Respir. Med and Res 78 (2020) 100782

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Elsevier Masson France
EM|consulte
www.em-consulte.com

Letter to the Editor

Immunosuppression in a lung transplant recipient with COVID-19? Lessons from an early case

ARTICLE INFO

Keywords:
SARS-CoV-2
Lung transplantation
Immunosuppressants
Protease inhibitors
Therapeutic drug monitoring

1. Introduction

A severe consequence of SARS-CoV-2 infection is acute respiratory distress syndrome. In mid-March 2020 for lung transplant recipients there were very little data on the clinical course and therapeutic options to treat SARS-CoV-2 infection and its consequences. Lopinavir/ritonavir was an option for patients with severe pneumonia based on data from Sars-Cov-1 outbreaks [1]. Ritonavir is widely used as a potentiator in combination with other protease inhibitors, such with lopinavir. The metabolization of immunosuppressants such as mTor and calcineurin inhibitors by cytochrome P450 3A4 (CYP3A4) is inhibited by lopinavir/ritonavir. The case reported here illustrates the dangerous interaction between lopinavir/ritonavir and immunosuppressants in a lung transplant recipient with COVID-19 in a context of uncertainty in the choice of antiviral regimen.

2. Case report

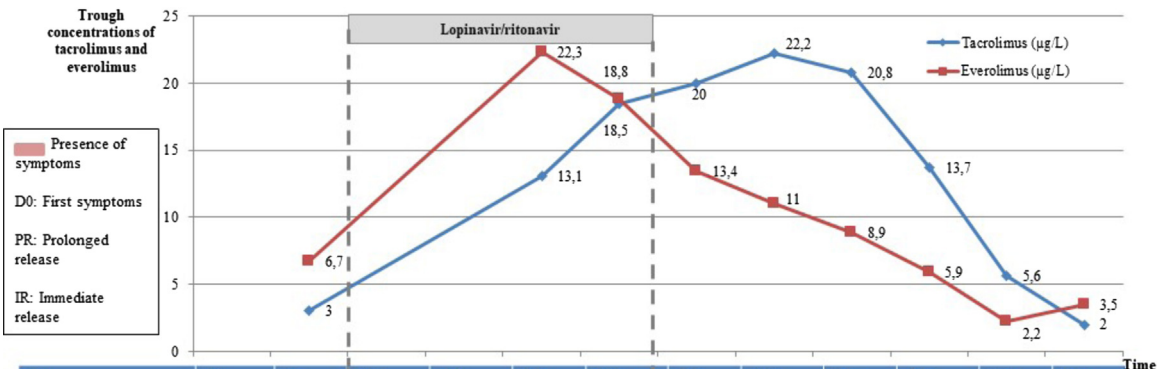
We report the case of a 69-year old caucasian-woman with a history of single right lung transplantation in August 2008 for pulmonary lymphangioleiomyomatosis complicated by pulmonary hypertension. She received substitution therapy for hypothyroidism, citalopram for depression, azithromycin and montelukast to prevent chronic lung allograft dysfunction and treatment for hypertension. Her lung function has been stable (percent predicted forced expiratory volume in 1 second –ppFEV1– was 37) since the transplantation, without need for oxygen therapy. Her immunosuppressive regimen consisted of everolimus (1.25 mg twice a day), tacrolimus ER (extended release) 1 mg daily and prednisone 5 mg per day. The tacrolimus and everolimus target trough concentrations were respectively 2–4 and 5–8 μg/L.

Myalgia and headaches appeared on March 16, 2020 (day 0) after contact with a SARS-CoV-2 carrier five days before. The SARS-CoV-2 nasal PCR test was positive. She was directly admitted to our intensive care unit on day 11 for febrile dyspnea requiring 8 L/min oxygen therapy. The chest X-ray showed major alveolar syndrome in the transplanted right lung. The clinical course and biological data are reported in Fig. 1. On day 11, we initiated lopinavir/ritonavir, and the dosage of immunosuppressants was adapted. Citalopram and azithromycin were stopped because of the risk of QT lengthening. On day 15, clinical symptoms worsened and a chest X-ray revealed increased opacities in the transplanted right lung. On day 13, she suffered severe vomiting and from day 14 experienced tremor, vomiting and diarrhea. Those symptoms were associated with tacrolimus and everolimus levels three to seven times greater than the target trough concentrations under antiviral treatment. Consequently, we prematurely stopped lopinavir/ritonavir after 8 doses (5 days) and intravenously rehydrated the patient, leading to improvement in renal function, and the disappearance of symptoms. Liver function remained stable during her hospital stay. On day 18, the patient was discharged with continued monitoring of liver and renal functions and the concentrations of immunosuppressives. Since discharge, the patient has been in good health.

3. Discussion

In this case of COVID-19 in an immunocompromised lung transplant recipient, given the insufficient scientific data about specific treatments and in view of the potential benefits, we decided to introduce lopinavir/ritonavir due to the patient's critical state. Reducing the SARS-CoV-2 viral load may reduce the severity of symptoms, as has been shown for SARS-Cov-1 [1]. At this early stage in the pandemic we decided to use lopinavir/ritonavir despite little data on the efficacy and safety of the various therapeutics tested in COVID-19 [1]. In 2004, Chu et al showed that lopinavir/ritonavir decreased mortality and acute respiratory distress syndrome in SARS-CoV-1 infected patients [1]. By March 18, 2020, Cao B. et al had demonstrated in a large Chinese randomized clinical trial on hospitalized patients with severe COVID-19 that the combination of lopinavir/ritonavir was not associated with significant clinical improvement, either in terms of lower mortality rates or of SARS-CoV-2 RNA levels, when given at a late stage of COVID-19 following standard care [2]. However, Wit E. et al had shown that the early introduction of remdesivir was needed for efficiency in MERS-CoV infected macaques [3]. Lopinavir might therefore have some effect if introduced early enough. Unfortunately, lopinavir/ritonavir dramatically increases blood concentrations of calcineurin and mTor inhibitors as it strongly inhibits CYP3A4 which metabolizes immunosuppressants, leading to altered pharmacokinetics due to drug interactions. This interaction has already been described in liver transplant patients living with HIV [4] and more recently in renal transplant recipients having COVID-19 and treated with chloroquine and lopinavir/ritonavir [5]. The observed difference in pharmacokinetics between tacrolimus and everolimus might be explained by a difference in their half-lives. Therefore, they recommended decreasing the dose of tacrolimus by at least 50% one day before starting lopinavir/ritonavir, and suspending tacrolimus

https://doi.org/10.1016/j.resmer.2020.100782



Days	D0	D7	D11	D12	D13	D14	D15	D16	D17	D28	D20	D21
Saturation (%)		94	94	91	93	87	96	98	98	100	99	99
02 Litres (ml/min)		0	6	5	8	5	6	5	3	2	1	0
Fever (>38°C)												
Digestive disorder												
Headache												
Tremors												
Myalgia												
Serum creatinine (µmol/L)	84	84	123		136	93	109	97		91	101	82
Lopinavir/ritonavir (200mg/50mg) dose/day			1	2	2	2	1					
Tacrolimus dose/day (mg/24h)		1 (PR)	1 (PR) decreased to 0,5 (IR)	0,5 (IR)	0,5 (IR)	0,5 (IR)	0,2 (IR)			1 (PR)	1 (PR)	1 (PR)
Everolimus dose/day (mg/24h)		1,25 X2	1,25 X2 decreased to 0,1 X2	0,1 X2	0,1 X2	0,1 X2	0,1			1,25 X2	1,25 X2	1,25 X2
Lopinavir trough concentration (mg/L)								6,8				
Ritonavir trough concentration (mg/L)								< 0,1				

Fig. 1. History of symptoms and blood parameters.

for the following days. This pharmacodynamic interaction has also been reported in a SARS-CoV-2 infected kidney transplant patient [6]. During this potentially fatal pandemic, resorting to unproven therapies without waiting for clinical trial data is a dilemma for physicians [7]. In the present case, we chose to introduce antiviral treatment despite the risk of adverse events. Indeed, considering the rapid deterioration in the patient's health, it seemed urgent to act. At that time, we had no strong evidence regarding their efficacy but in our opinion it appeared to be the best choice.

4. Conclusion

This case reveals the dangerous interaction between lopinavir/ritonavir and tacrolimus/everolimus despite close monitoring of the drug trough concentrations. We do not recommend the use of lopinavir/ritonavir under these conditions. However, we had to find a balance between waiting for strong evidence regarding the treatment's efficacy and acting quickly in an emergency. Therefore, in solid organ transplant recipients requiring COVID-19 treatment the rigorous management of immunosuppressants (blood concentrations) is essential. Practicians should be aware of the potential severe interaction between immunosuppressants and antiviral drugs in these life-threatening situations.

Disclosure of interest

The authors declare that they have no competing interest.

Acknowledgments

The authors thank Alison Mary Foote and Thomas Saillard for reviewing the manuscript.

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J. Raëth [a,b]
A. Tomio [a,b]
A. Eugene [b,c]
A. Mouffak [b,g]
M. Durand [e]

R. Hamidfar[a]
C. Pison[a,b,*]
H. Pluchart[b,c,d]
A.L. Mounayar[f]
[a] *Pôle thorax et vaisseaux, service hospitalier universitaire pneumologie, CHU Grenoble Alpes, Grenoble, France*
[b] *Université Grenoble Alpes, Grenoble, France*
[c] *Pôle pharmacie, CHU Grenoble Alpes, Grenoble, France*
[d] *TIMC-IMAG UMR5525/ThEMAS, CNRS, université Grenoble Alpes, Grenoble, France*
[e] *Pôle anesthésie réanimation, CHU Grenoble Alpes, Grenoble, France*
[f] *Pôle urgence médecine aiguë, service des maladies infectieuses et tropicales, CHU Grenoble Alpes, Grenoble, France*
[g] *Centre régional de pharmacovigilance, centre hospitalier universitaire Grenoble-Alpes, 38000 Grenoble, France*

[*] Corresponding author. Pôle thorax et vaisseaux, service hospitalier universitaire pneumologie physiologie, CHU Grenoble Alpes, CS10217, 38043 Grenoble cedex 9, France.
E-mail address: cpison@chu-grenoble.fr (C. Pison)

Received 15 May 2020

Received in revised form 9 July 2020

Accepted 23 July 2020
Available online 3 August 2020