Original Article

Effect of Telmisartan on Histological Activity and Fibrosis of Non-alcoholic Steatohepatitis: A 1-Year Randomized Control Trial

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ABSTRACT

Background/Aim: Telmisartan can attenuate two hit pathogenesis of non-alcoholic steatohepatitis (NASH). This study aimed to observe the effect of Telmisartan on non-alcoholic fatty liver disease (NAFLD) activity score (NAS) and fibrosis score in NASH patients. **Patients and Methods:** A total of 50 NASH patients were randomized; 35 of group 1 were treated with Telmisartan 40/80 mg once daily with life style modification (TL) and 15 of group 2 underwent only life style modification (L) for 1 year. At the end, 20 of TL group and 10 of L group were analyzed. Those who showed NAS improvement ≥ 2 or NAS improvement ≥ 1 with fibrosis improvement ≥ 1 were considered as responders. **Results:** Baseline alanine aminotransferase (ALT), aspartate aminotransferase (AST), insulin resistance index, components of metabolic syndrome, age, and sex were similar in both groups. At the end of study, NAS improvement in TL and L groups was 2.15 ± 1.66 and 1.10 ± 0.57 (P = 0.017) and fibrosis improvement was 0.65 ± 0.93 and –0.30 ± 0.48 (P = 0.001), respectively. NAS improved by ≥ 2 in 13 (65%) and 2 (20%) patients and fibrosis score improved by ≥ 1 in 8 (40%) patients and none of the patients in TL group and L group, respectively. Telmisartan and life style modification could improve steatosis, ballooning, lobular inflammation, and fibrosis. Life style modification could improve ballooning only, but fibrosis deteriorated. TL group showed improvement in NAS and fibrosis score [P value: 0.035; odds ratio (OR) =92.07, confidence interval (CI) =1.39–6106] to the level of response by regression analysis. Weight reduction and improvement of metabolic syndrome did not influence the response. There were similar minor adverse events in both groups. **Conclusion:** Telmisartan improved NAS and fibrosis score in NASH with insignificant adverse events.

Key Words: Bangladesh, fatty liver, fibrosis, histological activity, non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, Telmisartan

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Non-alcoholic fatty liver disease (NAFLD) is a condition pathologically linked to metabolic syndrome with the contribution of insulin resistance (IR), characterized by hepatic steatosis in the absence of significant alcohol use, hepatotoxic medications, or other known liver disease.[1] The spectrum of NAFLD is broad, extending from simple steatosis through non-alcoholic steatohepatitis (NASH) to cirrhosis and liver failure. NASH is a distinct clinical entity characterized by steatosis, varying degrees of lobular inflammation, and fibrosis of the liver, which can potentially progress.[2] NAFLD is the most common cause of chronic liver disease in United States. The estimated prevalence of NAFLD is 20–30% and NASH is 3.5–5%.[3] NAFLD occurs in patients of both genders, all ethnicities, and in all age groups, including children.[4] Reports have also suggested that the prevalence of NAFLD among Asian Indians is comparable to that seen in the West.[5,6] NASH probably causes around 80% of cases of cryptogenic cirrhosis and progresses to advanced fibrosis in 32–37% of patients.[7] Between 5 and 20% of noncirrhotic NASH patients develop cirrhosis during a 10-year follow-up,[8] and perhaps 1 in 200 NASH patients develop hepatocellular carcinoma (HCC) over a 7-year follow-up.[9] The pathogenesis of NASH involves initial

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insult that leads to development of macrovesicular steatosis with accumulation of hepatic fat. IR is the main contributing factor of this dysregulation of lipid metabolism. The second hit involves oxidative stress from mitochondrial reactive oxygen species, leading to secretion of pro-inflammatory cytokines that cause hepatic stellate cell activation, which results in fibrosis.[10]

Currently, most hepatologists attempt to manage NASH using life style changes to reverse the consequences of metabolic disease, such as weight reduction with or without exercise, as well as standard therapeutic interventions to control associated diseases such as hyperlipidemia, hypertension, and Type 2 diabetes mellitus (DM). Pharmacological therapies including thiazolidinediones, which up-regulate the activity of the transcription factor peroxisome proliferator-activated receptor (PPAR)-γ, lipid-lowering agents, cytoprotective agents (ursodeoxycholic acid), antioxidants (vitamin E, hepatic iron reduction, betaine, *S*-adenosyl methionine, *N*-acetyl cysteine), etc., improve certain aspects of the liver damage associated with NASH. Nevertheless, the persistent underlying or residual pathology underscores the need for more effective innovative treatments.[11]

Telmisartan is a unique angiotensin receptor blocker (ARB) that blocks both the hits by modulating PPAR-γ activity and thereby increasing insulin sensitivity, which decreases hepatic fat accumulation,[12] as well as by blocking angiotensin II receptor, which inhibits hepatic stellate cell activation and thus suppresses hepatic fibrogenesis.[13] Telmisartan is also effective in mild to moderate hypertension, improves insulin sensitivity in Type 2 DM, and improves cholesterol and triglyceride levels. As most of the patients of NAFLD have features of metabolic syndrome, Telmisartan can be used for treatment of NASH with metabolic syndrome.[14,15] We designed this randomized control trial (RCT) to observe the changes of histological activity and fibrosis in NASH patients after 1 year of Telmisartan therapy.

PATIENTS AND METHODS

Patient selection and randomization

This was an open-label RCT. Duration of the study was from January 2012 to September 2014. Patients of age 18–65 years in whom NAFLD activity score (NAS) was greater than or equal to 5 in liver histology were selected as the sample of our study. Exclusion criteria were: 1. alcohol intake >20 g/day; 2. Presence of co-morbid conditions such as, chronic hepatitis of other causes, chronic obstructive pulmonary disease, chronic kidney disease, cogestive cardiac failure; history of recent myocardial infarction, hypothyroidism, 3. Decompensated cirrhosis of liver; 4. Alanine aminotransferase (ALT) more than five times of upper normal limit; 5. History of taking angiotensin receptor blocker or angiotensin converting enzyme inhibitors. Group 1 patients received 40 mg of Telmisartan once daily and underwent life style modification (TL) and group 2 patients underwent life style modification alone, for 1 year. Liver biopsy was repeated after 1 year. Moderate exercise consisting of 30 min of walk daily with dietary advice to avoid fatty foods and excessive sugar-containing diet were followed by patients in both groups. Diabetic patients were treated with life style modifications and if needed, Gliclazide or Glimepiride was added. Lipid-lowering agents were put on hold for the first 3 months, as literature shows that Telmisartan has mild lipid-lowering effect.[14] If the patient was still dyslipidemic [total cholesterol (TC) >200 mg/dl, triglyceride (TG) >150 mg/dl], then statin was added. If the patient was still hypertensive after taking 40 mg Telmisartan, then the doses were increased up to 80 mg/day. In case further antihypertensive was needed, then atenolol or amlodipine was added.

Totally 50 patients were selected for randomization (35 of group 1/TL arm and 15 of group 2/L arm) and were followed for the next 1 year. Fifteen patients of group 1 and five patients of group 2 withdrew from the study due to lack of interest in doing end-of-study liver biopsy. So, a total 30 patients (20 in group 1 and 10 in group 2) were considered for statistical analysis, as per study protocol [Figure 1].

Biochemical analysis

Estimation of fasting blood sugar (FBS), ALT, aspartate aminotransferase (AST), gamma-glutamyl transpeptidase (GGT), bilirubin (B), TC, TG, low-density lipoprotein-cholesterol (LDL-C), and high-density lipoprotein-cholesterol (HDL-C) in fresh serum was conducted in the university biochemistry laboratory using autoanalyzer. Serum samples obtained after an overnight fast of at least 12 h and immediately frozen at −20°C were used to determine the levels of immunoreactive insulin (IRI) by a chemiluminescence immunoassay. We determined IR using the homeostasis model assessment 2 (HOMA 2-IR) calculator.[16]

Histopathology analysis

All liver biopsies were done within 15 days of laboratory investigations with full resuscitation facilities. Samples were

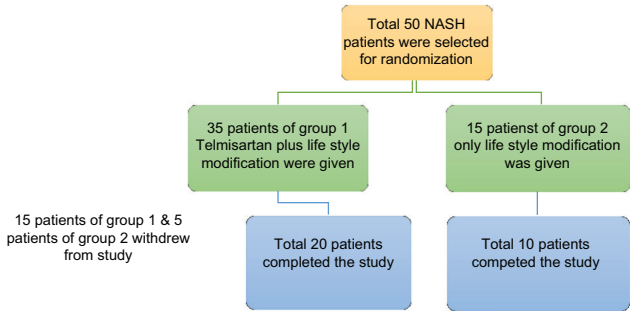

Figure 1: Flowchart for patient selection for the study

immersed in 10% formalin and stained with hematoxylin–eosin and Masson's trichrome. Biopsies were evaluated by an experienced pathologist, who was not aware of allocation of treatment as well as the clinical and biochemical parameters of any patient, using the scoring system validated by Kleiner.[17] This histological scoring system quantifies steatosis, lobular inflammation, and ballooning resulting in NAS that ranged between 0 and 8. Scores greater than or equal to 5 are largely diagnostic for NASH. Fibrotic changes were evaluated separately from NAS, with scores ranging from 0 (no fibrosis) to 4 (cirrhosis).

Study schedule and surveillance parameters

After screening, the included patients were followed for 12 months. Patients were followed months for the initial 3 months and then every three monthly for the next 9 months. Each visit consisted of clinical examination, blood pressure (BP), and body mass index (BMI) determinations. Serum was collected for CBC, erythrocyte sedimentation rate (ESR), FBS, blood sugar 2 hours after breakfast, ALT, AST, prothrombin time (PT) with international normalised ratio (INR), GGT, TC, TG, HDL, LDL, and IRI determinations in the first and last visits. FBS, 2HABF, and lipid profile for diabetic and dyslipidemic patients were monitored according to need. Also, the first visit comprised recording of the results of the index liver biopsy, while the last visit ended with second liver biopsy, performed at maximum 2 weeks after the end of treatment.

Statistical analysis

All data were presented as mean ± SD and analyzed by SPSS (version 20). Qualitative data were analyzed by Chi-square test and quantitative data by Student's *t*-test/Mann–Whitney U test. All quantitative and qualitative data were analyzed between responders and non-responders. Univariate and multivariate logistic regression analyses were done to find the best predictor of patient response. A statistically significant result was considered when *P* value was less than 0.05.

Operational definitions

NASH

NAS by liver biopsy greater than or equal to 5 was considered as NASH.

Non-NASH fatty liver

NAS by liver biopsy less than 5 was considered as non-NASH fatty liver (NNFL).

Weight reduction

During 1 year of study time, losing 10% or more of original body weight was considered as significant weight reduction.

Metabolic syndrome

If the patient met three or more of the following five criteria, he/she was considered as having metabolic syndrome: (i) Waist circumference (WC) in male ≥90 cm and in female ≥80 cm; (ii) TG ≥ 150 mg/dl; (iii) HDL in male < 40 mg/dl and in female <50 mg/dl; (iv) systolic BP ≥ 130 mm of Hg and/or diastolic BP ≥ 85 mm of Hg and/or patient on antihypertensive; and (v) fasting blood glucose ≥5.6 mmol/l and/or patient on antidiabetic agents.

Histological responder

Patients with NAS improvement ≥2 or NAS improvement ≥1 with fibrosis score improvement ≥1 were considered as histological responder.

Ethical consideration

Ethical clearance for the study was obtained from the Institutional Review Board (IRB) of the Medical University (BSMMU/2013/3401). The aims and objectives of the study along with its procedure, risks, and benefits were explained to the study subjects, and signed informed consent was taken from every patient, in accordance with the Helsinki declaration. The study subjects were assured about privacy and confidentiality of the information, freedom to withdraw at any time from the study, and were also ensured that this would not be a barrier to get the available standard treatment.

RESULTS

Baseline characteristic of patients

Most of our patients were either young or middle-aged; mean age in group 1 was 43.30 ± 11.03 years and in group 2 was 38.00 ± 8.23 years (*P* value = 0.188). Most of them were females (74.2%). According to Asian criteria (BMI ≥ 25 kg/m^2 considered as obese), totally 19 patients (63.3%) were obese, of which 14 patients were in group 1 (70%) and 5 patients were in group 2 (50%) (*P* = 0.284). Twenty four patients (80%) had increased WC; of them, 16 patients were in group 1 and 8 were in group 2 (*P* = 1.000). So, baseline anthropometric characteristics were similar in both groups. Eight patients were diabetic during enrollment (26.7%); of them, seven patients were in group 1 (35%) and one patient was in group 2 (10%) (*P* = 0.144). Overall, 11 patients (36.7%) were hypertensive, of whom 9 were in group 1 (45%) and 2 were in group 2 (20%) (*P* = 0.180). Baseline liver function tests did not differ significantly between the two groups. ALT was 50.00 ± 36.04 U/l and 45.80 ± 24.93 U/l in groups 1 and 2, respectively (*P* = 0.744); AST was 47.30 ± 32.27 U/l and 47.70 ± 32.21 U/l in groups 1 and 2, respectively (*P* = 0.971); and GGT was 54.55 ± 30.61 U/l and 49.69 ± 19.56 U/l (*P* = 0.646) in groups 1 and 2, respectively.

FBS was 5.77 ± 1.30 mmol/l and 5.39 ± 0.93 mmol/l, HOMA-2 IR 1.87 ± 1.62 and 1.40 ± 0.42, TG was 269.50 ± 101.08 mg/dl and 254.90 ± 236.78 mg/dl, and HDL was 37.15 ± 21.51 mg/dl and 48.20 ± 35.02 mg/dl in groups 1 and 2, respectively. So, all the baseline biochemical markers did not differ significantly between the groups [Table 1].

Histological improvement

In group 1, there was significant improvement of NAS from 5.80 ± 0.70 to 3.65 ± 1.5 [t (19) =5.782, $P < 0.0005$]. Histology improved in all components of NAS; steatosis improved from 2.30 ± 0.66 to 1.35 ± 0.93 ($P = 0.002$), ballooning from 1.50 ± 0.51 to 0.90 ± 0.64 ($P = 0.002$), and lobular inflammation from 2.00 ± 0.46 to 1.35 ± 0.49 ($P < 0.001$). In group 2, there was improvement of NAS from 5.20 ± 0.42 to 4.10 ± 0.56 [t (9) =6.128, $P < 0.005$], but it could not reach the level of response in 8 (80%) patients. Of the components of NAS, no significant improvement in steatosis, lobular inflammation, and fibrosis was observed ($P = 0.343$, 0.104, and 0.081, respectively), but significant improvement was observed in ballooning from 1.40 ± 0.52 to 0.90 ± 0.32 [t (9) =3.000, $P = 0.015$]. In group 1, mean NAS improvement at the end of study was 2.15 ± 1.66, whereas in group 2, it was 1.10 ± 0.57. The difference in NAS improvement between two groups was statistically significant ($P = 0.017$).

Fibrosis decreased in group 1 from 1.55 ± 0.76 to 0.90 ± 0.45 [t (19) =3.115, $P = 0.006$]. In this group, mean fibrosis score improvement was 0.65 ± 0.93, whereas in group 2, it was –0.30 ± 0.48. The difference in fibrosis score improvement between group 1 and group 2 was statistically significant ($P = 0.001$). Fibrosis score deteriorated from 1.20 ± 0.79 to 1.50 ± 0.85 in group 2.

NAS ≥ 2 or NAS ≥ 1 with fibrosis score ≥1 was defined as responder. So, 15 patients responded out of 20 patients (75%) in group 1 and 2 patients out of 10 patients (20%) responded in group 2 (*P* value: 0.004). Among the 13 non-responders, 5 patients were in group 1 (25%) and 8 patients were from group 2 (80%) [Figure 2]. In group 1, NAS ≥ 2 improved in 13 patients (65%), whereas in group 2, it improved in 2 patients (20%) (*P* value: 0.020). In TL group, fibrosis score ≥1 improved in eight patients (40%), whereas, in L group, no patient had such improvement (0%) (*P* value: 0.020).

Dynamic characteristic improvement

The mean BMI improvement in group 1 was 2.26 ± 2.50 kg/m^2 and in group 2 was 1.77 ± 1.99 kg/m^2 ($P = 0.599$). The mean WC improvement in the two groups was 1.90 ± 4.40 cm and 0.60 ± 5.21 cm, respectively ($P = 0.479$). Also, the mean improvement in TG was 17.50 ± 160.03 mg/dl and 24.00 ± 248.98 mg/dl and the mean HDL change was −5.05 ± 21.88 mg/dl and 18.70 ± 111.97 mg/dl, respectively. So, the difference in mean TG and HDL improvement between the two groups did not reach a significant level ($P = 0.931$ and 0.522, respectively). Mean

Table 1: Baseline characteristics of patients

Variables	Group 1 (*n*=20) (mean±SD)*	Group 2 (*n*=10) (mean±SD)**	*P* value
Age (years)	43.30±11.03	37.90±8.67	0.188
Sex-male/female (%)	4/16 (20/80)	3/7 (30/70)	0.542
Obesity-present/absent (%)	14/6 (70/30)	5/5 (50/50)	0.284
Waist circumference increased-yes/no (%)	16/4 (80/20)	8/2 (80/20)	1.000
Diabetes-present/absent (%)	7/13 (35/65)	1/9 (10/90)	0.144
Hypertension-present/absent (%)	9/11 (45/55)	2/8 (20/80)	0.180
BMI (kg/m^2)	27.09±4.19	26.24±5.33	0.634
Waist circumference (cm)	94.05±8.64	93.20±11.19	0.820
Bilirubin (µmol/l)	9.85±3.22	9.30±2.36	0.636
ALT (U/l)	50.00±36.04	45.80±24.93	0.744
AST (U/l)	47.30±32.27	47.70±32.21	0.971
GGT (U/l)	54.55±30.61	49.69±19.56	0.646
Alkaline phosphatase (U/l)	96.45±28.69	96.70±14.98	0.980
FBS (mmol/l)	5.77±1.30	5.39±0.93	0.423
HOMA-2 IR	1.87±1.62	1.40±0.42	0.249
Cholesterol (mg/dl)	215.35±42.12	185.30±60.02	0.122
LDL (mg/dl)	133.88±49.02	104.38±57.87	0.245
HDL (mg/dl))	37.15±21.51	48.20±35.02	0.293
Triglycerides (mg/dl)	269.50±101.08	254.90±236.58	0.813

*Group 1: Telmisartan and life style modification; **Group 2: Only life style modification. SD: Standard deviation; BMI: Body mass index; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; GGT: Gamma-glutamyl transpeptidase; FBS: Fasting blood sugar; HOMA-2 IR: Homeostasis model assessment 2; LDL: Low-density lipoprotein; HDL: High-density lipoprotein

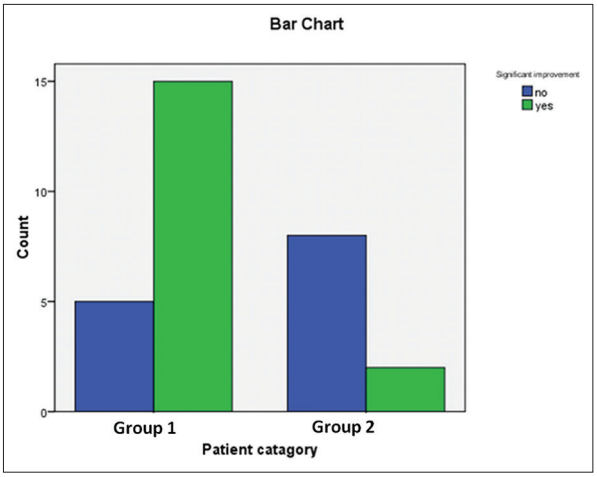

Figure 2: In group 1 (Telmisartan and life style modification), histological response was obtained in 75% of patients and in group 2 (life style modification only), the response was obtained in 20% of patients (*P* value: 0.004)

improvement in ALT and GGT between the two groups did not differ significantly as well (*P* values: 0.482 and 0.439, respectively) [Table 2].

Factors associated with response of the patient

The overall NAS improvement in responder was 2.71 ± 1.26 and in non-responder was 0.62 ± 0.65. Overall fibrosis score improved to 0.76 ± 0.97 in responder and deteriorated to 0.23 ± 0.44 in non-responder. The mean differences in age and sex between responders and non-responders were not significant. The mean baseline BMI in responders was 26.93 ± 4.85 kg/m^2 and in non-responders was 26.65 ± 4.26 kg/m^2 (*P* value: 0.869) and the mean WC in responders was 94.60 ± 10.80 cm and in non-responders was 92.69 ± 7.42 cm (*P* value: 0.542), which were similar. Baseline metabolic characteristics such as diabetes, hypertension, hypertriglyceridemia, metabolic syndrome, or obesity had no significant effect on patients' response: 64.7% of patients were obese among responders, whereas 61.5% of the non-responders were obese; 41.2% of the responders were hypertensive, whereas 30.8% of the non-responders were hypertensive; 35.3% of responders and 15.4% of non-responders were diabetic. There were no significant differences in baseline ALT, AST, and GGT between responders and non-responders. Baseline FBS, 2HABF, and IRI between responders and non-responders did not differ significantly (*P* values: 0.645, 0.063, and 0.154, respectively). Mean BMI improvement of responders was 2.37 ± 2.64 kg/m^2 and of non-responders was 1.73 ± 1.85 kg/m^2 (*P* value: 0.459). Weight loss of 10% or more from baseline was observed in 13 patients; 9 (69.2%) of them had significant histological improvement, whereas 4 (30.8%) of them had no significant improvement. On the other hand, 17 patients did not show weight reduction of 10% or more; 8 of them (47.1%) had significant improvement and 9 (52.9%) had no significant improvement. Thus, weight reduction of 10% or more within 1 year did not have effect on patient response (*P* value = 0.225). Mean WC improvement of responders was 1.76 ± 4.90 cm and of non-responders was 1.08 ± 4.43 cm (*P* value = 0.695). HOMA-2 IR change did not significantly differ between responders and non-responders (*P* value = 0.167). ALT change could not differentiate responders and non-responders. GGT improved to 17.94 ± 31.22 U/l in responders and deteriorated to 3.00 ± 38.35 IU in non-responders (*P* value = 0.110) [Table 3].

Table 2: Improvement in dynamic characteristics

Improvement	Group 1 (mean±SD)*	Group 2 (mean±SD)**	*P* value
NAS	2.15±1.66	1.10±0.57	0.017$^+$
Fibrosis score	0.65±0.93	−0.30±0.48	0.001$^+$
BMI (kg/m^2)	2.26±2.50	1.77±1.99	0.599
WC (cm)	1.90±4.40	0.60±5.21	0.479
TG (mg/dl)	17.50±160.03	24.00±248.98	0.931
Cholesterol (mg/dl)	43.45±49.40	6.30±65.36	0.092
HDL (mg/dl)	−5.05±21.88	18.70±111.97	0.522
LDL (mg/dl)	33.00±53.62	−7.00±66.55	0.132
FBS (mmol/l)	−0.22±1.55	0.24±1.14	0.418
2HABF (mmol/l)	−0.54±2.59	−0.91±2.39	0.708
HOMA-2 IR	−0.86±1.16	−0.45±1.47	0.458
ALT (U/l)	−11.40±62.71	3.80±33.71	0.482
GGT (U/l)	5.25±42.04	16.10±15.32	0.439

*Group 1: Telmisartan and life style modification; **Group 2: Only life style modification. $^+$Improvement of non-alcoholic fatty liver disease activity score and fibrosis score was significantly higher in Telmisartan and life style modification group than that in the group with life style modification only. NAS: Non-activity score; BMI: Body mass index; WC: Waist circumference; TG: Triglyceride; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; FBS: Fasting blood sugar; HOMA-2 IR: Homeostasis model assessment 2; ALT: Alanine aminotransferase; GGT: Gamma-glutamyl transpeptidase; 2HABF: 2 hours after breakfast (blood sugar)

Predictors of patient response

Logistic regression analysis was performed to find the best predictor of patient response. As given in Table 4, all important dynamic factors as well as patient groups were considered for logistic regression analysis. Univariate analysis showed only group 1 to be the significant predictor [*P* = 0.009; odds ratio (OR) =12.00, confidence interval (CI) =1.86–76.38] of patient response. Improvement in other factors such as BMI (*P* = 0.447), WC (*P* = 0.683), TG (*P* = 0.829), cholesterol (*P* = 0.334), HDL (*P* = 0.497), FBS (*P* = 0.188), HOMA-2 IR (*P* = 0.161), and GGT (*P* = 0.159) did not predict patient response significantly. Multivariate logistic regression analysis was done to see the effects of all confounding variables together. Multivariate analysis also showed that only TL group showed significant histological response (*P* value: 0.035; OR = 92.07, CI = 1.39–6106). So, both univariate and multivariate analyses revealed that only Telmisartan could has led to the response.

Probable side effects

Adverse events noticed during the study were mild headache, dizziness, and abdominal pain and they were similar in both groups. In TL group, no patient developed hypotension. No patient required treatment discontinuation for any adverse event.

DISCUSSION

This open-label, prospective RCT was conducted on 20 NASH patients, in whom Telmisartan plus life style modification were introduced, and 10 NASH patients, in whom only life style modification was introduced. So, total 30 patients were followed for 1 year and comparison was made between index and end-of-study liver biopsy of the patients. This study was performed to observe the effect of Telmisartan on the histological activity of NASH patients and, in fact, it is the first RCT that was

Table 3: Comparison of clinical, laboratory, and clinical characteristics of responders and non-responders

Factors	Responders (*n*=17) (mean±SD)	Non-responders (*n*=13) (mean±SD)	*P* value
Baseline factors			
Category of patient-group 1/group 2 (%)	15/2 (75/20)	5/8 (25/80)	0.004*
Age (years)	43.12±10.65	39.38±10.27	0.342
Sex-male/female (%)	3/14 (17.6/82.4)	4/9 (30.8/69.2)	0.400
BMI (kg/m^2)	26.93±4.85	26.65±4.26	0.869
WC (cm)	94.60±10.80	92.69±7.42	0.592
Obesity-yes/no (%)	11/6 (64.7/35.3)	8/5 (61.5/38.5)	0.858
Hypertension-yes/no (%)	7/10 (41.2/58.8)	4/9 (30.8/69.2)	0.558
Diabetic-yes/no (%)	6/11 (35.3/64.7)	2/11 (15.4/84.6)	0.222
Hypertriglyceridemia (mg/dl) (%)	14/4 (77.8/22.2)	10/3 (76.9/23.1)	0.955
Metabolic syndrome-yes/no (%)	11/6 (64.7/35.3)	8/5 (61.5/38.5)	0.858
ALT (U/l)	56.71±39.65	38.00±14.86	0.118
AST (U/l)	55.53±32.53	36.85±14.76	0.046
GGT (U/l)	55.71±27.74	49.23±27.06	0.527
FBS (mmol/l)	5.73±1.33	5.52±1.01	0.645
2HABF (mmol/l)	9.15±2.85	7.44±1.61	0.063
IRI	1.99±1.73	1.33±0.52	0.154
TG (mg/dl)	252.00±112.81	281.15±201.95	0.619
HDL (mg/dl)	37.71±23.34	44.92±31.00	0.472
Dynamic factors			
NAS improvement	2.71±1.26	0.62±0.65	0.000
Fibrosis improvement	0.76±0.97	−0.23±0.44	0.001
BMI improvement (kg/m^2)	2.37±2.64	1.73±1.85	0.459
Weight reduction 10% or more-yes/no (%)	9/8 (69.2/47.1)	4/9 (30.8/52.9)	0.225
WC improvement (cm)	1.76±4.90	1.08±4.43	0.695
FBS improvement (mmol/l)	0.25±1.25	−0.47±1.58	0.176
2HABF improvement (mmol/l)	0.08±1.71	−1.58±3.01	0.074
IRI improvement	−0.38±0.70	−1.11±1.61	0.167
TG improvement (mg/dl)	26.12±161.82	11.23±228.08	0.836
HDL improvement (mg/dl)	−4.65±23.58	12.69±97.72	0.329
ALT improvement (U/l)	−3.41±71.60	−10.15±18.58	0.744
GGT improvement (U/l)	17.94±31.22	−3.00±38.35	0.110

SD: Standard deviation; BMI: Body mass index; WC: Waist circumference; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; GGT: Gamma-glutamyl transpeptidase; FBS: Fasting blood sugar; HOMA-2 IR: Homeostasis model assessment 2; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; TG: Triglyceride; IRI: immunoreactive insulin; NAS: Non-activity score; 2HABF: 2 hours after breakfast (blood sugar)

Table 4: Logistic regression analysis of laboratory and histological parameters among responders

Predictors	Univariate analysis		Multivariate analysis	
	P value	OR (95% CI)	*P* value	OR (95% CI)
Category of patient (group 1/group 2)	0.009*	12.00 (1.86-76.38)	0.035*	92.07 (1.39-6106)
BMI improvement	0.447	1.14 (0.82-1.58)	0.825	0.93 (0.49-1.78)
WC improvement	0.683	1.03 (0.88-1.21)	0.670	1.09 (0.74-1.61)
TG improvement	0.829	1.00 (1.00-1.00)	0.352	1.01 (0.99-1.02)
HDL improvement	0.497	1.00 (0.98-1.00)	0.388	0.98 (0.94-1.02)
FBS improvement	0.188	1.48 (0.83-2.67)	0.867	1.11 (0.33-3.77)
HOMA-2 IR improvement	0.161	1.72 (0.81-3.65)	0.275	2.75 (0.45-16.98)
GGT improvement	0.159	1.02 (0.99-1.06)	0.509	1.07 (0.92-1.20)

*Histological improvement influenced only by Telmisartan and life style modification. BMI: Body mass index; WC: Waist circumference; FBS: Fasting blood sugar; HOMA-2 IR: Homeostasis model assessment 2; HDL: High-density lipoprotein; TG: Triglyceride; GGT: Gamma-glutamyl transpeptidase

carried out in Bangladeshi NASH patients. It revealed that Telmisartan significantly improved the histology of NASH patients.

The assessment of therapeutic agents for NASH is a complex process. Because there are no validated biomarkers of response to treatment, one must rely on histological assessment of liver biopsy tissue.[18,19] Both NAS and fibrosis score were taken into consideration to assess histological improvement in this study. NAS improvement was significantly higher with Telmisartan and life style modification than that observed with only life style modification. Similarly, fibrosis score improved in the first group, but deteriorated in the second group. Zein *et al*. reported in a RCT that Pentoxyphylline improved NAS ≥ 2 in 50% of patients.[20] In 2010, Sanyal *et al*. found in a large RCT that Vitamin E improved NAS ≥ 2 in 43% of patients.[21] Our RCT revealed that Telmisartan improved NAS ≥ 2 in 65% of patients. So, regarding improvement of NAS, Telmisartan is more effective than Pentoxyphylline or Vitamin E.[20,21]

Our study revealed that Telmisartan improved both histological activity and fibrosis of NASH patients. In Yokohama *et al*.'s study, seven patients with NASH and hypertension were treated with 50 mg/day of Losartan for 48 weeks. Hepatic necroinflammation improved in five patients and hepatic fibrosis reduced in four patients.[22] Reduction of fibrosis could be explained from Bataller *et al*.'s study that activated human hepatic stellate cells (HSCs) express the renin–angiotensin system and synthesize angiotensin II. So, angiotensin II receptor antagonist could attenuate the progression of hepatic fibrosis by direct inhibition of activated HSCs.[23] Fujita *et al*. reported on the effect of the angiotensin II type 1 receptor antagonist Telmisartan on the development of NASH in a rat model. Telmisartan, but not the angiotensin receptor antagonist valsartan, markedly attenuated hepatic steatosis, inflammation, and fibrosis in these rats. The quantitative attenuation of hepatic steatosis and fibrosis of the liver were also similar to that of Telmisartan.[24] These reports strongly support our findings of decrease in histological activity and fibrosis observed.

In the second group, there was significant NAS improvement, but only two patients had NAS improvement of ≥2, that is, up to the level of operational definition of response. During 1 year of the study period, these two patients had lost 16% and 18% of their body weight, respectively. Significant weight loss was probably the underlying cause of histological improvement observed in these two patients. In 2010, Musso *et al*. described in a meta-analysis that weight reduction through life style modification had significant effect on histological improvement of NASH patients. But the meta-analysis could not quantify the cut-off value of weight reduction at which steatosis or NAS improved.[25] As life style modification is considered the standard approach of patient management, the present study included this approach for both groups.

In the present study, 10% or more body weight reduced in 13 out of 30 patients. Among them, 9 (69.2%) had significant histological improvement, whereas 4 (30.8%) had no significant histological improvement. On the other hand, 17 patients did not lose weight of 10% or more; of them, 8 patients (47.1%) had significant histological improvement and 9 patients (52.9%) had no significant histological improvement. So, body weight loss of 10% or more could not affect the patient response significantly (*P* value: 0.225). The underlying cause was not clear, but these findings strengthen our study findings that the histological improvement caused by Telmisartan was more significant than that caused by weight reduction. Improvement in biochemical parameters such as HOMA-2 IR, ALT, GGT, TG, and HDL did not differ significantly between histological responders and non-responders. These findings reveal that biochemical improvement does not correlate with histological improvement. HOMA-2 IR deteriorated more in non-responders than in responders (-0.38 ± 0.70 vs -1.11 ± 1.61), but could not reach statistically significant level (*P* value: 0.167).

Change in serum ALT was not different between responders and non-responders. On the contrary, serum GGT improved to 17.94 ± 31.22 U/l in responders and changed to -3.00 ± 38.35 U/l in non-responders. So, the present study shows GGT as a more reliable dynamic marker than ALT to assess improvement of NASH patients. These findings were not consistent with the findings of Zein *et al*. and Sanyal *et al*. In these two RCTs, histological improvement was consistent with serum ALT improvement.[20,21] GGT was a more reliable marker of liver histology than ALT, which was previously described in another study also.[18]

Regarding the safety profile, it was observed that Telmisartan had minimum side effects and they were similar in both groups. It has never caused significant hypotension in hypertensive and non-hypertensive NASH patients. Another study revealed that high systemic levels of Telmisartan, which were well tolerated, can be attained in normotensive adults of any age and in hypertensive subjects as well.[15] None required treatment discontinuation after development of side effects in our study. Previous reports also suggested that Telmisartan was well tolerated with a low incidence of drug-related adverse events.[26] Another report also revealed that the adverse effect encountered with Telmisartan was less frequent than with other ARB or ACE inhibitors.[27]

The study limitations were the small sample size and the high number of drop-outs. With these small numbers of patients, it is very difficult to predict treatment response confidently. All patients recruited in this study were from a single tertiary-level hospital. So, the present study suffered from lack of multicenter, different ethnic categories of patients.

CONCLUSION

In conclusion; Telmisartan, an ARB, improved the overall histology of NASH patients significantly. It improved significantly NAS and fibrosis score. This histological improvement with Telmisartan was independent of weight reduction. Telmisartan was similarly effective in hypertensive and non-hypertensive NASH patients. Its therapeutic effect was unaltered, irrespective of metabolic factors such as diabetes, dyslipidemia, obesity, or metabolic syndrome. It had very minimum side effects during 1 year of treatment. We recommend conducting large multicenter, double-blinded RCTs to consolidate the findings of this study.

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