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Generic Obeticholic Acid for Management of Fatty Liver - A Prospective, Real-Life Study from Bangladesh

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ABSTRACT:

Introduction: Fatty liver has become a pandemic with potential of progression to liver cirrhosis and hepatocellular carcinoma. Till date lifestyle modification remains the

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mainstay of management of fatty liver.

Materials & Methods: We included 68 fatty liver patients in this prospective, real-life study. They were randomized into two groups. One group (case group') included 48 patients who were prescribed generic obeticholic acid 20 mg orally, daily plus lifestyle modification. The other group (control') included 20 fatty liver patients. They were advised only lifestyle modification. Patients were followed up at 6 months. Serum alanine aminotransferase and aspertate aminotransferase levels, in addition to ultrasonography of hepatobiliary system and fibroscan were done at baseline and at 6 months.

Results: We observed significant reduction in hepatic fat content in the case group compared to the control group. Conclusion: Our real-life study shows promising results with generic obeticholic acid in fatty liver management. Larger clinical trials in the future will be needed to validate our findings.

Keywords: Fatty liver, obeticholic acid, generic, hepatic fat content, hepatic fibrosis

Introduction

Fatty liver is now days a very common cause of chronic liver disease across the globe responsible for increased numbers of hepatocellular carcinoma (HCC) and liver-related deaths [1, 2, 3]. The overall global prevalence of fatty liver (MAFLD) is 25.2% [4]. It has been estimated that approximately 15-20% of patients with MAFLD suffer from MASH [5]. They progress to develop liver cirrhosis at a rate of 25% in 7-8 years. Hepatic decompensation develops in 10 years at 25% rate and HCC at a rate of 1% per year [6]. In Bangladesh the situation is equally worrisome as the prevalence of MAFLD here has been estimated at 18.5% [7].

Prevention of development of cirrhosis therefore remains one of the corner stones of MAFLD management. Obeticholic acid (OCA) is a potent and selective farnesiod X receptor (FXR) agonist. It is derived from the primary bile acid chenodeoxycholic acid [8]. FXR is a ligand-activated nuclear receptor which is predominantly expressed in liver and small intestine [9]. In the liver, it is expressed in the hepatocytes, Kupffer cells and endothelial cells [9, 10]. Activation of FXR leads to

increased utilization of glucose and decreased lipogenesis and decreased inflammation [11]. FXR activation reduces fibrosis and exerts anti-fibrotic effect on hepatic stellate cells [9]. Therefore, a school of thought exists that OCA may be beneficial for MAFLD patients.

Material & Methods

In this prospective, real-life study from Bangladesh, 68 treatment naïve, fatty liver patients were included. Fatty liver was diagnosed by ultrasonography of hepatobiliary system and fibroscan. Infection of hepatitis B and C viruses, alcohol consumption and liver cirrhosis were excluded. Patients were between 21 to 70 years of age. The patients were randomized by block randomization method into 2 groups. In 'case group', there were 48 patients, who were prescribed OCA 20 mg orally, daily in addition to lifestyle modification. Generic version of OCA is available in Bangladesh. The other group (control') included 20 patients, who were advised lifestyle modification only. Patients were followed up at 6 months to assess response. Serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels, in addition to ultrasonography of hepatobiliary system and fibroscan were done.

Results

Age and sex distribution of patients included in the case and control groups are shown in Figure 1-4. At baseline, there were no significant differences between groups for ALT (cases: 50.8 ± 39.7 vs. controls: 62.9 ± 40.9; p = 0.262), whereas controls had significantly higher AST (45.6 ± 28.4 vs. 34.0 ± 17.6; p = 0.045) and CAP values (318.9 ± 34.9 vs. 294.1 ± 36.8; p = 0.012). LSM values were significantly higher in the case group compared with controls (6.48 ± 2.70 vs. 5.46 ± 1.05; p = 0.027) (Table 1).

At 6 months, the main 'between-group difference' at 6 months was CAP, with controls having higher CAP. ALT and AST differences were no longer statistically significant between groups at 6 months. LSM was similar between groups at 6 months (Table 2).

Within groups, both groups showed significant decreases in ALT and CAP at 6 months. Decreases were numerically larger in the control group for ALT, AST and CAP. Only the case group showed statistically significant reduction in LSM ($p = 0.018$). In control group, LSM did not change significantly.

After 6 months, ALT and AST levels decreased in both groups. In the control group, ALT declined from 62.9 ± 40.9 to 44.4 ± 22.0 (mean change −18.5; $p = 0.010$) and AST from 45.6 ± 28.4 to 33.5 ± 9.9 (mean change −12.1; $p = 0.023$). In the case group, ALT decreased from 50.8 ± 39.7 to 38.3 ± 29.8 (mean change −12.5; $p = 0.040$), while the reduction in AST did not reach statistical significance (34.0 ± 17.6 to 29.4 ± 11.2; $p = 0.113$).

For CAP, both groups showed significant reductions. In case group, CAP decreased from 294.1 ± 36.8 to 274.7 ± 45.3 (mean change −19.4; $p = 0.010$) and in control group from 318.9 ± 34.9 to 305.5 ± 33.2 (mean change −13.5; $p = 0.009$). 'Between-group' comparison at 6 months showed significantly higher CAP values in the control group (305.5 ± 33.2 vs. 274.7 ± 45.3; $p = 0.008$).

Regarding LSM, significant reduction was observed only in the case group (6.48 ± 2.70 to 5.49 ± 1.61; mean change −0.99; $p = 0.018$), whereas no significant change occurred in the controls (5.46 ± 1.05 to 5.38 ± 1.00; $p = 0.585$). At 6 months, there was no significant difference in LSM between groups ($p = 0.779$) (Figure-5) (Tables 3-4).

Discussion

Currently lifestyle modification and dietary changes to induce weight reduction and improve insulin sensitivity are recommended for MAFLD/MASH management [12, 13]. The fundamentals of lifestyle modification include diet, exercise and weight reduction. Exercise includes brisk walking, aerobic exercise, swimming and cycling [14]. If one loses >7% body weight, this will lead to resolution of excess hepatic fat content, while >10% weight reduction can lead to disappearance of hepatic fibrosis [15]. However long-term outcome of such interventions remains debatable as many patients are unable to maintain dietary and lifestyle changes [12, 16]. Besides, rebound weight gain is also a natural phenomenon in many cases [17].

However, finding the appropriate drug remains a challenge. Resmetirom a partial activator of a thyroid hormone receptor, which reduces hepatic fat has recently been approved by the United States Food and Drug Administration (USFDA) as the first drug for the management of MAFLD/MASH [18]. Most recently a phase III clinical trial has shown excellent results with semaglutide in MAFLD/MASH management [19].

OCA has generated enthusiasm for MAFLD/MASH management. Although the drug did not make it to the USFDA, several clinical trials have yielded promising results with OCA in fatty liver. A large, international, multi-center, phase III clinical trial which is termed 'REGENERATE', included 2500 patients. Analysis of data of initial 931 patients showed that OCA at a dose of 25 mg, orally, resulted in a 1-stage reversal of hepatic fibrosis without worsening of MASH, compared to those patients who received OCA 10 mg, orally, daily or placebo (23% versus 18% versus 12%). OCA was also found to be superior to placebo in improving lobular inflammation and hepatocyte ballooning [20]. Similar improvement in hepatic histology was also observed in an earlier, smaller, phase IIb clinical trial of OCA in fatty liver, which is known as 'FLINT' trial [21]. In this later study, improvement of serum ALT was also observed in OCA-treated fatty liver patients compared to those receiving placebo (66% versus 36%). Another clinical trial involving 283 fatty liver patients demonstrated significant improvement in hepatic histology at 72 weeks of treatment in OCA treated patients compared to those receiving placebo (45% versus 23%) [5]. In our case, we observed improvement in both hepatic fat content and fibrosis in OCA treated patients, however the latter was not statistically significant when compared with the 'control' group.

The most common, dose dependent adverse event with OCA is pruritus seen in 19-28% patients, which is rarely severe, but can still lead to treatment discontinuation. Increase in low density lipoprotein (LDL) level is associated with 1-month treatment with OCA, which is easily managed with statins. There is little evidence of hepatotoxicity of OCA including those with compensated liver cirrhosis [22].

Generic version of OCA approved by the Directorate General of Drug Administration (DGDA) of Bangladesh and is produced and widely used in Bangladesh for treating

fatty liver. The country is long known for its generic drugs which have wide access into the global market too. From a local context, it is therefore felt necessary to access the response to generic OCA among Bangladeshi fatty liver patients. We selected serum ALT and serum AST levels and assessed hepatic fat content (i.e. CAP) and fibrosis (i.e. LSM) by fibroscan for documenting response to OCA. Liver biopsy remains 'gold standard' for assessment of hepatic inflammation and fibrosis. Our group performs this procedure frequently. However, its acceptability is limited to more conservative colleagues who prefer to avoid this safe, but invasive procedure. LSM and CAP by fibroscan are useful and widely accepted alternatives for assessment of hepatic fat content and fibrosis [23, 24, 25, 26]. We however did not rely on ultrasonography of hepatobiliary system, as it is subject to intra- and inter-observer variability specially in Bangladesh, where it is often performed by non-qualified practitioners.

We observed improvement of markers of hepatic necro-inflammation, fat content and fibrosis with life-style modification. However, patients taking OCA showed significant reduction of fat in the liver. This is an important real-life observation, not to mention that it also demonstrates efficacy of Bangladeshi generic OCA in fatty liver.

Conclusion

Identifying effective pharmacotherapy for MAFLD/MASH management remains elusive. Newer drugs are often expensive. Bangladesh, like other countries of the region, faces the non-communicable fatty liver pandemic. It is rightly anticipated that the consequent increased burden of chronic liver disease will eventually pose huge obstacles in our quest for ensuring healthy life for our population in the not-too-distant future. We therefore ought to try a different approach in addition to lifestyle modification for management of MAFLD/MASH. This is a small real-life study, but it generates hope and assurance. It also paves the way for conducting multi-center clinical trials with generic OCA and other generic pharmacologic agents in fatty liver patients.

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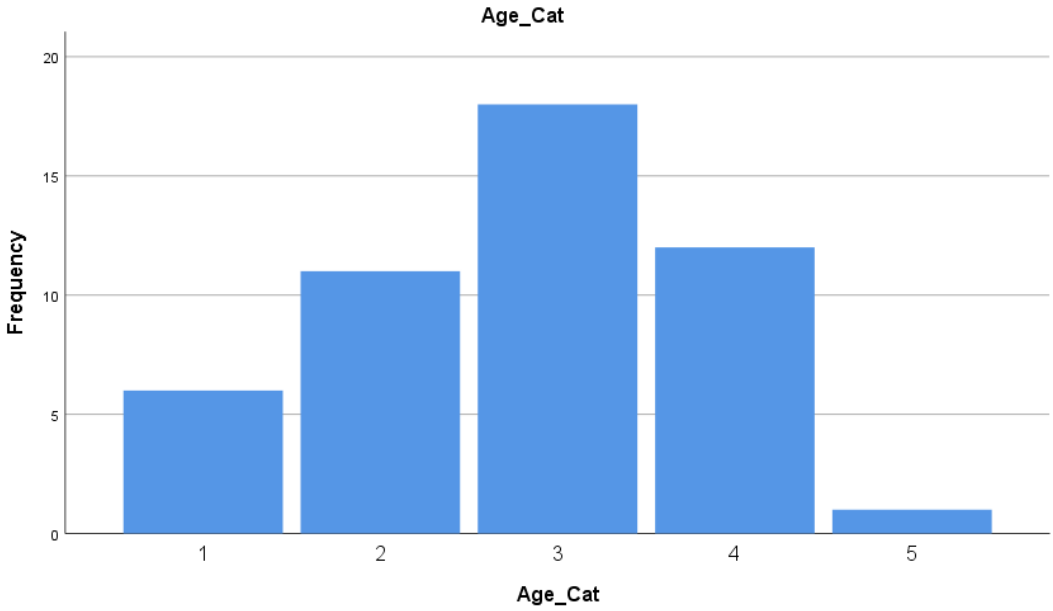

Figure -1: Age distribution of case.

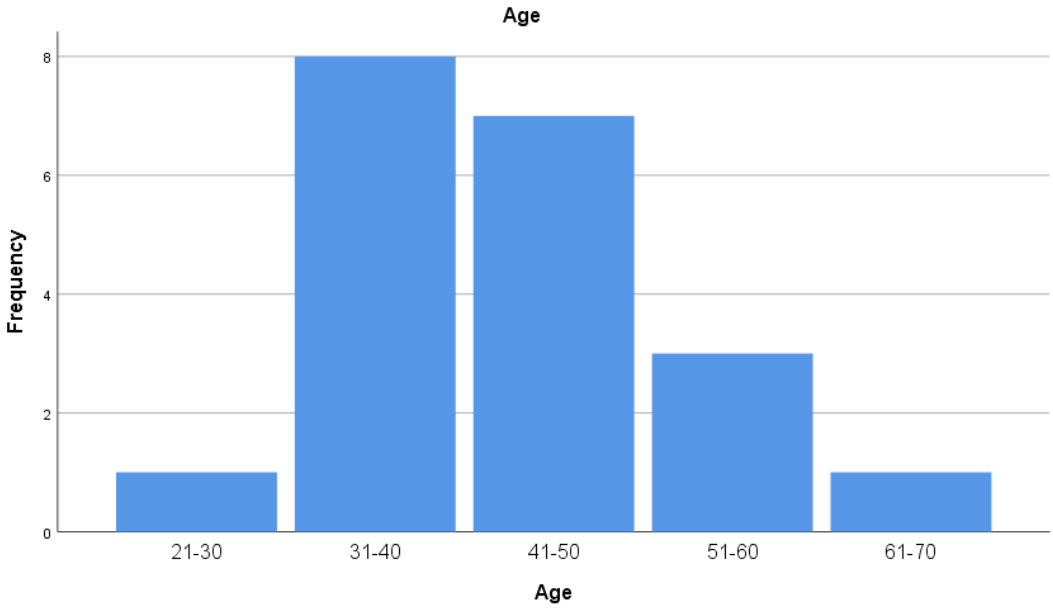

Figure-2: Age distribution of control.

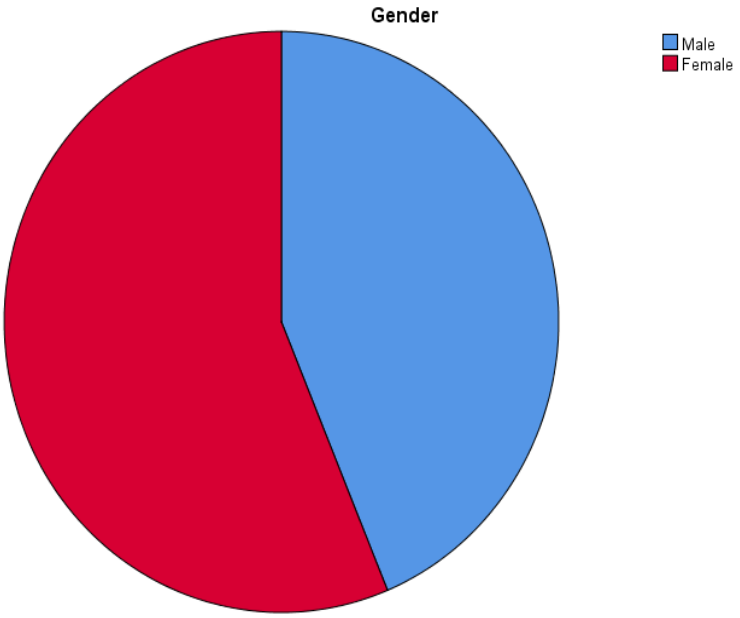

Figure-3: Gender distribution of case.

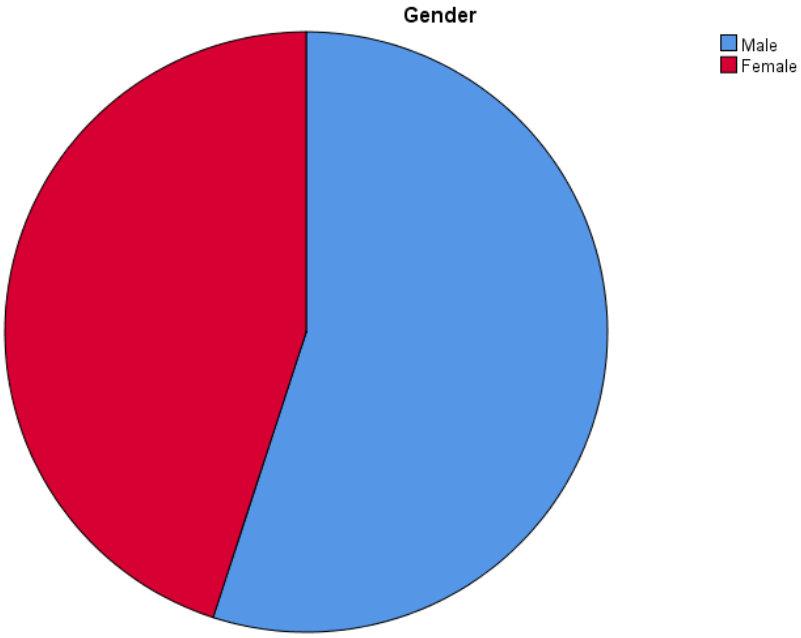

Figure-4: Gender distribution of control.

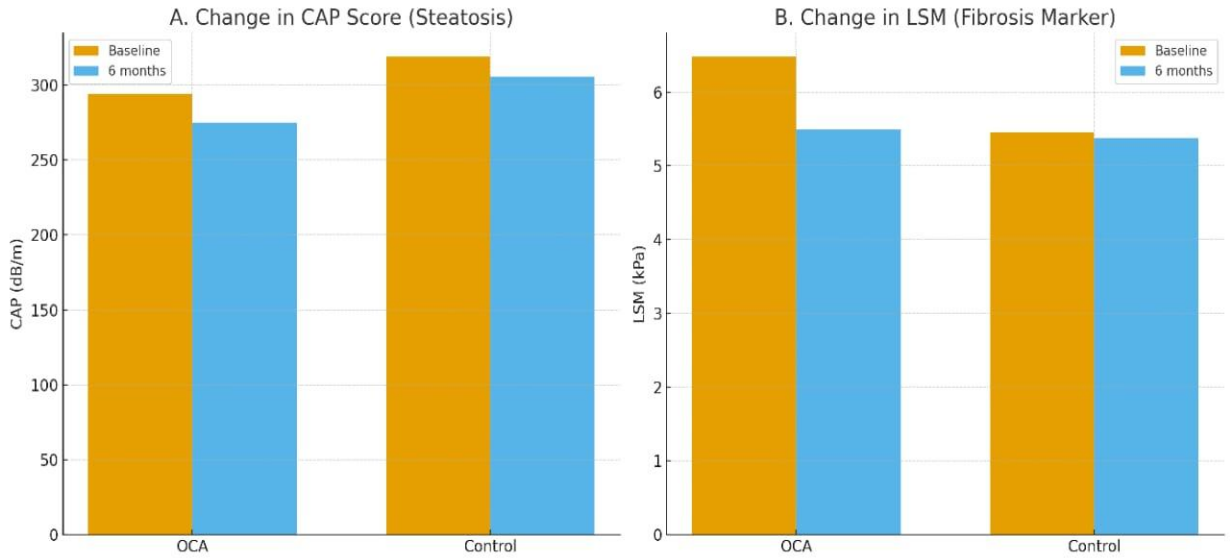

Figure-5: Change in CAP and LSM between case and control groups.

Table-1: Baseline Values of both case and control groups.

Variable	OCA (Mean ± SD) N=48	Control (Mean ± SD) N=20	t-test p-value
ALT	50.8 ± 39.7	62.9 ± 40.9	0.262
AST	34.0 ± 17.6	45.6 ± 28.4	0.045*
CAP	294.1 ± 36.8	318.9 ± 34.9	0.012*
LSM	6.48 ± 2.7	5.46 ± 1.0	0.027*

(Independent t-test between groups)

Table-2: Liver function tests of case group and control group at 6 months

Variable	OCA (Mean ± SD) N=48	Control (Mean ± SD) N=20	p-value
ALT	38.3 ± 29.7	44.4 ± 22.0	0.413
AST	29.4 ± 11.2	33.5 ± 9.9	0.165
CAP	274.7 ± 45.24	305.5 ± 33.2	0.008*
LSM	5.48 ± 1.6	5.38 ± 1.0	0.779

(Independent t-test)

Table-3: Comparison within control group at baseline and 6 months.

Variable	Baseline (Mean ± SD)	6m (Mean ± SD)	p-value
ALT	50.8± 39.7	38.3± 29.7	0.040*
AST	34.0± 17.5	29.4± 11.2	0.113
CAP	294.1± 36.7	274.7± 45.2	0.010*
LSM	6.48± 2.69	5.49± 1.6	0.018*

(Paired t-test)

Table-4: Comparison within case group at baseline and 6 months.

Variable	Baseline (Mean ± SD)	6m (Mean ± SD)	p-value
ALT	62.9± 40.8	44.4± 22.0	0.010*
AST	45.6± 28.3	33.5± 9.9	0.023*
CAP	319.0± 34.8	305.5± 33.2	0.009*
LSM	5.45± 1.0	5.38± 1.0	0.585

(Paired t-test)