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Clinical efficacy and mechanism of polyene phosphatidylcholine combined with atorvastatin in treating metabolic associated fatty liver disease

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Abstract: **Background**: Metabolic associated fatty liver disease (MAFLD) is mainly caused by liver cell steatosis or fat storage due to lipid metabolism disorders. It may induce the diseases such as liver cirrhosis and liver cancer. **Objectives**: Our study aimed to explore the efficacy and mechanism of polyene phosphatidylcholine (PPC) combined with atorvastatin (ATV) in treating MAFLD. **Methods**: Ninety-two MAFLD patients were divided into control and observation groups which received PPC alone and PPC combined with ATV for six months. The total therapeutic efficiency, liver function indicators, blood lipid indicators, inflammatory factors and liver injury indexes were evaluated and compared between two groups. **Results**: After treatment, comparing to the control group, in the observation group the total effective rate was significantly increased and the liver function indicators, blood lipid indicators, inflammatory factors and liver injury index transforming growth factor-β (TGF-β) and nuclear transcription factor-κB (NF-κB) levels were significantly improved (all $P < 0.05$). **Conclusion**: PPC combined with ATV is superior to PPC alone in improving the liver function, lipid metabolism, inflammation and liver injury without increasing the adverse reactions. It may represent a safe adjunct strategy in MAFLD management.

Keywords: Atorvastatin; Inflammatory; Liver function; MAFLD; Polyene phosphatidylcholine

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INTRODUCTION

Metabolic associated fatty liver disease (MAFLD) is mainly caused by liver cell steatosis or fat storage due to lipid metabolism disorders. MAFLD may induce the diseases such as liver cirrhosis and liver cancer (Badmus *et al*., 2022). With the changes in people's dietary structure and living standards, the normal dietary structure is gradually being broken. In addition, the unhealthy lifestyle or work habits such as prolonged sitting and less exercise have gradually occupied the main time in people's daily life. These factors increasingly increase the incidence rate of MAFLD (Vespoli *et al*., 2023). The main pathological mechanism of MAFLD is not fully understood. In order to reduce the temporary and long-term pressures caused by MAFLD on patients themselves, families and society, it is urgent to make accurate diagnosis of this disease and improve the treatment effectiveness. At present, there is no standard therapy or specific drugs for the clinical treatment of MAFLD. The main purpose of treatment is to reduce the liver fat accumulation, reduce the damage caused by fat oxidation to liver tissue and control the progression of liver injury and other pathological changes (Nassir, 2022). The medication remains the preferred treatment for MAFLD (Guo *et al*., 2022). The clinical practice has shown that, the combination of two or more drugs is more effective than only one drug for treatment of some diseases.

Polyene phosphatidylcholine (PPC) is a drug for liver diseases. It can repair the liver cell membranes, regulate the liver energy stability, promote the liver tissue regeneration, convert the cholesterol and neutral fats into the easily metabolized forms and stabilize the bile (Li *et al*., 2022; Lu *et al*., 2022). However, for some MAFLD patients the efficacy of using this drug alone is not ideal. Atorvastatin (ATV) is the most representative lipid-lowering drug in clinical practice, especially in patients with hyperlipidemia. After medication, it can reduce the TG level and lower the low-density lipoprotein cholesterol (LDL-C) level (Chen *et al*., 2025). Our study aimed to investigate the clinical efficacy of PPC combined with ATV in treating MAFLD.

MATERIALS AND METHODS

Patients

This was a retrospective analysis on ninety-two MAFLD patients who were treated in our hospital between August 2020 and August 2022. According to treatment method, the patients were grouped to the control group (46 cases) and the observation group (46 cases). The post-hoc power analysis showed that, with the current sample size, this study achieved a statistical power of over 80% for

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detecting the effect value, which met the methodological requirements. The control group included 38 males and 8 females. The age was 41-72 years (60.28±9.36 years). The disease course was 3-15 years (9.58±3.57 years). The body mass index (BMI) was 25.11±2.06 kg/m^2. The observation group included 34 males and 12 females. The age was 42-70 years (61.13±10.19 years). The disease course was 2-18 years (10.33±2.19 years). The BMI was 24.78±3.11 kg/m^2. There was no significant difference in gender, age, disease course or BMI between the two groups ($P > 0.05$). This study had received the approval from our hospital ethics committee. The patients had provided the informed consent.

Inclusion and exclusion criteria

Inclusion criteria

(1) Meeting the MAFLD criteria; (2) With complete medical records; (3) Not receiving other medication treatment within two weeks prior to inclusion in the study.

Exclusion criteria

(1) Other liver diseases; (2) Serious lesions in major organs; (3) Cognitive impairment or mental illness; (4) Contraindications for the drugs involved in this study.

Treatment

In the control group, the patients were treated using PPC capsules (Sanofi (Beijing) Pharmaceutical Co., Ltd., Beijing, China) by oral administration, 456 mg per time, three times per day. In the observation group, the patients were treated using ATV tablets by oral administration (Zhejiang Lepu Pharmaceutical Co., Ltd., Taizhou, China), 10 mg per time, once per day and PPC capsules (Sanofi (Beijing) Pharmaceutical Co., Ltd., Beijing, China) by oral administration, 456 mg per time, three times per day. The treatment was performed lasting six months. The patients were given normal diet and reasonable exercise during the treatment. The adverse reactions occurring during the treatment were monitored.

Evaluation of total therapeutic efficiency

At the end of treatment, the total therapeutic efficiency was evaluated as follows: remarkably effective: the symptoms disappeared and the MAFLD-related indicators returned to normal; effective: the clinical symptoms mitigated and the MAFLD-related indicators were improved by ≥ 30%; ineffective: the clinical symptoms did not mitigate and the MAFLD-related indicators did not change. The total effective rate (%) was obtained by ratio of sum number of remarkably effective and effective cases to total case number.

Blood index detection

Fasting venous blood was taken before and after treatment, respectively. The liver function indicators including serum alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (ALP) were detected with the fully automatic blood analyzer. The normal reference ranges of ALT, AST and ALP were 5-50 U/L, 8-45 U/L and 40-130 U/L, respectively (due to the differences in test methods, instruments and populations, they may have slight difference among different hospitals and laboratories). The blood lipid indicators such as including high-density lipoprotein cholesterol (HDL-C), LDL-C, triglycerides (TG) and total cholesterol (TC), inflammatory factors such as tumor necrosis factor α (TNF-α) and hypersensitive C-reactive protein (hs-CRP) levels and liver injury indexes such as transforming growth factor-β (TGF-β) and nuclear transcription factor-κB (NF-κB) were detected by ELISA. The detection processes were in accordance with the kit instructions.

Statistical analysis

SPSS 22.0 software was used for statistical analysis. The measurement data (mean±standard deviation) were analyzed using t test. The counting data (number or rate) were analyzed using χ^2 test. P value less than 0.05 showed the statistically significant difference.

RESULTS

Total therapeutic efficiency

At the end of treatment, the total effective rate in the observation group was 91.30%, which was significantly higher than 73.90% in the control group ($P < 0.05$) (Table 1).

Liver function indicators

Before treatment, no significant difference in liver function indicators existed between two groups. After treatment, in two groups each liver function indicator was significantly decreased compared with before treatment. In addition, each index in the observation group was significantly decreased compared with the control group (all $P < 0.05$) (Table 2).

Blood lipid indicators

Before treatment, each blood lipid indicator presented no significant difference between the control and observation groups. After the treatment, in two groups the HDL-C was significantly increased and the LDL-C, TG and TC were significantly decreased, respectively. With comparison to the control group, in the observation group the HDL-C was further increased and the LDL-C, TG and TC were further decreased, respectively (all $P < 0.05$) (Table 3).

Inflammatory factors

No significant difference in each inflammatory factor was observed between two groups before treatment. After treatment, in each group each factor was significantly decreased and that in the observation group was further decreased compared with the control group (all $P < 0.05$) (Table 4).

Table 1: Total therapeutic efficiency

Group	n	Remarkably effective (n)	Effective (n)	Ineffective (n)	Total effective rate (%)
Control	46	20	14	12	73.90
Observation	46	24	18	4	91.30
χ^2					4.842
P					0.028

Table 2: Liver function indicators

Index	Group	n	Before treatment	After treatment	t	P
ALT (U/L)	Control	46	91.45±17.27	55.19±12.16	11.643	< 0.001
	Observation	46	88.20±20.17	47.63±8.06	12.668	< 0.001
	t		0.830	3.515		
	P		0.409	0.001		
AST (U/L)	Control	46	58.64±9.81	42.95±9.16	7.933	< 0.001
	Observation	46	60.28±11.23	36.17±12.63	9.676	< 0.001
	t		0.746	2.947		
	P		0.457	0.004		
ALP (U/L)	Control	46	71.63±13.69	52.39±7.32	8.411	< 0.001
	Observation	46	69.18±12.15	43.66±8.24	11.790	< 0.001
	t		0.908	5.379		
	P		0.366	< 0.001		

ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase.

Table 3: Blood lipid indicators

Index	Group	n	Before treatment	After treatment	t	P
HDL-C (mmol/L)	Control	46	0.92±0.28	1.18±0.24	4.782	< 0.001
	Observation	46	0.94±0.18	1.34±0.26	8.579	< 0.001
	t		0.408	3.067		
	P		0.685	0.003		
LDL-C (mmol/L)	Control	46	4.12±0.78	3.51±0.65	4.075	< 0.001
	Observation	46	4.36±0.93	2.67±0.55	10.609	< 0.001
	t		1.341	6.691		
	P		0.183	< 0.001		
TG (mmol/L)	Control	46	4.03±0.78	2.92±0.44	8.406	< 0.001
	Observation	46	3.89±0.75	2.33±0.53	11.521	< 0.001
	t		0.877	5.809		
	P		0.383	< 0.001		
TC (mmol/L)	Control	46	5.81±1.12	4.26±0.84	7.461	< 0.001
	Observation	46	6.03±1.24	3.87±0.79	9.964	< 0.001
	t		0.934	2.294		
	P		0.353	0.024		

HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides; TC, total cholesterol.

Table 4: Inflammatory factors

Index	Group	n	Before treatment	After treatment	t	P
TNF-α (ng/L)	Control	46	5.21±1.01	4.16±0.84	5.378	< 0.001
	Observation	46	5.03±0.89	3.58±0.93	7.590	< 0.001
	t		0.908	3.126		
	P		0.367	0.002		
hs-CRP	Control	46	8.17±2.81	6.49±1.38	3.650	< 0.001
(mg/L)	Observation	46	7.65±1.57	4.29±0.88	12.662	< 0.001
	t		1.099	9.117		
	P		0.275	< 0.001		

TNF-α/tumor necrosis factor α; hs-CRP/hypersensitive C-reactive protein.

Table 5: Biochemical factors

Index	Group	n	Before treatment	After treatment	t	P
TGF-β (ng/L)	Control	46	7.25±1.45	4.13±0.95	12.324	< 0.001
	Observation	46	7.47±1.33	3.64±0.73	17.122	< 0.001
	t		0.758	2.604		
	P		0.450	0.011		
NF-κB (ng/L)	Control	46	2.83±0.66	2.14±0.43	5.941	< 0.001
	Observation	46	2.76±0.51	1.87±0.39	9.402	< 0.001
	t		0.569	3.154		
	P		0.571	0.002		

TGF-β/transforming growth factor-β; NF-κB/nuclear transcription factor-κB.

Table 6: Adverse reactions

Group	n	Liver area discomfort (n)	Weakness (n)	Anorexia (n)	Incidence (%)
Control	46	1	1	1	6.52
Observation	46	2	1	2	10.87
χ^2					0.548
P					0.460

TGF-β and NF-κB

Before treatment, the serum TGF-β and NF-κB levels showed no significant difference between two groups. After the treatment, the serum TGF-β and NF-κB levels in each group were significantly decreased compared with before treatment, respectively and they in the observation group were further decreased compared with the control group (all $P < 0.05$) (Table 5).

Adverse reactions

During the treatment, the adverse reactions including weakness, liver area discomfort, weakness and anorexia occurred in two groups. These adverse reactions were transient and self-limited and the treatment did not need to be discontinued or adjusted. The incidence of adverse reactions showed no significant difference between two groups (Table 6).

DISCUSSION

Our study investigated the efficacy of PPC combined with ATV in treating MAFLD. It was found that, at the end of treatment, comparing to the control group, in the observation group the total effective rate was further increased, the ALT, AST and ALP were further decreased, the HDL-C was further increased and the LDL-C, TC and TC were further decreased. This indicates that, for treating MAFLD, compared with PPC alone, PPC combined with ATV improves the efficacy, improve the liver function and lower the blood lipid levels. PPC has the direct liver protective effect and indirect lipid-lowering effect and ATV has the direct lipid-lowering effect and indirect liver protective effect. Their combined use can enhance the liver protective and lipid-lowering effects, thus improving the treatment efficacy. During the treatment, there were some adverse reactions such weakness, liver area discomfort, weakness and anorexia in two groups. The incidence of adverse reactions presented no significant difference between two groups. This suggests that, PPC combined with ATV cannot increase the adverse reactions. These adverse reactions are due to the normal and mild side effects of drugs. They are transient and self-limited and do not require the special treatment or affect the long-term use of the planned therapy.

Inflammation is closely related to MAFLD. In MAFLD patients, the accumulation of fatty acids and lipid peroxides cause the inflammatory damage is to liver cells, leading to the increased inflammatory factor levels which in turn exacerbate the fat accumulation and steatosis (Badmus *et al*., 2022). TNF-α is an important inflammatory factor and the liver is the important target organ of TNF-α. TNF-α can not only directly damage the liver cells, but also bind to receptors on the liver cell membrane and induce the liver cell death (Kim *et al*., 2022). hs-CRP is an inflammatory marker that can sensitively reflect the level of inflammation activity and is proportional to the severity of inflammation (Eisenach *et al*., 2024). Research has shown that PPC has obvious anti-inflammatory effect, but this is considered one of its downstream effects or core mechanisms for repairing liver cells and protecting the liver (Mak and Shekhar, 2024). ATV also has the anti-inflammatory effect. This effect is not directly targeted at inflammatory factors, but rather through its main pharmacological action - inhibiting the cholesterol synthesis pathway - indirectly producing a pleiotropic effect (Inia *et al*., 2023). In our study, after treatment, the serum TNF-α and hs-CRP in the observation group significantly decreased comparing to the control group. It is suggested that, compared with PPC alone, PPC combined with ATV exerts the synergistic anti-inflammatory effect, thus enhancing the therapeutic efficiency for MAFLD.

Biochemical factor TGF-β and NF-κB are closely related to liver disease. The activation of TGF-β signaling can promote the liver fibrosis (Guo *et al*., 2023). In addition, the activated hepatic stellate cells can continuously release TGF-β which causes the liver injury (Dewidar *et al*., 2019). NF-κB is activated under the stimulation of immune inflammation, thereby enhancing the expression of liver endotoxin receptors. This can produce various inflammatory cells and endotoxins, leading to the liver function damage and liver fibrosis (Luedde and Schwabe, 2011). Previous study has shown that, ATV can decrease the vascular TGF-β level (Guimarães *et al*., 2015) and inhibit NF-κB signaling for reducing the contrast media-induced pyroptosis of renal tubular epithelial cells (Yue *et al*., 2023). In our study, in two groups the TGF-β and NF-κB after treatment significantly decreased comparing with before treatment. Compared with control group, in observation group each index was further decreased. This indicates that, compared with PPC alone, PPC combined with ATV can further reduce the TGF-β and NF-κB levels, thus preventing the liver injury.

In this study, we do not use single ATV as another control. The main reasons are as follows: MAFLD is a disease closely related to liver injury due to lipid metabolism disorders. The accumulation of liver fat is only a superficial manifestation and its core is a complex liver injury. ATV is just a lipid-lowering drug, whose main function is to strongly inhibit the cholesterol synthesis in the liver, thereby significantly reducing the LDL-C in the blood. It can also reduce the TG to a certain extent (Khokhar *et al*., 2022). Simply lowering blood lipids, especially LDL-C, cannot directly solve the fundamental problem of MAFLD. ATV may indirectly reduce the liver fat content and improve liver function through the improving blood lipid-lowering, anti-inflammatory and antioxidant effects (Solmaz *et al*., 2020). Therefore, the single ATV cannot be used for treating MAFLD and it should be combined with other drugs to enhance the efficacy.

This study still has the some limitations. Firstly, this is a single-center study, with relatively small sample size, which may affect the reliability of results. In the future, the sample size should be expanded through the multi-center design, especially to provide a sufficient statistical power for further verifying the efficacy of this treatment strategy. Secondly, the patients are treated and observed for only six months. The persistence of benefit after the treatment is unknown. In next study, the long-term follow-up should be performed for confirming the persistent effect of this treatment strategy.

CONCLUSION

In conclusion, PPC combined with ATV is superior to PPC alone in improving the liver function, lipid metabolism, inflammation and liver injury without increasing the adverse reactions. It may represent a safe adjunct strategy in MAFLD management. The specific action mechanisms still need to be further clarified by in-depth research.

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Author's contributions
Chao Cheng designed the study, Liguo Wang collected and analyzed the data, and Jinju Xie wrote the manuscript the manuscript.

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Data availability statement
The data that support the findings of this study are available on request from the corresponding author.

Ethical approval
This study was approved by the ethics committee of Guang'an People's Hospital (LWSC-2023-011). Written informed consent was obtained from all participants.

Conflict of interest
The authors declare no conflict of interest.

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