Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Co-infections: testing macrolides for added benefit in patients with COVID-19

Co-infections and pulmonary inflammation are potentially life-threatening consequences of COVID-19. We believe that for the management of co-infections, macrolide antibiotics are particularly useful. Although azithromycin is actively being pursued,[1] we would also like to suggest josamycin as a worthwhile alternative. Both macrolides are indicated for the treatment of a variety of respiratory infections including pharyngolaryngitis, acute bronchitis, and pneumonia, and the minimum inhibitory concentration of these drugs for the treatment of these infections are rapidly reached in the lungs.[2] With regards to COVID-19, macrolides are well known for their anti-inflammatory and immunomodulatory effects, observed in pulmonary inflammatory disorders such as diffuse panbronchiolitis, asthma, and cystic fibrosis.[3]

Recently, we have been particularly interested in josamycin, and we have assembled further evidence (appendix pp 1–7) of its antifibrotic and anti-inflammatory effects. On the basis of this evidence, we therefore consider that josamycin could be a good choice for patients with COVID-19, as these patients often develop fibrosis-related comorbidities and serious inflammatory symptoms. The UK National Institute for Health and Care Excellence (NICE) treatment guidance for pneumonia is the broad-spectrum antibiotic amoxicillin–clavulanic acid (co-amoxiclav) plus a macrolide. We concur with the opinion expressed by Michael Cox and colleagues[4] that further longitudinal surveillance data would improve antimicrobial stewardship throughout the course of the COVID-19 pandemic. Furthermore, however, we suggest that the choice of the supplemental macrolide antibiotic should be evaluated through interventional clinical trials and the choice of candidates be guided by their antifibrotic and anti-inflammatory secondary effects. The primary endpoint of such studies should be patient survival and the secondary endpoint the duration of stay in the intensive-care unit. Assessments of morbidity specifically due to lung function deterioration would also be important. For research on predictors of such adverse effects, specific biomarker sampling procedures have been suggested.[5]

As for the macrolide antibiotics to be evaluated, we suggest the following: local standard-of-care antibiotics; co-amoxiclav supplemented with clarithromycin, following NICE guidance; co-amoxiclav supplemented with azithromycin; and co-amoxiclav supplemented with josamycin. Our preference for azithromycin and josamycin is justified by their antifibrotic, anti-inflammatory, and immunomodulatory effects and their pharmacokinetic properties leading to effective concentrations in the target tissue (appendix). In conclusion, any primary antiviral and antibiotic treatment is not the only possibility in fighting COVID-19 pharmacologically, and it would be a shame if secondary positive effects of macrolides were missed in cases of patients who require antibiotic treatment anyway.

NU is an ex-employee (retired) of Astellas Pharma Europe. All other authors declare no competing interests.

*Katharina Anna Sterenczak, Israel Barrantes, Thomas Stahnke, Oliver Stachs, *Georg Fuellen, Nasrullah Undre*
fuellen@uni-rostock.de

Department of Ophthalmology (KAS, TS, OS) and Institute for Biostatistics and Informatics in Medicine and Ageing Research (IB, NU, GF), Rostock University Medical Center, Rostock 18057, Germany

1 Bleyzac N, Goutelle S, Bourguignon L, Tod M. Azithromycin for COVID-19: more than just an antimicrobial? *Clin Drug Investig* 2020; **40:** 683–86.
2 Parnham MJ, Erakovic Haber V, Giamarellos-Bourboulis EJ, Perletti G, Verleden GM, Vos R. Azithromycin: mechanisms of action and their relevance for clinical applications. *Pharmacol Ther* 2014; **143:** 225–45.
3 Zimmermann P, Ziesenitz VC, Curtis N, Ritz N. The immunomodulatory effects of macrolides—a systematic review of the underlying mechanisms. *Front Immunol* 2018; **9:** 302.
4 Cox MJ, Loman N, Bogaert D, O'Grady J. Co-infections: potentially lethal and unexplored in COVID-19. *Lancet Microbe* 2020; **1:** e11.
5 Fuellen G, Liesenfeld O, Kowald A, et al. The preventive strategy for pandemics in the elderly is to collect in advance samples & data to counteract chronic inflammation (inflammaging). *Ageing Res Rev* 2020; **62:** 101091.

Published **Online** November 2, 2020 https://doi.org/10.1016/S2666-5247(20)30170-1

See **Online** for appendix