Original paper

Comparative study of the effects of Abexol and atorvastatin in patients with non-alcoholic fatty liver disease

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Abstract

Aim of the study: To investigate the efficacy and safety of Abexol and atorvastatin in patients with non-alcoholic fatty liver disease (NAFLD).

Material and methods: The present study had a monocentric, randomized, double-blinded, comparative design with 4 parallel groups – group 1 (Abexol), group 2 (atorvastatin), group 3 (combined therapy) and group 4 (placebo) – to which dietary recommendations and physical activity practice were provided twice a day, for 24 weeks. Significant changes in the ultrasound analysis of the liver were considered a primary efficacy variable. Insulin resistance improvement (HOMA2-IR) was considered as a co-primary efficacy criterion. Significant changes in the serum levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST), lipid profile variables and the anthropometric variables were evaluated as secondary variables of effectiveness. Statistical analysis of all data was according to the intention to treat method.

Results: The groups were statistically homogeneous at baseline conditions. At the end of the 6 months of treatment about 50% of the patients in all groups showed a decrease of at least one degree in echogenicity, while the rest remained the same. There were no significant changes in the values of liver enzymes or anthropometric variables evaluated. Treatment with atorvastatin and combined therapy significantly reduced levels of low-density lipoprotein-cholesterol (LDL-C) and total cholesterol. The treatments were safe and well tolerated, although in the atorvastatin group the number of adverse events reported was greater than in the rest of the groups.

Conclusions: Abexol and atorvastatin showed comparable efficacy and safety in patients with NAFLD, with advantages for treatment with atorvastatin with respect to its effects on the lipid profile of these patients.

Key words: atorvastatin, Abexol, non-alcoholic fatty deposition liver disease, liver echogenicity, HOMA index.

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Introduction

Non-alcoholic fatty liver disease (NAFLD) has become a major public health problem due mainly to its frequent increase in obesity. NAFLD results from the presence of fat in the liver parenchyma not accompanied by inflammation, in the absence of excessive alcohol consumption, and is considered as one of the components of the metabolic syndrome. NAFLD may be influenced, among other factors, by age, gender, the presence of diabetes, genetic polymorphism and, according to more recent data, also by the intestinal microbiome [1].

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From the etiological point of view, two types of liver diseases are distinguished: due to non-alcoholic fat deposition, and related to the ingestion of alcoholic beverages or alcoholic fatty liver disease [2-4].

NAFLD is the most common liver disease, but its prevalence in the general population is not known exactly, since many cases occur asymptomatically. However, it is estimated that it affects between 10% and 24% of the general population. Although no age, sex or race can be excluded, NAFLD occurs most frequently between 47 and 53 years and is more common in women (65-83%) [5, 6].

NAFLD is usually asymptomatic, being detected incidentally during abdominal ultrasound examinations, liver function tests or by hepatomegaly in the routine clinical examination, although in some cases it is accompanied by diffuse symptoms, such as discomfort in the upper right quadrant of the abdomen or diffuse abdominal discomfort [7].

Abdominal ultrasonography is the most widely used diagnostic method in this disease because it is more economical and standardized, although other imaging modalities have also been used, such as computed tomography, magnetic resonance imaging, and transient elastography with the controlled attenuation parameter [8].

There is no proven effective medical therapy for NAFLD and it is recommended that future therapeutic trials be double-blind, randomized and controlled with diet-exercise indications, with a greater number of patients and more prolonged treatment, including checking the degree of injury [9-13]. However, there is some limited evidence in relation to some alternatives therapies such as decreased body weight, the use of lipid-lowering agents, the use of insulin-sensitizing drugs, angiotensin converting enzyme inhibitors, nutritional supplements and antioxidants [14, 15].

Statins are lipid-lowering drugs, inhibitors of hydroxy-methyl-glutaryl coenzyme A reductase (HMG-CoA reductase), the enzyme that regulates cholesterol synthesis in the liver, but they are also recommended for the treatment of NAFLD, including atorvastatin. It is the only one that has been shown to be able to reduce cardiovascular morbidity in patients with this liver condition. Although there is no information about the mechanism of action of statins in NAFLD improvement, it is likely that it could be associated with the hepatic clearance regulation of serum lipoproteins [16].

On the other hand, Abexol (D-002), a mixture of primary aliphatic alcohols purified from beeswax (*Apis mellifera*) [17], is a nutritional supplement that produces moderate anti-inflammatory effects [18] in addition to marked antioxidant [19] and gastroprotective effects [20, 21].

Randomized, double-blind, placebo-controlled clinical studies have shown that Abexol improves the duodenal ulcer healing process and reduces the ulcer associated symptoms [22], reduces the frequency of gastrointestinal symptoms in patients under therapy with non-steroidal anti-inflammatory drugs [19] and exerts antioxidant effects in healthy volunteers and in middle-aged and elderly subjects, reducing lipid peroxidation and markers of protein oxidation and increasing the total antioxidant state of the plasma, as well as being safe and very well tolerated [23-27].

Taking into account that Abexol has been experimentally shown to be an effective inhibitor of microsomal lipid peroxidation [19], that in a previous clinical trial it positively modified the liver ultrasound of patients with NAFLD [27] and that the search for new alternatives or treatments for NAFLD is justified, it is reasonable to carry out comparative studies with other products used for the same purpose.

The aim of the study was to investigate the efficacy and safety of Abexol and atorvastatin in patients with liver disease due to non-alcoholic fatty deposition.

Material and methods

The study was conducted according to the principles reflected in the Helsinki Declaration, as revised in 2000, as well as the recommendations of the World Health Organization and the Cuban regulations on Good Clinical Practices. The study protocol was approved by the Ministry of Public Health and by the Ethics Committee in Clinical Research of the National Gastroenterology Institute, and was registered in the Cuban Public Registry of Clinical Trials (RPCEC-00000221).

Study design

The study had a monocentric, randomized, double-blinded, comparative design with 4 parallel groups to which dietary recommendations and physical activity practice for the reduction of body weight were provided. Group 1 received a tablet of Abexol (50 mg) + 1 tablet of placebo-atorvastatin, twice a day, group 2 received a tablet of atorvastatin (10 mg) + 1 tablet of placebo-Abexol, twice a day, group 3 received combined Abexol therapy (50 mg) + atorvastatin (10 mg), twice a day and group 4 (control group) received 1 tablet of placebo-Abexol + 1 tablet of placebo-atorvastatin, twice a day, for 24 weeks.

The study consisted of 6 consultations: recruitment, inclusion, and 4 follow-up consultations at 6, 12, 18 and 24 weeks of treatment.

Recruitment/diagnosis criteria

Outpatients of both sexes, aged between 20 and 70 years who attended an outpatient consultation of the Institute of Gastroenterology, were recruited after signing the informed consent and with a history of liver enzyme elevation in routine examinations, obesity or overweight, diabetes, dyslipoproteinemias or with an ultrasound history of liver disease due to non-alcoholic fat deposition.

Inclusion criteria

NAFLD ultrasound patients according to standard criteria accepted by the American Gastroenterology Association [28].

Exclusion criteria

Patients with current alcohol consumption, hepatitis C and B virus infection, autoimmune liver disease, hemochromatosis, hepatotoxicity, human immunodeficiency virus (HIV), secondary causes of NAFLD, cirrhotic patients, pregnant or nursing women, diabetic non-compensated patients were excluded from the study.

Primary efficacy endpoints

The primary efficacy endpoints were: 1) improvement in NAFLD as noted by ultrasound described as a decrease in hepatic echogenicity based on renal echogenicity; and/or absence of attenuation; and presence of differentiation of the periportal reinforcement and of the vesicular wall due to the decrease of parenchymal hyperechogenicity, the degree of involvement being standardized by a semi-quantitative scale of the degree of hepatic refringement [28] and 2) a statistically significant reduction in the values of the insulin resistance index (HOMA2-IR) with respect to their baseline values and a statistically significant reduction compared to the control group (diet + physical exercise) (co-primary efficacy variable).

Secondary efficacy endpoints

The secondary efficacy endpoints included: 1) a statistically significant improvement in the serum levels for the liver enzymes alanine aminotransferase (ALT) and aspartate aminotransferase (AST) as well as the lipid profile variables and 2) a statistically significant decrease among the evaluated anthropometric variables compared to baseline values as well as a statistical significant decrease when comparing the changes to the control group (diet + physical exercise).

Safety and tolerability

Data from physical examination (determination of bodyweight, body mass index (BMI), pulse rate and arterial pressure), laboratory tests and requests for adverse event (AE) were included for safety and tolerability analysis.

Adverse event was defined as any undesirable experience or exacerbation of any common pathological condition that a patient reported during their participation in the trial, whether or not it was considered related to the study medication.

The clinical manifestations of AE were assessed by the doctor and recorded on the data collection sheet, classifying their intensity as follows: mild: one that did not require antidote or treatment, or suspension of the investigated treatment; moderate: one that required suspension of the investigated treatment by decision of the doctor and/or treatment; severe or serious (SAE): one that could endanger the life of the patient and therefore necessarily required the suspension of the study drug, leading to the hospitalization of the patient. Within the SAE, those that caused death were considered fatal. The information on AE was recorded in the Data Collection Form (CRF), describing its moment of appearance, intensity, and the behavior followed for its management.

Treatment with AE depended on its intensity (perceived by the subject and assessed by the doctor) and duration. In the cases that required treatment, these were symptomatic.

AE that persisted less than five days, but whose intensity disturbed the patient's condition, were defined as a cause for suspension of treatment, and similarly those that did not subside within five consecutive days were considered, and the procedure was not envisaged, dose reduction as this was a study that evaluated a single dose in a small number of subjects.

Furthermore, according to their possible relationship with treatment, AE were classified according to the following algorithm [29]:
- probably related: those that were directly related to the pharmacological effect, appeared with the treatment and did not disappear when the treatment was withdrawn;

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- possibly related: Those that had a mediating relationship with the pharmacological effect, appeared with the treatment, but their disappearance was not related to the withdrawal of the treatment;
- doubtful: those that did not meet the above criteria.

Although there were no SAEs in the study, the protocol provided that in the event of SAEs occurring, they would proceed according to the form of presentation of the AE and urgently contact the monitor responsible for the investigation, filling in the SAE notification form.

Laboratory analysis

Liver enzymes (ALT, AST, and γ-glutamyl-transferase – GGT), insulin, glycosylated hemoglobin, creatine-phospho-kinase (CK), serum glucose, creatinine, cholesterol, high-density lipoprotein cholesterol (HDL-C) and triglycerides were determined by enzymatic methods using reagent kits (Roche, Switzerland), and low-density lipoprotein cholesterol (LDL-C) values calculated with the Friedewald equation [30].

The Insulin Resistance Index (HOMA2-IR) was calculated:

$$HOMA2\text{-}IR = \frac{Fasting\ insulin\ (\mu U/ml) \times Fasting\ blood\ glucose\ (mmol/l)}{22.5}$$

Statistical analyses

Data were analyzed according to the intention to treat method. Then, data of all randomized patients were analyzed. Sample size was calculate by assuming to detect a difference of 10% between the groups in relation to the main efficacy variable, with a power β of 0.8 and a value α of 0.05, for which a sample of 100 cases was estimated (approximately 25 in each group).

The data were presented as mean ± standard deviation. Changes within each group of the continuous variables as well as comparisons between groups were analyzed using the ANOVA and Scheffé statistical tests. Categorical variables were analyzed with Fisher's exact probability test. All statistical tests used were two-tailed. A priori a level of α = 0.05 was established for statistical significance.

Results

Baseline characteristics and homogeneity of the groups

In this study, 100 patients were recruited, of whom 92 were included in the active treatment phase. The causes of non-inclusion were: 1 patient by normal ultra-sonography, 2 patients for not having ultrasonography and 5 patients for not having complementary laboratory studies. Table 1 shows the main baseline characteristics of the study population. The groups were statistically homogeneous in all the comparisons made.

The average age of the population studied was 52 years and the most prevalent personal history was atrial hypertension (62%). Other personal antecedents present in the study population (≥ 20%) were obesity (51.1%), overweight (35.9%), diabetes (33.7%) and dyslipidemia (32.1%). In addition, 69.6% had a family history of diabetes mellitus, dyslipidemia (41.3%) and obesity (38%).

93.3% of patients consumed some medication, the most frequent being angiotensin converting enzyme inhibitors (42.4%) and diuretics (27.2%), as expected according to the number of hypertensive patients, as well as oral hypoglycemic agents (20.7%) according to the number of diabetics.

Of the 92 patients included, 75 completed the treatment, and 17 patients were discharged: one due to adverse events, 11 patients for not wishing to continue and 5 patients for trips abroad. Comparisons between groups were not significant.

The adherence to treatment was satisfactory and comparable between the groups, since the patients consumed > 85% of the treatment that corresponded to them. Adherence to treatment was evaluated by the doctor questioning the patient and counting the remaining tablets at follow-up visits and was considered good if at least 85% of the tablets were consumed.

Primary efficacy endpoints

The results of the ultra-sonographic evaluation of the liver are shown in Table 2. At the beginning the evaluation was comparable in all groups and no included patient presented normality criteria (score = 0). At the end of treatment about 50% of patients in all groups showed a decrease by at least one degree in echogenicity, while the rest remained the same. There were no significant differences between groups in the comparisons made.

There were no significant changes in the HOMA index with respect to baseline values in any of the treatment groups evaluated, although there was an increase in this index in all groups at the end of treatment. Comparisons between groups were not significant (Table 3).

Secondary efficacy endpoints

Treatment with atorvastatin and combined therapy (Abexol + atorvastatin) significantly reduced levels of LDL-C and total cholesterol, compared to the rest of the treatments, which did not modify these parame-

Table 1. Baseline characteristics of study patients

Parameters	Abexol (n = 22)		Atorvastatin (n = 23)		Combined therapy (n = 24)		Diet + exercise (n = 23)	
Age (years) (X ± SD)	51 ±8		50 ±11		54 ±11		52 ±7	
Body mass index (BMI) (kg/m²)	31.5 ±4.9		30.9 ±4.9		29.4 ±3.7		30.0 ±3.7	
Hip circumference (cm)	106.4 ±8.9		107.4 ±12.2		106.8 ±12.6		102.7 ±11.2	
Body weight (kg)	83.8 ±14.9		82.7 ±16.2		81.9 ±14.9		84.1 ±15.0	
Pulse (beats/min)	76.4 ±9.2		77.7 ±7.4		74.2 ±8.5		78.2 ± 6.5	
Diastolic blood pressure (mmHg)	80.0 ±10.7		79.6 ±6.4		81.7 ±9.5		79.8 ±7.8	
Systolic blood pressure (mmHg)	123.6 ±10.9		124.8 ±9.9		127.9 ±16.1		126.5 ±11.5	
Aspartate aminotransferase (U/l)	30.9 ±10.7		38.5 ±21.1		29.7 ±14.3		33.3 ±13.8	
Alanine aminotransferase (U/l)	42.4 ±20.6		57.4 ±32.9		37.6 ±20.1		48.3 ±31.0	
γ-glutamyl transferase (U/l)	76.6 ±45.5		76.4 ±69.2		47.3 ±42.0		83.5 ±69.6	
Creatine phosphokinase (U/l)	163.0 ±93.1		132.2 ±68.7		307.5 ±355.7*		122.1 ±70.8	
Serum glucose (mmol/l)	5.9 ±1.4		5.6 ±0.6		6.0 ±1.7		5.7 ±1.4	
Creatinine (µmol/l)	76.8 ±15.6		78.9 ±17.1		79.7 ±17.2		82.5 ±23.6	
Glycosylated hemoglobin (%)	5.2 ±0.8		4.8 ±0.9		5.3 ±1.2		5.1 ±1.0	
Insulin (mg)	21.7 ±10.5		23.6 ±11.0		17.1 ±9.3		19.7 ±11.8	
	n	%	*n*	%	*n*	%	*n*	%
Gender: Female	14	63.6	13	56.5	13	54.2	11	47.8
Gender: Male	8	36.4	10	43.5	11	45.8	12	52.2
Personal history								
Obesity (BMI ⩾ 30 kg/m²)	13	59.1	11	47.8	11	45.8	12	52.2
Overweight (BMI ⩾ 25, < 30 kg/m²)	7	31.8	9	39.1	9	37.5	8	34.8
Hypertension	12	54.5	16	69.6	14	58.3	15	65.2
Diabetes mellitus	8	36.4	6	26.1	10	41.7	7	30.4
Dyslipidaemia	7	31.8	9	39.1	7	29.2	7	30.4
Smoking	4	18.2	4	17.9	3	12.5	0	0.0
Family history								
Diabetes mellitus	16	72.7	16	69.6	16	66.7	16	69.6
Dyslipidaemia	11	50.0	15	65.2	6	25.0	6	26.1
Obesity	8	36.4	12	52.2	9	37.5	6	26.1
Concomitant medications (CM)								
Patients consuming CM	22	100	20	87.0	21	87.5	22	95.7
Diuretics	4	18.2	7	30.4	7	29.2	7	30.4
ACEI	9	40.9	11	47.8	9	37.5	10	43.5
Oral hypoglycaemic drugs	7	31.8	1	4.3	7	29.2	4	17.4
Nitrovasodilator	0	0.0	1	4.3	3	12.5	0	0.0
β-blockers	4	18.2	4	17.9	3	12.5	1	4.3
Antiplatelet drugs	3	13.6	2	8.7	0	0.0	1	4.3
Antiulcer	1	4.5	0	0.0	2	8.3	1	4.3
Calcium antagonists	2	9.1	1	4.3	2	8.3	2	8.7

X – mean, SD – standard deviation, ACEI – angiotensin converting enzyme inhibitors.
*The table includes CM consumed by ⩾ 2 patients, *p < 0.05 comparison between groups (ANOVA test)*
The rest of the comparisons were not significant (ANOVA test, Fisher probability exact test, p > 0.05)

ters. Atorvastatin also significantly reduced triglyceride levels compared to the control group (diet + exercise) (Table 4).

There were no significant changes in liver enzyme values (ALT, AST) or the anthropometric variables investigated during the study in any of the treatment

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Table 2. Effects on ultrasonographic evaluation

Degree of severity	Abexol (*n* = 22)		Atorvastatin (*n* = 23)		Combined therapy (*n* = 24)		Diet + exercise (*n* = 23)	
	Baseline	24 weeks	Baseline	24 weeks	Baseline	24 weeks	Baseline	24 weeks
Normal	0	2	0	2	0	2	0	6
Mild	5	7	2	6	4	12	7	7
Moderate	11	10	14	12	18	8	12	8
Severe	6	3	7	3	2	2	4	2
	n	%	*n*	%	*n*	%	*n*	%
Patients who remained the same at 24 weeks	10	45.5	12	52.2	11	45.8	12	52.2
Patients with reduction of echogenicity by at least one degree at 24 weeks	10	45.5	11	47.8	11	45.8	11	47.8

n – number of patients
All comparisons were not significant (Fisher probability exact test, p > 0.05)

Table 3. Effects on HOMA index (X ± SD)

Treatment	Baseline	12 weeks	24 weeks
Abexol	6.1 ±4.1	6.2 ±4.1	6.6 ±3.3
Atorvastatin	5.9 ±3.0	5.9 ±2.7	6.1 ±4.0
Combined therapy	4.9 ±4.0	6.3 ±7.1	6.7 ±9.8
Diet + exercise	5.2 ±3.9	5.5 ±4.4	7.4 ±9.2

X – mean, SD – standard deviation
All comparisons were not significant (ANOVA test, p > 0.05)

groups evaluated, or in any of the comparisons made (Table 5).

Safety and tolerability analysis

Both treatments were safe, as there were no significant changes in the physical or laboratory indicators investigated during the study. We should point out that the creatine-phosphokinase (CK) values at the beginning of the study in the group treated with the combined therapy were significantly higher than in the rest of the treatment groups, this parameter being non-homogeneous in baseline conditions. However, at the end of the treatment no differences between groups in the comparisons made were found (data not shown for simplicity).

A single patient in the control group (diet + exercise) reported a severe adverse event (paralytic ilium), in addition to another moderate adverse event (abdominal distension), while a patient in the atorvastatin group also reported another moderate adverse event (dizziness), which required treatment, while the rest of the adverse events reported were classified as mild. There were no differences between the groups in the

comparisons made, although it should be noted that in the atorvastatin group, the number of adverse events reported was greater than in the rest of the groups, because four patients reported more than one adverse event (Table 6).

Tolerability was classified by doctors as very good in 76 patients (82.6%) for not presenting adverse events, good for 14 patients (15.2%) for presenting mild adverse events, regular for 1 patient (1.1%) for presenting a moderate adverse event and poor in 1 patient (1.1%) for presenting a severe adverse event. The groups were comparable, without significant differences in the comparisons made.

Discussion

The adequate treatment of patients with liver disease due to non-alcoholic fatty deposition should be carried out on the basis of comprehensive and multidisciplinary care; therefore, a change in lifestyle along with diet, exercise and medications constitute the basic pillars for its management [3, 7].

In this study, the distribution by sex was homogeneous in all groups, with a greater percentage of wom-

Table 4. Effects on lipid profile (X ± SD)

Treatment	Baseline	12 weeks	24 weeks	Changes (%)
Total cholesterol (mmol/l)				
Abexol	4.6 ±0.8	4.5 ±0.7	4.6 ±0.7	0.0
Atorvastatin	4.8 ±0.7	3.5 ±0.9*a	4.0 ±0.9*a	−16.7
Combined therapy	4.5 ±0.9	3.4 ±0.8*a	3.9 ±0.9*a	−13.3
Diet + exercise	5.1 ±0.9	4.7 ±0.9	4.8 ±0.9	−5.9
LDL-C (mmol/l)				
Abexol	2.9 ±0.8	2.9 ±0.7	2.9 ±0.7	0.0
Atorvastatin	3.1 ±0.5	2.0 ±0.9*a	2.4 ±1.0*a	−22.6
Combined therapy	2.8 ±0.8	2.0 ±0.7*a	2.1 ±0.9*a	−25.0
Diet + exercise	3.0 ±0.8	3.1 ±1.0	3.1 ±1.0	+3.3
HDL-C (mmol/l)				
Abexol	1.0 ±0.4	0.9 ±0.3	0.9 ±0.3	−10.0
Atorvastatin	1.0 ±0.3	1.0 ±0.3	1.0 ±0.3	0.0
Combined therapy	1.0 ±0.2	1.0 ±0.3	1.1 ±0.3	+10.0
Diet + exercise	1.0 ±0.3	0.9 ±0.3	1.0 ±0.3	0.0
Triglycerides (mmol/l)				
Abexol	1.7 ±0.8	1.7 ±0.9	1.7 ±0.7	0.0
Atorvastatin	1.8 ±0.9	1.2 ±0.4*b	1.2 ±0.5*b	−33.3
Combined therapy	1.6 ±0.8	1.3 ±0.6	1.5 ±0.7	−6.3
Diet + exercise	1.8 ±1.1	1.8 ±1.2	1.9 ±1.3	+5.6

X – mean, SD – standard deviation, *$p < 0.05$ comparison between groups (ANOVA test)
[a]$p < 0.05$ comparison atorvastatin group and combined therapy group vs. Abexol group and vs. diet + exercise group (Scheffé test)
[b]$p < 0.05$ comparison atorvastatin group vs. diet + exercise group (Scheffé test)

en (55.4%) than men (44.6%). Although this difference was not significant, it is partly a reflection of what happens in routine clinical practice, in which women are more motivated to participate in clinical trials and are more discipline [31].

The most prevalent personal history among the study patients was the presence of obesity and overweight (87.0%), which coincides with the fact that obesity is the greatest risk factor described for NAFLD. The number of patients with hypertension was also high (62%), which is consistent with the concomitant consumption of antihypertensives (ACEI: 42.4%, diuretics: 27.2%).

Type 2 diabetes mellitus frequently coexists in this population, as they share risk factors such as adiposity and insulin resistance. However, the prevalence of type 2 diabetes mellitus is 20 to 35% in patients with NALFD [32], so the existence of 33.7% in the population studied is within the estimated range.

Dyslipidemia was present in 41.3% of the patients, of which none was consuming any lipid-lowering therapy, a significant fact, as it was suggested by the data

of cholesterol values at the start of the study (most patients presented normal figures), who were on a diet or using some lipid-lowering therapy prior to inclusion in the study.

The efficacy analysis showed satisfactory and similar results for the treatments evaluated, in relation to the primary efficacy variable. At the beginning of the study, all patients presented some degree of steatosis, confirming that they were well included according to the ultrasound performed. However, the results of the ultra-sonographic evaluation of the liver showed that the number of patients who managed to reduce echogenicity by at least one degree or remained the same at the end of the study (24 weeks) were similar in the treatment groups investigated, without significant differences in the comparisons made, while with respect to the co-primary efficacy variable HOMA index, the treatments investigated did not produce significant changes at the end of the study with respect to baseline values.

It is known that inflammation is closely related to NAFLD, so some inflammation-mediating substances have been investigated as potential diagnostic tools [33].

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Table 5. Effects on liver enzymes (X ± SD)

Treatment	Baseline	12 weeks	24 weeks
Aspartate aminotransferase (AST) (U/l)			
Abexol	30.9 ±10.7	28.3 ±12.0	32.0 ±14.3
Atorvastatin	38.5 ±21.1	28.1 ±18.8	31.3 ±20.5
Combined therapy	29.7 ±14.3	25.0 ±11.9	25.7 ±9.7
Diet + exercise	33.3 ±13.8	23.8 ±11.9	30.2 ±14.8
Alanine aminotransferase (ALT) (U/l)			
Abexol	42.4 ±20.6	39.2 ±19.0	40.5 ±17.9
Atorvastatin	57.4 ±32.9	36.7 ±26.3	41.0 ±25.5
Combined therapy	37.6 ±20.1	28.5 ±10.9	31.6 ±16.7
Diet + exercise	48.3 ±31.0	38.1 ±25.1	45.2 ±27.8

X – mean, SD – standard deviation
All comparison were not significant (ANOVA test, p > 0.05)

There is experimental evidence of the anti-inflammatory effects of Abexol, through the inhibition of the activity of the cycle and lipoxygenase enzymes causes inhibition of the synthesis of eicosanoids: prostaglandins and thromboxane by the cyclooxygenase route, and leukotrienes and lipoxins by the lipoxygenase pathway. Abexol has an effect on COX, specifically on COX-2 and on 5-LOX; the latter is involved in the production of leukotrienes B4, which constitutes a potent chemotactic factor for neutrophils, promoting the development of acute inflammation. The inhibition of both enzymes, referred to as a dual anti-inflammatory effect, blocks the synthesis of eicosanoids and prevents inflammation associated with the development of NAFLD [34].

Atorvastatin has also shown a hepatoprotective and useful effect in reducing liver fat content in patients with NAFLD [16].

The treatments did not produce significant changes in the serum levels of liver enzymes (ALT, AST), although there was a tendency to reduce these values, a very positive effect in this type of patient. The average ALAT values improved to normal in the groups treated with Abexol, atorvastatin and combined therapy, unlike the control group (diet + exercise), in which these values remained high.

There were also no significant changes in the anthropometric variables evaluated with respect to the baseline level and the control group that received diet + physical exercise as a therapy, although there is also a tendency to reduce body weight and reduce hip circumference, aspects which stand out in the multifactorial treatment of these patients. However, the fact that the patients' body weight remained without significant changes at the end of the study, despite the fact that a group of patients achieved a weight reduction of ≥ 5%, comparable between the groups, indicates that the patients did not properly follow the recommended diet and exercise and reinforces the hypothesis that the effects obtained in this study are attributable to the pharmacologic treatments.

On the other hand, in another study only the intake of a 1500 kcal diet and daily walks of 1 km maintained for 24 weeks were evaluated, so this factor may have influenced the results obtained in all groups, taking into account that weight loss is a factor that depends on changes in lifestyle, diet and adherence to exercise, as well as the results of a study conducted where the role of weight loss after changes in the life style was evaluated and which recommended with level of evidence (A1) that motivation, comorbidity and patient preference should be considered to achieve a loss in 12 months of 7-10% of body weight, which leads to improvements in liver disease parameters due to the non-alcoholic fat deposit, obtaining maximum benefits when a loss > 10% of body weight is achieved [35].

With regard to the lipid profile, treatment with atorvastatin and combined therapy (Abexol + atorvastatin) significantly reduced levels of LDL-C and total cholesterol, compared to the rest of the treatments that did not modify these parameters, and atorvastatin also significantly reduced triglyceride levels compared to the control group (diet + exercise). These results confirm the lipid-lowering efficacy profile described for atorvastatin, a HMG-CoA reductase inhibitor, an enzyme that regulates the synthesis of cholesterol in the liver, and which is useful as a treatment in the reduction of hyperlipidemia in patients with NAFLD [16].

The treatments showed a satisfactory safety profile, since there were no significant changes in the physical and laboratory indicators investigated during the

Table 6. Adverse events reported during the study

Adverse events (AE)	Abexol (n = 22)		Atorvastatin (n = 23)		Combined therapy (n = 24)		Diet + exercise (n = 23)	
	n	%	n	%	n	%	n	%
Cephalea	0	0.0	0	0.0	1	4.2	0	0.0
Syncope	0	0.0	1	4.3	0	0.0	0	0.0
Decay	0	0.0	3	13.0	1	4.2	1	4.3
Diarrheal stools	0	0.0	3	13.0	2	8.3	0	0.0
Slight difficulty in breathing	1	4.5	0	0.0	0	0.0	0	0.0
Dyspepsia	1	4.5	0	0.0	0	0.0	0	0.0
Abdominal distention	0	0.0	0	0.0	0	0.0	1	4.3
Abdominal pain	0	0.0	0	0.0	0	0.0	1	4.3
Right upper quadrant pain	0	0.0	1	4.3	0	0.0	2	8.7
Foot pain when exercising	1	4.5	0	0.0	0	0.0	0	0.0
Leg muscle pain	1	4.5	0	0.0	0	0.0	0	0.0
Joint pain	0	0.0	1	4.3	0	0.0	0	0.0
Constipation	1	4.5	1	4.3	0	0.0	1	4.3
Fatigue	1	4.5	2	8.7	1	4.2	3	13.0
Paralytic ilium	0	0.0	0	0.0	0	0.0	1	4.3
Lack of appetite	1	4.5	1	4.3	0	0.0	0	0.0
Dizziness	0	0.0	1	4.3	0	0.0	0	0.0
Sickness	0	0.0	4	17.4	1	4.2	0	0.0
Pruritus	0	0.0	0	0.0	1	4.2	0	0.0
Disgust to smells	0	0.0	1	4.3	0	0.0	0	0.0
Vomiting	0	0.0	2	8.7	0	0.0	0	0.0
Total number of AE	7	31.8	21	91.3	7	29.2	10	43.5
Total number of patients reporting AE	4	18.2	4	17.4	5	20.8	3	13.0

n – number of patients
All comparisons were not significant (Fisher probability exact test, p > 0.05)

study, which coincides with previous results of the clinical evaluation of these treatments]16, 22-27].

Limitations of the study

The established treatment time (6 months) was relatively short to observe significant changes in liver echogenicity in abdominal ultrasonography of these patients.

On the other hand, taking into account the design of the study, another limitation is the insufficient number of patients expected per treatment group (*n* = 25), which was not fulfilled since of 100 patients planned for inclusion, 92 patients were included, as well as the number of patients who left the study prematurely (17 patients), which threatens to obtain significant intra- and intergroup differences.

Another fact to note is that no significant differences were found in the comparisons made between the investigated treatments (Abexol, atorvastatin, combined therapy) and the control group that indicated diet + exercise at the end of the 6 months of therapy, with the exception of the positive changes obtained in the lipid profile with the treatment with atorvastatin, which suggests that the treatments did not contribute anything significant to the conventional treatment indicated in these patients, or that the patients included in the study were not naive patients, but already

C.R. Domech, J.C.F. Travieso, Z.D. Guridi, M.I.C. Fernández, S.L. del Vallín, A.R.Carralero, E.F. Batallie, A.M.A. Alvarez, L.F. Dorta, J.I. Ferrer, S. M.Castaño, M.R. García, G.J. Rivero, Y.V. Alvarez

had a previous diagnosis of the disease and therefore had been treated prior to their inclusion in the study; therefore, the benefits to be obtained with the addition of Abexol and atorvastatin over conventional treatment were limited in these patients.

Conclusions

Abexol and atorvastatin showed comparable efficacy and safety in patients with non-alcoholic fatty deposition liver disease (NAFLD), with advantages for treatment with atorvastatin with respect to its effects on the lipid profile of these patients. However, to determine whether the use of these medications can help with NAFLD regression, future studies with a greater number of patients with NAFLD and a longer treatment time should be carried out to determine the true impact of these medications on treatment of NAFLD.

Disclosure

The authors declare no conflict of interest.

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