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THE COMPARATIVE STUDY BETWEEN OBETICHOLIC ACID AND URSODEOXYCHOLIC IN NONALCOHOLIC STEATOHEPATITIS (NASH) MANAGEMENT

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ABSTRACT

Objective: In this study our main goal is to evaluate the effectiveness of obeticholic acid and ursodeoxycholic in non alcoholic steatohepatitis management. **Method:** This cross sectional study was carried out at Tertairy Medical hospital January 2019 to January 2020. Where a total of 60 patients with a clinical and laboratory diagnosis of NASH, on a stable dose of UDCA for at least 6 months prior to screening, were randomly assigned (1:1:1) to one of three treatment groups for 85 days (3 months): OCA 10 mg, OCA 25 mg, OCA 50 mg or a matching placebo administered once daily. **Results:** During the study, out of 60 patients (40%) were 30 or below 30 years old, (26.6%) 31-40 years and (20%) 41-50 years and majority were male, 80%. C-reactive protein (CRP) showed significant reductions from baseline at the end of the study with OCA treatment. In OCA 25 mg group Improvement of fibrosis was 24% without worsening of NASH and 12% resolution cases of NASH with no worsening of fibrosis**. Conclusion:** Daily doses of OCA, ranging from 10 to 25 mg, significantly reduced levels of ALP, lipid profile, and alanine aminotransferase, compared to placebo, in patients with NASH who had inadequate responses to UDCA. Further study is needed for better outcome.

KEYWORDS: obeticholic acid (0CA), ursodeoxycholic, nonalcoholic steatohepatitis (NASH).

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD), a common pathologic condition characterized by lipid deposition in hepatocytes, can range from simple steatosis to non-alcoholic steatohepatitis (NASH) to fibrosis.[1]

NASH occurs in about one quarter of patients with NAFLD indicating disease progression and being a major cause of cryptogenic cirrhosis. A retrospective study showed that 41% of patients with NASH progressed to liver fibrosis and 5.4% to end-stage liver diseases.[2-3]

The prevalence of NASH has increased with increasing obesity and type 2 diabetes, and NASH is currently estimated to affect approximate 1% of the populations of Europe and North America.[4]

Ursodeoxycholic acid (UDCA), a secondary bile acid produced by intestinal bacteria as metabolic by product, has been shown effective in the non-surgical treatment of cholesterol gallstones and primary biliary cirrhosis (PBC).[5]

The clinical properties of UDCA include anti-apoptotic effects, lowering serum TNF-α concentrations, decreasing endoplasmic reticulum stress and improving hepatic insulin sensitivity, suggesting that UDCA may be effective in the treatment of NASH.[6]

Current FDA guidelines approve OCA for the treatment of PBC in patients who have failed treatment or are unable to tolerate UDCA. The clinical trials on the efficacy of OCA against PBC, PSC, NAFLD, NASH, and Type-II diabetes have all shown promising results. These reports suggest that OCA, whether administered either as a monotherapy or in conjunction with conventional therapy, may work to effectively manage and treat these diseases. The efficacy of OCA against

various other hepatic and pancreatic related disorders warrants more studies.[7-8]

OBJECTIVE

To assess the effectiveness of obeticholic acid and ursodeoxycholic in nonalcoholic steatohepatitis management.

METHODOLOGY

Types of study

- It was a cross sectional type.

Place and period of the study

- The study place was carried out at tertiary medical college hospital, Bangladesh. Where data were collected from January 2019 to January 2020.

Study Population

- A total of 60 patients with a clinical and laboratory diagnosis of NASH, on a stable dose of UDCA for at least 6 months prior to screening, were randomly assigned (1:1:1) to one of three treatment groups for 85 days (3 months): OCA 10 mg, OCA 25 mg, OCA 50 mg or a matching placebo administered once daily.

Data Analysis

- All collected data were coding and input in SPSS-25 for further analysis. Both descriptive and inferential statistics done. Descriptive statistics included frequency distribution, percent, mean, standard deviation; graph, tables, figures and inferential statistics.

RESULTS

In figure-1 shows age distribution of the patients, out of 60 patients (40%) were 30 or below 30 years old, (26.6%) 31-40 years and (20%) 41-50 years. The following figure is given below in details.

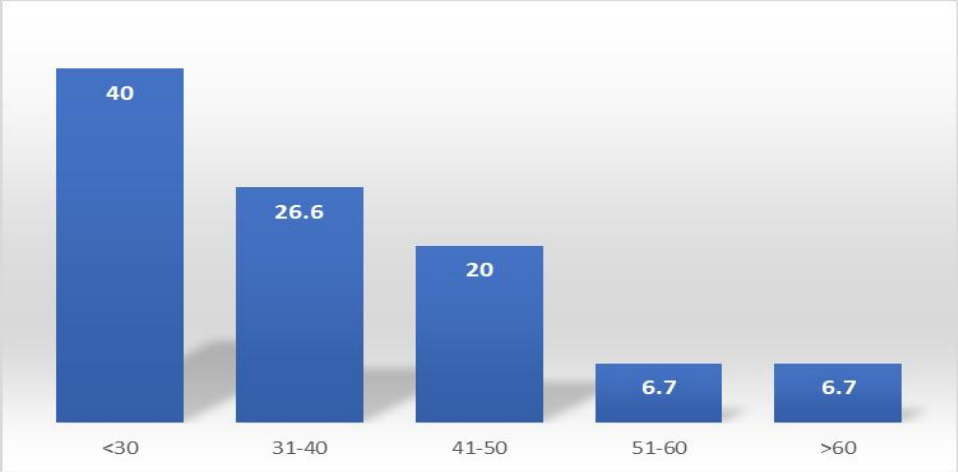

Figure-1: Age distribution of the patients.

In figure-2 shows gender distribution of the patients. Majority (80%) of the patients were male. The following figure is given below in details.

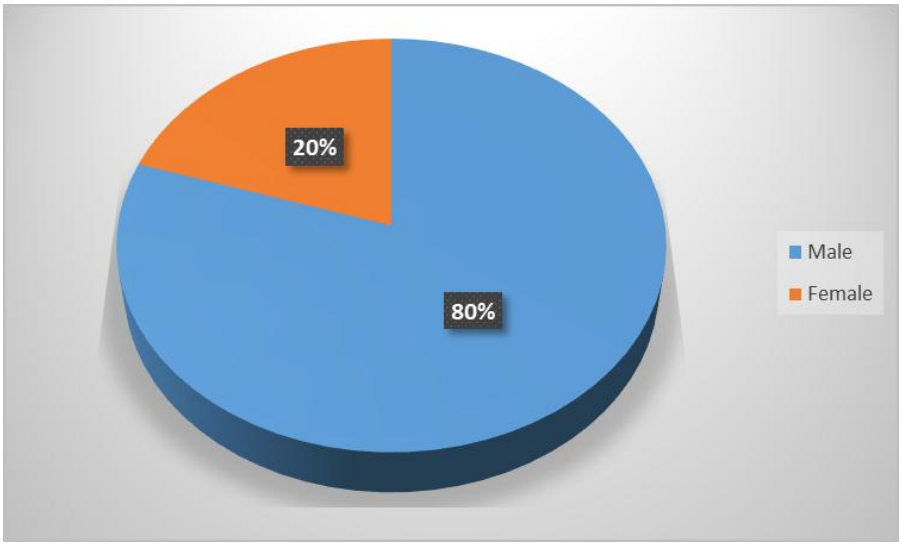

Figure-2: Gender distribution of the patients.

In table-1 shows baseline Characteristics of Patients.

Table 1: Baseline Characteristics of Patients.

Body Mass Index (kg/m2)	Placebo (N=320)	OCA 10 mg (N=20)	OCA 25 mg (N=20)
Mean (SD)	27.4 (5.2)	27.8 (4.7)	27.4 (5.1)
ALP (U/L) Mean (SD)	275.2 (102.7)	294.4 (149.4)	290.0 (123.6)
Bilirubin (mg/dL), mean	0.2 (0.2)	0.2 (0.2)	0.2 (0.1)
Albumin (g/dL), mean (SD)	4.2(0.3)	4.3(0.5)	4.0(0.4)
History of Increased ALP	94%	92%	93%

In table-2 shows biochemical Treatment Response Criteria Day 85 Response where in case of ALP ≤ 3x ULN or AST ≤ 2x ULN and tBili ≤ 1 mg/dL1, OCA 25 mg group day 85 baseline response was 71%. The following table is given below in detail.

Table 2: Biochemical Treatment Response Criteria Day 85 Response.

ALP ≤ 3x ULN or AST ≤ 2x ULN and tBili ≤ 1 mg/dL1	Placebo (N=20)	OCA 10 mg (N=20)	OCA 25 mg (N=20)
Day 85 % baseline non-responders with treatment effect	0	34%	71%
ALP ≤ 1.5x ULN and AST ≤ 1.5x ULN and tBili ≤ 1 mg/dL2	Placebo (N=20)	OCA 10 mg (N=20)	OCA 25 mg (N=20)
Day 85 % baseline non-responders with treatment effect	11%	33%	33%
ALP ≤ 1.67x ULN3	Placebo (N=20)	OCA 10 mg (N=20)	OCA 25 mg (N=20)
Day 85 % baseline non-responders with treatment effect	12%	44%	43%
ALP ≤ 1.76x ULN4	Placebo (N=20)	OCA 10 mg (N=20)	OCA 25 mg (N=20)
Day 85 % baseline non-responders with treatment effect	18%	40%	48%

In table-3 shows Liver Chemistry, Immunologic Markers and Lipids. C-reactive protein (CRP) and IgM values also showed significant reductions from baseline at the end of the study with OCA treatment. Median IgM values decreased by 14%, 21% and 18% at 10 mg, 25 mg, and 50 mg OCA (p=.0003 for 10 mg; p<.0001 for 25- and 50 mg compared to baseline), respectively, vs. a 19% increase in the placebo group. The following table is given below in detail.

Table 3: Liver Chemistry, Immunologic Markers and Lipids of the patients.

	Placebo (N=20)		OCA 10 mg (N=20)		OCA 25 mg (N=20)	
	Day 0	Day 85	Day 0	Day 85	Day 0	Day 85
ALT (U/L)	41 (28-53)	40 (26-63)	45 (30-60)	27 (22-41)	39 (30-59)	24 (19-38)
AST (U/L)	38 (30-49)	36 (27-48)	43 (32-57)	33 (27-40)	39 (30-47)	29 (24-42)
CRP (mg/L)	3.4 (1.6-7.9)	5.5 (1.4-8.1)	5.5 (3.1-9.5)	4.7 (2.8-6.4)	6.1 (2.8-8.9)	2.4 (1.4-4.7)
Cholesterol (mg/dL)	239 (201-258)	246 (204-268)	218 (190-251)	20s6 (179-244)	231 (196-272)	208 (184-259)
LDL (mg/dL)	133 (104-162)	137 (113-160)	130 (104-159)	128 (107-172)	133 (105-157)	139 (108-165)
HDL (mg/dL)	70 (55-86)	72 (61-87)	65 (54-80)	57 (42-68)	67 (59-81)	56 (45-74)
Triglycerides (mg/dL)	119 (101-154)	106 (85-137)	113 (81-148)	108 (86-139)	114 (83-150)	97 (76-130)

In table-3 shows clinical outcome of the patients where in OCA 25 mg group Improvement of fibrosis was 24% without worsening of NASH and 12% resolution cases of NASH with no worsening of fibrosis. Fibrosis was detected by Fibro scan.

The following table is given below in detail.

Table 3: clinical outcome of the patients.

	Placebo (N=20)	OCA 10 mg (N=20)	OCA 25 mg (N=20)
Improvement of fibrosis with no worsening of NASH	13%	19%	24%
Resolution of NASH with no worsening of fibrosis	9%	11%	12%

DISCUSSION

Treatment with obeticholic acid 25 mg met the primary endpoint of improvement in fibrosis with no worsening of NASH in patients with stage F2 or F3 fibrosis, at the month-18 interim analysis. The robust antifibrotic effect of obeticholic acid was dose dependent and consistent across different patient populations and subgroups, and was further supported by fibrosis-related secondary endpoints, including an improvement in fibrosis of at least two stages. Per the draft guidance from the FDA on efficacy endpoints for clinical trials in NASH, improvement in fibrosis by at least one stage with no worsening of NASH is reasonably.[10]

Although the percentage of patients achieving NASH resolution was not significant between obeticholic acid and placebo, more patients receiving obeticholic acid 25 mg showed improvements in immunogenic and lipid profiles of the prespecified NASH resolution endpoint. These data are relevant to other studies.[6]

Additionally, C-reactive protein (CRP) showed significant reductions from baseline at the end of the study with OCA treatment.[7]

CONCLUSION

Daily doses of OCA, ranging from 10 to 25 mg, significantly reduced levels of ALP, lipid profile, and alanine aminotransferase, compared to placebo, in patients with NASH who had inadequate responses to UDCA. Further study is needed for better outcome.

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