

Reply Letter – “Safety and efficacy of oral lopinavir/ritonavir in pediatric patients with coronavirus disease: a nationwide comparative analysis”

A. DE VITO, G. MADEDDU

Department of Medical, Surgical and Experimental Sciences, Unit of Infectious Diseases, University of Sassari, Sassari, Italy

Dear Editor,

We have read with great interest the manuscript “Safety and efficacy of oral lopinavir/ritonavir in pediatric patients with coronavirus disease: a nationwide comparative analysis” by Lu et al¹. Since the start of the outbreak, the number of people with SARS-CoV-2 infection increased exponentially, as well as the number of deaths due to COVID-19. Therefore, the scientific community started to find effective approaches to prevent and treat COVID-19²⁻⁵ millions of people have been infected with thousands of deaths. Few data regarding factors that increase the risk of infection are available.

However, even if moderate to severe COVID-19 has been reported in children, data on pediatric patients’ treatment are scarce.

The authors conducted a retrospective case-control study to evaluate the efficacy and safety of lopinavir/ritonavir (LPV/r) in a pediatric population, compared with standard of care (symptomatic treatment). More in details, the investigators retrospectively enrolled 23 children who have been treated with LPV/r (12 mg/kg for 7-15 kg; 10 mg/kg for 15-40 kg; maximum dose 400/100 mg; twice a day), and 92 participants treated only with aerosol inhalation therapy with interferon- α 2b.

LPV/r is a protease inhibitor commonly used in HIV treatment and has been tested to treat SARS and MERS, and now different trials and cohort studies have analysed its efficacy against SARS-CoV-2. Nowadays, LPV/r is not the first choice for HIV treatment because new antiretroviral drugs, more effective and safe, are available for both naïve and experienced patients, despite patients’ comorbidity⁶⁻¹⁰. Unfortunately, all these drugs are not tested yet against SARS-CoV-2.

Lu et al¹ reported that LPV/r could cause prolonged hospitalization in children and increase recovery time, compared with aerosol inhalation therapy with interferon. Furthermore, most of the children who assumed LPV/r had gastrointestinal adverse effects that could explain hospitalization length. The gastrointestinal adverse reaction rate in the LPV/r group was 69.6% (16/23), which was significantly higher than the equivalent rate in the control group (2.2%). The gastrointestinal adverse effect, especially diarrhea, is common in HIV patients during treatment; therefore, clinicians may suggest a specific diet¹¹. In addition to gastrointestinal reactions, the adverse drug reactions included abnormal elevation of aspartate transaminase (AST) or alanine transaminase (ALT), which may lead to longer discharge times.

Previous studies on adults have shown how the increase in AST and ALT and their ratio could be associated with a worst outcome in patients with COVID-19¹².

Lu et al¹ have not reported children’s symptoms in the two groups, neither how many days between the symptoms’ development and the start of treatments occurred. The lack of these data could represent an important bias of the study. However, although the study’s retrospective nature does not allow to link cause and effect and based on previous safety data, the high occurrence of adverse events suggests caution in the administration of LPV/r in children with COVID-19.

Conflict of Interest

The Authors declare that they have no conflict of interests.

References

- 1) Lu JM, Zhou AF, Zhang XB, Xu H, Wang XF, Ye QF, Shang FN, He YL, Ma SL, Cui YX, Chen RJ, Li XY, Zhai XW, Xu H, Li ZP. Safety and efficacy of oral lopinavir/ritonavir in pediatric patients with coronavirus disease: a nationwide comparative analysis. *Eur Rev Med Pharmacol Sci* 2021; 25: 549-555.
- 2) De Vito A, Geremia N, Princic E, Fanelli C, Panu Napodano CM, Muredda AA, Flore V, Maida I, Fois AG, Babudieri S, Madeddu G. Does Angiotensin II receptor blockers increase the risk of SARS-CoV-2 infection? A real-life experience. *Eur Rev Med Pharmacol Sci* 2021; 25: 523-526.
- 3) De Vito A, Geremia N, Fiore V, Princic E, Babudieri S, Madeddu G. Clinical features, laboratory findings and predictors of death in hospitalized patients with COVID-19 in Sardinia, Italy. *Eur Rev Med Pharmacol Sci* 2020; 24: 7861-7868.
- 4) Perrella A, Carannante N, Berretta M, Rinaldi M, Maturo N, Rinaldi L. Editorial - Novel Coronavirus 2019 (SARS-CoV2): A global emergency that needs new approaches? *Eur Rev Med Pharmacol Sci* 2020; 24: 2162-2164.
- 5) WHO Solidarity Trial Consortium, Pan H, Peto R, Henao-Restrepo AM, Preziosi MP, Sathiyamoorthy V, Abdool Karim Q, Alejandria MM, Hernández García C, Kieny MP, Malekzadeh R, Murthy S, Reddy KS, Roses Periago M, Abi Hanna P, Ader F, Al-Bader AM, Alhasawi A, Allum E, Alotaibi A, Alvarez-Moreno CA, Appadoo S, Asiri A, Aukrust P, Barratt-Due A, Bellani S, Branca M, Cappel-Porter HBC, Cerrato N, Chow TS, Como N, Eustace J, García PJ, Godbole S, Gotuzzo E, Griskevicius L, Hamra R, Hassan M, Hassany M, Hutton D, Irmansyah I, Jancoriene L, Kirwan J, Kumar S, Lennon P, Lopardo G, Lydon P, Magrini N, Maguire T, Manevska S, Manuel O, McGinty S, Medina MT, Mesa Rubio ML, Miranda-Montoya MC, Nel J, Nunes EP, Perola M, Portolés A, Rasmin MR, Raza A, Rees H, Reges PPS, Rogers CA, Salami K, Salvadori MI, Sinani N, Sterne JAC, Stevanovikj M, Tacconelli E, Tikkinen KAO, Trelle S, Zaid H, Røttingen JA, Swaminathan S. Repurposed antiviral drugs for Covid-19 - Interim WHO solidarity trial results. *N Engl J Med* 2021; 384: 497-511.
- 6) Zanet E, Berretta M, Benedetto F Di, Talamini R, Ballarin R, Nunnari G, Berretta S, Ridolfo A, Lleshi A, Zanghi A, Cappellani A, Tirelli U. Pancreatic cancer in HIV-positive patients: a clinical case-control study. *Pancreas* 2012; 41: 1331-1335.
- 7) Rossetti B, Baldin G, Sterrantino G, Rusconi S, De Vito A, Giacometti A, Gagliardini R, Colafigli M, Capetti A, d'Ettorre G, Celani L, Lagi F, Ciccullo A, De Luca A, Di Giambenedetto S, Madeddu G. Efficacy and safety of dolutegravir-based regimens in advanced HIV-infected naïve patients: results from a multicenter cohort study. *Antiviral Res* 2019; 169: 104552.
- 8) Borghetti A, Baldin G, Capetti A, Sterrantino G, Rusconi S, Latini A, Giacometti A, Madeddu G, Picarelli C, De Marco R, Cossu MV, Lagi F, Cauda R, De Luca A, Di Giambenedetto S; Odoacre Study Group. Efficacy and tolerability of dolutegravir and two nucleos(t)ide reverse transcriptase inhibitors in HIV-1-positive, virologically suppressed patients. *AIDS* 2017; 31: 457-459.
- 9) Di Benedetto F, De Ruvo N, Berretta M, Masetti M, Montalti R, Di Sandro S, Quintini C, Codeluppi M, Tirelli U, Gerunda GE. Don't deny liver transplantation to HIV patients with hepatocellular carcinoma in the highly active antiretroviral therapy era. *J Clin Oncol* 2006; 24: e26-27.
- 10) Zanet E, Berretta M, Martellotta F, Cacopardo B, Fisichella R, Tavio M, Berretta S, Tirelli U. Anal cancer: focus on HIV-positive patients in the HAART-era. *Curr HIV Res* 2011; 9: 70-81.
- 11) Nunnari G, Coco C, Pinzone MR, Pavone P, Berretta M, Di Rosa M, Schnell M, Calabrese G, Cacopardo B. The role of micronutrients in the diet of HIV-1-infected individuals. *Front Biosci (Elite Ed)* 2012; 4: 2442-2456.
- 12) Zinellu A, Arru F, De Vito A, Sassu A, Valdes G, Scano V, Zinellu E, Perra R, Madeddu G, Carru C, Pirina P, Mangoni AA, Babudieri S, Fois AG. The De Ritis ratio as prognostic biomarker of in-hospital mortality in COVID-19 patients. *Eur J Clin Invest* 2020; 51: e13427.