

CURRENT DEVELOPMENTS IN BIOMEDICAL AND CLINICAL SCIENCES

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VEKLURY® (REMDESIVIR) FORMULATIONS INHIBIT INITIAL MEMBRANE-COUPLED EVENTS OF SARS-COV-2 INFECTION DUE TO THEIR CYCLODEXTRIN CONTENT

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Kitti Kurtan is a fifth year medical student at the University of Debrecen. Kitti joined a research team at the Department of Biophysics and Cell Biology at the University of Debrecen under the supervision of Florina Zakany MD, PhD in 2019. Kitti's research focuses on highlighting the potential beneficial effects of cholesterol-depleting cyclodextrins on the membrane-coupled events of SARS-CoV-2 infection. Presenting her research work at the local and national Student's Research Society Conferences, she was awarded 1st and 2nd prizes several times.

Aim: Up until now there is no effective therapy for severe COVID-19 disease caused by SARS-CoV-2. Remdesivir (REM), formulated under the trade name Veklury® as a powder or concentrated solution for intravenous infusion, was the first approved drug for the treatment of severe COVID-19. In addition to the same amount of REM, both formulations contain a significant amount (3 vs. 6 g) of sulfobutylether- β -cyclodextrin (SBECD) as a vehicle that can reach millimolar serum concentrations during therapy. However, the two formulations were considered equivalent in the clinical practice in spite of their different SBECD contents. Cyclodextrins (CDs), through their cholesterol-depleting ability, can reduce lipid raft localization of various proteins (e.g. ACE2 and TMPRSS2) by disrupting membrane microdomains. Therefore, we examined how different CDs and Veklury® formulations affect the association of ACE2 and TMPRSS2 with lipid rafts; furthermore the ACE2 binding and cellular uptake of SARS-CoV-2 spike proteins.

Methods: We evaluated ACE2-TMPRSS2-lipid raft colocalizations using quantitative confocal microscopy, ACE2 binding of spike receptor-binding domains with flow cytometry, and spike trimer internalizations using confocal microscopy and quantitative 3D image analysis in HEK cells stably expressing ACE2 and TMPRSS2 (HEK/ACE2+TMPRSS2) and as a more physiological model system of infection, Calu-3 human lung adenocarcinoma cells

Results: Clinically relevant CDs (MBCD, HPBCD, SBECD) and Veklury® formulations significantly reduced the association of ACE2 with lipid rafts and TMPRSS2 at therapeutically relevant concentrations, whereas REM alone exerted no such effect. Furthermore, CDs and Veklury® formulations dose-dependently reduced ACE2 binding of wild-type, delta and omicron spike proteins, and similarly, they inhibited the uptake of spike trimers.

Conclusions: CDs inhibit ACE2 receptor binding and uptake of different variants of SARS-CoV-2 spike proteins by reducing association of ACE2 with TMPRSS2 and lipid rafts. Furthermore, given that the Veklury® solution inhibited ACE2 binding of spike proteins more efficiently due to its twice higher SBECD content our findings call for the differentiation of Veklury® formulations that were treated equivalent thus far, and also raise the possibility of adjuvant cyclodextrin therapy, even at higher doses, in COVID-19 disease.