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Pentoxifylline for Treatment of Nonalcoholic Fatty Liver Disease (NAFLD) : A Randomized, Placebo-Controlled Study

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ABSTRACT

Background: Insulin resistance plays an important role in pathogenesis of NAFLD. Adiponectin has antilipogenic and anti-inflammatory effects, while TNF-α reduces insulin sensitivity and has proinflammatory effects. The aims of this study are to determine the efficacy and safety of pentoxifylline, a TNF-α inhibitor, compare with placebo

Methods: Thirty-two patients had biopsy-confirmed NASH and NAFLD with other causes of liver disease and secondary causes of NASH excluded. All patients had persistently elevated ALT (>1.5 times for more than 6 months, after dietary treatment for 2 months) were randomized into 2 groups. The first group was given pentoxifylline at a dosage of 400 mg t.i.d. plus dietary treatment and the second group was given placebo with dietary treatment for 6 months. The changes in ALT, AST, insulin resistance index (homeostatic metabolic assessment insulin resistance (HOMA IR) index, waist/hip ratio), TNF-α and adiponectin level from baseline to at the end of treatment were compared between 2 groups.

Results: The 32 patients had a mean age of 48.9 ± 11.7 yr. Nineteen patients (59%) were male, Five patients (15.6%) were obese (BMI >30 kg/m^2) with mean BMI 26.5 ± 3.2 kg/m^2, Five patients (15.6%) were type II DM, twelve patients (37.5%) were hypertension and twenty seven (84.4%) were dyslipidemia. There were no baseline demographic differences between both groups. The mean changes of serum alanine, aspartate aminotransferase and fasting plasma glucose levels difference significantly from baseline in the pentoxifylline group compared to the placebo group. (ALT + 68.2 ± 40.7 vs. + 18.2± 34.2, p = 0.001; AST + 27.3 ± 20.4 vs. + 7.9 ± 19.8, p = 0.008; FBS + 9.1 ± 10.7 vs. - 0.7 ± 5.7, p = 0.003, respectively) The pentoxifylline groups showed more improvement in BMI, waist/hip ratio and serum TNF-α, compared with the placebo groups, without any statistically significant. Adinopectin levels were not changed significantly between both groups. There was no serious adverse events occurred.

Conclusions: Pentoxifylline therapy effectively achieved significant improvement in aminotransferase level among patients with NAFLD when compared to placebo.

Key words : pentoxifylline, Nonalcoholic fatty liver disease, NAFLD

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Nonalcoholic fatty liver disease (NAFLD) has recently emerged as the most common cause of abnormal liver function tests seen in patients. The overall prevalence of NAFLD and nonalcoholic steatohepatitis (NASH) in the developed country estimated to be between 20-30% and 2-3%, respectively in general population.[1,2] The realization that a proportion of patients with NAFLD can progress through steatohepatitis and fibrosis to cirrhosis and liver cancer.[3-5] NAFLD is associated strongly with obesity, insulin resistance, and metabolic syndrome.[6] The prevalence of obesity, diabetes and hyperlipidemia in NAFLD and NASH patients are 39-95%, 21-55%, and 20-92%, respectively.[7-12] In Thailand, the prevalence of NAFLD and NASH patients with non-HBV, non-HCV chronic hepatitis was 54.3% and 76.1%, respectively.[13] The pathogenesis of NASH is not well defined. A "two hit" hypothesis has been proposed; whereby fat accumulation in the liver is the "first hit". The primary cause of steatosis is thought to be insulin resistant, which causes increased lipolysis and delivery of free fatty acids to the liver. Reactive oxygen species (ROS) and lipid peroxidation represent the "second hit" that lead to steatohepatitis.[14,15] Several bioactive proteins or adipokines include leptin, TNF-α, resistin, and adiponectin have been implicated in the pathogenesis of both nonalcoholic steatohepatitis and insulin resistance.[16] The goals of therapy include correction of the underlying risk factors, avoidance of factors that promote progression of liver disease and pharmacologic treatment.[17] Despite its common occurrence, there is no proven pharmaceutical therapy for patients. Until now, weight loss remains the standard of care.[18,19] Owing to the pathogenesis of NAFLD and NASH, TNF-α is involved in mediating insulin resistance and plays a proinflammatory role in development of NASH.[20,21] Pentoxifylline inhibits TNF-α production and has been found to be effective in the treatment of alcoholic hepatitis patients.[22,23] From 2 pilot trials of pentoxifylline therapy, there was a significant improvement or normalization of aminotransferase at the end of treatment (6-12 months) and there were no serious adverse effects occurred.[24,25] In this first randomized, double-blind, placebo-controlled study, we investigated the effect of pentoxifylline on improvement in biochemical and metabolic parameters of NAFLD and NASH.

Materials and Methods

Subjects

We recruited the participants between November 2005 and August 2006 from Division of Gastroenterology and Tropical Medicine at Ramathibodi Hospital. All participants fulfilled the following enrollment criteria, were included.

Inclusion Criteria

Patients aged between 18 and 75 years, both male and female, who had elevated aminotransaminase level >1.5 times of upper limit of normal on 2 occasions at least 6 months apart and had liver biopsy proven NAFLD by were included[31].

Exclusion Criteria

Patients who had alcohol abuse more than 20 gm per week in previous 6 months, or had evidence of viral or autoimmune hepatitis, primary biliary cirrhosis, Wilson's disease, hemochromatosis, decompensated liver disease, or received medications: amiodarone, tamoxifen, methotrexate, antioxidants, metformin, glitazone, theophylline and warfarin, or had other comorbid conditions such as congestive heart failure, pregnancy, COPD were excluded.

A total of 32 patients fulfilled the selection criteria and were enrolled. All patients gave written informed consent.

Study design

At baseline, all patients had clinical evaluation including height, weight, blood pressure, and measurement of body mass index (BMI), waist/hip ratio along with hemogram and biochemical tests. These included CBC, coagulogram, serum aminotransferase, alkaline phosphatase, gamma glutamyl transferase, total bilirubin, hepatitis B serology, anti-HCV, antinuclear antibody, antimitochondrial antibody, iron profile, ceruloplasmin, cholesterol, triglycerides, fasting plasma glucose, serum adiponectin and TNF-α level. An abdominal ultrasound was performed to assess the liver parenchyma, biliary tree, vascular patency and presence of ascites or portal hypertension, and also exclude the possibility of hepatocellular carcinoma.[26]

During the 8 weeks run-in period, the patients were instructed to lose weight, follow a healthy diet, and stop taking over-the-counter vitamin, mineral or herbal supplements. Patients received standard nutri-

tion counseling in 20 to 30 minute individual session by a trained dietitian emphasizing a healthy lifestyle, gradual weight loss, an increase in physical activity. After completion of the pretreatment evaluation and life style modification, patients who had persistently elevated serum aminotransferase and who had no exclusion criteria were double-blinded randomly assigned into 2 study groups using block-random sampling numbers with computer-generated and the investigators were unaware of the treatment assignments. The first group was given pentoxifylline at a dosage of 400 mg t.i.d. plus dietary treatment and the second group was given placebo with dietary treatment for 6 months. The compliance was assessed by means of a pill count on follow up visits.

Measurements

During therapy, patients were followed up at monthly interval for the initial 2 months and subsequently at 2-month intervals for the duration of the treatment. At every visit, adverse events, concurrent medication, and compliance of the study medication were assessed. Liver biochemistry was performed at every visit. Body mass index, homeostatic metabolic assessment insulin resistance (HOMAIR) index (fasting serum insulin (μIU/ml) × fasting serum glucose (mmol/l) ÷ 22.5), waist/hip ratio, serum fasting glucose, serum TNF-α and adiponectin level was evaluated at baseline (prior treatment) and at 6 months follow up. (Figure 1)

Serum TNF-α level was measured by chemiluminescent immunomectric assay using a standard kit (IMMULITE/IMMULITE 1000 TNF-α, EURO/DPC Ltd.) The antibody is highly specific for TNF-α. The analytical sensitivity is 1.7 pg/ml. Paired samples were available for the estimation of TNF-α in all patients at baseline and at 6 months follow-up.

Serum adiponectin levels were measured in duplicate by radioimmunoassay (Linco Research, St. Charles, MO). The lowest level of human adiponectin that can be detected by this assay is 1 ng/ml when using a 100 μl sample size.

Histological Evaluation

Liver biopsy was performed in every patient at the baseline for the diagnosis of NASH. The necroinflammatory grade and stage of fibrosis were assessed according to the method given by Brunt, *et al*. Steato-

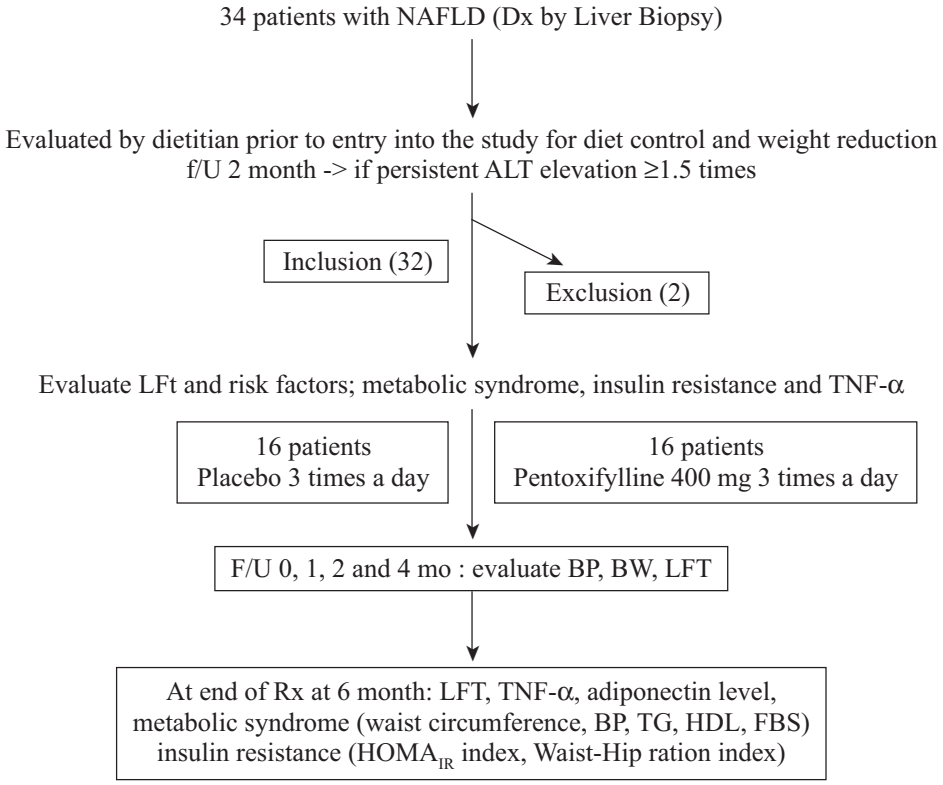

Figure 1 Protocol flow chart

sis was graded as: grade 0 = none, grade 1 = up to 33%, grade 2 = 33-66%, grade 3 ≥66%. Each biopsy was analyzed and graded by one pathologist who unknown the patients' clinical or laboratory data.

Statistical Analysis

The main end point of the study was to compare improvement by 50% or normalization of aminotransferase at the end of the study between treatment group and placebo group. Data were summarized in frequencies (or percentages) for categorical variables and as means ± SD for continuous variables. The chi-square (or Fisher's exact) test and a two sample T-test was used to compare differences between the groups for categorical and continuous variables, respectively. A p value of less than 0.05 was accepted as statistically significant.

RESULTS

Subject Characteristics

Thirty-two patients completed the study protocol successfully. Two patients were excluded due to normalization of aminotransferase after 8 weeks run-in period. The demographic data are shown as in Table 1.

The mean serum aminotransferase were significantly higher in the treatment group. Other baseline biochemical and metabolic parameters were similar in both groups. (Table 2) Among all patients, 17 patients (53%) and 15 patients (47%) had the histological findings of steatosis and steatohepatitis, respectively. The mean histopathological necro-inflammatory activity grade is slightly higher in the treatment group, but there was no statistically significant (1.625 vs. 1.57, p = 0.847).

Biochemical and Metabolic Response

A significant decrease was noted in the mean serum alanine aminotransferase, aspartate aminotransferase, fasting plasma glucose at the end of treatment in the pentoxifylline group. (Table 3, Figure 2,3) Serum AST levels decreased by 41% in patients who received pentoxifylline, as compared with 16% in subjected who received placebo (p = 0.008), AST levels reduced by 46.7% in patients who received pentoxifylline, as compared with 17% in subjected who received placebo (p = 0.001), and FBS levels decreased by 8.6% in patients who received pentoxifylline, as compared with increased 0.72% in subjected who received placebo (p = 0.003). Improvement in BMI, mean Waist/Hip ratio and serum TNF-α were observed in the pentoxifylline group, but there was no statistically significant (P >0.05). The other serum parameters including serum adiponectin, insulin, and HOMAIR index did not change significantly between both groups.

Subject Compliance and Adverse Events

Compliance with the study medication was 95.3%, with exception of one subject who received pentoxifylline (55.1% compliance due to nausea and

Table 1 Demographic Characteristics of the patients

Parameters	Pentoxifylline group (N = 16)	Placebo group (N = 16)	P value
Gender (male/female)	12/4	7/9	0.07
Mean Age ± SD (yr)	48.4 ± 11.4	49.5 ± 12.2	0.79
Mean BMI ± SD (kg/m^2)	25.8 ± 2.4	27.1 ± 3.8	0.29
Mean Waist/Hip ratio ± SD	0.9 ± 0.05	0.9 ± 0.07	0.26
Steatosis/NASH	8/8	9/7	0.72
Mean SBP ± SD (mmHg)	130.2 ± 11.6	128.5 ± 21.0	0.79
Mean DBP ± SD (mmHg)	81.4 ± 10.3	80.5 ± 11.7	0.81
Mean MAP ± SD (mmHg)	97.7 ± 9.7	96.4 ± 14.5	0.76
DM (%)	3 (18.7)	2 (12.5)	1.00
HT (%)	5 (31.2)	7 (43.7)	0.46
Hypercholesterolemia (%)	15 (93.7)	12 (75)	0.33
Hypertriglyceridemia (%)	9 (56.2)	8 (50)	0.72

Table 2 Baseline Biochemical and Metabolic Parameters

Parameters (Units)	Pentoxifylline group (N = 16)	Placebo group (N = 16)	P value
ALT ± SD (U/L)	146.1 ± 57.9	106.1 ± 25.9	0.02*
AST ± SD (U/L)	66.4 ± 24.1	48.1 ± 16.4	0.02*
ALP ± SD (U/L)	84.2 ± 29.2	92.5 ± 26.9	0.43
Bilirubin ± SD (mg/dl)	0.71 ± 0.28	0.7 ± 0.27	0.89
Albumin ± SD (g/L)	44.9 ± 11.6	47.8 ± 2.1	0.35
FBS ± SD (mmol/L)	5.8 ± 1.1	5.7 ± 0.97	0.69
Insulin level (μIU/ml)	19.9 ± 7.9	25.5 ± 15.7	0.67
$HOMA_{IR}$ index ± SD	5.3 ± 2.6	6.5 ± 4.2	0.71
Cholesterol ± SD (mg/dl)	217.1 ± 50.9	225.5 ± 27.5	0.56
Triglyceride ± SD (mg/dl)	249.1 ± 193.9	166.0 ± 68.1	0.39
HDL (mg/dl) ± SD	38.0 ± 10.1	42.6 ± 18.2	0.39
TNF-α (pg/ml) ± SD	11.14 ± 6.64	8.5 ± 6.5	0.28
Adiponectin (μg/ml) ± SD	7.3 ± 2.8	8.2 ± 4.2	0.49

*p <0.05

Table 3 Mean changes in parameters at the end of treatment of both groups

Parameters	Pentoxifylline (N = 16)			Placebo (N = 16)			P value**
	Baseline	Mean change At the end of treatment	P value	Baseline	Mean change At the end of treatment	P value	
ALT (U/L)	146.2 ± 57.9	-68.2 ± 40.7	0.000*	106.1 ± 25.9	-18.1 ± 34.2	0.278	0.001*
AST (U/L)	66.4 ± 24.1	-27.3 ± 20.4	0.000*	48.1 ± 18.0	-7.9 ± 19.7	0.353	0.008*
Glucose (mg/dL)	106.2 ± 20.2	-9.1 ± 10.7	0.005*	103.5 ± 17.6	0.7 ± 5.7	0.223	0.003*
BMI (kg/m^2)	25.8 ± 2.4	-1.0 ± 1.0	0.002*	27.1 ± 3.8	-0.6 ± 0.6	0.002*	0.217
Mean Waist/Hip ratio	0.9 ± 0.0	0.0 ± 0.0	0.644	0.9 ± 0.0	0.0 ± 0.0	0.004*	0.123
Insulin (μIU/mL)	19.9 ± 7.9	-8.2 ± 8.5	0.002*	25.5 ± 15.7	-10.3 ± 11.3	0.002*	0.56
$HOMA_{IR}$ index	5.3 ± 2.6	-2.4 ± 2.6	0.003*	6.5 ± 4.2	-2.6 ± 3.0	0.004*	0.866
Adiponectin (μg/ml)	7.3 ± 2.8	-0.0 ± 1.5	0.943	8.2 ± 4.2	0.1 ± 1.1	0.667	0.75
TNF-α (pg/ml)	11.1 ± 6.6	-1.64 ± 11	0.601	8.5 ± 6.5	-0.46 ± 3.3	0.603	0.70

*p <0.05
** Difference of mean change in parameters at the end of treatment of both groups

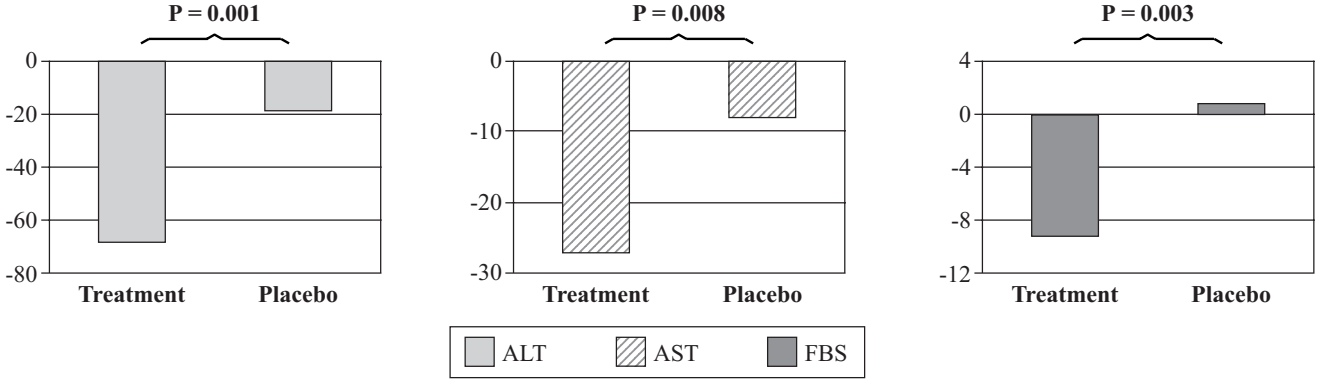

Figure 2 Mean changes in parameters at the end of treatment of both groups

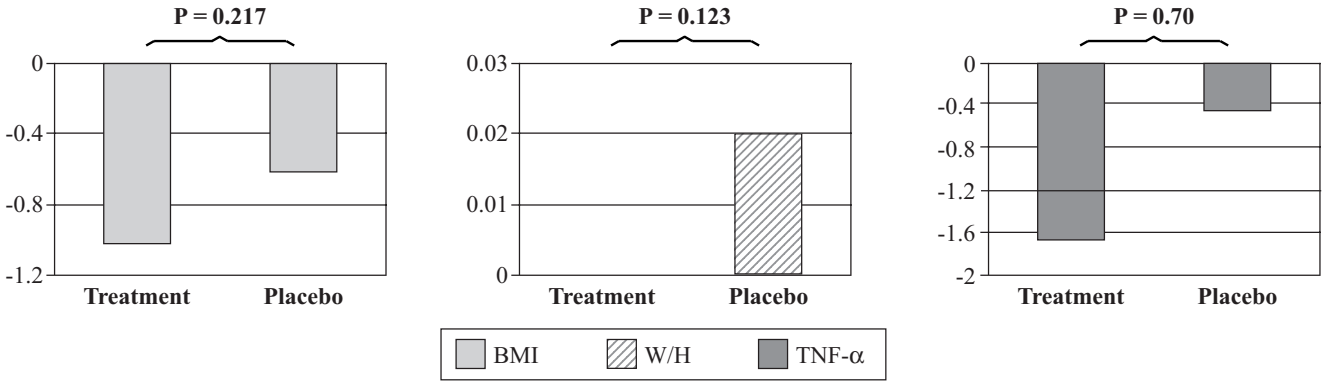

Figure 3 Mean changes in parameters at the end of treatment of both groups

Table 4 Adverse Effects

Number Affected (%)	Adverse Effects		P value
	Pentoxifylline (N = 16)	Placebo (N = 16)	
Nausea/vomiting	4 (25%)	1 (6.2%)	0.144
Bloating	0 (0%)	2 (12.5%)	0.144
Headache	1 (6.2%)	0 (0%)	0.310
Dizziness	0 (0%)	1 (6.2%)	0.310
Rash	0 (0%)	1 (6.2%)	0.310

vomiting). Most of the patients (97%) tolerated the drug well without serious adverse effects. Minor side effects were detected in 9 patients (28%), 4 (25%) patients in the pentoxifylline group and 5 (31.3%) patients in the placebo group. Gastrointestinal disturbances such as nausea, vomiting, bloating and epigastrium discomfort were the most troublesome on initiation of the pentoxifylline (Table 4). But there was no significant differences when compared to the placebo group (p = 0.144).

DISCUSSION

This is the first randomized, double-blind, placebo-controlled study, which investigated the effect of pentoxifylline on improvement in biochemical and metabolic parameters of NAFLD and NASH. TNF-α interferes with insulin signaling, thereby favoring steatosis, and may play a proinflammatory role in the pathogenesis of NASH and NAFLD.[27] Pentoxifylline, a methylxanthine compound that inhibits TNF-α production by several mechanisms; inhibited cytokine and chemokine synthesis and reduced expression of adhesion molecule on endothelial cells, reduced activation and proliferation of neutrophils, and proliferation and transmigration of leucocytes.[28-30] In our study, patients with nonalcoholic liver disease who received pentoxifylline for 6 months had demonstrated significant improvement/normalization of aminotransferase when compared to the placebo group at the end of 6 months. This result reflects that pentoxifylline may have a beneficial effect in glucose metabolism in NAFLD patients. The two pilots studies showed that pentoxifylline therapy had effectively achieved significant improvement in aminotransferase level. In this study, there was only minimal adverse effects. One patient had less than 60% compliance due to nausea and vomiting. Compared to the previous pilots studies, the rate of adverse effects of pentoxifylline in this study is closed to study of[25] (25% vs. 22%), but they were significantly decreased when compared to the study of[24] (25% vs. >60%). However, serum TNF-α and adiponectin level were not significantly different correlated to aminotransferase level in the pentoxi-

Table 5 The end point of the study at the end of treatment

Endpoints	Pentoxifylline group (N = 16)	Placebo group (N = 16)	P value
Primary			
Normalization of aminotransferase	7	2	0.049*
50% improvement of aminotransferase	7	1	0.014*
Secondary			
FBS (mg/dL) (mean change)	-9.1 ± 10.7	0.7 ± 5.7	0.003*
Insulin (μIU/mL)	-8.2 ± 8.5	-10.3 ± 11.3	0.56
BMI (kg/m^2) (mean change)	-1.0 ± 1.0	-0.6 ± 0.6	0.217
Waist/Hip ratio (mean change)	0.00 ± 0.03	0.02 ± 0.03	0.123
$HOMA_{IR}$ index	-2.4 ± 2.6	-2.6 ± 3.0	0.866
TNF-α (pg/ml) (mean change)	-1.6 ± 11	-0.4 ± 3.3	0.70
Adiponectin (μg/ml)	-0.0 ± 1.5	0.1 ± 1.1	0.75

fylline group which may be from the small numbers of patients or it may need longer duration of treatment to demonstrate the improvement.

In conclusion, addition to its safety, pentoxifylline effectively achieved significant improvement in aminotransferase and fasting plasma glucose level among patients with NAFLD compared to placebo. A larger clinical trials and longer duration are needed to be continued.

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