



Original Article

Dual Drug Therapy for Fatty Liver: Outcome of a Prospective, Real Life Study from Bangladesh

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ABSTRACT

Introduction: Fatty liver remains a global healthcare concern as it, on one hand has reached pandemic proportions and on the other hand has potential of progression to liver cirrhosis and hepatocellular carcinoma. However, till date lifestyle modification remains the mainstay of management of fatty liver. **Materials & Methods:** We included 93 fatty liver patients in this prospective, real life study. They were randomized into two groups. One group (Group-A) included 44 patients who were prescribed obeticholic acid 20 mg daily plus saroglitazar 4 mg daily, both orally in addition to lifestyle modification. The other group (Group-B) included 49 fatty liver patients. They were advised lifestyle modification only. Patients were followed up at 6 to 12 months. Serum alanine aminotransferase and aspartate aminotransferase levels, in addition to ultrasonography of hepatobiliary system and fibroscan were performed at baseline and at follow up. **Results:** We observed significant improvement in liver enzyme levels as well as significant reduction of fibroscan parameters in the treatment group (Group-A) compared to the lifestyle only modification group (Group-B). **Conclusion:** Our study shows promising results and paves the way for larger studies to validate our observations.

Keywords: Fatty liver, dual drug therapy, hepatic inflammation, hepatic fat content, hepatic fibrosis.

INTRODUCTION

It has been estimated that approximately 25% patients with fatty liver (MAFLD) suffer from chronic hepatitis (MASH). More importantly they progress to developing liver cirrhosis at a rate of 25% in 7-8 years. Hepatic decompensation develops in 10 years again at 25% rate and hepatocellular carcinoma (HCC) at a rate of 1% per year [1]. The prevalence of fatty liver is 27.4% in Asia. In Bangladesh the situation is equally worrisome as the prevalence of MAFLD here has been estimated at 18.5% [2]. In obese and diabetics, the prevalence has been estimated at 70-75% [3, 4]. Since obesity and diabetes are both on the rise in the global perspective, it's only expected that we shall be seeing more patients with MAFLD/MASH in the coming times [5, 6].

MATERIALS & METHODS

We included 93 naïve, fatty liver patients in this prospective, real life study from Bangladesh. Diagnosis of fatty liver was made at ultrasonography of hepatobiliary system and fibroscan. Infection of hepatitis B and C viruses, alcohol consumption and liver cirrhosis were excluded. Patients were between 20 to 73 years of age. Among them 39 were males and rest 54 females. They were randomized by block randomization method into 2 groups. In Group-A there were 44 patients, who were prescribed obeticholic acid 20 mg daily plus saroglitazar 4 mg daily, both orally in addition to lifestyle modification. Generic versions of both drugs are available in Bangladesh. There is no report of any drug to drug interaction between these two agents. The other group (Group-B) included 49 patients, who were advised lifestyle modification only. Patients were followed up at 6 to 12 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

All results were analyzed by SPSS (version 27.0 IBM Corp: Armonk NY USA). The mean age in Group-A was higher (47.0 ± 12.9 years) compared to Group B (41.6 ± 8.8 years), with age ranges of 21–73 years and 20–62 years, respectively. The statistical comparison of age distribution between the groups showed no significant difference ($p = 0.115$) (Table-1). In Group A, 43.2% were male and 56.8% were female, while in Group B, 40.8% were male and 59.2% were female. The difference in sex distribution between the two groups was also not statistically significant ($p = 0.817$) (Table-2).

After treatment, patients in Group A showed significantly lower AST (27.7 ± 13.2 vs. 38.8 ± 20.0 , $p = 0.002$) and ALT (31.0 ± 16.6 vs. 51.3 ± 28.9 , $p < 0.001$) levels compared to Group B (Table 3). Additionally, liver stiffness (kPa) and fat content (CAP) values were significantly improved in Group A ($p < 0.001$ for both), indicating better reductions in fibrosis and hepatic steatosis (Table 3).

Pre- and post-treatment comparisons of liver function tests and imaging-based liver health markers within each group were done. In Group A, there were statistically significant reductions in AST ($p = 0.004$), ALT ($p < 0.001$), liver stiffness (kPa; $p < 0.001$), and CAP ($p < 0.001$) after 6 to 12 months, indicating meaningful improvement in liver function, fibrosis, and steatosis. In Group B, AST ($p = 0.003$) and ALT ($p = 0.001$) levels also decreased significantly over time, but no significant change was observed in liver stiffness ($p = 0.467$). CAP values however showed significant reduction ($p = 0.003$) (Table 4).

Table-1: Age Distribution of patients (N = 93)

Age group (years)	Group A (n=44)	Group B (n=49)	p-value
20-29	2(4.5%)	4(8.2%)	0.115
30-39	11(25.0%)	14(28.6%)	
40-49	11(25.0%)	20(40.8%)	
50-59	12(27.3%)	9(18.4%)	
>60	8(18.2%)	2(4.1%)	
Total	44(100.0%)	49(100.0%)	
Mean±SD	47.0±12.9	41.6±8.8	
Range (min – max)	(21-73)	(20-62)	

(p-value obtained by Chi-square test, $p < 0.05$ was considered as *significant)

Table-2: Sex distribution of patients (N = 93)

Sex	Group A (n=44)	Group B (n=49)	p-value
Male	19(43.2%)	20(40.8%)	0.817
Female	25(56.8%)	29(59.2%)	
Total	44(100.0%)	49(100.0%)	

(p-value obtained by Chi-square test, $p < 0.05$ was considered as *significant)

Table-3: Comparison of liver enzymes (AST, ALT), liver stiffness (kPa) and steatosis (CAP) between two groups at baseline and follow up (N = 93)

Variables	Group A (n=44)	Group B (n=49)	p-value
Baseline			
AST	35.8±22.9 (10-120)	46.8±25.4 (19-139)	0.032*

ALT	49.1±38.8 (16-168)	63.5±37.5 (17-182)	0.072
k.Pa	8.9±7.6 (3.7-50.8)	7.9±2.4 (4.3-12.8)	0.358
CAP	298.9±38.9 (231-391)	310.1±33.8 (237-385)	0.143
After 6 months to 1 year			
AST	27.7±13.2 (10-90)	38.8±20.0 (12-135)	0.002*
ALT	31.0±16.6 (12-84)	51.3±28.9 (13-136)	<0.001*
k.Pa	5.7±2.4 (2.5-16.3)	7.7±2.9 (3.9-16.4)	<0.001*
CAP	239.4±43.0 (129-354)	299.2±33.9 (220-370)	<0.001*

(Data were expressed as mean ± SD and range (min-max)
(p-value obtained by Unpaired t- test, p<0.05 was considered as *significant)

Table-4: Within-group comparison of AST, ALT, liver stiffness (kPa) and steatosis (CAP) at baseline and after 6 to 12 months (N = 88)

	Baseline (n=44)	After 6 months to 1 year (n=44)	p-value
Group A			
AST	35.8±22.9 (10-120)	27.7±13.2 (10-90)	0.004*
ALT	49.1±38.8 (16-168)	31.0±16.6 (12-84)	<0.001*
k.Pa	8.9±7.6 (3.7-50.8)	5.7±2.4 (2.5-16.3)	<0.001*
CAP	298.9±38.9 (231-391)	239.4±43.0 (129-354)	<0.001*
Group B			
AST	46.8±25.4 (19-139)	38.8±20.0 (12-135)	0.003*
ALT	63.5±37.5 (17-182)	51.3±28.9 (13-136)	0.001*
k.Pa	7.9±2.4 (4.3-12.8)	7.7±2.9 (3.9-16.4)	0.467
CAP	310.1±33.8 (237-385)	299.2±33.9 (220-370)	0.003*

(Data were expressed as mean ± SD and range (min-max)
p-value obtained by Paired t- test, p<0.05 was considered as *significant)

Table-5: Regulatory role of FXR in MAFLD/MASH

Metabolism	Inflammation	Liver fibrosis
Decrease lipogenesis	Reduce inflammation	Inhibit hepatic stellate cell activation
Decrease gluconeogenesis	Decrease NF-κB	Reduce collagen deposition
Increase glucose oxidation	Decrease hepatocyte apoptosis	
Increase glycogen synthesis		
Increase β oxidation of fatty acids		
Increase triglyceride clearance		

DISCUSSION

Currently lifestyle modification remains the mainstay of management of MAFLD/MASH, the fundamentals of lifestyle modification being diet, exercise and weight reduction. Exercise may be many fold including brisk walking, aerobic exercise, swimming and cycling [7]. It has been seen that if one can lose >7% body weight, this may lead to resolution of hepatic excess fat content, while >10% weight reduction may lead to disappearance of fibrosis from the liver [8]. Having said so, this has to be kept in mind that sustaining reduced body weight remains a challenge, rebound weight gain being a natural phenomenon in many cases [9].

Therefore, pharmacotherapy remains an option, however once again finding the drug of choice remains an even greater challenge. Resmetirom is a partial activator of a thyroid hormone receptor. The activation of this receptor by resmetirom in the liver reduces liver fat accumulation. This has recently received approval from the United States Food and Drug Administration (USFDA) as the first drug for the management of MAFLD/MASH, but is yet to be available in many parts of the world including in Bangladesh [10]. Most recently a phase III clinical trial has shown excellent results with semaglutide in MAFLD/MASH management [11]. Pioglitazone and vitamin E are two drugs with promising results in clinical trials MAFLD/MASH [12, 13, 14, 15]. Unfortunately, neither could stand the test of time as there are safety concerns with pioglitazone including pedal oedema, weight gain, bone loss, pancreatitis and heart failure to name a few [9]. Vitamin E has been tested only in non-diabetic fatty liver. None of these two agents have been tested in MASH cirrhosis [9].

A recent enthusiasm is obeticholic acid (OCA), a synthetic analogue of farnesoid X receptor (FXR). FXR is a member of the bile acid-activated-receptor super family (BAR), which is detected in hepatocytes and hepatic stellate cells. In addition, FXR is also found in small intestinal enterocytes, kidney, ovary and adrenal glands [9]. It is capable of regulating several metabolic, inflammatory and fibrotic pathways in the liver (Table-4). However, OCA, ultimately failed to make it to the USFDA.

Another drug that attracted much attention in recent times is saroglitazar, a peroxisome proliferator activated receptor (PPAR)- α and γ agonist, that has been approved by the The Central Drugs Standard Control Organization (CDSCO) for MAFLD/MASH management, but not by the USFDA yet [16]. Saroglitazar acts on PPAR- α receptors present in hepatocytes and prevents hepatic steatosis and steatohepatitis by inhibiting intra-hepatic fatty acid accumulation. It also acts on PPAR- γ receptors in adipocytes and decreases hepatic fat availability by improving insulin sensitivity and lipid oxidation. It thus reduces hepatic steatosis, inflammation and fibrosis [17, 18, 19].

For assessing response to our treatment regimen, we opted for serum ALT and serum AST levels and plus assessment of hepatic fat content and fibrosis by fibroscan. Although liver biopsy remains the gold standard for assessment of hepatic inflammation and fibrosis and is extensively employed by our group for these purposes, its acceptability is limited in many cases by colleagues as those with more conservative approach prefer to avoid percutaneous liver biopsy, which is a safe, but invasive procedure. In this context, LSM and CAP by fibroscan may be useful alternatives for assessment of hepatic fat content and fibrosis [20, 21, 22, 23]. We did not consider ultrasonography of hepatobiliary system, as it is subject to intra and inter observer variability and particularly in Bangladesh, is not performed by qualified specialists in many cases. Therefore, it is no wonder that ultrasonography findings are often inconsistent, which we also observed in our cohort.

There are several clinical trials that show beneficial role of OCA in MAFLD/MASH. These include FLINT study, REGENERATE trial and REVERSE trial. Not going into details, this much can be said that these studies showed either improvement or non-deterioration of hepatic fibrosis, improvement of NAS score and reduction in serum liver enzymes [24, 25, 26]. On the other hand, several studies have reported reduction of LSM with saroglitazar [27, 28]. Similarly CAP reduction with saroglitazar has also been reported [29].

We observed improvement of markers of hepatic necro-inflammation and hepatic fat content with life style modification. However, when we used the dual drug regimen, in addition to improvement of hepatic inflammation and fat content we achieved reduction in hepatic fibrosis, which is the mainstay of treatment of any chronic liver disease including fatty liver and that to within a short span of time. This is the most important finding of our real life study, not to mention that it also established the safety of combination obeticholic acid and saroglitazar in fatty liver patients.

CONCLUSION

Improvement of hepatic inflammation and fibrosis remains the holy grail for MAFLD/MASH management. While researchers are busy across the globe looking for the correct answer, our approach has been different. Overburdened with high volume of MAFLD/MASH patients, we hypothesized that since the disease itself has many faces, we ought to try a different approach with multiple potentials pharmacologic agents in addition to lifestyle modification for management of

MAFLD/MASH in order to try to bring this non-communicable pandemic to a halt. Our's is a small study, but with huge hopes and our results are promising. We look forward to larger, multi-centre clinical trials with similar or more innovative approaches with the expectation that we shall soon be able to contain MAFLD/MASH.

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