

Clinical efficacy of lopinavir/ritonavir in the treatment of Coronavirus disease 2019

X.-T. YE¹, Y.-L. LUO¹, S.-C. XIA², Q.-F. SUN¹, J.-G. DING¹, Y. ZHOU¹, W. CHEN¹, X.-F. WANG¹, W.-W. ZHANG¹, W.-J. DU², Z.-W. RUAN³, L. HONG¹

¹Department of Infection, Rui'an People's Hospital, Rui'an, China

²Leading Group for COVID-19, Rui'an People's Hospital, Rui'an, China

³Emergency Intensive-Care Unit, Rui'an People's Hospital, Rui'an, China

Xiaoting Ye and Yunling Luo are co-first authors

Abstract. – **OBJECTIVE:** The Coronavirus disease 2019 (COVID-19) which outbreaked in December 2019 is highly contagious with a low cure rate. In view of this, there is an urgent need to find a more appropriate therapeutic scheme against COVID-19. The study aimed to investigate whether lopinavir/ritonavir (LPV/r) in combination with other pneumonia-associated adjuvant drugs has a better therapeutic effect on COVID-19.

PATIENTS AND METHODS: Totally 47 patients with COVID-19 infection who were admitted to Rui'an People's Hospital between January 22 and January 29, 2020 were collected. The patients were divided into the test group and the control group according to whether they had been treated with LPV/r or not during hospitalization. Patients in the test group were treated with LPV/r combined with adjuvant medicine, while those in the control group were just treated with adjuvant medicine. The changes of body temperature, blood routine and blood biochemistry between the two groups were observed and compared.

RESULTS: Both groups achieved good therapeutic effect with the body temperature of patients decreased gradually from admission to the 10th day of treatment. But the body temperature of patients in the test group decreased faster than that of the control group. Blood routine indexes showed that compared with the control group, the abnormal proportion of white blood cells, lymphocytes and C-reactive protein of the test group could be reduced to some extent. Blood biochemical indexes exhibited that the proportion of patients with abnormal alanine aminotransferase and aspartate aminotransferase in the test group were lower than the control group. The number of days for nCoV-RNA turning negative after treatment was significantly decreased in the test group than that in the control group.

CONCLUSIONS: Compared with the treatment of pneumonia-associated adjuvant drugs alone, the combination treatment with LPV/r and adjuvant drugs has a more evident therapeutic effect

in lowering the body temperature and restoring normal physiological mechanisms with no evident toxic and side effects. In view of these conclusions, we suggested that the use of LPV/r combined with pneumonia-associated adjuvant drugs in the clinical treatment for patients with COVID-19 should be promoted.

Key Words:

Clinical trial, Coronavirus, Lopinavir/ritonavir, COVID-19, China.

Introduction

Coronavirus is a general term referring to a class of viruses and it has caused two severe respiratory infectious diseases in the past two decades: Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS). SARS emerged at the end of 2002 is caused by a novel coronavirus called SARS-CoV and a large-scale epidemic was developed in China at that time. By the time of August 15, 2003, a total of 8,422 confirmed cases of SARS infection had been reported worldwide and 916 people had died of the disease, with a fatality rate around 10%^{1,2}. Another highly pathogenic disease MERS is caused by MERS-CoV virus that was initially identified in middle-east in 2012³. The MERS-CoV virus can induce severe infection of lower respiratory tract leading to a mortality up to 35%. Although great efforts had been made in containing the virus from global transmission, infected people have emerged in over 27 countries⁴. In view of these, the coronavirus pneumonia is a severe disease of both high infection and fatality rate.

At the end of December in 2019, the first case of novel coronavirus pneumonia was identified

in people with pneumonia who had been associated with a seafood and live animal market in the city of Wuhan (Hubei, China). According to the World Health Organization (WHO), the novel coronavirus pneumonia has been given an official name called Coronavirus Disease 2019 (COVID-19). The 2019 Novel Coronavirus (2019-nCoV) that causes COVID-19 is a type of β -coronavirus, whose genetic characteristics are significantly discriminative compared to those of MERSr-CoV or SARSr-CoV, with nucleotide homology up to approximately 50% and 78%, respectively⁵. COVID-19 is highly infectious and the viral transmission is predominantly realized in the way of spreading by droplets or from unprotective contacts⁵. In January 9, 2020, the first case of COVID-19 death occurred. By the time of February 16, 2020, totally 68,694 confirmed cases of COVID-19 infection had been reported in China and the deaths had been up to 1,667. Although the fatality rate of COVID-19 is only 2.4% lower than that of SARS, the number of deaths is much bigger due to the massive infectious population. It has been reported that the main clinical symptoms of patients with COVID-19 are fever, dry cough, myalgia, fatigue, and diarrhea⁶. In addition, breathing difficulties and a decrease of leucocytes, as well as lymphocytes, were developed in most people, and nearly all sufferers were detected with the appearance of ground-glass opacity in chest CT⁷. Currently, no specific medicine against COVID-19 has been developed, and the way we can manage the patients is limited in the symptomatic treatment and the use of the drugs already in the market for treatment and clinical trials. Therefore, it is urgent to find appropriate therapeutic medicine.

Lopinavir/ritonavir (LPV/r) is a kind of protease inhibitor that has been widely applied in the clinical treatment for HIV-1 infection⁸. At present, LPV/r is one of the drugs used for second-line treatment on anti-retrovirus. LPV/r interferes with HIV protease to cause dysregulation of structural and functional proteins in virus core, contributing to the generation of immature and noninfectious virus particles, in turn achieving the inhibition of HIV replication⁹. When LPV/r is used combined with other antiviral drugs, patients with HIV-1 infection who have undergone initial treatment or antiviral treatment can receive effective response, such as the decrease of viral load in plasma and the improvement of immunity. In addition, good efficacy can also be received when LPV/r is used alone in clinic⁹. It has been reported that LPV/r

has certain therapeutic effect on early SARA patients^{10,11}. Chu et al¹² made a comparison on the effect of different therapeutic regimens on patients with SARA infection, and found that the occurrence rate of adverse outcomes was significantly lower after combined use of LPV/r and ribavirin relative compared to that after treatment with ribavirin alone, and physical symptoms were seen to be much more improved. Besides, Arabi et al¹³ used the treatment combined with interferon β -1b, lopinavir and ritonavir (LPV/r) for patients with MERS infection in Saudi Arabia (with the placebo as control), which suggested a good response of patients with MERS infection to LPV/r. Given that LPV/r has produced good response in prior clinical trials, this study focused on the role of LPV/r in patients with COVID-19.

In the present study, totally 47 patients with COVID-19 admitted in Rui'an People's Hospital were recruited. Meanwhile, the efficacy patients received after the combination treatment with LPV/r and routine adjuvant therapeutic drugs was evaluated.

Patients and Methods

Patient Collection and nCoV-RNA Positive Test

A total of 47 patients with COVID-19 infection (including 22 males and 25 females) who were admitted to Rui'an People's Hospital from January 22 to 29, 2020 were recruited. Nucleic acid samples were collected from the respiratory tract and the nCoV-RNA was test to be positive by quantitative PCR. The patients aged between 5 and 68, of which 9 were under 30 and 38 were over 30. According to whether they had been treated with LPV/r or not during hospitalization, patients were classified into the test group (n=42) and control group (n=5). The general clinical data of the patients including gender, hypertension, diabetes, CT abnormality, body temperature at admission, oxygen saturation, hemoglobin (Hb) concentration, C-reactive protein (CRP) are detailed in Table I.

Therapeutic Schemes

Control group was treated with adjuvant drugs only. Interferon aerosol inhalation (Schering-Plough Pharmaceutical Co., Ltd, Shanghai, China) and arbidol tablets (Suzhou Pharmaceutical Factory of Jiangsu Wuzhong Pharmaceutical Group Corporation, Jiangsu, China) were used for

Table 1. General clinical data of the patients.

Features	Test group (n=42)	Control group (n=5)	p-value
Gender			0.3525
Male	21	1	
Female	21	4	
Hypertension			0.9977
Yes	7	1	
No	35	4	
Diabetes mellitus			0.9986
Yes	7	1	
No	35	4	
CT abnormality			1.0000
Yes	27	4	
No	12	1	
Body temperature at admission (°C)	37.36±0.67	37.92±0.61	0.7762
Oxygen saturation	97.4±1.52	95.72±9.06	0.6840
Hemoglobin (g/dL)	129.5±10.24	141.06±16.73	0.1399
C-reactive protein (CRP)			0.2670
<10 mg/L	27	2	
>10 mg/L	8	2	

anti-viral treatment. Usage and dosage of interferon aerosol inhalation: 5 MU or equivalent dose for adults, adding 2 ml sterile water for injection, twice a day. Usage and dosage of arbidol tablets: 2 tablets (0.2 g) once for adults, 3 times a day, oral. Asmeton (Compound Methoxyphenamine Capsules, Daiichi Sankyo (Shanghai) Holdings Co., Ltd., Shanghai, China), eucalyptol limonene and pinene enteric soft capsules (Beijing Jiuhe Pharmaceutical Co., Ltd, Beijing, China) along with moxifloxacin (moxifloxacin hydrochloride tablets/injection, Bayer, Beijing, China) were used against infection and inflammation (including cough, sputum and wheezing). Usage and dosage of asmeton: 2 tablets for patients over 15 years old and 1 tablet for patients over 8 years old and less than 15 years old, after meals, 3 times a day, oral. Usage and dosage of eucalyptol limonene and pinene enteric soft capsules: 1 tablet (0.3 g) for acute patients (adult), 3-4 times a day and 1 tablet (0.3 g) for chronic patients, twice a day, taken with cold water half an hour before meals. Usage and dosage of moxifloxacin: 0.4 g for once a day, oral or intravenous injection. Effective oxygen therapies including nasal cannula, mask oxygen inhalation and high-flow nasal cannula oxygen, if necessary, were used for dyspnea.

The test group was treated with LPV/r (AbbVie Ltd, North Chicago, IL, USA) and adjuvant drugs. The per ml of LPV/r oral liquid contained 80 mg lopinavir and 20 mg ritonavir. Usage and dosage: 5 ml/time (400/100 mg) for adults, twice a day or 10 ml/time (800/200 mg) once a day with

food. The schemes of adjuvant drugs were the same as the control group.

All patients rested in bed and daily sufficient caloric intake was ensured. The balance of water-electrolyte in the patients was guaranteed and the stability of internal environment was maintained by fluid infusion. To prevent occurrence of new infections, antibiotics should not be used continuously for more than 5 days, and therapy in combination with broad-spectrum antibiotics should be avoided. In addition, glucocorticoids can be used in a short period of time (3-5 days) at doses not exceeding 1-2 mg/kg/d, depending on the patients' situation.

Evaluation Indexes

Body temperature: the daily temperature changes of the patients since admission were recorded. In this study, the temperature of each patient was recorded for 10 days (some patients failed to record for 10 days due to their own sake, and the unrecorded days were not included in the subsequent data statistics). The maximum body temperature of each day was taken for daily data.

Blood routine: including Hb (g/dL), total white blood cells (WBC) ($10^9/L$), granulocyte ($10^9/L$), platelets (PLT, $10^9/L$), lymphocyte count ($10^9/L$) and CRP (mg/L). The data were recorded before and during treatment (three times), respectively.

Blood biochemistry: including alanine aminotransferase (ALT, U/L) and aspartate aminotrans-

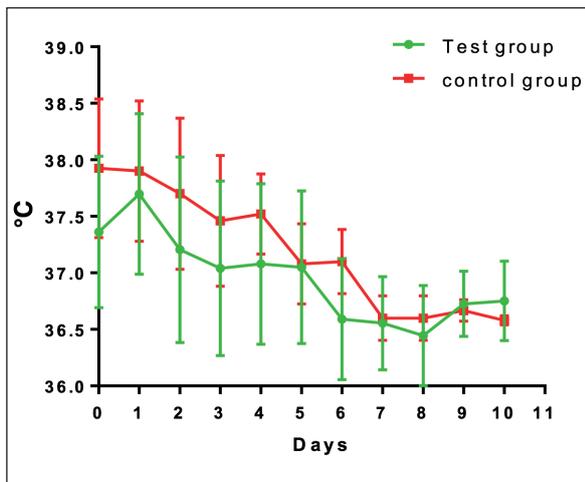


Figure 1. Daily temperature variations of patients in the two groups during 10-day hospitalization period.

ferase (AST, U/L). The data were recorded before and after treatment (three times), respectively.

Statistical Analysis

SPSS 22.0 software (IBM Corp., Armonk, NY, USA) was used for statistical analysis of all the data. Fisher’s exact test was used for compar-

ative analysis of the enumeration data of the test group and the control group. $p < 0.05$ was considered statistically significant.

Results

Comparison of Treatment Effects in Patients

Since most patients had developed a fever, we firstly recorded the daily temperature of patients for a total of 10 days since the patients had received treatment. The results exhibited that the body temperature of the patients in the test group decreased faster than that in the control group, but there was no significant difference ($p > 0.05$; Figure 1). In addition, patients whose body temperature was higher than 37.5°C at admission in the test and control groups were compared in the number of days of patients’ temperature recovering to 37.5°C during treatment. The results indicated that compared with the control group, the patients in the test group returned to normal body temperature in a shorter time (test group: 4.8 ± 1.94 days vs. control group: 7.3 ± 1.53 days, $p = 0.0364$). These results suggested that patients who were treated with LPV/r combined with pneumonia-as-

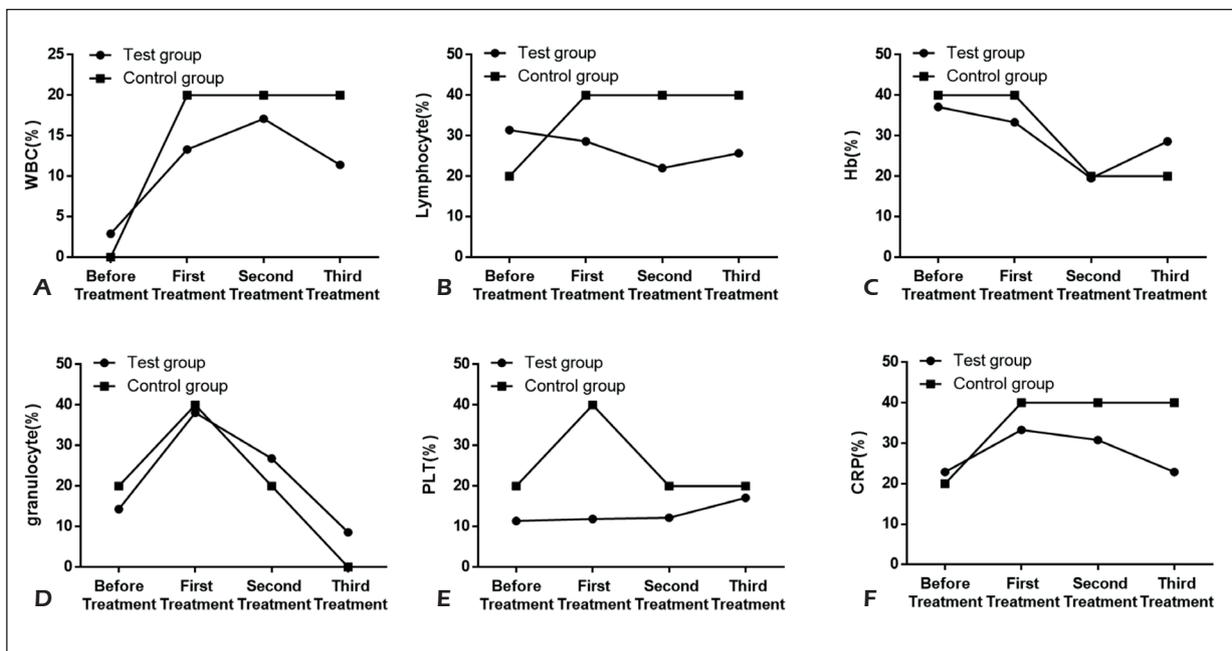


Figure 2. The percentage of patients with abnormal blood routine indexes measured three times before and after treatment from all the patients in each group. The percentage of patients in the test and control groups with abnormal indexes including WBC (A), lymphocyte (B), Hb (C), granulocyte (D), PLT (E) and CRP (F) was measured before and after treatment for three times. The normal reference values: Hb, 115-150 g/L, WBC, $3.5-9.5 \times 10^9/L$, granulocyte, $1.8-6.3 \times 10^9/L$, PLT, $125-350 \times 10^9/L$, lymphocyte, $1.1-3.2 \times 10^9/L$ and CRP, 0-5 mg/L. The values beyond or below the normal reference values were considered abnormal.

sociated adjuvant drugs were more likely to return to normal body temperature.

After comparing the difference towards fever in patients with COVID-19 infection in the control group and the test group, we analyzed the blood routine indexes before and after treatment as well as the days of nCov-RNA turning negative after treatment in the two groups. The results displayed that the abnormal proportion of WBC, lymphocytes, CRP and PLT in the test group was generally lower than that in the control group after three treatments (Figure 2). Moreover, the abnormal proportion of lymphocyte, Hb, granulocyte and CRP in the test group was gradually decreased from the first test to the third test (Figure 2). The number of days required for nCoV-RNA turning negative was compared and the result implied that the patients in the test group are able to turn negative in a shorter period of time (test group: 7.8 ± 3.09 days vs. control group: 12.0 ± 0.82 days, $p=0.0219$). These results suggested that the use of LPV/r-combined therapy could reduce the abnormal values of biochemical indexes in patients and was more effective than use of adjuvant therapy only.

ALT and AST Indexes of Patients

The results of the body temperature and the blood routine demonstrated that the therapeutic effect of LPV/r-combined therapy was better than that of the therapy without LPV/r. After that, blood biochemical tests were conducted for the toxic and side effects of the drugs on liver. The main indexes of the test were ALT and AST of patients in the control group and the test group. By comparing the percentage of patients with abnormal indexes in the first test after treatment, we found that the abnormal percentage of ALT and AST in the test group was lower than that in the control

group (Table II). For the test group, we concluded that there was no significant difference in the proportion of patients with indexes abnormality in the three measurements except for a remarkable increase in the proportion of patients with ALT abnormality at the third measurement. These results indicated that there were no adverse effects in liver toxic and side effects compared with the control group after the combination treatment with LPV/r and adjuvant drugs.

Discussion

The main purpose of this study was to evaluate the clinical effect of LPV/r combined with the routine adjuvant therapeutic drugs on patients with COVID-19. As revealed, the time of body temperature returning to normal was much shorter in patients receiving LPV/r. In addition, blood biochemical test suggested that the number of patients with abnormal ALT and AST in the test group was not significantly increased with the treatment duration, and the corresponding percentage was lower than that in the control group. This indicated that there might be no evident toxic and side effects produced on liver after the combined use of adjuvant medicine and LPV/r. Moreover, in patients receiving the combination treatment, accelerated remission could be seen in some clinical symptoms, such as abnormality of WBC, lymphocyte and C-reactive protein. Meanwhile, the nCoV-RNA in patients undergoing the combination treatment could be turned negative in a shorter time. However, due to the small sample size of the control group and the missing of relevant data, the results above are of some uncertainties to some extent.

Table II. The percentage of patients with abnormal ALT and AST in the test group and control group.

Time	Test group	Control group
<i>The first measurement after treatment</i>		
ALT	9.5%	25%
AST	19%	25%
<i>The second measurement after treatment</i>		
ALT	11.1%	NA
AST	16.7%	NA
<i>The third measurement after treatment</i>		
ALT	22.7%	NA
AST	18.2%	NA

Note: the normal reference values: ALT: male, 9-50 U/L and female, 7-40 U/L. AST: male, 15-40 U/L and female 13-35 U/L. The values beyond or blow the normal reference values were considered abnormal. NA means no data.

A report¹⁴ published in *The Lancet* in January 30, 2020 describes 99 cases with early COVID-19 who admitted in Wuhan Jinyintan Hospital from January 1 to 20, 2020, and reveals that fever, cough and tachypnea are the most common symptoms occurring in sufferers. Consistently, over 80% patients in this study also developed fever. Furthermore, similar to a previous study on the epidemic of COVID-19⁵, most patients in our research harbored imaging characteristic of viral pneumonia and a relative lower count of WBC in the early stage. Our statistical result further verified the typical symptoms of patients with COVID-19.

It is established that SARS-CoV, MERS-CoV, and 2019-nCoV are coronavirus and they are all RNA viruses like HIV that can be translated into functional viral proteins in the way of protease hydrolysis during viral replication and assembly process, which makes it possible to impede viral replication process via inhibiting protease hydrolysis. An article published in the *Nature Reviews Drug Discovery*¹⁵ in February 2020 describes that the non-structural proteins encoded by 2019-nCoV genome are key players involved in the viral life cycle, such as 3-chymotrypsin-like protease, papain-like protease, helicase and RNA-dependent RNA polymerase, and these four proteases have been observed to have highly conservative catalytic sites. In addition, structural analysis in this article reveals that the key drug-binding pockets across SARS-CoV, MERS-CoV and 2019-nCoV proteases might be conservative and can be used as potential antiviral targets. Thus, it prompts us to pay more attention on the potential of the antiviral agents that have been approved or are in development for treating infections caused by HIV, hepatitis B virus (HBV), hepatitis C virus (HCV) and influenza. Among the drugs, LPV/r, darunavir and ASC09/Ritonavir are all HIV protease inhibitors and have been studied in this research.

At present, there is no available specific medicine against COVID-19. LPV/r is generally used in the treatment for HIV infection and it is able to cause the suppression of HIV-1 replication¹⁶. Chu et al¹² indicated that use of LPV/r can significantly lead to the reduction of acute respiratory distress syndrome development and mortality that caused by SARS infection. In addition, for the therapeutic response of patients with COVID-19 to LPV/r, some scholars have paid much attention on and made some discussions recently, yet the specific results have not been reported¹⁷. In the present study, LPV/r was used for COVID-19 treatment and good responses were achieved in

the remission of fever and inflammation. However, there are some limitations that mainly refer to the small sample size of the control group. Besides, the missing data during treatment make the results not precise enough, and no statistical analysis has been performed towards the side effects of LPV/r on gastrointestinal track like diarrhea. Therefore, for future analysis, sample size should be enlarged to make the results more accurate and a systemic study should be carried out on whether LPV/r can cause side effects on gastrointestinal track in patients with COVID-19 infection.

Conclusions

We proved that the combination treatment of LPV/r and routine adjuvant medicine against pneumonia could produce much better efficacy on patients with COVID-19 infection compared to treatment with adjuvant medicine alone. Hence, we suggest to widely apply the combination treatment in treating patients with COVID-19 infection.

Ethics Committee Approval

Ethical approval was given by the Medical Ethics Committee of Rui'an People's Hospital, with the following reference number: YJ2020013.

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Conflict of Interests

The authors declare that they have no conflict of interests.

References

- 1) PEIRIS JS, LAI ST, POON LL, GUAN Y, YAM LY, LIM W, NICHOLLS J, YEE WK, YAN WW, CHEUNG MT, CHENG VC, CHAN KH, TSANG DN, YUNG RW, NG TK, YUEN KY; SARS study group. Coronavirus as a possible cause of severe acute respiratory syndrome. *Lancet* 2003; 361: 1319-1325.

- 2) CHENG VC, LAU SK, WOO PC, YUEN KY. Severe acute respiratory syndrome coronavirus as an agent of emerging and reemerging infection. *Clin Microbiol Rev* 2007; 20: 660-694.
- 3) ZAKI AM, VAN BOHEEMEN S, BESTEBROER TM, OSTERHAUS AD, FOUCHIER RA. Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. *N Engl J Med* 2012; 367: 1814-1820.
- 4) HUI DS, AZHAR EI, KIM YJ, MEMISH ZA, OH MD, ZUMLA A. Middle East respiratory syndrome coronavirus: risk factors and determinants of primary, household, and nosocomial transmission. *Lancet Infect Dis* 2018; 18: e217-e227.
- 5) SPECIAL EXPERT GROUP FOR CONTROL OF THE EPIDEMIC OF NOVEL CORONAVIRUS PNEUMONIA OF THE CHINESE PREVENTIVE MEDICINE ASSOCIATION. [An update on the epidemiological characteristics of novel coronavirus pneumonia COVID-19]. *Zhonghua Liu Xing Bing Xue Za Zhi* 2020; 41: 139-144.
- 6) WU YC, CHEN CS, CHAN YJ. Overview of the 2019 novel coronavirus (2019-nCoV): the pathogen of severe specific contagious pneumonia (SS-CP). *J Chin Med Assoc* 2020. doi: 10.1097/JCMA.000000000000270. [Epub ahead of print].
- 7) LIU J, ZHENG, X, TONG Q, LI W, WANG B, SUTTER K, TRILLING M, LU M, DITTMER U, YANG D. Overlapping and discrete aspects of the pathology and pathogenesis of the emerging human pathogenic coronaviruses SARS-CoV, MERS-CoV, and 2019-nCoV. *J Med Virol* 2020. doi: 10.1002/jmv.25709. [Epub ahead of print].
- 8) SHEAHAN TP, SIMS AC, LEIST SR, SCHAFFER A, WON J, BROWN AJ, MONTGOMERY SA, HOGG A, BABUSIS D, CLARKE MO, SPAHN JE, BAUER L, SELLERS S, PORTER D, FENG JY, CIHLAR T, JORDAN R, DENISON MR, BARIC RS. Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. *Nat Commun* 2020; 11: 222.
- 9) SABBATANI S, LEGNANI G, FULGARO C. [First evaluations of LPV/RTV (Kaletra) efficacy on HIV-positive patients treated with multiple drugs]. *Infez Med* 2003; 11: 18-24.
- 10) STOCKMAN LJ, BELLAMY R, GARNER P. SARS: systematic review of treatment effects. *PLoS Med* 2006; 3: e343.
- 11) NUKOOLKARN V, LEE VS, MALAISREE M, ARUKSAKULWONG O, HANNONGBUA S. Molecular dynamic simulations analysis of ritonavir and lopinavir as SARS-CoV 3CL(pro) inhibitors. *J Theor Biol* 2008; 254: 861-867.
- 12) CHU CM, CHENG VC, HUNG IF, WONG MM, CHAN KH, CHAN KS, KAO RY, POON LL, WONG CL, GUAN Y, PEIRIS JS, YUEN KY; HKU/UCH SARS Study Group. *Thorax* 2004; 59: 252-256.
- 13) ARABI YM, ALOTHMAN A, BALKHY HH, AL-DAWOOD A, ALJOHANI S, AL HARBI S, KOJAN S, AL JERAISY M, DEEB AM, ASSIRI AM, AL-HAMEED F, ALSAEDI A, MANDOURAH Y, ALMEKHLAFI GA, SHERBEENI NM, ELZEIN FE, MEMON J, TAHA Y, ALMOTAIRI A, MAGHRABI KA, QUSHMAO I, AL BSHABSHE A, KHARABA A, SHALHOUB S, JOSE J, FOWLER RA, HAYDEN FG, HUSSEIN MA; the Saudi Critical Care Trials Group. Treatment of Middle East respiratory syndrome with a combination of lopinavir-ritonavir and interferon-β1b (MIRACLE trial): study protocol for a randomized controlled trial. *Trials* 2018; 19: 81.
- 14) CHEN N, ZHOU M, DONG X, QU J, GONG F, HAN Y, QIU Y, WANG J, LIU Y, WEI Y, XIA J, YU T, ZHANG X, ZHANG L. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* 2020; 395: 507-513.
- 15) LI G, CLERCO ED. Therapeutic options for the 2019 novel coronavirus (2019-nCoV). *Nat Rev Drug Discov* 2020; 19: 149-150.
- 16) BONGIOVANNI M, BINI T, CHIESA E, CICCIONI P, ADORNI F, MONFORTE D'ARMINIO A. Lopinavir/ritonavir vs. indinavir/ritonavir in antiretroviral naive HIV-infected patients: immunovirological outcome and side effects. *Antiviral Res* 2004; 62: 53-56.
- 17) HUANG C, WANG Y, LI X, REN L, ZHAO J, HU Y, ZHANG L, FAN G, XU J, GU X, CHENG Z, YU T, XIA J, WEI Y, WU W, XIE X, YIN W, LI H, LIU M, XIAO Y, GAO H, GUO L, XIE J, WANG G, JIANG R, GAO Z, JIN Q, WANG J, CAO B. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020; 395: 497-506.