Antibacterials/antivirals

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Off-label use in COVID-19 pneumonia, and induction of resistance through mutation selection: case report

A 66-year-old woman received off-label treatment with azithromycin, ceftriaxone, hydroxychloroquine and lopinavir/ritonavir for COVID-19 pneumonia. Additionally, she developed drug resistance, to which ceftolozane/tazobactam and off-label azithromycin contributed by mutation selection.

The woman, who was admitted to the ICU of hospital in Spain in March 2020 due to COVID-19 pneumonia, received off-label treatment with ceftriaxone, azithromycin, hydroxychloroquine and lopinavir/ritonavir. Eleven days following hospitalisation, she developed ventilator-associated pneumonia (VAP) due to *Pseudomonas aeruginosa*. The strain was resistant only to ceftazidime and piperacillin/tazobactam, and she was therefore treated with meropenem 2 g/8h for 8 days and ceftolozane/tazobactam 2 g/8h and 1 g/8h for two additional weeks. Subsequently, intermediate cultures were negative. However, a bronchial aspirate cultured was found to be again positive for *Pseudomonas aeruginosa*. Therefore, treatment was switched to piperacillin/tazobactam and amikacin; however, she died of respiratory complications after 2 weeks. The *Pseudomonas aeruginosa* strain (HC-20-232), which was isolated following treatment with ceftolozane/tazobactam treatment, was found to be resistant to meropenem and ceftolozane/tazobactam. Also, the strain was resistant to other β-lactams and fluoroquinolones. Whole-genome sequencing showed that the strain, belonging to ST274, had acquired a nonsense mutation leading to truncated carbapenem porin OprD (W277X), a 7-bp deletion (nt213D7) in NfxB (negative regulator of the efflux pump MexCD-OprJ) in addition to two missense mutations (Q178R and S133G) located within the first large periplasmic loop of MexD. Eventually, resistance to the novel cephalosporin-β-lactamase inhibitor combinations had been caused by the modification of MexD substrate specificity. It was noted that off-label azithromycin played a role in the induction of resistance since azithromycin is associated with the frequent selection of mutations leading to the overexpression of MexCD-OprJ because azithromycin is a major substrate of this efflux pump. Thus, it was considered that azithromycin possibly led to the selection of the nfxB mutation, leading to the overexpression of the efflux pump. Also, the subsequent treatment with ceftolozane/tazobactam might have selected the mutations leading to the structural modification of MexD.

Gomis-Font MA, et al. Emergence of Resistance to Novel Cephalosporin-beta-Lactamase Inhibitor Combinations through the Modification of the Pseudomonas aeruginosa MexCD-OprJ Efflux Pump. Antimicrobial Agents and Chemotherapy 65: 1-5, No. 8, Aug 2021. Available from: URL: http://doi.org/10.1128/AAC.00089-21 803600585