N-acetylcysteine and/or ursodeoxycholic acid associated with metformin in non-alcoholic steatohepatitis: an open-label multicenter randomized controlled trial

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ABSTRACT – **Background** – Nowadays, pharmacological treatment of non-alcoholic fatty liver disease (NAFLD) is still limited and it is based on the treatment of conditions associated comorbities. Oxidative stress and insulin resistance are the mechanisms that seem to be mostly involved in its pathogenesis. **Objective** – To evaluate the efficacy of N-acetylcysteine (NAC) in combination with metformin (MTF) and/or ursodeoxycholic acid (UDCA) for treatment of non-alcoholic steatohepatitis (NASH). **Methods** – Open-label multicenter randomized trial was conducted for 48 weeks. It included patients with biopsy-proven NASH. The patients were randomized into three groups: NAC (1.2 g) + UDCA (15 mg/kg) + MTF (850-1500 mg/day) (n=26); UDCA (20 mg/kg) + MTF (850-1500 mg/day) (n=13); NAC (1.2g) + MTF (850-1500 mg/day) (n=14) for 48 weeks. Clinical, laboratory and the second liver biopsies were performed after 48 weeks. **Results** – A total of 53 patients were evaluated; 17 (32.1%) were males; median age ±54 (IQR=15, 21-71) years. In the baseline, no difference was seen between groups according clinical and histological parameters. The groups differed only in cholesterol, LDL and triglycerides. No significant differences in biochemical and histologic parameters were found between these the three groups after 48 weeks of treatment. In the intragroup analysis (intention-to-treat) comparing histological and biochemical features, there were significant improvements in the steatosis degree (*P*=0.014), ballooning (0.027) and, consequently, in the NAFLD Activity Score (NAS) (*P*=0.005), and in the ALT levels at the end of the treatment only in the NAC + MTF group. No significant evidence of modification in the liver fibrosis could be observed in any of the groups. **Conclusion** – This multicenter study suggests that the association of NAC + MTF could reduce the liver disease activity in patients with NASH. These data stimulate further controlled studies with this therapy for these patients.

HEADINGS – Non-alcoholic fatty liver disease. Acetylcysteine. Ursodeoxycholic acid. Metformin.

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is a clinical condition with a broad spectrum of manifestations. It can be histologically classified as simple steatosis and non-alcoholic steatohepatitis (NASH), whose severity may vary according to the degree of fibrosis, evolution to cirrhosis and complications such as hepatocellular carcinoma. Histologically, what differentiates the two forms of the disease is the presence of signs of hepatocellular damage such as hepatocyte ballooning, present only in the NASH[1].

Currently, the NAFLD treatment is based on the control of associated conditions such as: obesity, diabetes mellitus and hypertriglyceridemia, as well as discontinuation of hepatotoxic drugs. The recommendation of the loss of excess weight and physical exercises should always be recommended, regardless of the histopathological grade of the patient's liver biopsy. Gradual weight loss leads to improved insulin sensitivity and may decrease hepatic steatosis and the degree of inflammation. The recommended loss weight should be 5%–10% to improve histological features[2,3].

Nowadays, pharmacological treatment of NAFLD is still limited and it is based on the treatment of conditions associated comorbities. Despite the high prevalence of hepatic steatosis and the potential to disease progress to NASH, fibrosis and cirrhosis, no specific treatment is still universally accepted.

A variety of hepatoprotective agents used in other liver diseases have been evaluated in patients with NAFLD. Ursodeoxycholic acid (UDCA), a quenodeoxycholic bile acid epimer, has anti-inflammatory, immunological and anti-apoptotic properties and is widely used in chronic cholestatic liver diseases. However, after promising results from a number of pilot studies in which reduction of aminotransferases and histological improvement with steatosis reduction in NASH patients were observed, a double-blind, randomized, 2-year study showed that the results of UDCA treatment were not significantly better than those observed in the control group[4]. Recently, however, a French multicenter study[5] tested high UDCA doses (28 to 35 mg/kg) in 126 patients randomized to placebo or UDCA for one year. The results confirm a significant reduction in alanine aminotransferase (ALT) and gamma glutamyl transferase (GGT)

concentrations in the UDCA group and a reduction in FibroTest (Biopredictive, Paris, France). Also, in this same study, surprisingly, there was an improvement in glycemia, HbA1c, and markers of IR (serum insulin and HOMA levels) that were independent of weight variation. N-acetylcysteine (NAC), a precursor of glutathione, an important intracellular antioxidant, has been tested in pilot studies in humans for treatment of NASH, showing improvement in serum aminotransferases levels[6,7]. The present study aimed to evaluate the efficacy of NAC in combination with metformin (MTF) and/or UDCA to treat NASH. Biochemical and histological parameters were evaluated after 12 months of treatment.

METHODS

Design and population study

An open-label therapeutic clinical trial was done in fifty-three NASH biopsy-proven patients from three Brazilian centers, randomized in a proportion of 2:1:1 to receive MTF associated with UDCA plus NAC or UDCA or NAC only during 12 months.

• Inclusion criteria

The patients enrolled presented the following criteria: age 18-70 years; absence of alcohol consumption [<20 g (woman) and 40 g (man) ethanol], drug addiction, schistosomiasis, hepatitis B or C; absence of autoantibodies titers; serum iron, ferritin and transferrin saturation as well ceruloplasmin and copper, alpha1-antitrypsin levels were normal. Histological analyzes were performed according the Pathology Committee of the NASH Clinical Research Network[8]. Biopsies obtained until 12 months before the baseline of the study were accepted, provided that the patients had not presented weight loss greater than 5% of body weight during the last 12 months or had been treated with any new medication that could modify the histological parameters.

• Exclusion criteria

Exogenous poisoning by oxidizing agents, pregnancy and lactation; prothrombin time <70 % or platelets <50.000/mm^3 and refusal to collaborate with the research. In addition, all of the patients had elevated ALT and/or aspartate aminotransferase (AST) levels on at least two occasions over six months prior to enrollment.

Specific informed consent was obtained of all patients for the study and the protocol was approved by the Internal Review Board of the University of São Paulo (São Paulo, Brazil), Federal University of São Paulo (São Paulo, Brazil) and Federal University of Bahia (Bahia, Brazil).

The diagnosis of diabetes type II, hypertension, and dyslipidemia were based on the criteria of the American Diabetes Association (fasting glucose 100 mg/dL; triglyceride 150 mg/dL; high density lipoprotein (HDL) <40 mg/dL in men or <50 mg/dL in women; and 130 mmHg systolic or mmHg diastolic)[9]. Anthropometric parameters including height, weight, and BMI were also performed.

Study groups

After histological diagnosis all patients were randomized in a proportion of 2:1:1 to receive MTF (850-1500 mg/day) associated with: UDCA plus NAC or UDCA or NAC according the groups: Group 1: NAC (1.2 g/day) + UDCA (15 mg/kg/day) (n=26); Group 2: UDCA (20 mg/kg/day) (n=13) and Group 3: NAC (1.2 g/day) (n=14) for 48 weeks. After this period, patients performed the second liver biopsy.

All patients will be informed about diet, exercise and encouraged to lose weight, avoid alcohol intake, and medications such as anti-inflammatories, corticosteroids, herbal products among others.

Histological diagnosis

The liver tissue was fixed in 4% formaldehyde and processed for hematoxylin–eosin and Masson trichrome stains for histological analysis. All specimens were scored by a two experient liver pathologist with expertise in NAFLD. The specimens were blindly scored according to the NASH activity score (NAS) devised by the Pathology Committee of the NASH Clinical Research Network[8]. According to the NAS, scored parameters included macro- and microvacuolar fatty change, zonal distribution, foci of necrosis, portal and perivenular fibrosis, and inflammatory and fibrotic infiltrate with zonal distribution.

Statistical analysis

Sample size was calculated on the basis of a previous clinical trials with MTF and NAC where a significant reduction in serum levels of liver enzymes could be reached with only 20 patients included in the trial[10]. Because the aim was to evaluate the impact of NAC + UDCA, used in combination, on the histological improvement of hepatic biopsy and there are no studies related to this result, the stratification method includes 3 groups (each group with 20 patients), assuming a loss of 10%–15% for follow-up. This sample size allows us to estimate the impact of these drugs on hepatic histology. Sample size was calculated on the basis of a previous clinical trials with MTF and NAC[10].

The main selection was the population that completed the study (per-protocol sample). The analyses were conducted with the software IBM SPSS Statistics for Windows version 20 (Chicago, IL, USA), all tests were conducted at .05 two-sided level. Continues variables are presented as mean ± standard deviation (SD) and categorical variables as frequency and percentage. ANOVA test complemented by Bonferroni test was used for the comparison between continuous variable and Chi-square or Fisher's test for categorical variables, during the different periods of the study. Paired Student t test or Wilcoxon test was utilized for comparison between, respectively, continuous or categorical variables in each group before and after treatment. Descriptive level of $P<0.05$ was considered significant.

RESULTS

Fifty-three patients meeting the inclusion criteria were enrolled in the study and were randomized into three groups in a proportion of 2:1:1 to receive MTF associated with: UDCA plus NAC or UDCA or NAC for 48 weeks. However, 14 (27%) patients did not complete all the study protocol by adverse effects or no acceptance the second liver biopsy. The patients were analyzed per group (FIGURE 1). The majority of patients that presented adverse effects and stopped the protocol were in the group UDCA plus Metformin. They presented severe diarrhea. Five patients refused to do the second liver biopsy.

Seventeen (32.1%) were males with median age ±54 years (IQR=15, 21-71 years). In the baseline, no difference was seen between groups according clinical and histological parameters, although the groups differed in total cholesterol, LDL and triglycerides (TABLE 1). The rate of significant fibrosis (F2-F4) was around 50% in each group, P=1.00 (TABLE 2).
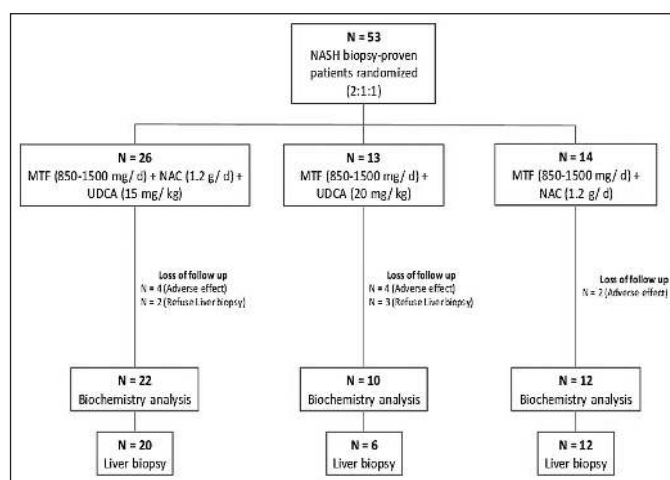
FIGURE 1. Consort diagram of nonalcoholic steatohepatitis patients randomized to receive oral N-acetylcysteine (NAC) in combination with metformin (MTF) and/or ursodeoxycholic acid (UDCA).

The intergroup analysis there is no differences among the three groups according biochemical and histologic parameters after 48 weeks treatment (TABLE 3). However, in the other hand, in the intention-to-treat intragroup analysis, comparing baseline with post-treatment data there was improvement in ALT level as well in histology in the NAC + MTF group, with significant improvements in steatosis degree, ballooning and, consequently, in the NAFLD Activity Score (NAS) (TABLE 2, FIGURE 2). There were significant improvements in steatosis degree (*P*=0.014), ballooning (0.027) and, consequently, in the NAFLD Activity Score (NAS) (*P*=0.005) in the NAC + MTF group (FIGURE 2). In the other variables, in the intention-to-treat analysis, there was no progression of fibrosis and inflammation in each group with no significant difference between them.

DISCUSSION

This Brazilian multicenter randomized controlled trial showed that the association of NAC and MTF improved liver histology including NAFLD Activity Score (NAS) and ALT in patients with

TABLE 1. Clinical and laboratory characteristics of nonalcoholic steatohepatitis patients from N-acetylcysteine (NAC) in combination with metformin (MTF) and/or ursodeoxycholic acid (UDCA) at baseline.

Characteristic	MTF (850-1500 mg/d) + NAC (1.2 g/d) + UDCA (15 mg/Kg/d) (n=26)	MTF (850-1500 mg/d) + UDCA (20 mg/Kg/d) (n=13)	MTF (850-1500 mg/d) + NAC (1.2 g/d) (n=14)	*P*-value
Demographics				
Age, median (IQR)	49 (10)	56 (15)	56 (15)	**0.004**
Male, n (%)	11 (42.3)	2 (15.4)	4 (28.6)	0.224
BMI, kg/m², median (IQR)	31.2 (6)	31.2 (10)	29.9 (6)	0.728
Comorbidities, n (%)				
Diabetes mellitus	10 (38.5)	9 (69.2)	9 (64.3)	0.117
Arterial hypertension	9 (34.6)	5 (38.5)	5 (35.7)	0.972
Hyperlipidemia	15 (57.7)	10 (76.9)	12 (85.7)	0.149
Metabolic syndrome	7 (26.9)	3 (23.1)	7 (50.0)	0.239

NAC: N-acetylcysteine; MTF: metformin; UDCA: ursodeoxycholic acid; BMI: body mass index; IQR: interquartile range.

TABLE 2. Comparison between baseline and post-treatment histological parameters (intragroup comparison).

	Baseline	Post-treatment	z-value	*P*-value
MTF (850-1500 mg/d) + NAC (1.2 g/d) + UDCA (15 mg/Kg/d) (n=21)				
Steatosis (0/1/2/3)	0/1/12/8	4/8/9	-0.632	0.527
Inflamation (0/1/2/3)	0/13/4/4	1/8/10/2	-0.25	0.803
Balooning (0/1/2)	1/10/10	1/9/11	-0.302	0.763
Fibrosis (0/1/2/3/4)	1/9/6/4/1	2/8/4/6/1	-0.243	0.808
NAS (3/4/5/6/7/8)	0/7/6/2/3/2	3/3/4/6/4	0	1
MTF (850-1500 mg/d) + UDCA (20 mg/Kg/d) (n=6)				
Steatosis (0/1/2/3)	0/0/1/5	0/2/2/2	-1.633	0.102
Inflamation (0/1/2/3)	0/2/3/1	0/2/4/0	-0.577	0.564
Balooning (0/1/2)	0/2/4	0/0/6	1.414	0.157
Fibrosis (0/1/2/3/4)	0/3/2/0/1	0/2/1/2/1	-1.732	0.083
NAS (4/5/6/7/8)	0/2/1/2/1	1/2/1/2/0	-1.134	0.257
MTF (850-1500 mg/d) + NAC (1.2 g/d) (n=12)				
Steatosis (0/1/2/3)	0/1/2/9	0/4/5/3	-2.46	0.014*
Inflamation (0/1/2/3)	0/3/9/0	0/8/4/0	-1.667	0.096
Balooning (0/1/2)	0/2/10	1/7/4	-2.333	0.020*
Fibrosis (0/1/2/3/4)	0/6/2/4/0	0/4/2/5/1	-1.155	0.248
NAS (2/4/5/6/7/8)	0/0/3/3/5/1	1/5/4/1/1	-2.754	0.006*

Inflamation: lobular inflammation; NAS: NAFLD Activity Score; z: Wilcoxon test score for related samples. * *P*-value <0.05.

TABLE 3. Comparison between baseline and post-treatment endpoints (intragroup comparison).

	MTF (850-1500 mg/d) + NAC (1.2 g/d) + UDCA (15 mg/Kg/d) (n=26)	MTF (850-1500 mg/d) + UDCA (20 mg/Kg/d) (n=13)	MTF (850-1500 mg/d) + NAC (1.2 g/d) (n=14)	P-value
Glucose, mg/dL				
Baseline	111.6±42.0	132.7±33.0	124.3±75.7	.411
Final	116.0±45.5	124.1±34.3	115.6±40.2	.908
P-value	.329	.590	.281	
Insuline, μU/mL				
Baseline	19.5±13.2	21.3±8.4	19.9±7.6	.168
Final	17.7±16.2	20.4±5.0	20.4±9.9	.889
P-value	.370	.782	.902	
ALT, U/L				
Baseline	90.7±63.8	63.3±31.3	100.3±78.2	.523
Final	66.4±38.9	57.0±43.2	57.9±32.2	.863
P-value	.151	.751	**.042**	
AST, U/L				
Baseline	61.8±38.4	50.5±33.1	83.2±97.0	.493
Final	48.0±27.8	44.5±22.8	39.6±19.5	.779
P-value	.163	.668	.108	
GGT, U/L				
Baseline	94.7±115.0	161.7±113.6	114.0±111.1	.378
Final	48.5±37.3	72.2±35.4	90.2±75.7	.110
P-value	.072	.063	.428	
Alkaline phosphatase, U/L				
Baseline	85.9±88.6	71.5±15.5	98.6±55.4	.736
Final	63.0±21.8	64.5±7.7	84.9±27.4	.502
P-value	.260	.414	.307	
Total cholesterol, mg/dL				
Baseline	178.3±40.9	167.8±42.3	218.6±53.5	.049
Final	186.0±40.3	175.5±41.7	199.6±55.1	.556
P-value	.411	.552	.228	
HDL cholesterol, mg/dL				
Baseline	44.7±13.2	50.7±8.2	43.9±10.3	.426
Final	47.2±14.7	50.7±14.3	42.8±7.4	.426
P-value	.123	1.000	.715	
LDL cholesterol, mg/dL				
Baseline	105.6±32.5	91.5±28.5	139.2±46.9	**.034**
Final	108.5±37.8	95.7±29.8	125.2±47.1	.319
P-value	.754	.733	.308	
Triglycerides, mg/dL				
Baseline	141.4±44.3	164.7±35.3	196.3±80.2	**.039**
Final	160.7±66.8	138.2±28.2	177.6±115.2	.627
P-value	.230	.220	.608	

NAC: N-acetylcysteine; MTF: metformin; UDCA: ursodeoxycholic acid; ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma glutamyl transferase.
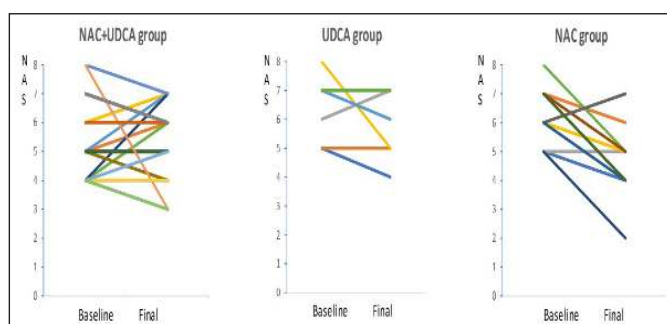
FIGURE 2. NAFLD Activity Score (NAS) at baseline and 6 months after treatment with N-acetyl cysteine (NAC group), Ursodeoxicholic acid (UDCA group) or both (NAC+ UDCA group).

NASH after 48 weeks of treatment. In previous pilot study that included 20 patients, Oliveira et al.[10] used the same dose of MTF 850 mg to 1 g/day + NAC 1.2 g/day for the same period of time and showed the same results: improvement in biochemical and histological parameters of patients with NASH.

NAFLD has a crescent prevalence around the world and a potential to progress to fibrosis, cirrhosis and hepatocellular carcinoma. Specific pharmacological treatment is not universally accepted; however, several therapeutics drugs trials are under development, with single drug or drug combination.

The ideal candidate drug should be at least one that present the following properties: to correct the underlying insulin resistance (IR) and lipotoxicity by targeting also extrahepatic tissues (gut, adipose tissue, pancreas and muscle); to have anti-fibrotic effects in the liver; improve survival (liver related and cardiovascular disease; and to have few adverse effects. This current study, controlled with liver biopsy before and after the treatment, demonstrated the improvement of lipotoxicity and few side effects in NAC plus MTF group.

Acetylcysteine (NAC) is the N-acetyl derivative of the amino acid L-cysteine and is the agent of choice to prevent hepatotoxicity associated with acetaminophen overdose[11]. It is a precursor of glutathione, the most powerful antioxidant in the liver because is a donor of the sulfhydryl group that crosses the cell membrane and restores GSH levels by providing cysteine for its synthesis[12]. Recently, a meta-analysis of prospective clinical trials evaluated the safety and efficacy of NAC in patients with acute liver failure (ALF) not related to acetaminophen poisoning. The study concluded that NAC cannot improve the overall survival, however it could prolong patients' survival with native liver without transplantation and survival after transplantation beyond is safe for NAI-ALF[13]. In addition, NAC has been used clinically to treat various other diseases related to oxidative stress and/or GSH deficiency, such as HIV infection[14,15]. Besides, in severe alcohol hepatitis, Nguyen-Khac et al.[16] compared the effects of the combination of NAC and prednisolone vs prednisolone and placebo, while NAC was administered intravenously for five days demonstrated significantly reduced the 6-month incidence of hepatorenal syndrome and infections in the association of NAC and prednisolone compared with prednisolone with placebo.

In previous experimental studies in rats improvement of liver histopathology and reduction of oxidative stress by NAC in NAFLD have reported[17,18]. In another recent experimental study the authors demonstrated also, improvement in histological findings of NASH with the combination of NAC + MTF[19] as well our present study.

The treatment of NASH with NAC has been evaluated in other studies. Pamuk and Sonsuz[20] demonstrated significant decreases in ALT, AST and GGT levels after a 4-week treatment period with NAC; however, no liver biopsy was performed to determine histological effects. Another small human study, that included 11 NASH patients treated with diet regimen followed by NAC therapy, showed some improvement aminotransferases, although also without histological evaluation[21]. The study didn't observe statistical improvement in histology in others two groups such as UDCA + MTF and UDCA + MTF + NAC. The most relevant result in these patients group was the improvement of GGT.

In the literature, UDCA has shown rather limited clinical benefits in the treatment of NAFLD/NASH. A pilot study demonstrated that UDCA (~15 mg/kg/day) reduced alkaline phosphatase (AP), ALT, and GGT after 12 months of treatment[22], but a 2-year randomized controlled trial was not able to demonstrate effects with a similar dose[23]. Another trial with a higher dose (28 mg/kg/day) showed a reduction in lobular inflammation but no differences in fibrosis or in the overall histology score[4]. Thus, in clinical practice, according current EASL-EASD-EASO NAFLD guidelines and AASLD guidelines NASH patients are currently not treated with UDCA, which is in line with the, since UDCA failed to demonstrate consistent histological benefits[3]. Although, we added MTF to UDCA or NAC, the patients did not demonstrate histology improvement and the groups of UDCA had more adverse events such are diarrhea and gastrointestinal intolerance.

One limitation of this study is the small number of patients that completed the study and performed the second liver biopsy, manly in the UDCA groups. About 27% the patients lost the follow up in these groups. We know that this loss is very high in randomized trials. Both, UDCA and MTF, are known for having diarrhea as an adverse event in therapeutic doses[24,25]. However, it is the first study that combine MTF + UDCA in high doses, and this combination promoted severe diarrhea in these patients impairing adhesion. All others clinical trials with high doses of UDCA did not add MTF[4,21,22].

In patients with NASH, the presence of hepatic fibrosis has been considered the most important prognostic factor. Hepatic fibrosis has been related to the greater morbidity and mortality of the patients. Thus, one of the main goals of the therapeutic trials involving patients with NASH has been the regression or stabilization of fibrosis, since the natural history of the evolution of the disease to this stage is already well defined. It is estimated that 40% of NASH patients already have fibrosis and that 20% have regression potential, albeit sluggish, in a period also estimated to be 3.7 ± 6.6 years[26,27]. In the present study involving 53 patients treated for 48 weeks with no worsening progression of fibrosis was observed in the three groups of patients.

Although the limited number of patients and perhaps limited time of observation should be considered, these results are important because they suggest that the association of drugs, notably NAC with MTF, has good perspectives in the treatment of NASH with and without fibrosis.

In conclusion, these results stimulate the developed of new multicenter controlled trials with NAC + MTF with large number and follow up of patients with NASH. These drugs association improved histology observed by NAS without fibrosis progression. Despite the limitations of this study, significant improvement in main parameters of injury without or significant side effects is very encouraging for more controlled studies in patients with NASH for to test combination therapy versus placebo.

Authors' contribution

Oliveira CP, Cotrim HP and Parise ER were responsible for study design, data collection, analysis and interpretation as well as writing the manuscript. Stefano JT, Siqueira ACG and Salgado ALA were responsible for data collection at their institution. Parise ER was responsible for statistical data analysis and Oliveira CP, Cotrim HP and Parise ER helped on the revision of the manuscript.

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RESUMO – **Contexto** – Atualmente, o tratamento farmacológico da doença hepática gordurosa não alcoólica (DHGNA) ainda é limitado e baseia-se no tratamento de condições associadas às comorbidades. O estresse oxidativo e a resistência à insulina são os mecanismos que parecem estar mais envolvidos em sua patogênese. **Objetivo** – Avaliar a eficácia da N-acetilcisteína (NAC) em associação à metformina (MTF) e/ou ácido ursodesoxicólico (UDCA) no tratamento da EHNA. **Métodos** – Estudo randomizado, multicêntrico e aberto, conduzido por 48 semanas. Incluiu pacientes com esteato-hepatite não alcoólica (EHNA) comprovada por biópsia. Os pacientes foram distribuídos aleatoriamente em três grupos: NAC (1,2 g) + UDCA (15 mg/kg) + MTF (850-1500 mg/dia) (n=26); UDCA (20 mg/kg) + MTF (850-1500 mg/dia) (n=13); NAC (1,2 g) + MTF (850-1500 mg/dia) (n=14) durante 48 semanas. Os dados clínicos, laboratoriais e as segundas biópsias hepáticas foram realizados após 48 semanas. **Resultados** – Um total de 53 pacientes foram avaliados; 17 (32,1%) eram do sexo masculino; idade mediana de ±54 (IQR=15, 21-71) anos. No baseline, nenhuma diferença foi observada entre os grupos de acordo com parâmetros clínicos e histológicos. Os grupos diferiram apenas em colesterol, LDL e triglicerídeos. Não foram encontradas diferenças significativas nos parâmetros bioquímicos e histológicos entre os três grupos após 48 semanas de tratamento. Contudo, na análise intragrupos (intenção de tratar) comparando características histológicas e bioquímicas, houve melhora significativa no grau de esteatose (*P*=0,014), balonização (*P*=0,027) e, consequentemente, no *NAFLD Activity Score* (NAS) (*P*=0,005), e nos níveis de ALT no final do tratamento apenas no grupo NAC+MTF. Nenhuma evidência significativa de modificação na fibrose hepática pôde ser observada em nenhum dos grupos. **Conclusão** – Este estudo multicêntrico sugere que a associação de NAC+MTF poderia reduzir a atividade da doença hepática em pacientes com EHNA. Esses dados estimulam estudos adicionais controlados com essa terapia para esses pacientes.

DESCRITORES – Hepatopatia gordurosa não alcoólica. Acetilcisteína. Ácido ursodesoxicólico. Metformina.

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