Is it safe to use remdesivir in combination with a combined p-glycoprotein and CYP3A4 inhibitor?

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) was detected in Wuhan, China about 1 year ago and caused a pandemic that has been ongoing for about 10 months. Optimal antiviral therapy has not yet been established in the treatment of coronavirus disease 2019 (COVID-19) caused by this virus.

Remdesivir is one of the most commonly used antiviral drugs in the treatment of COVID-19 worldwide. Remdesivir, a prodrug, converts to its active phosphate form and inhibits RNA-dependent RNA polymerase that enables the replication of the SARS-CoV-2.[1] In vitro studies have demonstrated that remdesivir is a substrate for the cytochrome P450 (CYP450) enzymes CYP3A4, CYP2D6 and CYP2C8, as well as the organic anion carrying polypeptide (OATP) 1B1, OATP1B3 and p-glycoprotein.[2] However, the clinical significance of the metabolism of remdesivir with CYP3A4 and p-glycoprotein is unknown because drug–drug interactions of remdesivir have not been studied clinically.

Leegwater *et al* reported that hepatotoxicity occurred on day 5 of remdesivir treatment in a COVID-19 patient >60 years old. Amiodarone treatment was started in the patient due to atrial fibrillation 3 days before the development of hepatotoxicity. As alanine aminotransferase (ALT) and aspartate aminotransferase (AST) enzymes decreased rapidly after remdesivir was stopped, the authors thought that hepatotoxicity might have developed due to the possible interaction of amiodarone and remdesivir. COVID-19 and amiodarone seem to be less likely to cause hepatotoxicity due to the time of development of hepatotoxicity, the rapid recovery after remdesivir discontinuation, and the low total dose of amiodarone. It was proposed that amiodarone, a p-glycoprotein inhibitor, may cause high concentrations of remdesivir in hepatocytes by reducing the efflux of remdesivir from hepatocytes to the bile duct.[3]

Amiodarone is also a moderate CYP3A4 inhibitor.[4] Remdesivir–amiodarone interaction may result from amiodarone inhibiting both p-glycoprotein and CYP3A4. It has been stated in the literature that caution should be exercised when using remdesivir combined with CYP3A4 inducers such as rifampicin, phenytoin and carbamazepine.[5] There were no warnings about the concomitant use of CYP3A4 or p-glycoprotein inhibitors and remdesivir. However, as reported in the case above, concomitant use of remdesivir with a combined p-glycoprotein and CYP3A4 inhibitor may cause hepatotoxicity.

Since remdesivir is a substrate for both p-glycoprotein and CYP3A4, studies are needed to demonstrate the safety of its simultaneous use with p-glycoprotein inhibitors (eg, azithromycin, carvedilol), CYP3A4 inhibitors (eg, voriconazole) or combined p-glycoprotein and CYP3A4 inhibitors (eg, amiodarone, diltiazem, clarithromycin, verapamil). Clinicians should be careful in regard to the combined use of remdesivir and these drugs, and should closely monitor patients for drug toxicity.

Ömer Faruk Bahçecíoğlu, Selim Gök, Mefküre Durmuş

Clinical Pharmacy, Inonu University, Malatya, Turkey

Correspondence to Ömer Faruk Bahçecíoğlu, Clinical Pharmacy, İnönü Üniversitesi, Malatya, Turkey; omerfb92@hotmail.com

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

To cite Bahçecíoğlu ÖF, Gök S, Durmuş M. *Eur J Hosp Pharm* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/ejhpharm-2021-002680

Eur J Hosp Pharm 2021;**0**:1. doi:10.1136/ejhpharm-2021-002680

ORCID iD

Ömer Faruk Bahçecíoğlu http://orcid.org/0000-0002-4045-4555

REFERENCES

1 Gordon CJ, Tchesnokov EP, Woolner E, *et al*. Remdesivir is a direct-acting antiviral that inhibits RNA-dependent RNA polymerase from severe acute respiratory syndrome coronavirus 2 with high potency. *J Biol Chem* 2020;295:6785–97.
2 NIH. COVID-19 treatment guidelines, 2021. Available: https://www.covid19treatmentguidelines.nih.gov/antiviral-therapy/remdesivir/ [Accessed cited 03 Jan 2021].
3 Leegwater E, Strik A, Wilms EB. Drug-induced liver injury in a COVID-19 patient: potential interaction of remdesivir with P-glycoprotein inhibitors. *Clin Infect Dis* 2020.
4 McDonald MG, Au NT, Rettie AE. P450-based drug-drug interactions of amiodarone and its metabolites: diversity of inhibitory mechanisms. *Drug Metab Dispos* 2015;43:1661–9.
5 Gandhi Z, Mansuri Z, Bansod S. Potential interactions of remdesivir with pulmonary drugs: a Covid-19 perspective. *SN Comprehensive Clinical Medicine* 2020;2:1707–8.