Zidovudine (azidothymidine, AZT) unexpressed clinical potential against multidrug-resistant Gram-negative isolates

Sir,

We read with great interest the article by Foletto et al. published in the *International Journal of Antimicrobial Agents* [1]. The authors conducted a nice systematic review of studies published in the last 20 years on the efficacy of non-antibiotic drugs as antimicrobials. Their survey was carried out up to 30 September 2020. The subject is of great interest and it is not easy to systematically cover such a large topic.

We would like to shed some light on the potential of the antiviral zidovudine, also know as azidothymidine (AZT), as an antimicrobial agent. Foletto et al. cited only one study on the repositioning of AZT as an antibacterial, but there are others that deserve to be mentioned. We are pleased to briefly summarise them here in order to contribute to the comprehensiveness of the systematic review on this hot topic.

In 2017, Ng et al. screened more than 1000 drugs for activity against a clinical carbapenem- and multidrug-resistant *Escherichia coli* isolate. The lead candidate was determined to be AZT. Time–kill assay revealed that AZT was rapidly bactericidal against *E. coli*, achieving a 6-log kill at 4× minimum inhibitory concentration (MIC) within 3 h [2].

In early 2018. Peyclit et al. assessed the efficacy of AZT against 40 bacterial strains including 16 *E. coli* (12 colistin-resistant, 3 carbapenem-resistant and 1 susceptible isolate) and 22 *Klebsiella pneumoniae* (11 colistin-resistant, 9 carbapenem-resistant, 1 colistin- and carbapenem-resistant and 1 susceptible isolate). They demonstrated that all tested Enterobacteriaceae strains were susceptible to AZT with MICs ranging from 0.2–6.25 μM (0.05–1.67 μg/mL) [3].

In mid 2018, Loose et al. tested, by time–kill curves, the combination of colistin sulphate and AZT both against colistin-susceptible and colistin-resistant Enterobacteriaceae. They demonstrated that AZT accelerated the killing of colistin-resistant *E. coli* or showed bactericidal activity even if the substances alone were not bactericidal [4].

In 2018, Hu et al. tested the combination of colistin and AZT against multidrug-resistant Enterobacteriaceae both using the checkerboard method and time–kill analysis as well as a murine peritoneal infection model. The fractional inhibitory concentration index (FICI) from the checkerboard assay demonstrated that AZT synergised with colistin against 61% and 87% of extended-spectrum β-lactamase (ESBL)-producing *E. coli* and *K. pneumoniae* strains, respectively, 100% of NDM-1-producing strains, and 92% of MCR-1-producing *E. coli* strains. Time–kill analysis demonstrated significant synergistic activities when AZT was combined with colistin. Moreover, the murine peritoneal infection model showed augmented activities of both drugs when given in combination against NDM-1-producing *K. pneumoniae* and MCR-1-producing *E. coli* infections [5].

In 2019, Falagas et al. reported the results of testing in vitro the combination of colistin and AZT against 100 clinical strains of colistin-resistant *K. pneumoniae* isolates collected in 2015–2017. Using the mini checkerboard broth microdilution method, they found synergistic activity in 79% (79/100) of isolates and additive activity in the remaining 21% (21/100) [6].

In mid 2019, Loose et al. published another paper on the topic, this time a phase 1 clinical study of seven healthy subjects. The subjects received intravenous colistin methanesulfonate and AZT alone and in combination. In an ex vivo study, urinary bactericidal titres and time–kill curve determinations were performed in artificial urine spiked with colistin sulfate and AZT using four *mcr-1*-positive colistin-resistant and five colistin-susceptible Gram-negative isolates. Combination with AZT increased urinary bactericidal titres by up to two dilution steps each for the Enterobacteriaceae and *Acinetobacter* but not for the *Pseudomonas* strains. In time–kill curves, the combination showed bactericidal activity against colistin-resistant strains even when the substances alone were not bactericidal [7].

In 2020, DeSarno et al. published a study conducted in vitro and in vivo (in *Galleria mellonella* larvae) using two *K. pneumoniae* strains producing either the NDM-1 or KPC-3 carbapenemase. In vitro, both strains were resistant to meropenem but susceptible to AZT. Although the combination of meropenem and AZT was not synergistic in vitro, the authors found the combination to prevent bacterial proliferation in an in vivo model [8].

In 2021, Antonello et al. reported the results of testing the combination of fosfomycin and AZT against 36 clinical isolates of multidrug-resistant Enterobacteriaceae. The in vitro study showed synergistic activity for the combination fosfomycin + AZT in 69% of the tested strains. Moreover, in 7 of 8 fosfomycin-resistant strains (MIC > 32 mg/L) the addition of AZT restored fosfomycin susceptibility. In an in vivo study using a *G. mellonella* model, the combination of fosfomycin and AZT resulted in greater larval survival (20–50%) than monotherapy [9].

We believe that AZT is a molecule with unexpressed clinical potential against multidrug-resistant bacterial infections, especially as part of combination therapy.

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Competing interests

None declared.

Ethical approval

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