A Double-Blind Randomized Placebo-Controlled Trial of Orlistat for the Treatment of Nonalcoholic Fatty Liver Disease

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Background & Aims: Few controlled studies have addressed the issue of effective medical treatment for nonalcoholic fatty liver disease (NAFLD). We herein assessed the effect of orlistat in patients with NAFLD.

Methods: We performed a randomized, double-blind, placebo-controlled study on 52 patients with NAFLD diagnosed by ultrasound (US) and confirmed by liver biopsy (40 patients). The patients were randomized to receive either orlistat (120 mg 3 times daily for 6 months) or placebo. All patients participated in an identical behavioral weight loss program. All patients underwent monthly evaluation by abdominal US; liver enzyme levels, lipid profiles, insulin levels, and anthropometric parameters were monitored, and all patients underwent nutritional follow-up evaluation. Twenty-two patients underwent a second liver biopsy examination at the end of the study.

Results: Fifty-two patients were recruited and 44 (mean age, 47.7 y; mean body mass index, 33) completed the study. Serum glucose and insulin levels ($P<.03$) were significantly higher in the orlistat group, which also presented a higher degree of fibrosis. Body mass index was reduced significantly in each group, with a nonsignificant difference between the groups. Serum alanine transaminase (ALT) levels decreased significantly in both groups, with an almost 2-fold reduction in the orlistat group (48% vs 26.4%). There was a statistically significant reversal of fatty liver by US only in the orlistat group ($P<.05$).

Conclusions: Orlistat improves serum ALT levels and steatosis on US in NAFLD patients, beyond its effect on weight reduction.

In recent years nonalcoholic fatty liver disease (NAFLD), the most common form of liver disease, has been recognized as the hepatic manifestation of the metabolic syndrome. In view of the epidemic of obesity, the prevalence of NAFLD is expected to continue to increase in coming years.

Although lifestyle modification is sufficient in many patients, resistant cases of NAFLD may require pharmacologic therapy. Several studies have investigated various medications for the treatment of NAFLD. Most of these studies were not randomized placebo-controlled trials and some lacked follow-up biopsy examinations. Hence, the drug of choice for the treatment of primary NAFLD has yet to be found.

Patient medications for the treatment of NAFLD should lead to weight reduction, decreased free fatty acid (FFA) flux to the liver, and improved insulin sensitivity, without hepatotoxic adverse effects.

Orlistat, a gastrointestinal lipase inhibitor that possesses these characteristics, is useful in the treatment of obesity and type 2 diabetes mellitus. In the present randomized placebo-controlled study we evaluated the role of orlistat in the treatment of patients with primary NAFLD.

Patients and Methods

Design

We conducted a double-blind, randomized, placebo-controlled study of orlistat at a dose of 120 mg 3 times a day for 6 months or placebo in patients with NAFLD. Both groups underwent an identical behavioral weight-loss intervention program. Patients with even research code numbers were allocated to the orlistat treatment group. The pharmacist was unaware of the randomization system. The placebo tablets supplied by the drug company (Roche, Basel, Switzerland) were indistinguishable from the orlistat tablets.

Abbreviations used in this paper: ALT, alanine transaminase; FFA, free fatty acid; NAFLD, nonalcoholic fatty liver disease; US, ultrasound. 
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Patients

Fifty-two patients, aged 18–75 years, were recruited from our fatty liver clinic between January and December 2003 and 44 completed the study. The diagnosis of NAFLD was based on ultrasound (US)-guided liver biopsy examination (n = 40) or US only (n = 4). Patients with a known cause for their increased liver enzyme levels such as viral hepatitis (B or C), autoimmune/chronic immune hepatitis, primary biliary cirrhosis, metabolic and genetic hemochromatosis, Wilson’s disease, or α-1 antitrypsin deficiency were excluded from the study, as were those who suffered from thyrotoxicosis, consumed alcohol in excess, were taking hepatotoxic drugs, or were pregnant. The study conformed with the declaration of Helsinki and was approved by the ethics committee of the medical center. All patients gave written informed consent to participate in the study.

Weight Loss Program

Nutritional therapy was based on a balanced low-energy diet prescribed by a nutritionist. The diet included 104.5 kJ/day for ideal body weight, with an emphasis on reduced intake of both fat (≤30% of daily calories) and simple carbohydrates. Patients were encouraged to perform physical activity 3–4 weeks times a week (40 minutes of walking at 5–6 km/h).

The nutritionist interviewed all study participants at the time of their monthly clinic visit. Weight and waist circumference were checked at baseline and at each follow-up visit.

Biochemical Assessments

All patients underwent baseline and monthly tests of fasting serum levels of total bilirubin, aspartate and alanine transaminases (ALT), alkaline phosphatase, a lipid profile, glucose levels, and insulin levels.

Ultrasound Assessments

Two expert radiologists performed the abdominal US examinations. All patients underwent monthly examinations, always by the same radiologist who did the baseline procedure. Fatty liver was identified qualitatively using accepted methods including a bright hepatic echo pattern, a homogenous or coarse echo pattern, increased attenuation of the US beam, loss of intrahepatic architectural details, and a nodular appearance of the liver surface. The radiologic end point was qualitative and was considered positive only if the echogenic features resolved.

Histologic Assessments

Patients who gave consent underwent a US-guided liver biopsy examination (16-gauge Klatskin needle) at randomization and again at the end of the study. A liver specimen of 15 mm with at least 10 portal tracts was considered adequate for evaluation. One expert histopathologist (E.B.) graded and staged the biopsy specimens according to Brunt. The pathologist was blinded to each patient’s treatment group affiliation and to the sequence of the biopsy examination.

Statistical Analyses

Statistical analyses were performed using the SPSS software program version 11 (SPSS, Inc., Chicago, IL). Data are presented as mean ± SD. Paired t tests were used to evaluate within-group changes from baseline to end of treatment. Independent sample t tests were used for between group comparisons. The Wilcoxon signed-rank test or the Mann–Whitney test were used if nonparametric tests were required. Statistical significance was set at a P value of less than .05 throughout. Multivariate analysis of variance for repeated measurements was used to determine the shape of the relationship between the outcomes (log of ALT, insulin, and homeostasis model assessment levels) and time, with covariates (age and sex). Because the ALT distribution was skewed we used the log transformation to obtain a normal distribution.

The Greenhouse–Geisser adjustment was used for violations of the assumption of sphericity. To handle missing values in the repeated-measurement analysis we used the last-observation-carried-forward method.

Results

Patients

Fifty-two patients with primary NAFLD were randomized to receive either orlistat or placebo, of whom 44 have completed the 6-month follow-up period (23 in the placebo group). Eight subjects withdrew from the study, 5 from the orlistat group and 3 from the placebo group (lost to follow up evaluation, gastrointestinal side effects, and unrelated pancreatic and urologic diseases). Sixty-two percent of the orlistat group were women compared with 52% in the placebo group.

Baseline Anthropometric and Biochemical Characteristics

Eighty-six percent of the patients in the orlistat group were obese (body mass index ≥30 kg/m²), compared with 61% in the placebo group. Three patients (2 in the placebo group and 1 in the orlistat group) had a body mass index within the normal range (20–25 kg/m²). There were no significant differences between the groups at baseline in body mass index, lipid profile, or liver enzyme levels. Blood glucose and serum insulin levels were significantly higher in the orlistat group. Only the orlistat group had patients with impaired glycemic control at baseline, including 4 patients with treated diabetes mellitus. These patients were on oral hypoglycemic drugs for at least 6 months before the study and were instructed to adhere to the same regimen throughout the study. In all, 62.8% of the patients had hyperinsulinemia (>25 μU/mL), 80% in the orlistat group and 47.8% in the placebo group (P < .03) (Table 1).
Liver Biopsy Examinations

Forty patients underwent liver biopsy examination at randomization and 22 had a repeat biopsy examination at the end of the study (11 in each group). Of these, 9% of the placebo group had histologic grade 0 at baseline compared with none in the orlistat group, however, 27.3% in the placebo group had histologic grade 3 compared with only 9% in the orlistat group (Figure 1).

In contrast, the orlistat group had a higher level of fibrosis: 27.3% had histologic stage 4 and only 9% had stage 0, whereas no patient in the placebo group had histologic stage 4 and 54.5% had stage 0 (Figure 2).

Treatment Outcomes

Weight loss and waist circumference. Body mass index decreased significantly within each group (P < .01) with no significant difference between the groups (P = .26). The mean weight loss was 7.7 (±6.8) kg (8% body weight) in the orlistat group compared with 5.9 (±5.9) kg (6% body weight) in the placebo group. Waist circumference also decreased significantly (P < .001) in both groups, 8.7 (±5.2) cm in the orlistat group compared with 5.5 (±5.7) cm in the placebo group, with no significant difference between the groups (Table 2 and Figure 3).

Biochemical tests. Serum ALT and aspartate transaminase levels decreased significantly in both groups (P < .05). The percentage of ALT reduction was almost double in the orlistat group (48% vs 26.4%) (Table 2). The reduction in ALT level occurred earlier in the orlistat group. In both groups the reduction in log ALT level over time was significant. However, the shape

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**Table 1. Characteristics of Patients at Randomization**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Orlistat (n = 21)</th>
<th>Placebo (n = 23)</th>
<th>Pa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, % men</td>
<td>38</td>
<td>48</td>
<td>.5</td>
</tr>
<tr>
<td>Age, y</td>
<td>48.4 ± 8.1 (28–62)</td>
<td>47.0 ± 12.2 (22–68)</td>
<td>.7</td>
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<tr>
<td>BMI, kg/m² (normal, 20–25)</td>
<td>34.8 ± 5.0 (24–41)</td>
<td>31.5 ± 5.8 (23–48)</td>
<td>.06</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>96.0 ± 17.5 (69–138)</td>
<td>91.6 ± 24.5 (57–178)</td>
<td>.5</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>106.7 ± 11.4 (90–137)</td>
<td>99.6 ± 13.6 (74–140)</td>
<td>.07</td>
</tr>
<tr>
<td>Glucose level, mg/dL (normal, 70–110)</td>
<td>112.5 ± 44.6 (78–273)</td>
<td>89.8 ± 13.3 (70–114)</td>
<td>.04</td>
</tr>
<tr>
<td>Insulin level, μU/mL (normal, 5–25)</td>
<td>52.5 ± 42.1 (15–200)</td>
<td>29.0 ± 12.7 (13–68)</td>
<td>.02</td>
</tr>
<tr>
<td>HOMA score</td>
<td>15.7 ± 19.2 (3–92)</td>
<td>6.4 ± 3.3 (3–18)</td>
<td>.05</td>
</tr>
<tr>
<td>Triglyceride level, mg/dL (normal, 50–175)</td>
<td>202 ± 73.0 (70–327)</td>
<td>195 ± 108.5 (49–510)</td>
<td>.8</td>
</tr>
<tr>
<td>Cholesterol level, mg/dL (normal, 150–200)</td>
<td>231.5 ± 43.8 (148–336)</td>
<td>218 ± 38.6 (125–273)</td>
<td>.3</td>
</tr>
<tr>
<td>ALT level, U/L (normal, 5–39)</td>
<td>63.8 ± 61.0 (15–267)</td>
<td>48.2 ± 29.2 (10–108)</td>
<td>.3</td>
</tr>
<tr>
<td>Aspartate transaminase level, U/L (normal, 5–40)</td>
<td>47.0 ± 33.0 (17–124)</td>
<td>37.6 ± 21.0 (11–106)</td>
<td>.3</td>
</tr>
<tr>
<td>γ-glutamyltransferase level, U/L (normal, 5–50)</td>
<td>63.5 ± 48.2 (9–165)</td>
<td>69.5 ± 101.2 (11–432)</td>
<td>.8</td>
</tr>
</tbody>
</table>

NOTE. For all variables other than sex, data are presented as mean ± SD, with the range in parentheses. BMI, body mass index; HOMA, homeostasis model assessment. *Independent samples t test.

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Figure 1. Histologic characteristics at randomization for grading. Data are presented as the percentage of patients within every category of grading. A liver specimen of 15 mm with at least 10 portal tracts was considered adequate for evaluation. One expert histopathologist (E.B.) graded and staged the biopsy specimens for grade of nonalcoholic steatohepatitis according to Brunt.22

Figure 2. Histologic characteristics at randomization for staging. Data are presented as the percentage of patients within every category of staging. A liver specimen of 15 mm with at least 10 portal tracts was considered adequate for evaluation. One expert histopathologist (E.B.) graded and staged the biopsy specimens according to Brunt.22
of reduction was linear in the placebo group \((P = .005)\) compared with an exponential decrease in the orlistat group \((P = .04)\) (Figure 4).

The reduction in serum insulin level paralleled that of ALT level, with a faster rate in the orlistat group (Figure 5). The equivalent homeostasis model assessment plot showed a similar pattern (data not shown).

**Radiologic.** There was a statistically significant reversal of fatty liver by US in the orlistat group only \((P < .05)\). At the end of treatment, 24\% in the orlistat group had normal echogenicity vs 17.4\% in the placebo group (Figure 6).

**Histopathologic.** The degree of steatosis decreased by about 50\% in each group \((P < .01)\). The grading improved in 4 patients in the placebo group and in 2 patients in the orlistat group, but did not reach statistical significance in either group \((P > .1)\).

A comparable improvement in the degree of fibrosis (staging) was noted with both orlistat and placebo \((P = .07\) vs .1\), with at least 1 degree of improvement in 5 of the 11 follow-up biopsy examinations in the orlistat group compared with 3 in the placebo group.

### Table 2. Changes From Baseline to End of Treatment in Each Group

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Orlistat (^a) (n = 21)</th>
<th>Placebo (^a) (n = 23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight, kg</td>
<td>(-7.7 \pm 6.8^b)</td>
<td>(-5.9 \pm 5.9^b)</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>(-8.7 \pm 5.2^b)</td>
<td>(-5.5 \pm 5.7^b)</td>
</tr>
<tr>
<td>Glucose, mg/dL (normal, 70–110)</td>
<td>(-15.5 \pm 31.4^c)</td>
<td>(-2.3 \pm 7.6)</td>
</tr>
<tr>
<td>Insulin, µU/mL (normal, 5–25)</td>
<td>(-13.5 \pm 39.3)</td>
<td>(-3.1 \pm 12.4)</td>
</tr>
<tr>
<td>HOMA score</td>
<td>(-6.2 \pm 19.6)</td>
<td>(-8.0 \pm 3.0)</td>
</tr>
<tr>
<td>Triglyceride level, mg/dL (normal, 50–175)</td>
<td>(-23.8 \pm 102.4)</td>
<td>(-21.6 \pm 71.0)</td>
</tr>
<tr>
<td>Cholesterol level, mg/dL (normal, 150–200)</td>
<td>(-13.3 \pm 28.8^c)</td>
<td>(+5.1 \pm 30.0)</td>
</tr>
<tr>
<td>ALT level, U/L (normal, 5–39)</td>
<td>(-30.6 \pm 59.0^c)</td>
<td>(-12.7 \pm 26.6^c)</td>
</tr>
<tr>
<td>Aspartate transaminase level, U/L (normal, 5–40)</td>
<td>(-18.9 \pm 33.0^c)</td>
<td>(-8.8 \pm 17.2^c)</td>
</tr>
<tr>
<td>(\gamma)-glutamyltransferase level, U/L (normal, 5–50)</td>
<td>(-22.3 \pm 42.2^c)</td>
<td>(-10.7 \pm 34.6)</td>
</tr>
</tbody>
</table>

**NOTE.** Mean change shown \(\pm\) SD.

HOMA, homeostasis model assessment.

\(^a\)Paired samples \(t\) test.

\(^b\)\(P < .01\).

\(^c\)\(P < .05\).

Figure 3. Rate of change in weight over 6 months of treatment. Weight decreased significantly within each group \((P < .01)\), with no significant difference between the groups. The mean weight loss was \(7.7 \pm 6.8\) kg (8\% body weight) in the orlistat group compared with \(5.9 \pm 5.9\) kg (6\% body weight) in the placebo group. ●, Placebo; ○, orlistat.

Figure 4. Rate of change in ALT level over 6 months of treatment. Serum ALT levels decreased significantly in both groups \((P < .05)\), however, the shape of reduction was linear in the placebo group \((P = .005)\) in contrast to an exponential decay in the orlistat group \((P = .04)\). Multivariate analysis of variance for repeated measurements was used to determine the shape of the relationship between log ALT levels and time, with covariates (age and sex). ●, Placebo; ○, orlistat.

Figure 5. Rate of change in insulin level over 6 months of treatment. The reduction in serum insulin level paralleled that of ALT level. ●, Placebo; ○, orlistat.
Discussion

Orlistat is an approved drug for the management of obesity, with improvement of glycemic control reported. This benefit is ascribed to weight loss because orlistat acts in the intestinal lumen and is not believed to have direct systemic effects. Indeed, the effect of orlistat in NAFLD patients already has been tested in 2 small uncontrolled studies; however, very few randomized placebo-controlled studies have been conducted to evaluate treatment options for patients with NAFLD.

In the present study, patients who received orlistat showed a more pronounced reduction in serum ALT and insulin levels and a greater degree of reversibility of fatty liver by US. However, a comparable improvement in histopathology was noted in both the orlistat and placebo groups. This lack of difference between the groups could be explained by the limited power of the study owing to the relatively small number of patients who agreed to undergo a second liver biopsy examination.

Although it was reasonable to assume that the primary beneficial effect of orlistat on patients with NAFLD would be through weight reduction, there was no significant difference in this variable between the orlistat and the placebo groups. Therefore, other mechanisms of action should be considered.

Kelley et al suggested recently that at equivalent weight loss, the addition of orlistat results in a greater reduction in plasma FFA levels and insulin resistance. The greater reduction in plasma FFA levels achieved with orlistat therapy would seem to be the major factor in improved insulin sensitivity. Indeed, it is well established that FFAs modulate insulin sensitivity. Therefore, we propose that orlistat improves insulin sensitivity more than diet alone by decreasing insulin resistance via decreased FFA flux into the liver.

In the present study, a more pronounced, although insignificant, decrease in serum insulin levels and homeostasis model assessment was noted in the orlistat group than in the placebo group. The suggested effect of orlistat on FFAs was not manifested by a significant reduction in serum triglyceride levels, presumably because the baseline triglyceride levels were increased only mildly.

Interestingly, in the present study, ALT level decreased in a pattern that was very similar to insulin and homeostasis model assessment (Figures 5 and 6). A prospective study showed an association between increased ALT levels and decreased hepatic insulin sensitivity, expressed as accelerated hepatic glucose output, leading to an increased incidence of type 2 diabetes. Similarly, in animal models, decreased hepatic insulin sensitivity predisposed the liver to relative resistance to insulin action on suppression of gluconeogenesis. Because insulin suppresses genes encoding gluconeogenic enzymes, and ALT is a gluconeogenic enzyme, it is possible that ALT level is an indicator of impaired insulin signaling.

There are a few limitations in our study that should be noted. Only 22 patients agreed to undergo a second liver biopsy examination and the duration of the study may have been too short for liver fibrosis to be reversed. Therefore, ALT level and abdominal US were the 2 major end points. US is not the gold standard for the quantitative evaluation of severity, but is considered a sensitive method for the qualitative detection of NAFLD. Thus, in this study only complete reversal of fatty liver was considered as an ultrasonographic end point.

In conclusion, orlistat improves serum ALT level and features of steatosis on US in NAFLD patients beyond its effect on weight reduction. A larger number of follow-up biopsy examinations and a longer duration of treatment are necessary to determine the true extent of histologic improvement.
References


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