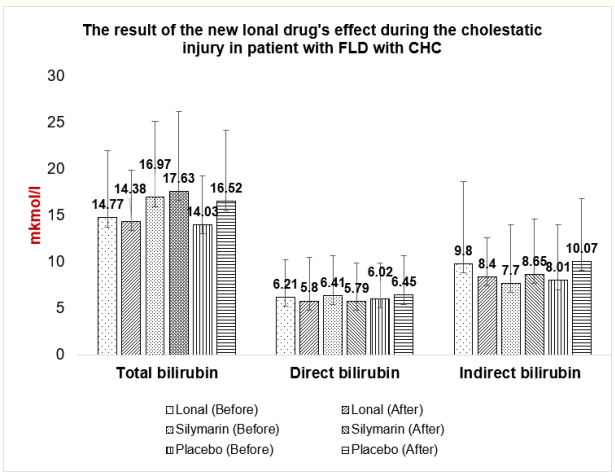

Figure 3: The result of new lonal drug's effect during the cholestatic injury in patient with FLD with CHC.

Before treatment of the participants used Lonal drug average of ALP was 158,22 ± 59,28 U/L, after treatment it was decreased 130,72 ± 65,23 U/L (p = 0.04). Before treatment, average of GGT was 58.5 ± 41.57 U/l, after treatment an average of GGT was reduced 53,8 ± 37,96 U/L (p = 0.445).

However Silymarin drug used participants average of ALP was 154,28 ± 48,17 U/L before treatment, after treatment it was decreased 147,41 ± 44,02 U/L (p = 0,989), before treatment average of GGT was 46,77 ± 18.20 U/L, after a treatment it was reduced 28,62 ± 14,28 U/l (p = 0.041).

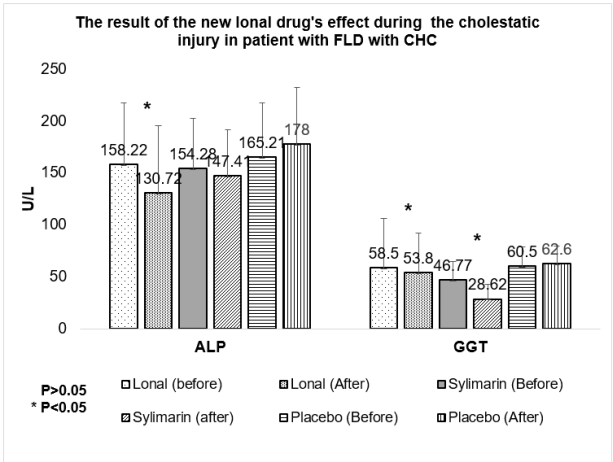

Figure 4: The result of the new lonal drug's effect during the cholestatic injury in patient with FLD with CHC.

The result of new lonal drug's some effect during the metabolic syndrome in patient with fatty liver desease associated with chronic hepatitis C

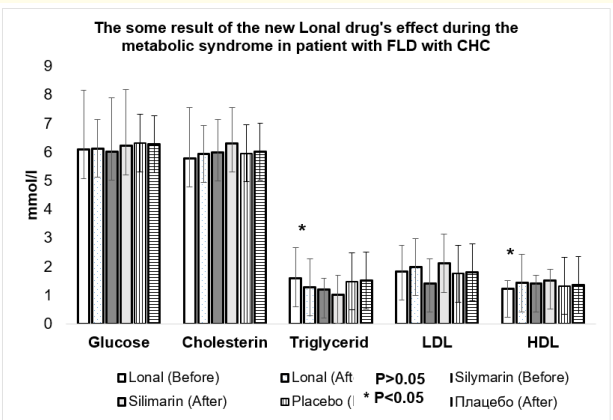

Figure 5: The result of new lonal drug's some effect during the metabolic syndrome in patient with FLD with CHC.

Using Lonal participants average of glucose was 6,08 ± 2.09 mmol / L before treatment, after treatment, their average of glucose was 6,13 ± 1,69 mmol/l (p = 0.851), average of TG was 1.59 ± 1.07 mmol / l before treatment, it was decreased 1.27 ± 1.05 mmol / l (p = 0,042) in after treatment, before treatment average of the cholesterol 5,77 ± 1.78 and it was increased 5,93 ± 1,41 mmol / l (p = 0,635). Before treatment, average of LDL was 1,82 ± 0.91 mmol / L after treatment average of LDL was 1,98 ± 0,81 mmol/l (p=0.545), and before treatment average of HDL was 1.22 ± 0.29 mmol/l after treatment it was increased 1,42 ± 0,27 mmol / l (p = 0.047).

However Silymarin drug used group's participants average of glucose before treatment it was 6,02 ± 1,89 mmol/l, after treatment it was increased 6,21 ± 1,98 mmol/l (p=0.563), before treatment average of cholesterol 6.0 ± 1.14 mmol / l after treatment it was increased 6.3 ± 1.25 mmol/l (p = 0.321), before treatment the average of TG 1.2 ± 0.39 mmol / l, after treatment it was 1.02 ± 068 mmol/l (p = 0.912). And before treatment average of HDL 1,4 ± 0,3 mmol/l after treatment it was 1,57 ± 0,38 mmol/l (p = 0.461), before treatment average of LDL was 1.4 ± 0.87 mmol / l after treatment it was 2.1 ± 1.02 mmol/l (p = 0.587).

The some results of the new lonal drug's effect for some complication in patient with fatty liver desease with chronic hepatitis C;

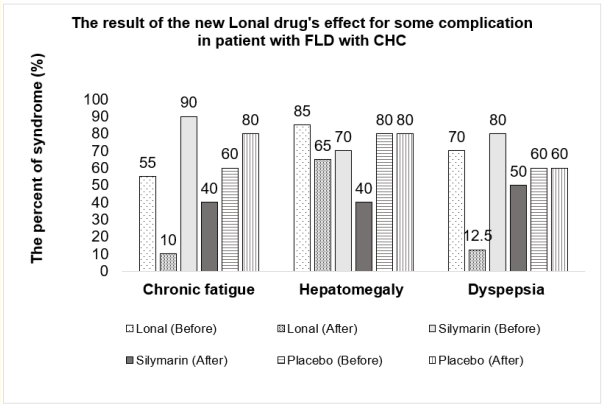

Figure 6: The result of the new lonal drug's effect for some complication in patient with FLD with CHC.

Before treatment in 55% of participants were used this group Lonal drug who had chronic fatigue syndrome, 85% of them were syndrome hepatomegaly (right rib bow in heavy flushes, painful), 70% of them were (dyspepsia syndrome) and after treatment they were reduced in 10%, 65% and 12.5%.

Control group's 10 participants have taken Silymarin drug 90% of patients were found chronic fatigue syndrome, 70% of them had syndrome hepatomegaly, 80% of them had dyspepsia syndrome, after treatment they showed in 50%, 40% and 50%.

The some results of the new lonal drug's effect for during hepatomegaly syndrome in patient with FLD with CHC (Figure 7).

We used abdominal ultrasound examination for to measure participant's liver right lobe's size. Before treatment, average of liver right lobe's size was 145,18 ± 15,84 mm, after a treatment it has been reduced 141,35 ± 15,22 mm (p = 0.024).

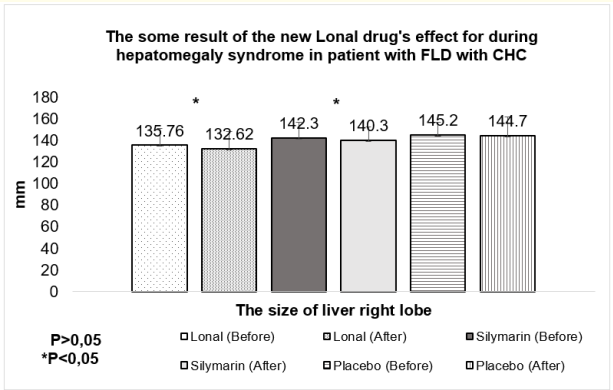

Figure 7: The some results of the new lonal drug's effect for during hepatomegaly syndrome in patient with FLD with CHC.

However, the participants who used Silymarin average of liver right lobe's size was 142,3 ± 18,25 mm after the treatment it was decreases 140,3 ± 17,56 mm (p = 0.04).

The lonal studied the results of tests by the fibroscan and liver biopsy in patient with fatty liver desease with chronic hepatitis C:

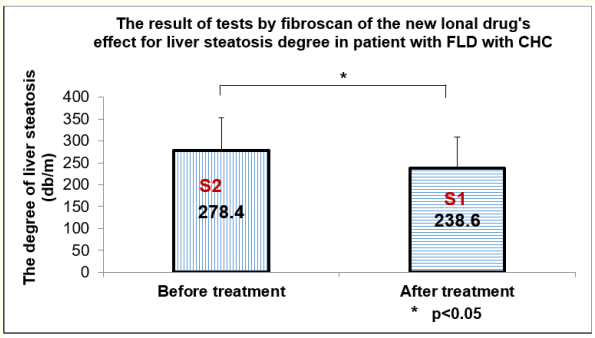

Figure 8: The result of the new lonal drug's effect for degree of liver steatosis tests by the fibroscan in patient with FLD with CHC.

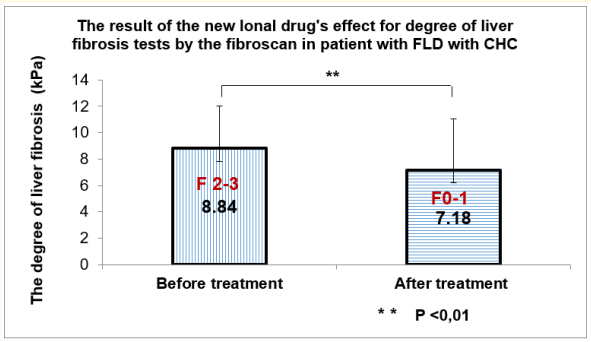

Figure 9: The result of the new lonal drug's effect for degree of liver fibrosis tests by the fibroscan in patient with FLD with CHC.

Participants with fatty liver disease associated with chronic hepatitis C have taken the Fibroscan and liver biopsy. That was compared to determine before and after treatment such as sreatosis and fibrosis degree. In fibroscan, steatosis degree was S2: 238.4 ± 75.3 dB/m before treatment and after treatment it was dropped from S1: 278.6 ± 70.4 dB/m ($p < 0.05$), before treatment, fibrosis degree was F0: 8.84 ± 3.2 kPa, after treatment it was decreased in F0: 7.18 ± 3.87 ($p < 0.01$).

In liver histology, comparing before and after treatment the results of hepatocellular inflammation and fibrosis area was reduced by 1,75 times and decreases hepatic steatosis degree (Strong fatty change was improved Mild fatty change) [3-22].

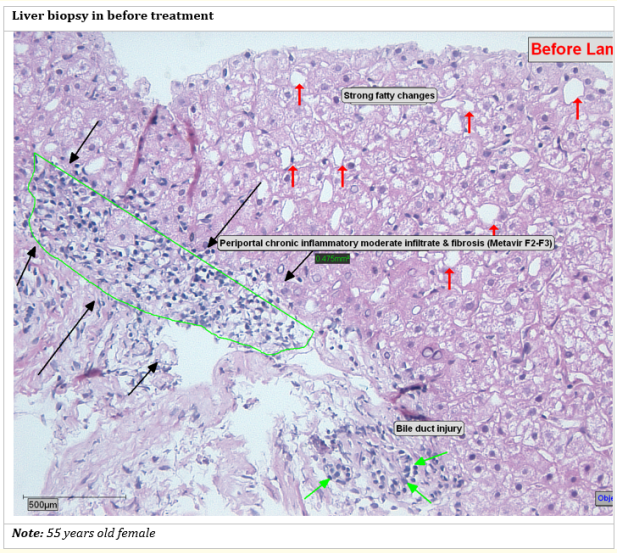

Figure 10: The comparative result of liver biopsy for hepatoprotective effect of the new lonal drug in patient with FLD with CHC.

Conclusion

The new lonal drug is decreasing hepatocellular injury, cholestatic injury and some criteria of the metabolic syndrome in patient with fatty liver disease associated with chronic hepatitis C. Also the new lonal drug decreses the degree of liver steatosis and fibrosis by Fibroscan and liver histology.

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