ECRONICON OPEN ACCESS

EC GASTROENTEROLOGY AND DIGESTIVE SYSTEM

Research Article

Efficacy and Safety of Obeticholic Acid in NASH Egyptian Patients

Mona El Amir*, Ehab Abd Elaty, Abdelkhalek Hamed, Gamal Shiha and Riham Elsayed

Department of Hepatology, Cairo University, Egypt

***Corresponding Author:** Mona El Amir, Department of Hepatology, Cairo University, Egypt.

Received: September 01, 2022; **Published:** September 30, 2022

Abstract

Background: Non-alcoholic steatohepatitis is an increasingly common cause of chronic liver disease worldwide and it is associated with increased liver-related mortality and hepatocellular carcinoma, even in the absence of cirrhosis [1-3].

Aim: To assess efficacy and safety of Obeticholic acid 10 mg once daily in NASH Egyptian patients for 12 months especially on ALT and AST parameters and fibrosis, steatosis score based on fibroscan.

Keywords: *Nonalcoholic Steatohepatitis (NASH); Nonalcoholic Fatty Liver Disease (NAFLD); ALT and AST*

Introduction

Nonalcoholic steatohepatitis (NASH)

Nonalcoholic fatty liver disease (NAFLD) can lead to a serious complication which is NASH (Non-alcoholic steatohepatitis) which consequently can lead to liver fibrosis, liver cirrhosis, hepatic failure, hepatocellular carcinoma and May end to death [4]. NASH is considered as a severe form of NAFLD and is a progressive chronic asymptomatic disease [5]. When diagnosed by imaging More than 25% of total populations suffers from NAFLD, From which 1.5% to 6.5% progress to NASH [6,7]. NASH is growing fast and will become one of the leading cause of liver transplant [8]. Fibrosis is the main histological feature predictor of severe outcomes [9,10]. From the severe outcomes is liver related death which is a normal progress from cirrhosis, decompensation, sepsis and hepatocellular carcinoma which is also a progress of fibrosis [6,7,11]. The main goal of NASH therapy is to prevent cirrhosis in advanced fibrotic patients. We have now an urging need to develop an effective pharmacological treatment for NASH due to high prevalence and aggressive progression of NASH to other complications.

Obeticholic acid

Obeticholic acid (OCA) is a potent, selective FXR agonist and is an analogue of chenodeoxycholic acid but more potent 100 times [12]. The efficacy and safety of OCA in NASH was validated in FLINT, a phase 2b, 18-month, placebo-controlled study [13]. The results of flint trial based on OCA 25 mg once daily resulted in significant improvement in histological features including hepatocellular ballooning, steatosis and lobular inflammation versus placebo [13]. There was a significant reduction in aminotransferases also. During OCA treatment there was no serious adverse events and generally was well tolerated and the most common adverse events from OCA was pruritis but was mild to moderate and didn't lead to drug discontinuation [13].

Non-invasive diagnosis of fibrosis and steatosis

Transient elastography (Fibroscan): One of the easiest non-invasive test which takes maximum 10 minutes and measures. The cutoff values used to identify stages of hepatic fibrosis are as follow: 7.1 kPa for F ≥ 2, 9.5 kPa for F ≥ 3 and 12.5 kPa for F4 [16]. There are some conditions that can lead to liver stiffness other than fibrosis as hepatic congestion and acute inflammation, Mass lesion in the liver. We experience some difficulties and reading unreliability in the following patients: obesity (BMI > 30 - 35 kg/m^2), older age, and presence of as- cites. No contraindication in this test but it must be used with caution in Pregnancy and in patients using pacemaker. Advises against the use of this device in pregnancy and in patients with a pacemaker and implantable defibrillators. Fibroscan now is considered one of the most important test to detect fibrosis and in the current guidelines in it is recommended in management [17].

Controlled attenuation parameter: It is a vibration based elastography which can predict and measure steatosis. CAP can detect significantly the presence and absence of steatosis but it is less accurate in differentiating different grades of steatosis [18]. But in real world practice it is valid to use CAP score to detect steatosis grade [19-21]. The optimal cut-off values of CAP for estimation of hepatic steatosis grades such as S1, S2 and S3 are ≥ 263 dB/m, ≥ 281 dB/m and ≥ 283 dB/m respectively [18]. Another study also graded hepatic steatosis de- pending on CAP value into S1 ≥ 238 dB/m, S2 ≥ 260 dB/m, and S3 ≥ 293 dB/m [22]. CAP is an excellent diagnostic tool for detecting presence and absence of hepatic steatosis by using a cutoff value of 241 dB/m in children with NAFLD but has limited value in evaluating grades of steatosis, especially in children with high BMI (> 30 kg/m^2) [24].

Materials and Methods

Study design

This study enrolled 112 patients at 4 participating medical centers in Egypt all are NASH confirmed by Fibroscan with CAP (Fibrosis and Steatosis), U/S and Clinical examination treated with Obeticholic acid 10 mg once daily for 12 months.

This study was conducted between March 2021 till July 2022. During a lower incidence of Covid-19 in Egypt.

Our observation during the study that Covid-19 has a direct impact on liver enzymes and lipid profile in NASH patients but with a minor changes on liver enzymes and liver stiffness measurement. But it seems important to do more studies to confirm the relation between Covid-19 and NASH and whether OCA can decrease hospitalization of NASH patients due to Covid-19.

Inclusion criteria:

1. 18 years or older with NASH of both sexes
2. Fibrosis stage from F1 to F3.

Exclusion criteria:

1. History of significant alcohol consumption
2. Patient with chronic liver disease
3. Not taking or on stable dose of TZDs/glitazones or Vit E
4. Patients with associated chronic HBV, HCV, schistosomiasis
5. Patients with cirrhosis, renal, cardiac or autoimmune disease.

Endpoint:

1. Improvement of liver enzymes parameters (ALT and AST) after 12 months
2. Improvement of fibrosis score after 12 months of treatment based on fibroscan
3. Improvement of steatosis score after 12 months of treatment based on fibroscan with CAP.

Results

Patient's characteristics

Clinical items	Patients
Age	30-71 years, mean 50.5 years
Sex	Male 78 Female 34
Fibrosis score	Mean K.p. 7.3
F0	N = 36
F1	N = 31
F2	N = 27
F3	N = 18
Steatosis score	
S0	N = 0
S1	N = 2
S2	N = 29
S3	N = 81
Type 2 DM	N = 94
Dyslipidemia	N = 78

Table 1: *Demographic data before OCA.*

Clinical items	
Fibrosis score	Mean K.p. 5.9
F0	N = 65
F1	N = 25
F2	N = 18
F3	N = 2
F4	N = 2
Steatosis score	
S0	N = 6
S1	N = 24
S2	N = 49
S3	N = 33
S4	

Table 2: *Fibrosis and steatosis score after OCA.*

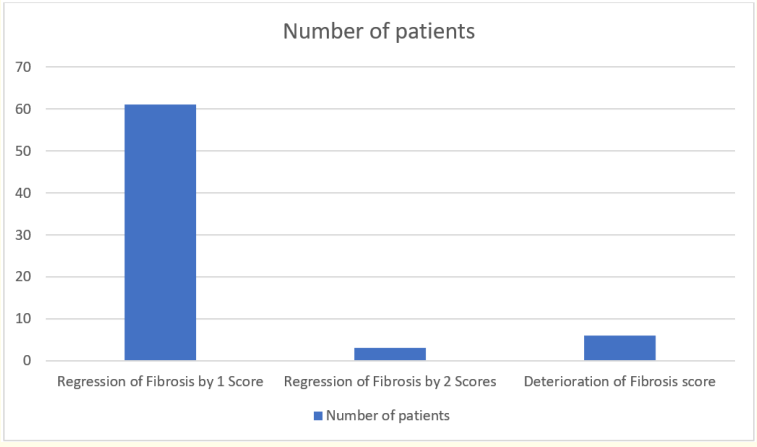
Lab. parameters	
S.ALT	Mean 48.8 U/L
S.AST	Mean 43.8 U/L
HBA1c	Mean 7.5%

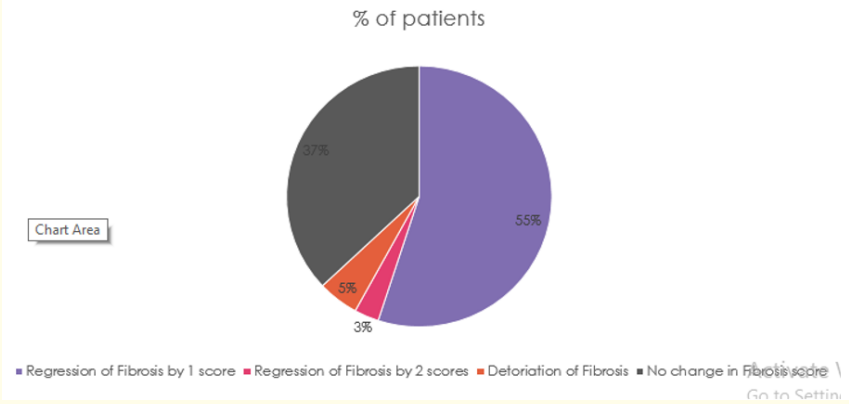
Table 3: *Laboratory data before OCA.*

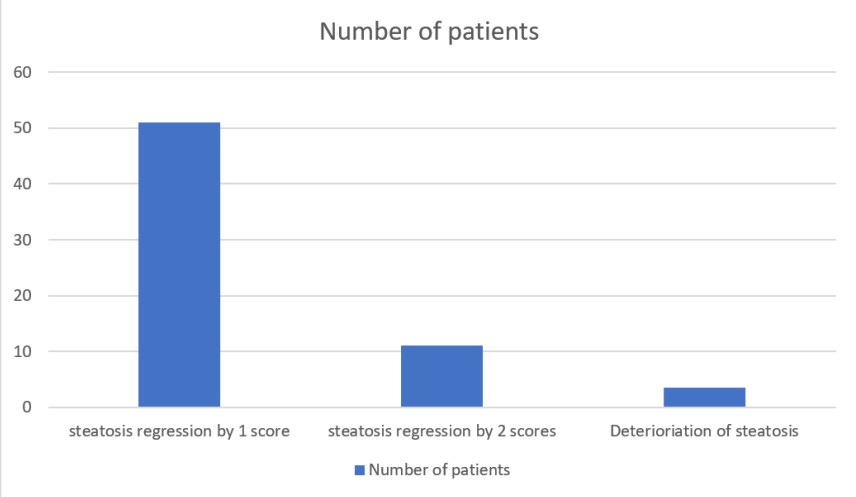
Lab. Parameters	
S.ALT	Mean 23.8 U/L
S. AST	Mean 23.4 U/L
HBA1c	Mean 7%

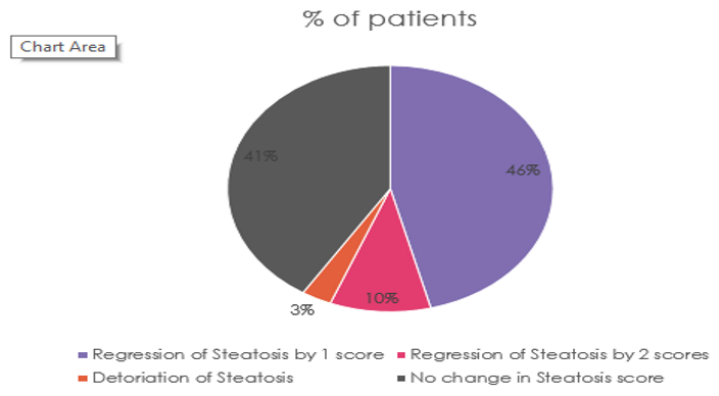
Table 4: *Laboratory data after OCA.*

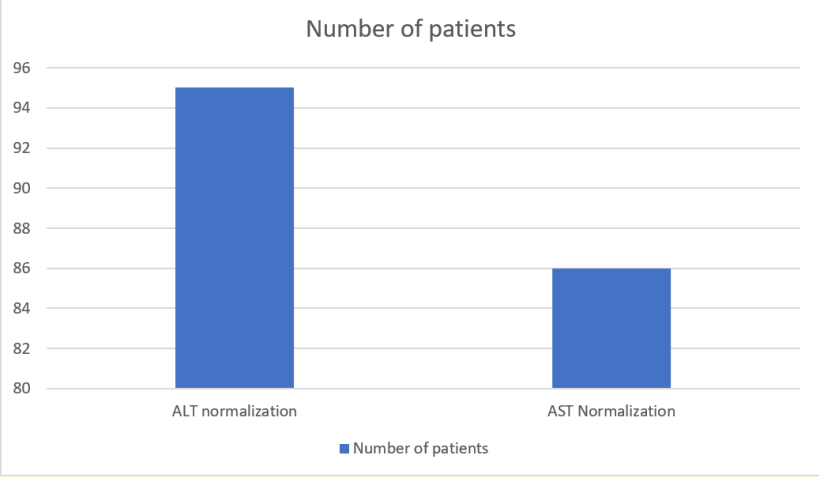
Study statistics






Number of patients
60
50
40
30
20
10
0
steatosis regression by 1 score
steatosis regression by 2 scores
Deterioration of steatosis
Number of patients


% of patients
Chart Area
41%
46%
10%
3%
Regression of Steatosis by 1 score
Regression of Steatosis by 2 scores
Detoriation of Steatosis
No change in Steatosis score


Number of patients
96
94
92
90
88
86
84
82
80
ALT normalization
AST Normalization
Number of patients

Obeticholic acid: Safety and tolerability

Few side effects have been reported in association with OCA. Those that have been reported were commonly mild to moderate, as a pruritus, dyslipidemia, fatigue, headache, and gastrointestinal side effects. Pruritus is the most common adverse effect reported in 1.7% of patients (2 patients only experienced pruritis) treated with OCA 10 mg. However, this symptom can be managed in most patients by the use of bile acid sequestrants, antihistamines.

Discontinuation of treatment due to pruritis side effects didn't happen during the trial.

Treatment with OCA has been associated with an increase in LDL-cholesterol and a decrease in HDL-cholesterol and triglycerides. This happened only in dyslipidemia patients and with the use of Statin in this population there was no significant difference between mean LDL and HDL levels before and after treatment.

Discussion

NAFLD is a multifaceted systemic disease, with a relevant epidemiological impact. Currently, lifestyle changes with dietary restrictions and physical activity remain the only recommended. Treatment for NAFLD, in all patients with increased body weight [14]. Presently, OCA is FDA approved in the treatment of Primary biliary cholangitis. However, FXR is a promising molecular target for NAFLD therapy. OCA has some side effects, such as elevated LDL levels and itching.

However, due to lack of specific treatment of NASH and the urging need for it the off-label use of obeticholic acid is likely to be great. We can conclude that, on the basis of this literature review, OCA appears to be a novel agent with promising potential that could be considered for future treatment protocols of NASH.

Conclusion

Patients treated with obeticholic acid showed improvements in results of established noninvasive tests of fibrosis and also improvement in steatosis scores and was safe and well tolerated.

Bibliography

1. Marrero JA., *et al*. "NAFLD may be a common underlying liver disease in patients with hepatocellular carcinoma in the United States". *Hepatology* 36 (2002): 1349-1354.
2. Page JM and Harrison SA. "NASH and HCC". *Clinics in Liver Disease* 13 (2009): 631-647.
3. Sanyal A., *et al*. "Population-based risk factors and resource utilization for HCC: US perspective". *Current Medical Research and Opinion* 26 (2010): 2183-2191.
4. G Vernon., *et al*. "Systematic review: the epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in adults, Aliment". *Pharmacology and Therapeutics* 34.3 (2011): 274-285.
5. M Khoonsari., *et al*. "Clinical manifestations and diagnosis of nonalcoholic fatty liver disease, Iran". *The Journal of Pathology* 12.2 (2017): 99-105.
6. N Chalasani., *et al*. "The diagnosis and management of nonalcoholic fatty liver disease: practice guidance from the American Association for the Study of Liver Diseases". *Hepatology* 67.1 (2018): 328-357.

7. ZM Younossi., *et al*. "Global epidemiology of nonalcoholic fatty liver disease: meta-analytic assessment of prevalence, incidence, and outcomes". *Hepatology* 64.1 (2016): 73-84.

8. MR Charlton., *et al*. "Dierkhising, Frequency and outcomes of liver transplantation for nonalcoholic steatohepatitis in the United States". *Gastroenterology* 141.4 (2011): 1249-1253.

9. ZM Younossi., *et al*. "Pathologic criteria for nonalcoholic steatohepatitis: interprotocol agreement and ability to predict liver-related mortality". *Hepatology* 53.6 (2011): 1874-1882.

10. P Angulo., *et al*. "Liver fibrosis, but no other histologic features, is associated with long-term outcomes of patients with nonalcoholic fatty liver disease". *Gastroenterology* 149.2 (2015): 389-397.

11. AJ Sanyal., *et al*. "Similarities and differences in outcomes of cirrhosis due to nonalcoholic steatohepatitis and hepatitis C". *Hepatology* 43.4 (2006): 682-689.

12. R Pellicciari., *et al*. "6alpha-ethyl-chenodeoxycholic acid (6-ECDCA), a potent and selective FXR agonist endowed with anticholestatic activity". *Journal of Medicinal Chemistry* 45.17 (2002): 3569-3572.

13. BA Neuschwander-Tetri., *et al*. "Farnesoid X nuclear receptor ligand obeticholic acid for non-cirrhotic, non-alcoholic steatohepatitis (FLINT): a multicentre, randomised, placebo-controlled trial". *Lancet* 385.9972 (2015): 956-965.

14. Puri P and Sanyal AJ. "Nonalcoholic Fatty Liver Disease: Definitions, Risk Factors, and Workup". *Clinics in Liver Disease* 1 (2012): 99-103.

15. Petta S., *et al*. "Serial combination of non-invasive tools improves the diagnostic accuracy of severe liver fibrosis in patients with NAFLD". *Alimentary Pharmacology and Therapeutics* 46 (2017): 617-627.

16. Castera L., *et al*. "Prospective comparison of transient elastography, Fibrotest, APRI, and liver biopsy for the assessment of fibrosis in chronic hepatitis C". *Gastroenterology* 128 (2005): 343-350.

17. Chalasani N., *et al*. "The diagnosis and management of nonalcoholic fatty liver disease: practice guidance from the American Association for the Study of Liver Diseases". *Hepatology* 67 (2018): 328-357.

18. Chan WK., *et al*. "Controlled attenuation parameter for the detection and quantification of hepatic steatosis in nonalcoholic fatty liver disease". *Journal of Gastroenterology and Hepatology* 29 (2014): 1470-1476.

19. Ahn JM., *et al*. "Relationship between controlled attenuation parameter and hepatic steatosis as assessed by ultrasound in alcoholic or nonalcoholic fatty liver disease". *Gut and Liver* 10 (2016): 295-302.

20. Yen YH., *et al*. "The correlation of controlled attenuation parameter results with ultrasound-identified steatosis in real- world clinical practice". *Journal of the Formosan Medical Association* 116 (2017): 852-861.

21. Machado MV. "Controlled attenuation parameter as a noninvasive method to detect and quantify hepatic steatosis in chronic liver disease: what is the clinical relevance?" *The GE – Portuguese Journal of Gastroenterology* 24 (2017): 157-160.

22. Sasso M., *et al*. "Controlled attenuation parameter (CAP): a novel VCTE (TM) guided ultrasonic attenuation measurement for the evaluation of hepatic steatosis: preliminary study and validation in a cohort of patients with chronic liver disease from various causes". *Ultrasound in Medicine and Biology* 36 (2010): 1825-1835.

23. Liu K., *et al*. "Prognostic value of controlled attenuation parameter by transient elastography". *The American Journal of Gastroenterology* 112 (2017): 1812-1823.

24. Shin J., *et al*. "Quick assessment with controlled attenuation parameter for hepatic steatosis in children based on MRI-PDFF as the gold standard". *BMC Pediatrics* 19 (2019): 112.

Volume 9 Issue 10 October 2022