

novaná terapia nirmatrelvirom/ritonaviirom a inhalačnými kortikoidmi v trvaní 5 dní je preferovaná v manažmente astmy (obzvlášť závažnej formy). Výhody tejto kombinovanej farmakoterapie sú preukázané a prevažujú nad rizikami spojenými s prerušením podávania inhalačných kortikoidov (29).

Riziko závažných liekových interakcií sme identifikovali pri kombinácii nirmatrelviru/ritonaviru s diazepamom, kvetiapiénom, domperidónom, tamsulosínom a salmeterolom. V prípade diazepamu a kvetiapiínu je ich súbežné podávanie kontraindikované podľa SmPC a liekovej databázy Lexicomp. Ide o silnú inhibíciu CYP3A4 ritonaviirom, ktorá výrazne prehĺbuje sedatívne účinky diazepamu a zvyšuje toxicitu kvetiapiínu. Diazepam je možné podať rektálne, vtedy je nižšia závislosť od metabolizmu liečiva cestou CYP3A4, v indi-

kácii pre urgentné ukončenie dlhotrvajúceho epileptického záchvatu (30). Pri kombinácii domperidónu s ritonaviirom významne narastá riziko vzniku závažných arytmií, ktoré sú klinicky veľmi významné (31, 32, 33). Súbežné podávanie salmeterolu s nirmatrelvir/ritonaviirom je vysoko rizikové, nakoľko už samotný salmeterol preukázateľne predlžuje QT interval (34) a zvyšuje riziko rozvoja ďalších kardiovaskulárnych nežiaducich účinkov (palpitácie, sínusová tachykardia). Inhibícia CYP3A4 ritonaviirom a následné zvýšenie plazmatickej koncentrácie salmeterolu uvedené riziká znásobuje. Riziko rozvoja závažných kardiovaskulárnych nežiaducich účinkov sa pri tejto kombinácii uvádza na úrovni 15 % (34). Pri začatí liečby nirmatrelvirom/ritonaviirom sa odporúča prerušiť podávanie salmeterolu a nahradiť ho bezpečnou alternatívou, napr. formoterolom.

Návrat k pôvodnej medikácii je možný 5 dní od ukončenia terapie ritonaviirom (34).

Záver

Podávanie kombinovaného antivirovika nirmatrelvir/ritonavir pacientom s chronickými ochoreniami je spojené so zvýšeným rizikom farmakoterapeutických komplikácií spôsobených liekovými interakciami. Vedomosti o mechanizme vzniku týchto interakcií, vyhodnotenie ich klinickej relevancie a návrh odporúčaných postupov na ich riešenie sú kľúčové k zabezpečeniu účinnej a bezpečnej farmakoterapie ochorenia COVID-19. Táto práca má slúžiť zdravotníckym pracovníkom na jednoduchú identifikáciu rizikových kombinácií liekov s najvyšším predpokladom interakcie a prispieť k optimalizácii farmakoterapie ambulantne liečených pacientov s ochorením COVID-19.

LITERATÚRA

- Săndulescu O, Apostolescu CG, Preotescu LL, et al. Therapeutic developments for SARS-CoV-2 infection – Molecular mechanisms of action of antivirals and strategies for mitigating resistance in emerging variants in clinical practice. *Front Microbiol.* 2023;14:1132501.
- Saravolatz L, Depcinski S, Sharma M. Oral coronavirus disease 2019 antiviral drugs. *Clin Infect Dis.* 2023;76(1):165-171.
- Kolář J, et al. Možnosti predchádzania a riešenia polyfarmazie. *Klin Farmakol Farm.* 2024;38(2):76-82.
- Súhrn charakteristických vlastností lieku Paxlovid. [Internet] [cited 2024 January 22]. Available from: https://www.sukl.sk/hlavna-stranka/slovenska-verzia/bezpenos-liekov/vakciny/vakciny-proti-covid-19/paxlovid-dokumenty?page_id=5792
- Chen N, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: A descriptive study. *Lancet.* 2020;395:507-513.
- Richardson S, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. *JAMA.* 2020;2052-2059.
- Cantudo-Cuenca MD, Gutiérrez-Pizarra A, Pinilla-Fernández, et al. Drug-drug interactions between treatment specific pharmacotherapy and concomitant medication in patients with COVID-19 in the first wave in Spain. *Scien Rep.* 2021;11(1):12414.
- Marzolini C, Kuritzkes DR, Marra F, et al. Prescribing Nirmatrelvir-Ritonavir: how to recognize and manage drug-drug interactions. *Ann Intern Med.* 2022;175:744-746.
- Marzolini C, Kuritzkes DR, Marra F, et al. Recommendation for the management of drug-drug interactions between the COVID-10 antiviral nirmatrelvir/ritonavir (Paxlovid) and comedications. *Clin Pharmacol Ther.* 2022;112(6):1191-1200.
- Lieková databáza Lexicomp, systém spoločnosti Wolters Kluwer Clinical Drug Information.
- Ontario COVID-19 Drugs and Biologics Clinical Practice Guidelines Working Group, University of Waterloo School of Pharmacy. Nirmatrelvir/Ritonavir (Paxlovid): What prescribers and pharmacists need to know. *Ontario COVID-19 Science Advisory Table.* 2022;3(58). <https://doi.org/10.47326/ocsat.2022.03.58.3.0>
- Shini Rubina SK, Anuba PA, Swetha B, et al. Drug interaction risk between cardioprotective drugs and drugs used in treatment of COVID-19: A evidence-based review from six databases. *Diabetes Metab Syndr.* 2022;16(3):102451.
- Azanza R J, Mensa J, González del Castillo J, et al. Interac-

- tions listed in the Paxlovid fact sheet, classified according to risks, pharmacological groups, and consequences. *Rev Esp Quimioter.* 2022;35(4):357-361.
- Lemaître F, Grégoire M, Monchaud C, et al. SFPT Therapeutic Drug Monitoring and Treatment Personalization group (STP-PT) of the French Society of Pharmacology and Therapeutics (SFPT), French Pharmacovigilance Network (CRPV), ANRS-MIE AC-43 Clinical Pharmacology Committee, joint working group, SFPT Therapeutic Drug Monitoring and Treatment Personalization group (STP-PT) of the French Society of Pharmacology and Therapeutics (SFPT), French Pharmacovigilance Network (CRPV), & ANRS-MIE AC-43 Clinical Pharmacology Committee, joint working group (2022). Management of drug-drug interactions with nirmatrelvir/ritonavir in patients treated for Covid-19: Guidelines from the French Society of Pharmacology and Therapeutics (SFPT). *Therapie.* 2022;77(5):509-521.
- IDSa COVID-19 Treatment and management guideline panel on behalf of the Infectious Diseases Society of America. Management of Drug Interactions With Nirmatrelvir/Ritonavir (Paxlovid®): Resource for Clinicians IDSA. 2022, Last Updated: May 6, 2022- Version 1.1. [Internet] Available from: <http://www.idsa.org/idsa-paxlovid-drug-interactions-resource-5-6-22-v1.1.pdf> (idsociety.org).
- Liverpool COVID-19 Interactions. COVID-19 Drug Interactions. 2024. [Internet] [cited 2024 January 12]. Available from: <https://www.covid19-druginteractions.org/checker>.
- Súhrn charakteristických vlastností lieku Sertralin Actavis 100mg. [Internet] [cited 2024 Jun 6]. Available from: https://www.adc.sk/databazy/produkty/spc/sertralin-actavis-100-mg-636492.html#kap_5_1.
- Marzolini C, Gibbons S, Khoo S, et al. Cobicistat versus ritonavir boosting and differences in the drug-drug interaction profiles with co-medications. *J Antimicrob Chemother.* 2016;71:1755-1758.
- Boppana U, Leonard T S, Jolayemi A, et al. Drug-Drug Interactions Between COVID-19 Treatments and Psychotropic Medications: An Updated Study. *Cureus.* 2023;15(12):e50469.
- Yalcin N, Allegaert K. COVID-19 and antiepileptic drugs: an approach to guide practices when nirmatrelvir/ritonavir is co-prescribed. *Eur J Clin Pharmacology.* 2022;78:1697-1701.
- Penzak S, Formentini E, Alfaro R, et al. Prednisolone Pharmacokinetics in the Presence and Absence of Ritonavir After Oral Prednisone Administration to Healthy. *J Acquir Immune*

Defic Syndr. 2005;40(5):573-580.

- Marrone A, Nevola R, Sellitto A, et al. Remdesivir plus dexamethasone versus dexamethasone alone for the treatment of COVID-19 patients requiring supplemental O2 therapy: a prospective controlled non-randomized study. *Clin Infect Dis.* 2022;75(1):e403-e409.
- RECOVERY Collaborative Group, Horby P, Lim WS, Emberson JR, et al. Dexamethasone in hospitalized patients with COVID-19. *N Engl J Med.* 2021;384:693-704.
- Keller MJ, Kitis EA, Arora S, et al. Effect of systemic glucocorticoids on mortality or mechanical ventilation in patients with COVID-19. *J Hosp Med.* 2020;15:489-493.
- Prescott HC, Rice TW. Corticosteroids in COVID-19 ARDS. Evidence and hope during the pandemic. *JAMA.* 2020;324:1292-1295.
- Štefan M, Chrdle A, Husa P, Beneš J, Dlouhý P. Covid-19: diagnostika a liečba. Doporučený postup Společnosti infekčního lékařství ČLS JEP (verze 06/10/2022). [Internet] Available from: https://infektologie.cz/Covid2019/DPcovid-19_SIL_0421.pdf.
- Wagner C. Systemic corticosteroids for the treatment of COVID-19: Equity-related analyses and update on evidence. *Cochrane Database Syst Rev.* 2022;17(11):CD014963.
- Selroos O, Halme M. Effect of a volumatic spacer and mouth rinsing on systemic absorption of inhaled corticosteroids from a metered dose inhaler and dry powder inhaler. *Thorax.* 1991;46:891-894.
- Carr TF, Fajt ML, Kraft M. Treating asthma in the time of COVID-19. *J Allergy Clin Immunol.* 2023;151(4):809-817.
- Noyman I, Ekstein D, Fahoum F. Using nirmatrelvir/ritonavir in patients with epilepsy: An update from the Israeli chapter of the International League Against Epilepsy. *Epilepsia.* 2022;63:1276-1278.
- Woosley RL, Heise CW, Romero KA (www.CredibleMeds.org). QTdrugs List. [18. 5. 2017]. AZCERT, Inc., 1822 Innovation Park Dr., Oro Valley, AZ 85755, USA.
- Rossi M, Giorgi G. Domperidon and long QT syndrome. *Curr Drug Saf.* 2010;5:257-262.
- Doggrell SA, Hancox JC. Cardiac safety concerns for domperidone, an antiemetic and prokinetic, and galactagogue medicine. *Expert Opin Drug Saf.* 2014;13:131-138.
- Guhan AR, et al. Systemic effects of formoterol and salmeterol: a dose-response comparison in healthy subjects. *Thorax.* 2000;55:650-656.