ORIGINAL ARTICLE

THE EFFECTIVENESS OF COMPLEX THERAPY WITH THE INCLUSION OF THE URSODEOXYCHOLIC ACID IN PATIENTS WITH NON-ALCOHOLIC FATTY LIVER DISEASE IN COMBINATION WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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ABSTRACT

The aim: Was increase the effectiveness of treatment in patients with non-alcoholic fatty liver disease (NAFLD) comorbid with chronic obstructive pulmonary disease (COPD) by using ursodeoxycholic acid (UDCA) in combination with ademethionine.

Materials and methods: Under observation was 98 patients with a diagnosis of NAFLD and COPD group II or their combination. Patients were divided into 3 groups: 1 (n = 36) – COPD + NASH – in addition to standard COPD therapy received UDCA 15 mg / kg / day – 6 months and ademethionine 1000 mg IV once a day for 10 days, followed by oral administration of 500 mg 2 times per day – 20 days, and group 2 (n = 32) – COPD + hepatic steatosis – in addition to standard therapy – UDCA 15 mg / kg / day – 6 months. Group 3 (n = 30) – COPD received standard therapy for COPD.

Results: UDCA with ademethionine on the background of standard COPD therapy reduces the clinical manifestations of NAFLD and normalizes liver function. The combination of UDCA with ademethionine not only has a positive effect on the course of NAFLD, but also reduces the intensity of dyspnea, systemic inflammation, improves the external respiration function and reduces anxiety and depression. Patients receiving UDCA + ademethionine for 6 months of follow-up had no exacerbations of COPD.

Conclusions: UDCA in combination with ademethionine in COPD courses have a positive effect on the course of NAFLD, and also reduces the intensity of dyspnea, improves the external respiratory function and reduces the frequency of COPD hospitalization.

KEY WORDS: NAFLD, COPD, UDCA, ademethionine, systemic inflammation

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INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is the most common chronic liver disease in the world, and continues to grow every year [1,2]. According to the European Respiratory Society (ERS), there is a steady increase in mortality and disability from chronic obstructive pulmonary disease (COPD) [3]. Pulmonary and extrapulmonary manifestations are observed in patients with COPD, in the pathogenesis of which there is immunological inflammation, which leads to chronic tissue hypoxia and to disruption of all organs and systems [4-6]. The World Health Organization classifies COPD as a major social burden [7]. The high prevalence of NAFLD and COPD causes a frequent combination of these pathological conditions. And the selection of a therapeutic approach should be carried out taking into account all the pathophysiological mechanisms of formation of these conditions.

Recently, for the treatment of various liver diseases, ursodeoxycholic acid (UDCA) drugs are used. Many randomized trials have proven the multifactorial effects of UDCA. Belgian researchers have concluded that UDCA reduces eosinophilic inflammation in the bronchopulmonary system [8]. Scientists from Turkey have demonstrated the effectiveness of UDCA in respiratory diseases by effectively modulating Th-2 cytokine derivatives [9], and experiments by Chinese scientists have shown that UDCA helps prevent edema and pulmonary fibrosis, which are common complications of COVID-19 [10]. Also of great interest is the drug ademethionine, which plays a central role in the biochemical reactions of transmethylation, transsulfation, aminopropylation and has antifibrotic activity. However, studies to study the concomitant use of UDCA and ademethionine in patients with comorbid liver disease have not been sufficiently studied.

THE AIM

The aim was to increase the effectiveness of treatment in patients with NAFLD comorbid with COPD by studying the possibility of using UDCA in combination with ademethionine.

MATERIALS AND METHODS

The observation revealed 98 patients who were treated at the Zakarpattia Regional Clinical Hospital named after

Andriy Novak during 2018-2020 with a diagnosis of NAFLD and COPD group II or their combination. Among the surveyed were 61.2% (60) men and 38.8% (38) women. The average age was 57.8 ± 1.5 years.

The studies were conducted with the informed consent of patients, and their methodology complies with the Helsinki Declaration of 1975 and its 1983 revision approved by the Local Bioethics Commission (Protocol №1 from 10.01.2020). The inclusion criteria in research study confirmed the diagnosis of chronic obstructive pulmonary disease COPD (GOLD II) and age over 40 years and less than 70 years and / or NAFLD. Exclusion criteria in the study were the presence of markers of viral hepatitis B and C, markers of autoimmune hepatitis, alcohol consumption, toxic liver damage.

The diagnosis of NAFLD was established according to the unified clinical protocol "Non-alcoholic steatohepatitis" (2014) and to the recommendations of the European Association for the Study of the Liver (EASL). The diagnosis of COPD was confirmed according to the order of the Ministry of Health of Ukraine №555 from 27.06.2013 "On approval of clinical protocols for medical care in the specialty" Pulmonology "and the provisions set out in the document GOLD [2017]. A modified Medical Research Council (mMRC) dyspnea scale and a COPD assessment test (CAT) were used to assess the clinical course of COPD and the intensity of the main symptoms.

The external respiration function was determined using a microprocessor device «Pulmovent-2» (Ukraine) with a bronchodilation test. Spirometry parameters such as: forced vital capacity (FVC), forced expiration volume in one second (FEV1) and their ratio, mean forced expiratory flow (FEF) between 25%, 50% and 75% of the expired vital capacity. The evaluation of these indicators was performed as a percentage of the corresponding values. FEV1 / FVC <0.7 after bronchodilation test became the basis for the diagnosis of COPD.

All patients with exacerbation of COPD received a basic treatment regimen, which included inhaled M-cholinolytic long-acting tiotropium bromide (drug in capsules with powder for inhalation 18 mcg with delivery device) and standard therapy for exacerbation of COPD: bronchodila-

Table I. Number of patients with persistent clinical syndromes after treatment depending on the treatment regimen

Syndromes 1 (n=36)		Groups, abs/%	
		2 (n=32)	
Asthenovegetative syndrome	a	33 / 91,7	29 / 90,6
	b	5 / 13,9*	7 / 21,9*
Dyspeptic syndrome	a	27 / 75,0	25 / 78,1
	b	6 / 16,7*	9 / 28,1*
Pain	a	21/ 58,3	19 / 59,4
	b	1 / 2,8*	5 / 15,6 *
Hepatomegaly	a	33 / 91,7	30 / 93,7
	b	2 / 5,5*	11 / 34,4*

Notes: *Significance of the difference (p <0.05); a - before treatment; b - after treatment.

Table II. Dynamics of biochemical parameters before and after treatment

Indexes		Groups		
		(n=30) Control group	1 (n=36) UDCA	2 (n=32) Ademethionine + UDCA
Bilirubin, mg/dL	a	15,3±1,4	29,2±3,7	30,9±1,2
	b		19,4±1,3*	12,4±0,8*,**
ALT, IU/L	a	22,1±3,7	147,8±42,7	122,1±3,4
	b		48,2±2,3*	32,6±1,3*,**
AST, IU/L	a	14,2±2,1	78,5±7,8	74,7±2,6
	b		57,4±1,6*	32,6±1,3*,**
ALP, IU/L	a	52,3±5,7	137,2±22,5	112,4±5,2
	b		69,2±1,5*	37,5±1,9*,**
GGT, IU/L	a	24,4±3,0	77,2±9,4	79,7±6,2
	b		46,1±3,1	21,7±5,1*,**

Notes: Significance of the difference: * - group I; **- group II (p values are calculated by Fisher's exact test, p <0,05-0,01). a - before treatment; b - after treatment

Table III. Assessment of the clinical symptoms according to mMRS and CAT scores before and after treatment

Groups		mMRC, point	CAT, point
Group 1	a	1,7± 0,4	16,8± 0,5
	b	1,1±0,5*	12,1±0,3*
Group 2	a	1,8±0,3	17,3±0,4
	b	1,3±0,1*	12,8±0,2*
Group 3	a	1,8±0,4	17,1±0,4
	b	1,6±0,2*	13,6±0,3*

Notes: *Significance of the difference (p <0.05); a - before treatment; b - after treatment.

Table IV. Dynamics of spirometry parameters during treatment

Groups		FVC, %	FEV1,%	FEV1 / FVC,%
Group 1	a	42,3± 3,2	48,4± 2,8	61,7±1,5
	b	62,4±2,5*	63,4±2,3*	69,2±1,7*
Group 2	a	42,4±4,3	49,2±3,3	63,5±1,3
	b	60,9,3±2,1*	60,2±3,6*	68,4±1,4*
Group 3	a	43,5±3,4	49,5±3,4	62,4±1,6
	b	60,2,6±2,3*	58,4±2,9*	66,5±1,5*

Notes: *Significance of the difference (p <0.05); a - before treatment; b - after treatment.

tor – methylxanthine – eufilin 2.4% solution – 10 ml IV in 10 – 20 ml of isotonic sodium chloride solution or teotard 200 mcg 2 times / day) and mucolytic (bromhexine 8 – 16 mg 3 times / day or ambroxol hydrochloride 30 mg 3 times) / day), as well as dexamethasone IV for 7 days.

In the sample in patients with COPD, depending on the stages of concomitant NAFLD, three groups of application of the following treatment complexes were identified:

Group 1 (n = 36) patients with COPD + NASH – in addition to standard therapy from the 7th day of treatment of COPD exacerbation (after elimination of the most acute phenomena of bronchoobstruction and systemic inflammation) on the background of lifestyle modification (weight loss, low-calorie diet, dosed physical activity) ademethionine 1000 mg IV once a day for 10 days, followed by oral administration of the drug (500 mg in the morning and at lunch) for 20 days and UDCA 15 mg / kg / day for two hours before bedtime.

Group 2 (n = 32) patients with COPD + hepatic steatosis – in addition to standard therapy from the 7th day of treatment of COPD exacerbation on the background of lifestyle modifications received UDCA 15 mg / kg / day two hours before bedtime. It should be noted that all patients

Table V. Dynamics of systemic immune inflammation activity under the influence of therapy

Inflammatory indexes		Group 1 (n=36)	Group 2 (n=32)	Group 3 (n=30)	Control group (n=30)
CRP, mg/L	a	16,4±0,5	18,2±0,7	17,4±0,6	2,7±0,9
	b	5,5±0,3*	8,6±0,4*	10,3±0,5	
IL-6, (normal 0-10 pg/mL)	a	45,4 ±1,3	49,5 ±0,8	47,8±1,7	3,9±1,2
	b	10,6±0,7*	16,3±0,6*	22,4±1,04	
TNF-a, (normal 0-6 pg/mL)	a	407,5 ±10,3	465,3 ±12,5	207,5 ±10,3	9,5±0,7
	b	53,8±0,61*	93,76±0,64*	77,71±0,83*	
Neopterin (normal up to 10 nmol / l)	a	447,3±0,3	378,6±1,5	109,5±1,8	7,2±1,2
	b	58,26±1,24*	104,88±0,5*	90,27±1,37	
IgG neutrophil elastase antibodies, IU / ml	a	49,2±5,2	47,4±3,8	48,5±4,6	3,2±0,8
	b	22,4±2,4*	24,5±2,5*	28,4±2,6	

Notes: *Significance of the difference (p <0.05); a - before treatment; b - after treatment.

Table VI. Dynamics of quality of life as a result of treatment

Indexes	Group 1		Group 2		Group 3	
	a	b	a	b	a	b
PF	77±2,5	86±1,4	72±1,2	79±1,8	77±2,1	81±1,7
RP	39±2,2	45±1,5	41±3,6	49±2,5	51±3,3	58±1,2
BP	35±41	42±1,7*	42±4,2	45±3,1	53±1,1	62±2,2
GH	36±3,5	45±4,4*	43±3,1	49±2,1	52±2,0	59±2,4
VT	37±4,2	46±5,4*	46±2,0	51±2,5	54±2,3	61±3,2
SF	45±1,2	50±2,5	52±2,5	58±2,7	59±2,0	69±4,4
RE	27±1,7	33±2,1*	33±2,5	39±2,1	41±2,1	45±2,6
MH	41±3,5	48±1,1*	44±3,3	48±2,0	51±1,9	60±1,7
PH	44±1,8	52±3,5	50±1,2	56±1,4	55±2,2	60±1,7
MH1	40±1,7	51±1,2	44±1,1	51±5,2	48±3,3	55±1,5

Notes: *Significance of the difference (p <0.05); a - before treatment; b - after treatment.

completed treatment on an outpatient basis. Taking UDCA 500 mg at night in group 1 and 2 continued for 6 months.

Group 3 (n = 30) – patients with COPD received the above standard exacerbation therapy.

Evaluation of the effectiveness of treatment was performed on the indicators of clinical course, liver tests, systemic inflammation (CRP, TNF-a, IL-6, neopterin, IgG antibodies to neutrophil elastase), respiratory function, quality of life. Quality of life (QOL) was assessed using a non-specific questionnaire «SF-36». Observation of included persons of the study lasted 12 months.

Enzyme-Immuno-Sorbent-Assay (ELISA) was used to determine levels of C-reactive protein (CPR), concentrations of TNF-a, IL-6, neopterin and IgG antibodies to neutrophil serum elastase. The results of the studies were taken into account on an automatic enzyme-linked immunosorbent assay "STATFAX" according to the instructions included with the reagent kits Diagnostics Biochem Canada and DRG (USA). To determine the degree of steatosis and liver fibrosis used a non-invasive method of diagnosis – FibroMax. The analysis and processing of the results was performed using Microsoft Windows 10 and STATISTICA application packages.

RESULTS

In groups 1 and 2 of patients, the treatment reduced the manifestations of dyspeptic syndrome, pain and hepatomegaly, with a predominance in patients receiving UDCA + ademethionine (table I).

Positive changes are registered not only in the well-being of patients, but also in the biochemical parameters of the blood. At the end of the treatment there is a decrease in the levels of total bilirubin, alkaline phosphatase, gamma-glutamyltranspeptidase in groups 1 and 2, compared with the levels of these parameters before treatment (table II).

In the course of treatment, positive dynamics of clinical features (reduction of dyspnea according to mMRC and intensity of the main symptoms according to CAT was revealed in all clinical groups (Table III). The changes were more pronounced in patients taking UDCA + ademethionine (group 1) at the same time, compared with group 2 and 3.

During the assessment of parameters of external respiration function under the influence of complex treatment, a significant increase in FVC, FEV1 and FEV1 / FVC in all clinical groups, with more pronounced dynamics in group 1 (Table IV).

After treatment, patients in all three groups tended to normalize the cytokine levels of the immune system. Decreased activity of pro-inflammatory cytokines, in particular TNF-α, IL-6 and neopterin, and decreased levels of IgG antibodies to neutrophil elastase. (Table V).

As a result of use the complex therapy with UDCA and ademethionine, the levels of TNF-α and neopterin were most significantly reduced by 7.5 and 7.7 times ($p < 0.01$) and IL-6 by more than 4 times ($p < 0.05$). The level of CRP decreased by almost 3 times ($p < 0.05$). Also, the level of IgG antibodies to neutrophil elastase decreased by 2 times ($p < 0.05$).

After a course of treatment in patients with COPD without NAFLD showed a tendency to improve all quality of life indicators (QOL). Analyzing the integrated index of physical and mental components of health on the whole SF-36 scale in patients with NAFLD combined with COPD by groups, we found the following dynamics: the average values of the integrated physical component of health (PH) in patients of group 1 showed maximum improvement – by 8 ± 1.7 points compared with pre-treatment index, and in patients of groups 2 and 3 increased by 5 ± 1.5 and 6 ± 0.2 points ($p < 0.05$). When assessing the integrated mental component of health (MH1), namely: in patients of group 1 the indicator increased by 11 ± 0.5 points, and in patients of groups 2 and 3 – by 7 ± 1.8 points and 7 ± 4.1 points (Table VI).

DISCUSSION

Two-thirds of the patients improved their general well-being and reduced pain in the right hypochondrium, apparently due to a normalization of the cytokine of the immune system. Hepatomegaly disappeared in almost all patients receiving concomitant ademethionine and UDCA. As a result of treatment in patients with NAFLD with comorbidity with COPD, a significant decrease in systemic inflammation was found, which is one of the common triggers for the progression of liver pathology and COPD, which is closely associated with the development of steatohepatitis and cardiovascular risk. [11,12]

It must be noted that the level of IgG antibodies to neutrophil elastase and the absence of exacerbation of COPD for 6 months in patients receiving ademethionine + UDCA, which proves the anti-inflammatory efficacy of the therapy.

The positive effect of the combined use of ademethionine and UDCA on the manifestations of asthenovegetative syndrome, characteristic of almost all patients at the beginning of the observation, was established.[13] During treatment in clinical groups of patients with NAFLD in combination with COPD, a positive dynamics of clinical and functional status was observed, which indicated a decrease in shortness of breath and intensity of COPD symptoms, as well as improvement of quality of life under the influence of treatment.

At the same time, the positive dynamics was more pronounced in the group of patients receiving additional UDCA + ademethionine in comparison with other groups. The most objective assessment of the effectiveness of treatment is the assessment of spirometry parameters of patients with NAFLD combined with COPD. Significant positive dynamics of both physical and mental components of QOL in groups of patients with COPD and NAFLD, which additionally used UDCA with ademethionine.

Significant reduction in dyspnea by mMRC and the intensity of the main symptoms in patients receiving complex therapy was accompanied by a decrease in the severity of depression and anxiety due to the antidepressant effect of ademethionine. [14]

CONCLUSIONS

The results showed that taking UDCA with ademethionine according to the proposed scheme helps to reduce the intensity, duration and frequency of the main manifestations of NAFLD. UDCA in combination with ademethionine has a positive effect not only on the course of NAFLD, but also improves the clinical and functional state in COPD. The positive effect on the clinical course of COPD is characterized by a decrease the intensity of dyspnea, improved respiratory function, reduces the intensity of the inflammatory process and leads to improved quality of life, reducing levels of anxiety and depression. The absence of side effects of therapy allows its widespread and long-term use in clinical practice.

The absence of side effects of therapy allows its widespread and long-term use in clinical practice. The proposed therapy may be an alternative for the treatment in patients with NAFLD comorbid with COPD not only at the stage of activation of the inflammatory process in the liver tissue, but also at the stage of maintenance therapy to prevent disease progression.

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