Oral Ursodeoxycholic Acid Therapy Failed to Mitigate SARS-CoV-2 Omicron Variants BA.5.2 Infection

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Research Article

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Abstract

Background

Ursodeoxycholic acid (UDCA) was reported to reduce susceptibility to SARS-CoV-2 infection by downregulating farnesoid X receptor (FXR) -ACE2 signaling. However, we found a different story in real-world clinical studies.

Objectives

We attempted to verify whether UDCA can effectively prevent SARS-CoV-2 transmission or have positive therapeutic effects in a real-world clinical study.

Methods

We performed a retrospective study, collected and assessed clinical presentation and laboratory data on patients with liver diseases infected with SARS-CoV-2 Omicron sub-variant BA.5.2 who had been treated with or without UDCA.

Results

Treatment with UDCA did not prevent infection with the Omicron sub-variant BA.5.2, failed in reducing the duration of infection and hardly mitigated the severity of COVID-19. Meanwhile, the severity of liver diseases, especially TBil, ALP, γ-GT, liver cirrhosis and Child-Pugh classification, should be considered as risk factors for severe COVID-19 in chronic hepatic patients.

Conclusion

UDCA failed to show inhibitory effects against SARS-CoV-2 infection in complex clinical settings. The regulatory mechanism of the novel UDCA-FXR-ACE2 pathway needs to be further investigated in real-world clinical studies.

Introduction

With the implementation of China's 10th newly epidemic prevention policy, the SARS-CoV-2 Omicron variant is sweeping through the country with the speed of a tsunami. Recently, eye-catching research demonstrated ursodeoxycholic acid (UDCA) reduced farnesoid X receptor (FXR) signaling, downregulated Angiotensin-converting enzyme 2 (ACE2) in humans and reduced susceptibility to SARS-CoV-2 infection[1]. Meanwhile, other studies reported UDCA and its derivatives activated repair mechanism to

alleviate the damage caused by SARS-CoV-2 spike protein-ACE2 interaction [2, 3]. However, this study lacked the necessary clinical evidence. During the recent COVID-19 wave, December 2022 through January 2023, patients in our Department of Liver Diseases have been gradually infected with the Omicron sub-variant BA.5.2, including persons who were previously taking UDCA. Therefore, we initiated this study to verify whether UDCA can effectively prevent SARS-CoV-2 transmission or have positive therapeutic effects in real-world clinical situations.

Results

As shown in Table 1, all patients were infected with Omicron sub-variant BA.5.2 regardless of whether they had taken UDCA during the peak of this wave. Although patients in the UDCA group had been taking UDCA for approximately 11 days, they were infected with SARS-CoV-2. Even though they continued to take UDCA after infection, there was no significant difference in the length for the nucleic acid test of SARS-CoV-2 to turn negative compared to the control group. UDCA showed limited effects in protecting against SARS-CoV-2 infection and shortening the duration.

Table 1. Baseline characteristics of patients

Basic characteristics	All patients (n=79)	UDCA group (n=35)	Control group (n=44)	P value
Age, years	49 (35, 65)	54 (45, 65)	45 (32, 63)	0.029
Sex				0.354
Women	43 (54%)	17 (48%)	25 (57%)	
Men	36 (46%)	18 (52%)	19 (43%)	
SARS-CoV-2 vaccinations				0.641
Zero time	7 (9%)	3 (8%)	4 (9%)	
Two times	25 (32%)	13 (37%)	12 (26%)	
Three times	47 (59%)	19 (55%)	27 (61%)	
SARS-CoV-2 nucleic acid				
Positive	79 (100%)	35 (100%)	44 (100%)	
Negative	0	0	0	
Signs and symptoms				
Fever	75 (95%)	34 (97%)	41 (93%)	0.428
Cough	72 (91%)	32 (91%)	40 (91%)	0.936
Expectoration	11 (14%)	6 (17%)	5 (11%)	0.464
Pharyngodynia	62 (78%)	26 (74%)	36 (82%)	0.402
Chest discomfort	8 (10%)	3 (9%)	5 (11%)	0.685
Muscular soreness	63 (80%)	24 (69%)	39 (89%)	0.028
Hypogeusia	0	0	0	-
Hyposmia	0	0	0	-
Laboratory findings				
Blood routine				

examination				
White blood cell count, ×10 /L	4.9 (3.7, 5.7)	5.2 (4.0, 6.3)	4.7 (3.6, 5.8)	0.098
Neutrophil count, ×10 /L	3.1 (2.1, 3.6)	3.2 (2.3, 3.7)	3.0 (2.0, 3.5)	0.129
Lymphocyte count, ×10 /L	1.3 (0.9, 1.6)	1.2 (0.9, 1.7)	1.3 (0.9, 1.7)	0.953
PLT, ×10 /L	129 (67, 164)	140 (63, 180)	121 (67, 145)	0.450
Liver function				
ALB, g/L	33.3 (28.3, 38.2)	34.2 (28, 38.8)	32.5 (28.0, 37.7)	0.225
TBil, μmol/L	73.6 (18.6, 75.7)	134.7 (43.3, 174.6)	25.0 (14.4, 29.1)	<0.001
ALT, U/L	133 (16.4, 69.2)	238.3 (16.4, 76.9)	49.2 (16.4, 57.5)	0.487
AST, U/L	136.9 (19.6, 49.3)	268.5 (19.5, 110.6)	38.3 (20.4, 42.2)	0.444
ALP, U/L	59.4 (17.3, 83.7)	84.8 (34.1, 119.4)	39.2 (11.8, 57.9)	0.001
γ-GT, U/L	65.1 (12.4, 72.7)	93.6 (23.7, 113.8)	42.4 (10.0, 39.3)	<0.001
Liver cirrhosis	24 (30%)	15 (43%)	9 (20%)	0.033
Child-Pugh				<0.001
A	62 (78%)	21 (60%)	41 (93%)	
B	11 (14%)	8 (23%)	3 (7%)	
C	6 (8%)	6 (17%)	0	
D-dimer, mg/L	1.3 (0.3, 1.5)	2.0 (0.3, 2.5)	0.8 (0.3, 0.9)	0.175

Classification of COVID-19				0.001
Asymptomatic carriers	1 (1.3%)	1 (2.9%)	0	
Mild	56 (70.9%)	16 (45.7%)	40 (91%)	
Moderate	20 (25.3%)	16 (45.7%)	4 (9%)	
Severe	2 (2.5%)	2 (5.7%)	0	
UDCA	35 (44.3%)	35 (100%)		
Treatment time before SARS-CoV-2 positive, Day	-	11 (5, 23)	-	
Duration from positive to negative SARS-CoV-2, Day	6 (4, 7)	6 (4, 9)	6 (5, 7)	0.972

There are details to be clarified. In the UDCA group, almost half were mild or moderate COVID-19, only one was asymptomatic and two were severe. In the control group, 91 percent were mild, and 9 percent were moderate cases. This phenomenon suggested that UDCA treatment did not prevent or mitigate the severity of COVID-19. Of course, there were other important factors needed to be considered. Further analysis showed that patients in the UDCA group had obvious higher level of total bilirubin (TBil), alkaline phosphatase (ALP) and γ-glutaminase (γ-GT) ($P \leq 0.001$), got severe liver cirrhosis than in the control group ($P = 0.033$). In Child-Pugh scale, there were 60% grade A, 23% grade B and 17% grade C in the UDCA group while 93% grade A and 7% grade B in the control group ($p < 0.001$). These results demonstrated that the severity of COVID-19 was significantly related to the severity of liver disease, which probably counteracted the efficacy of UDCA in treating COVID-19.

By the way, there was no difference between the groups in terms of sex, SARS-CoV-2 vaccination injection, signs and symptoms, in counts of white blood cells (WBC), neutrophils, lymphocytes, platelet (PLT), albumin (Alb), alanine transaminase (ALT), aspartate aminotransferase (AST), and D-dimer.

Discussion

ACE2 is a highly affinitive host receptor for SARS-CoV-2, functions as a key receptor-mediated internalization of virus and plays protective component during severe acute lung injury (4). Targeting ACE2 is emerging as a novel approach to prevent SARS-CoV-2 infection and brings a higher barrier to the emergence of resistance. Recently, Brevini T *et al.* identified the bile acid receptor farnesoid X receptor (FXR) as a direct regulator of ACE2 transcription, the use of UDCA or compound z-guggulsterone (ZGG) could reduce FXR signaling, downregulate ACE2 expression and limit SARS-CoV-2 infection [1]. The study

identified UDCA as a novel potential clinical application for the prevention of SARS-CoV-2 infection or its use in the treatment of COVID-19. However, whether this new regulatory pathway has a clinical effect is still questionable and needs to be validated in the real-world clinical studies.

To clarify the role of UDCA in the clinical prevention and treatment of COVID-19, we conducted this cohort. We found that UDCA neither prevent infection with Omicron sub-variant BA.5.2 nor shorten the duration of infection. We also found that UDCA treatment failed to prevent or mitigate the severity of COVID-19, although we do not know if the severity of liver diseases impacted the effects of UDCA in treating COVID-19. This is not to deny the inhibitory efforts of UDCA in SARS-CoV-2 infection, but rather to tell that the clinical problem is far more complex than hypothesis or experiments, and that some other factors may dominate the course of the COVID-19 in the real world. In our opinion, some reasons are under consideration: (1) FXR is widely distributed in the liver, gallbladder, intestine, kidney, and lungs, with a broad variety of functions, including bile acid and lipid metabolism, glucose homeostasis, fibrosis and inflammation [5, 6]. There should be multiple pathways in modulating FXR and UDCA is likely one of them in modulating the FXR-ACE2 pathway. (2) ACE2 is widely expressed in renal, cardiovascular, and gastrointestinal systems, type I and type II alveolar epithelial cells; ACE2 is regulated by multiple signaling pathways and is not limited to FXR [4, 7]; Competitive inhibition affects the regulation effort of the UDCA - FXR-ACE2 pathway. (3) Liver damage has been confirmed to associated with severe COVID-19, particularly decompensated cirrhosis is supposed as a risk factor for severe COVID-19 and death. We demonstrated the severity of COVID-19 in this cohort was closely associated with the severity of hepatic illness, especially the TBil, ALP, γ-GT, liver cirrhosis and Child-Pugh classification, which may outweigh the positive effects of the UDCA-FXR-ACE2 pathway[8–10].

In summary, our findings demonstrated that UDCA failed to prevent SARS-COV-2 infection and had no appreciable therapeutic effect in shortening the course of COVID-19 or reduce the severity of the disease in this real-world clinical study. Many factors are likely to affect this novel UDCA-FXR-ACE2 pathway, and more in-depth mechanistic studies and clinical validation are needed in future.

Material And Methods

Patients

Seventy-nine patients from the Liver Disease Inpatient Unit of the Second Affiliated Hospital of Nanchang University were included in the evaluation from December 10, 2022, to January 10, 2023. Thirty-five patients of them had been taking UDCA (Approval number: H20181059; 250 mg each time, three times a day) were selected by adopting a simple random sampling method for investigation, and no limit for the treatment time before. The rest forty-four patients were not treated with UDCA were randomly selected as controls. Clinical manifestations, including febrile symptoms, liver cirrhosis, Child-Pugh scale, classification of COVID-19 severity, laboratory tests, SARS-CoV-2 nucleic acid tests, SARS-CoV-2 vaccination, and time of SARS-CoV-2 turn negative were taken into consideration for statistical analysis. All medical laboratory data were generated from the Department of Clinical Laboratory of the Second

Affiliated Hospital of Nanchang University. The SARS-CoV-2 Omicron sub-variant was identified by Nanchang Center for Disease Control and Prevention (CDC).

Statistical analysis

Categorical data were summarized as frequencies (%) and compared by χ^2 test or Fisher's exact test when applicable. Continuous variables were described as median and interquartile ranges (IQR) values and compared with the Mann-Whitney U test. All analyses were performed with the SPSS 25.0 software (IBM, Chicago). Differences with $p < 0.05$ between group means were considered statistically significant.

Declarations

Availability of data and materials

The data that support the findings of this study are available from the corresponding author Sun-Shui Lin, upon reasonable request.

Declaration of competing interest

The authors have no competing interests to declare.

Fundings

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Ethical approval

This study was approved by the Ethics Committee of the Second Affiliated Hospital of Nanchang University (Ref 2022-115).

Author Contributions

DS Y, ZY S, and Y L collected the clinical data. WN X, GJ Z, and K S provided clinical cases. DS Y and YH L performed the statistical analysis. DS Y, YH L, and SL S designed the study and drafted the manuscript.

References

1. Anderson KM, Gayer CP. The Pathophysiology of Farnesoid X Receptor (FXR) in the GI Tract: Inflammation, Barrier Function and Innate Immunity. Cells 2021;10(11). doi: 10.3390/cells10113206.
2. Ashraf UM, Abokor AA, Edwards JM. SARS-CoV-2, ACE2 expression, and systemic organ invasion. 2021;53(2):51–60. doi: 10.1152/physiolgenomics.00087.2020.

3. Brevini T, Maes M. FXR inhibition may protect from SARS-CoV-2 infection by reducing ACE2. 2022. doi: 10.1038/s41586-022-05594-0.
4. Cabibbo G, Rizzo GEM. SARS-CoV-2 infection in patients with a normal or abnormal liver. 2021;28(1):4–11. doi: 10.1111/jvh.13440.
5. Dufour JF, Marjot T. COVID-19 and liver disease. 2022;71(11):2350–62. doi: 10.1136/gutjnl-2021-326792.
6. Fiorillo B, Marchianò S, Moraca F. Discovery of Bile Acid Derivatives as Potent ACE2 Activators by Virtual Screening and Essential Dynamics. 2022;62(1):196–209. doi: 10.1021/acs.jcim.1c01126.
7. Sun L, Cai J, Gonzalez FJ. The role of farnesoid X receptor in metabolic diseases, and gastrointestinal and liver cancer. 2021;18(5):335–47 doi: 10.1038/s41575-020-00404-2.
8. Sungnak W, Huang N, Bécavin C. SARS-CoV-2 entry factors are highly expressed in nasal epithelial cells together with innate immune genes. 2020;26(5):681–87. doi: 10.1038/s41591-020-0868-6.
9. Thuy PX, Bao TDD, Moon EY. Ursodeoxycholic acid ameliorates cell migration retarded by the SARS-CoV-2 spike protein in BEAS-2B human bronchial epithelial cells. Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie 2022;150:113021. doi: 10.1016/j.biopha.2022.113021.
10. Wanner N, Andrieux G. Molecular consequences of SARS-CoV-2 liver tropism. 2022;4(3):310–19. doi: 10.1038/s42255-022-00552-6.