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Safety and efficacy of oral lopinavir/ritonavir in pediatric patients with coronavirus disease: a nationwide comparative analysis

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Abstract. – OBJECTIVE: Because of the limited treatment options available, oral lopinavir/ritonavir (LPR) was used for treating coronavirus disease (COVID-19) in pediatric patients. This study aimed to assess the efficacy and safety of LPR in COVID-19 pediatric patients with mild symptoms.

PATIENTS AND METHODS: This retrospective multicenter analysis included hospitalized children with mild COVID-19 who received LPR at one of 13 hospitals in China from January 1, 2020, to June 1, 2020. Patients treated with LPR were matched with patients not treated with LPR (1:4) according to age, sex, and length of symptom onset and hospitalization. Descriptive statistics and non-parametric tests were applied to compare differences between groups. Kaplan-Meier probability curves and Cox regression models were used to analyze nasal swab turning negative time (recovery time) and hospital discharge days.

RESULTS: In total, 23 patients treated with LPR were matched with 92 untreated controls. The median age of patients was 6 years, and 56.52% of them were male. All patients were discharged from the hospital after being cured. The treatment group had a longer nasal swab turning negative time (hazard ratio [HR] 5.33; 95% CI: 1.94-14.67; $p = 0.001$) than the control group. LPR treatment was also associated with a longer hospitalization time (HR 2.01; 95% CI: 1.24-3.29; $p = 0.005$). After adjusting for the influence of LPR treatment, adverse drug reaction events were associated with a longer nasopharyngeal swab negative time (HR 4.67; 95% CI 1.35-16.11; $p = 0.015$).

CONCLUSIONS: For children with mild COVID-19, LPR is inferior to conventional treatment in reducing virus shedding time and hospitalization duration and is associated with increased adverse reactions.

Key Words:
Lopinavir/Ritonavir, COVID-19, Pediatric.

Introduction

Lopinavir/ritonavir (LPR) is an inhibitor of human immunodeficiency virus (HIV) protease and

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has been approved for treating HIV-1 infection. During the early stages of the coronavirus disease (COVID-19) pandemic in China, LPR was also recommended for the treatment of COVID-19, largely because it had shown some success against severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), and other treatment options were limited[1,2]. A recent trial[3] has provided evidence that the use of interferon (IFN)-β-1b + ribavirin + LPR triple therapy could accelerate the recovery of patients with mild-to-moderate COVID-19. The combination of LPR and ribavirin was previously shown to have a beneficial effect on SARS[4]. Moreover, LPR can increase the efficacy of IFNβ-1b against MERS[5,6]. *In vitro* and *in vivo* evidence indicating that LPR can inhibit severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) replication has recently been provided[7,8]. Thus, LPR may be useful clinically to treat patients with COVID-19.

However, the efficacy of LPR for the treatment of COVID-19 is controversial[9,10]. In a phase II clinical trial, the recovery time (from the start of treatment until two consecutive negative nucleic acid tests) was only 7 days with triple therapy, which was significantly lower than the 12 days in the LPR alone group. Nonetheless, the recovery time with LPR was shorter than that with placebo (12 *vs.* 15 days)[11]. In addition, a previous trial reported that LPR was inferior to arbidol in treating critically ill patients[12,13]. Therefore, the effectiveness of LPR needs to be clarified in controlled clinical trials.

Jiehao et al[14] found that most children with COVID-19 were asymptomatic or showed mild symptoms. Furthermore, it has been suggested that infected children should not take LPR or other antiviral medicines, as adverse drug reactions are even more prevalent in children. Indeed, Kredo et al[15] showed that the occurrence of adverse reactions with LPR was as high as 30%. In addition, the withdrawal rate due to LPR toxicity was as high as 9%[16]. Nonetheless, various drugs, including LPR, were prescribed for pediatric patients with COVID-19 during the early days of the outbreak in China. Thus, here, we conducted a national multicenter retrospective analysis to assess the efficacy of LPR in these children for the first time. As it would be difficult to obtain similar clinical trial data in the future for ethical reasons, it is important that this data set from the early days of COVID-19 is analyzed to evaluate the efficacy of LPR in children.

Patients and Methods

Patient Enrollment

This retrospective, multicenter analysis included all patients consecutively admitted to 13 hospitals in China with a diagnosis of mild COVID-19 from January 1, 2020, until June 1, 2020. The 13 tertiary hospitals included those in Shanghai (including 2 hospitals), Hangzhou, Wenzhou, Wuhan, Guangzhou (including 2 hospitals), Shenzhen, Guizhou, Qingdao, Henan, Yunnan and Hefei city in China. COVID-19 in pediatric patients was diagnosed based on the guidelines issued by the National Health Commission of the People's Republic of China. This study was approved by the Ethics Committee of each individual children's hospital (No. 2020-187) and was conducted in accordance with the Declaration of Helsinki.

Medication Procedures

According to an approved local protocol for off-label LPR administration, the following patients were enrolled: subjects under 18 years, with SARS-CoV-2 infection (diagnosed using real-time polymerase chain reaction on a rhino-pharyngeal swab), and showing mild clinical symptoms and signs (according to the Chinese Guidelines for the management of COVID-19). A *mild* case was defined as the presence of fever and respiratory tract infection (among other symptoms), but no signs of pneumonia in an imaging test.

All patients received LPR treatment for at least 5 days. The dosage of LPR (Abbvie, North Chicago, IL, USA) in children was adjusted according to their body weight: 12 mg/kg for 7-15 kg; 10 mg/kg for 15-40 kg; maximum dose 400/100 mg; twice a day. All patients or guardians of patients provided written informed consent for the compassionate use of LPR in local hospitals. All medicines used by patients during hospitalization were provided free of charge and were fully covered by the National Medical Insurance.

Statistical Analysis

Descriptive statistics (median and interquartile range [IQR] for continuous variables, absolute and relative [%] values for categorical variables) and non-parametric tests (Mann-Whitney U for continuous and chi-square test for categorical variables) were used to compare groups. Kaplan-Meier's probability curves and Cox regression models for virus clearance time and hospital discharge days were also generated. Two-tailed

p-values were calculated, and a *p*-value < 0.05 was used to assess statistical significance. Data management and analysis were performed using SPSS version 25 (IBM Corp. IBM SPSS Statistics for Windows, Armonk, NY, USA).

Results

In total, 31 patients who started LPR therapy were identified in our multicenter study. Eight patients were excluded because they did not meet the inclusion criteria. The process of patient selection and details of matching criteria are shown in Figure 1. Patients who received standard therapy were matched (4:1) with those treated with LPR according to age, sex, and length of time between symptom onset and hospital admittance. Standard treatment means that the child only receives symptomatic treatment, such as cough syrup and interferon atomization treatment. Of the 204 eligible patients who received standard therapy, 92 patients with defined criteria were matched. Table I shows the baseline demographic and clinical features of LPR-treated patients and matched controls. No significant differences were observed between the two cohorts regarding age, weight, or other physiological parameters (due to the nature of the matched design). Although the children in the control group did not receive any other oral antiviral medications, they all received aerosol inhalation therapy with interferon-α2b. All patients were discharged from the hospital after successful treatment.

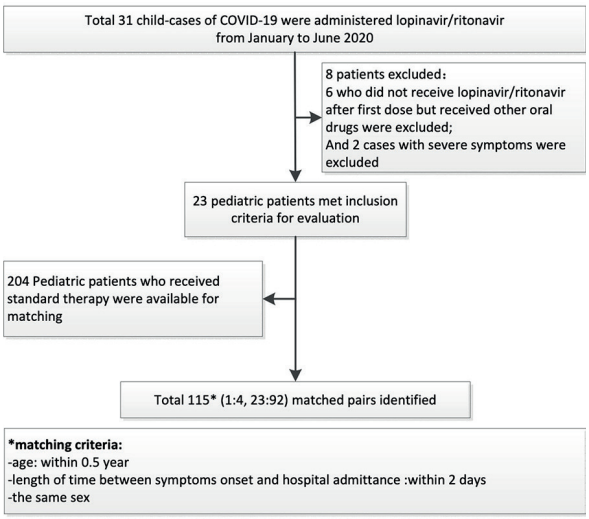

Figure 1. Flow diagram of patient selection process and matching criteria.

LPR did not seem to have any beneficial effects in reducing SARS-CoV-2 shedding time and total

Table I. Baseline parameters and treatment outcomes.

Variable	Control group (n = 92)	LPR group (n = 23)	*p*-value
Age (y), median (Q1, Q3)	8.85 (2.00,11.60)	8.66 (2.44,11.90)	.677
Weight (kg), median (Q1, Q3)	26.00 (11.25,50.65)	27.50 (10.75,46.50)	.893
Male sex, n (%)	52 (56.52%)	13 (56.52%)	1.00
[a]White blood cell count, × 10^9 per L	6.64 (5.75,8.80)	5.35 (4.48,6.58)	.392
[a]Lymphocyte count %	46.10 (34.30,58.30)	43.00 (39.80,48.88)	.539
Hemoglobin, g/L	130.00 (119.00,138.00)	137.50 (127.75,143.75)	.826
Platelet count,× 10^9 per L	233.50 (191.00,286.00)	288.00 (207.75,335.25)	.429
AST (15-40) IU/L	21.50 (16.50,30.75)	27.75 (20.13,39.13)	.533
ALT (9-50) IU/L	18.00 (11.00,47.00)	16.00 (9.58,18.48)	.218
[a]Creatinine, μmol/L	39.88 (27.15,60.05)	47.00 (36.25,50.25)	.994
[a]LDH, IU/L	215.50 (148.75,254.25)	222.50 (200.00,282.50)	.426
[b]ESR, mm/h	10.00 (7.00,11.10)	8.00 (6.00,19.50)	.981
Prothrombin time, (11-14.5)s	13.70 (11.33,15.53)	13.60 (13.30,13.70)	.273
APTT, (26-40) s	32.95 (25.60,38.60)	33.00 (31.90,36.20)	.460
D-dimer, (0-0.5) μg/mL	0.29 (0.11,0.55)	0.58 (0.48,0.68)	.773
Time to RT-PCR negative swab (d) median (Q1, Q3)	4.34 (1.50,5.50)	8.39 (4.50,12.00)	.000*
Duration of hospital stay (d), median (Q1, Q3)	8.05 (4.00,12.00)	12.21 (10.00,14.00)	.000*

Abbreviations: LPR, lopinavir/ritonavir; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; ESR, erythrocyte sedimentation rate; APTT, activated partial thromboplastin time; IQR, interquartile range. Data are presented as medians (interquartile ranges) or n (%). *$p < 0.05$ indicates a significant difference between groups. [a]Varied with age. White blood cells (×10^9/L): < 28 days, 10.0-24.0; 29 days-3 years, 8.0-12.0; > 3 years, 4.0-10.0; Lymphocytes (%): < 28 days, 30-40; 29 days-3 years, 50-70; > 3 years, 30-40; Hemoglobin (×109/L): < 28 days, 10.0-24.0; 29 days-3 years, 8.0-12.0; > 3 years, 4.0-10.0; LDH: 0-29 days, 290-2000; 30 days-23 months, 180-430; > 23 months, 110-290. [b]Varied with age and sex. Creatinine (μmol/L): ≤ 2 months, 22-90; 2 months-3 years, 11-34; 3-15 years, 21-65; > 15 years, male: 64-104, female: 49-90; ESR (mm/h): male: 0-21, female: 0-26.

hospitalization duration. In the overall survival analysis, the LPR group showed a disadvantage compared with the control group with a hazard ratio (HR) of 5.33 (95% CI: 1.94-14.67; $p = 0.001$) according to the Cox regression model. As shown in Figure 2A, the mean nasopharyngeal swab negative time (recovery time) was consistently lower in the LPR group at all time points, with a mean difference of 4 days. In addition, adverse drug reactions were associated with a longer nasopharyngeal swab negative time (HR, 4.67; 95% CI, 1.35-16.11; $p = 0.015$). In the overall hospital discharge time analysis, LPR use was associated with a longer (compared to no LPR use) overall discharge time (HR 2.01; 95% CI: 1.24-3.29; $p = 0.005$) according to the Cox regression model (Figure 2B). Sixteen cases with gastrointestinal complications were documented in 23 patients (69.6%) after LPR administration. The side effects were generally mild and self-limiting.

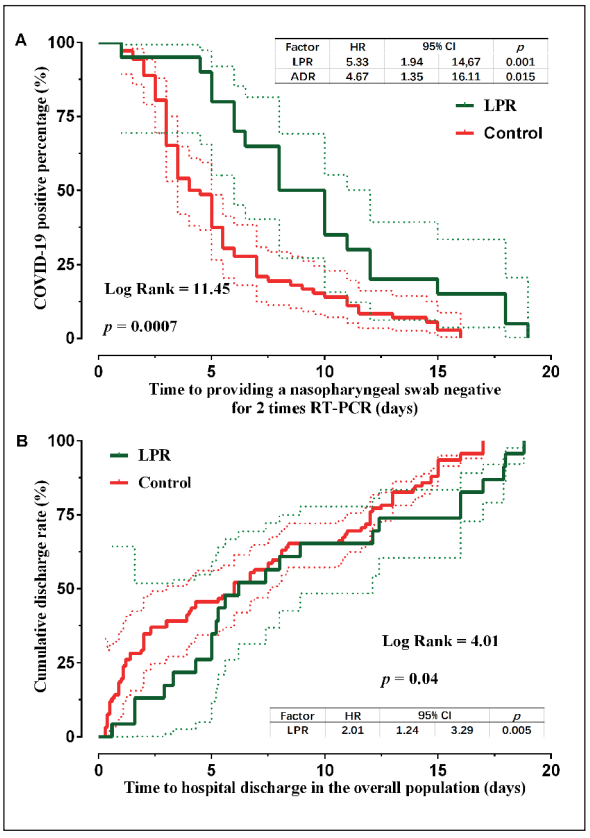

Figure 2. Kaplan-Meier plot of virologic viral clearance days in patients treated with oral LPR therapy (*green line*) and those treated with the standard treatment (*red line*). The dotted lines (of different colors) represent corresponding plots with a 95% confidence interval (Figure 2A). Figure 2B shows the Kaplan-Meier plot of hospital stays (days) in patients receiving oral LPR therapy (*green line*) and in patients receiving standard therapy (*red line*). The dotted lines (of different colors) represent corresponding plots with a 95% confidence interval. The table in the figure represents the influencing factors and Hazard Ratio (HR) analyzed by Cox regression model. ADR: adverse drug reaction.

Discussion

The results of this study demonstrate that pediatric patients with COVID-19 had a prolonged hospital stay and a prolonged nasal swab turning negative transition time after LPR administration. Consistent with our results, LPR did not reduce the SARS-CoV-2 shedding duration in adult patients with mild pneumonia in Taiwan[17]. Similarly, other studies[18] reported that the efficacy of LPR in the treatment of COVID-19 was inferior to that of the anti-influenza drug abidor. In contrast, a retrospective study[19] reported that the combination treatment with LPR and adjuvant drugs had a more evident therapeutic effect in lowering body temperature and restoring normal physiological parameters with no evident toxic or side effects. However, as the adjuvant drugs included IFN and arbidol hydrochloride, these combined drugs may have had a positive effect on treatment results. Zhang et al[20] found that the meantime to achieve negative nucleic acid testing and the mean hospitalization duration in patients treated with grazoprevir were significantly shorter than those in patients treated with LPR. Although LPR has been recommended for the treatment of COVID-19 owing to its inhibitory effect on SARS-CoV[21,22], we speculate that LPR may not be a good choice for the treatment of this infection.

As mentioned above, all children in the control group received aerosol inhalation therapy with interferon (IFN). Following viral infection, INFs are induced as the first line of innate immune defense, and these are essential for limiting viral replication[23]. IFN-α/β can induce the expression of more than 300 IFN-stimulating genes with antiviral, antiproliferative, and immunomodulatory functions[24]. In infected mice lacking the INF pathway, virus growth can reach high titers and cause severe pathological features[25]. Reportedly, the IFN response system in patients with severe COVID-19 is severely impaired and is characterized by low INF production and activity, as well as downregulation of genes stimulated by INF[26]. IFN has also been shown to be essential to maintain a balanced antiviral response in the respiratory tract and to limit initial infection[27]. Andreakos et al[28] confirm that IFN can fine-tune the antiviral

immune response before any signs of pneumonia occur or during the early stages of mild disease, preventing infection and minimizing collateral damage. Therefore, IFN is the most effective in the early stages of infection[29], where it can inhibit viral replication and reduce viral titers and inflammation in the body. Therefore, our study cannot rule out the beneficial influence of IFN aerosol treatment in the control group.

In addition to considering the efficacy of LPR, adverse reactions associated with LPR therapy in children were also considered in this study. It is already known that the incidence of gastrointestinal adverse reactions following LPR treatment can be as high as 62.5%[30]. According to our study, the gastrointestinal adverse reaction rate in the LPR group was 69.6% (16/23), which was significantly higher than the equivalent rate in the control group (2.2% [2/92]). Similarly, a study[31] comprising 178 cases of COVID-19 patients reported that adverse digestive tract symptoms were more severe after administering LPR than after administering the conventional treatment. In addition to gastrointestinal reactions, the adverse drug reactions included abnormal elevation of AST (glutamic oxalacetic aminotransferase) or ALT (glutamic-pyruvic aminotransferase), which may lead to longer discharge times. Another multicenter study[32] involving four hospitals found that LPR was not beneficial for the malignant progression of sickness in patients with SARS-CoV-2. Thus, two of five patients with severe symptoms treated with LPR deteriorated to progressive respiratory failure. In addition, four patients developed nausea and vomiting or diarrhea, and three developed abnormal liver function. The study of Cao et al[2] on 199 patients with SARS-CoV-2 infection, LPR treatment did not significantly accelerate clinical improvement or reduce mortality compared with standard treatment alone. Instead, a series of adverse gastrointestinal reactions occurred. Therefore, although the clinical benefits of LPR treatment among pediatric patients with mild COVID-19 are limited, the adverse events are significant.

There are several possible reasons why LPR treatment does not appear to be beneficial for pediatric patients with mild COVID-19. First, the benefits of LPR may be offset by an increased risk of residual viral replication[33]. Thus, although LPR may improve lung function, it does not reduce viral replication or change severe lung pathology[34]. In the later stages of COVID-19, lung damage is caused by inflammation (not pathogenicity of the virus)[35]. Second, LPR demonstrates deleterious effects on several organs and may interact with other drugs. In fact, LPR may cause renal dysfunction, such as electrolyte and acid-base disorders, and induce alterations in kidney morphology[36]. In addition, lopinavir is a potent inhibitor of cytochrome P450 (CYP450), CYP3A4, and CYP2C8, and ritonavir is a potent inhibitor of CYP2C8, CYP3A4, CYP3A5, and CYP3A7. Inhibition of CYP enzyme may cause more adverse drug reactions to other drugs. Third, LPR may affect the immunoregulation of the body. It has been reported that high lymphocyte counts are independent factors related to the rapid elimination of SARS-CoV-2 and that a decline in immune function leads to the early growth of the virus[37]. The limitation of this retrospective study is that the sample size in the study is small, and the randomization scheme is not used. This problem can be avoided if randomized controlled double-blind trials can be carried out in the future.

Conclusions

LPR is inferior to standard treatment in reducing virus shedding time and hospitalization duration in pediatric patients with mild COVID-19. Additionally, it significantly increases adverse events compared with standard therapy. Therefore, LPR is not recommended for use in pediatric patients with mild COVID-19.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Authors' Contribution

Conceptualization: Zhiping Li, Xiaowen Zhai, Hong Xu; Formal Analysis: Jinmiao Lu, Qiaofeng Ye, Feineng Shang; Funding Acquisition: Zhiping Li; Investigation: Feineng Shang, Hua Xu, Xianfeng Wang, Yanling He, Shuli Ma, Yuxia Cui, Ruijie Chen, Xuyuan Li; Methodology: Aifen Zhou, Xiaobo Zhang; Project Administration: Zhiping Li; Supervision: Zhiping Li, Xiaowen Zhai, Hong Xu; Writing

– original draft: Jinmiao Lu Writing – review, and editing: Zhiping Li, Jinmiao Lu, Qiaofeng Ye. All authors have read and approved the final version of this manuscript. The corresponding author, Zhiping Li, Xiaowen Zhai and Hong Xu had full access to all of the data in the study and takes complete responsibility for the integrity of the data and the accuracy of the data analysis.

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