The effects of Paxlovid on glycolipid immunometabolism in the patients with non-severe SARS-CoV-2 infection

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Abstract

A wave of SARS-CoV-2 infection speedily emerged in Shanghai, China, since late February 2022. Paxlovid is a therapeutic hybrid of different compounds and a novel SARS-CoV-2 protease inhibitor by blocking an enzyme required for viral protein synthesis. It could reduce the risk of hospitalization or death by 89% as well as being benefit for immunocompromised and severe COVID-19 patients. Our registry study indicated that the days of viral elimination and inflammation factors, such as IL-6, IL-10 and interferon-α levels could be lowered by paxlovid. Days of viral elimination may be associated with fasting blood glucose, NK cells count, interferon-α levels. Lipids profiles should be monitored before and after treatment of paxlovid, especially for those who have uncontrolled lipid disorder.

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Keywords: Paxlovid; glycolipid; immunometabolism; SARS-CoV-2

What is already known about this subject?

Paxlovid could reduce the risk of hospitalization or death by 89% as well as being benefit for immunocompromised and severe COVID-19 patients.

What this study adds?

1. The days of viral elimination and inflammation factors, such as IL-6, IL-10 and interferon-α levels could be lowered by paxlovid.
2. Days of viral elimination may be associated with fasting blood glucose, NK cells count, interferon-α levels.
3. Lipids profiles should be monitored before and after treatment of paxlovid, especially for those who have uncontrolled lipid disorder.

Abstract

A wave of SARS-CoV-2 infection speedily emerged in Shanghai, China, since late February 2022. Paxlovid is a therapeutic hybrid of different compounds and a novel SARS-CoV-2 protease inhibitor by blocking an enzyme required for viral protein synthesis. It could reduce the risk of hospitalization or death by 89% as well as being benefit for immunocompromised and severe COVID-19 patients. Our registry study indicated that the days of viral elimination and inflammation factors, such as IL-6, IL-10 and interferon-α levels could be lowered by paxlovid. Days of viral elimination may be associated with fasting blood glucose, NK cells count, interferon-α levels. Lipids profiles should be monitored before and after treatment of paxlovid, especially for those who have uncontrolled lipid disorder.

Introduction

The pandemic arising in the rapid spread of coronavirus disease 2019 (COVID-19) has influenced unparalleled public health emergency strategies from countries around the world (1). A wave of SARS-CoV-2 infection speedily emerged in Shanghai, China, since late February 2022. The comprehensive pandemic control strategies in Shanghai are therefore actually to reduce the number of people infected and to provide early diagnosis and appropriate treatment for severe COVID-19 (2).

Paxlovid is a therapeutic hybrid of different compounds and a novel SARS-CoV-2 protease inhibitor by blocking an enzyme required for viral protein synthesis. Recent studies indicated that it could reduce the risk of hospitalization or death by 89% as well as being benefit for immunocompromised and severe COVID-19 patients (3,4).

A meta-analysis indicated that paxlovid did not neither cause the adverse events nor aggravate the occurrence of adverse events. Its most common adverse events include nausea, diarrhea, headache, runny nose and muscle pain (5). Many studies also indicated that hyperglycaemia in patients with COVID-19 is a strong risk factor of worsening its prognosis and increasing the possibility of mortality (6,7). However, whether paxlovid affects the glycolipid immunometabolism in non-severe COVID-19 patients remains unknown.

Methods

A registry study to estimate the effects of paxlovid on glycolipid and immunometabolism was launched in South Campus, Renji Hospital from May 10, 2022 to June 7, 2022, with ethics board approval and written informed consents obtained from all patients. The study was open-labelled and observational in Shanghai, China (ChiCTR2200059743). The study protocol was approved by the ethics committees of Renji Hospital (KY2022-081-A). All the patients enrolled in this study following the Chinese guidelines (trial version 9 for COVID-19) (8). They were all treated by paxlovid for five days (day1-day5). Routine clinical and biochemical data collected from May 10, 2022 to June 7, 2022 and used in this study were their medical history, symptoms, vaccination status, age, sex, blood pressure, body mass index (BMI), liver function, kidney function, HbA1c, fasting blood glucose, total cholesterol, HDL cholesterol, non- HDL cholesterol, LDL cholesterol, triglycerides, inflammation factors as well as immunometabolism, such as B lymphocytes, T lymphocytes, Th lymphocytes, Ts lymphocytes. All the same glycolipid immunometabolism parameters were gained again at day 6 after paxlovid treatment. The Covid-19 virus were tested every day until both negative for ORF1ab and N genes (Ct value [?]35 by real-time quantitative PCR) in two consecutive days.

Results

Totally, 64 hospitalized patients with non-severe SARS-CoV-2, with a mean age of 37 years, a moderate

vaccination rate (65.63%) and a low comorbidity rate (4.69% for diabetes, 6.25% for hypertension, 3.13% for cancer) were treated by paxlovid (Table S1). Most enrolled patients with non-severe Covid-19 had different symptoms (20.31% for fever, 20.31% for cough, dizzy for 7.81%, myalgia for 6.25% et al, Table S1). Our result showed that the mean days of viral elimination treated by paxlovid was 7.90 ± 2.12, which was consistent with Shuang Ye et al'results (3). We also found that fasting blood glucose, serum high-density lipoprotein (HDL), interleukin-6 (IL-6), interleukin-10 (IL-10) and interferon-α were decreased after treatment (all$p$ <0.05, Table 1, Figure 1). At the same time, serum triglycerides, non-HDL levels and lymphocyte counts, such as B lymphocytes, T lymphocytes, Th lymphocytes, Ts lymphocytes as well as NK cells were statistically increased after 5 days treatment (all$p$ <0.05, Table 1, Figure 1).

Next, Cox proportional hazard regression model was used to assess the association between days of viral elimination and clinical parameters including the glycolipid immunometabolism factors, and to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs). We found that after adjusting for potential confounders, fasting blood glucose, NK cells count, interferon-α levels before paxlovid treatment and vaccine were related with days of viral elimination in all participants (Figure 2).

Discussion

This observational study indicated the days of viral elimination and inflammation factors, such as IL-6, IL-10 and interferon-α levels could be lowered by paxlovid. Days of viral elimination may be associated with fasting blood glucose, NK cells count, interferon-α levels and vaccine. Lipids profiles should be monitored before and after treatment of paxlovid, especially for those who have uncontrolled lipid disorder.

Compared with placebo, early initiation of Paxlvoid can significantly reduce the risk of hospitalization or death in mild-to-moderate cases compared with placebo (9). Paxlovid is recommended for patients with suitable indications (10), to prevent the disease progression as soon as possible by early implementation of antiviral therapy to inhibit viral replication. However, there are no clinical data on its implication in glycolipid and immunometabolism in adult.

A paxlovid registry study showed that paxlovid prescription within 5 days of diagnosis had a faster clearance of viral load measured by ORF1ab viral gene replication and a shorter time to viral elimination in immunocompromised patients. They also indicated that the linear correlation existed between timing of paxlovid initiation and viral elimination, which is consistent with our results (3).

Growing evidence indicates that SARS-CoV-2 induces mitochondrial dysfunction in immune cells. Acute SARS-CoV-2 infection resulted in rapid mitochondrial dysfunction in both CD4 and CD8 T cells, which compromised "T cell" functionality contributing to suppressed "T cell" immune responses to viral infection (11). Patients with SARS-CoV-2 infection displayed depolarized mitochondria and abnormal mitochondrial ultrastructure in monocytes, which was correlated with enhanced inflammatory responses (12). Our study further indicated that inflammation status sharply decreased and lymphocyte counts statistically increased in COVID-19 patients treated by paxlovid. It may be related to the compromised mitochondrial respiration and increased HIF-1α expression in alveolar macrophages (AMs) after viral infection in vivo (13), and the inhibition of pyruvate metabolism by mitochondrial pyruvate carrier inhibitor (MSDC) enhanced mitochondrial oxidative phosphorylation (OXPHOS) and fitness, which was associated with the reduction of proinflammatory cytokines (14). Thus, paxlovid may promote mitochondrial metabolic fitness and could be a novel therapeutic avenue for COVID-19.

Supplementary information

Table S1. Baseline characteristics of participants in a Paxlovid register study

Author contributions: All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Jiang Yue and Xu Zhang. The first draft of the manuscript was written by Jiang Yue,Yuan Gao as well as Jing Ma and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data Availability: The datasets will be available from the corresponding author on reasonable request.

Declarations

Competing interests

All the authors have declared no conflicts of interest.

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Table 1. Changes in clinical, glycolipid immunometabolism parameters treated by Paxlovid among non-severe COVID-19 patients in Renji hospital

Indicators	Prior treatment	Post treatment	p value
CRP (mg/L)	4.95 ± 6.31	1.99 ± 4.32	0.0002
SAA (mg/L)	35.64 ± 75.93	14.01 ± 47.17	0.0040
WBC ($\times 10^9$/L)	5.13 ± 1.71	5.44 ± 1.37	0.1855
Neutrophil cells ($\times 10^9$/L)	3.36 ± 1.71	3.08 ± 1.19	0.1913
Lymphocytes ($\times 10^9$/L)	1.24 ± 0.61	1.98 ± 0.55	0.0000

Indicators	**Prior treatment**	**Post treatment**	**p value**
Hb (g/L)	130.56 ± 13.66	128.93 ± 21.48	0.5512
IL-1β (pg/ml)	1.17 ± 0.84	1.29 ± 0.59	0.3965
IL-2 (pg/ml)	0.95 ± 0.74	0.96 ± 0.48	0.9052
IL-4 (pg/ml)	1.47 ± 0.97	1.64 ± 0.48	0.2225
IL-5 (pg/ml)	0.75 ± 0.40	0.85 ± 0.48	0.2279
IL-6 (pg/ml)	10.51 ± 15.47	2.45 ± 2.49	0.0083
IL-8 (pg/ml)	4.01 ± 2.85	3.36 ± 3.53	0.2496
IL-10 (pg/ml)	3.31 ± 1.77	2.43 ± 1.25	0.0018
IIL-12p70(pg/ml)	1.21 ± 0.96	1.28 ± 1.02	0.6859
IL-17A (pg/ml)	2.80 ± 2.30	2.54 ± 1.65	0.4863
TNF-α (pg/ml)	1.96 ± 1.32	2.22 ± 0.89	0.2145
Interferon α (pg/ml)	27.04 ±71.09	1.62 ± 2.45	0.0068
Interferon γ (pg/ml)	1.53 ± 0.94	1.35 ± 0.45	0.1635
B lymphocytes (CD3-CD19+) (%)	12.50 ± 6.86	13.34 ± 5.50	0.1808
T lymphocytes (CD3+) (%)	66.24 ± 9.84	70.91 ± 7.12	0.0000
Th lymphocytes (CD3+CD4+) (%)	36.48 ± 7.75	39.28 ± 6.73	0.0007
Ts lymphocytes (CD3+CD8+) (%)	25.69 ± 7.71	27.68 ± 7.28	0.0001
CD4/CD8 ratio	1.56 ± 0.56	1.55 ± 0.56	0.7654
NK cells (CD3-CD16+CD56+) (%)	17.86 ± 9.72	13.96 ± 6.95	0.0001
Absolute value of lymphocytes ($\times 10^9$/L)	1.28 ± 0.59	1.99 ± 0.53	0.0000
Absolute value of B lymphocytes (cells/uL)	163.40 ± 128.60	268.08 ± 161.03	0.0000
Absolute value of T lymphocytes (cells/uL)	876.63 ± 468.61	1408.11 ± 394.40	0.0000
Absolute value of Th lymphocytes (cells/uL)	485.64 ± 269.24	772.37 ± 218.19	0.0000
Absolute value of Ts lymphocytes (cells/uL)	334.58 ± 186.42	553.59 ± 212.39	0.0000
Absolute value of NK cells (cells/uL)	200.16 ± 111.93	276.98 ± 161.65	0.0003
ALT (IU/L)	24.35 ± 25.95	23.56 ± 20.68	0.7352
AST (U/L)	23.81 ± 10.99	21.56 ± 12.21	0.2298
LDH (U/L)	186.01 ± 37.86	170.23 ± 33.17	0.0021
ALP (U/L)	66.47 ± 18.84	61.48 ± 17.75	0.0093
γ-GT (U/L)	25.31 ± 31.80	28.89 ± 33.23	0.1597
TBil (umol/L)	9.92 ± 3.73	9.44 ± 2.98	0.4612
ChE (KU/L)	7.58 ± 1.64	8.00 ± 1.64	0.0010
Urea (mmol/L)	4.95 ± 7.10	4.25 ± 1.17	0.4467
Creatinine (umol/L)	64.30 ± 16.03	60.68 ± 12.63	0.0051
eGFR-EPI Cr (ml/min)	113.41 ± 21.96	113.79 ± 12.21	0.8539
UA (umol/L)	294.20 ± 80.97	296.46 ± 75.38	0.9977
TG (mmol/L)	1.41 ± 0.94	2.31 ± 1.56	0.0000
TC (mmol/L)	4.64 ± 0.81	4.78 ± 0.72	0.1062
HDL-C (mmol/L)	1.29 ± 0.28	1.11 ± 0.19	0.0000
LDL-C (mmol/L)	2.85 ± 0.64	3.03 ± 0.55	0.0036
non- HDL-C (mmol/L)	3.35 ± 0.81	3.67 ± 0.71	0.0003
Glucose (mmol/L)	5.90 ± 1.69	5.08 ± 0.76	0.0010
HbA1c (%)	5.50 ± 0.63	5.55 ± 0.39	0.8701

Data was expressed by mean ± SD. CRP:C-reactive protein; SAA:Serum amyloid A; WBC:White blood cell; Hb:Hemoglobin; PLT:Blood platelet; IL-1β:Interleukin-1β· IL-2:Interleukin-2; IL-4:Interleukin-4; IL-5:Interleukin-5; IL-6:Interleukin-6; IL-8:Interleukin-8; IL-10:Interleukin-10; IL-12p70:Interleukin-12p70; IL-17A:Interleukin-17A; TNF-α:Tumor necrosis factor-alpha-α· NK cells:Natural killer cells;ALT: Alanine aminotransferase; AST: Aspartate amino transferase; LDH: Lactic dehydrogenase; ALP: Al-

kaline phosphatase; γ-GT: γ-glutamyl transferase; TBil: Total bilirubin; ChE:Cholinesterase; UA:Uric acid; TG:Triglyceride; TC: Total cholesterol; HDL-C: High-density lipoprotein cholesterol;LDL-C:Low-density lipoprotein cholesterol; non- HDL-C:Non-high-density lipoprotein cholesterol;HbA1c:Glycosylated hemoglobin A1C

Figure legend

Figure 1 Significant Changes in glycolipid immunometabolism parameters treated by Paxlovid among non-severe COVID-19 patients in Renji hospital.

Figure 2 Cox proportional hazards regression for days of viral elimination* and clinical glycolipid immunometabolism factors among non-severe COVID-19 patients in Renji hospital.

* Viral elimination was defined as both negative for ORF1ab and N genes (Ct value [?]35 by real-time PCR) in two consecutive days. The second negative day was calculated as the time point of viral elimination. CI: confidence interval; IL-6: Interleukin-6; IL-10: Interleukin-10; TG:Triglyceride; TC: Total cholesterol; HDL-C: High-density lipoprotein cholesterol;LDL-C:Low-density lipoprotein cholesterol; non- HDL-C:Non-high-density lipoprotein cholesterol;