Eravacycline for treatment of complicated intra-abdominal infections: the fire is not ignited!

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The worldwide surge of multi-drug resistant (MDR) Gram-negative infections has become a real threat in postsurgical and critically ill patients. Among the most dreaded MDR Gram-negatives are extended-spectrum β-lactamase (ESBL) and carbapenemase producing Enterobacteriaceae and MDR Pseudomonas species (1,2). Carbapenem-resistant Enterobacteriaceae (CRE), in particular, are a steadily growing plague associated with increased morbidity and high mortality rates (3). Against this MDR Gram-negative epidemic stands a long period of antibiotic "starvation", interrupted only by the market introduction of tigecycline and doripenem (4). This often left clinicians with no other option than choosing for "older" polymyxins and/or aminoglycosides as primary treatment of complicated urinary, abdominal, pulmonary, and blood infections caused by MDR Gram-negative bacteria (5,6). Unfortunately, these two antibiotic classes have no well-defined or an unpredictable pharmacokinetic and pharmacodynamic profile which hampers their efficacy whilst enhancing the risk for adverse effects and toxicity.

Partial relief from this distressing situation was provided by joint initiatives of national healthcare agencies, governmental institutions, and the pharmaceutical industry, to reinvigorate the development of new potent antibiotics. Combinations of either an existing β-lactam with a novel β-lactamase inhibitor (ceftazidime-avibactam) (7) or vice versa (ceftolozane-tazobactam) already emerged from this pipeline (8).

Eravacycline is a novel fluorocycline antibiotic that has reached phase 3 study evaluation. Basically, eravacycline has a modified tetracycline core structure which enables to overcome tetracycline-specific resistance mechanisms such as efflux pumps and ribosomal hydrolysis (9) but also renders it 2- to 4-fold more potent *in vitro* than tigecycline against CRE (10). Eravacycline showed important activity against MDR Gram-positive and Gram-negative micro-organisms, including those expressing ESBL or carbapenem resistance mechanisms (11,12).

In a recent issue of *JAMA Surgery*, Solomkin *et al.* presented the results of the IGNITE 1 trial assessing efficacy and safety of eravacycline *vs.* ertapenem in complicated intra-abdominal infections (cIAIs). This large phase 3 study enrolled 541 patients who were randomized to receive either intravenous (IV) eravacycline (1.0 mg/kg/12 h; 270 patients) or IV ertapenem (1.0 g daily; 271 patients). At the test-of-cure visit in the microbiologically intent-to-treat population (446 subjects), the clinical cure rates were 86.8% and 87.6% respectively demonstrating non-inferiority of eravacycline to ertapenem (13).

Despite presenting treatment groups with very well-balanced patient characteristics, surgical techniques, and infection types at baseline, the IGNITE 1 trial is far from confirming a potential benefit of eravacycline in this particular indication. First, the investigators took care to include only severe cIAIs, yet the low mean acute physiology and chronic health evaluation (APACHE) II scores in both groups refer to a low global disease severity with a predicted hospital mortality between 0 and 5% (14,15). This is mainly

driven by the exclusion of more severely ill patients, in particular those with septic shock and acute kidney injury. Second, the number of CREs (18 in each group) is too low to positively evaluate a potential therapeutic superiority of eravacycline against these micro-organisms. Third, the less favorable response of *Enterococcus faecalis* to eravacycline is somewhat cumbersome for a drug with assumed good activity against MDR Gram-positive bacteria, including vancomycin-resistant enterococci. In contrast, eravacycline provided clinical cure in more than 80% of patients infected with *Pseudomonas aeruginosa* despite its known poor *in vitro* activity against this bacterium. This may be due to a favorable reaction on even a short anti-Pseudomonal β-lactam use in the perioperative phase in association with a rapid and adequate surgical source control. Finally, patients treated with eravacycline were more likely to have one of the particular well-defined reasons of clinical failure. In the margin of the current trial, it is notably that a phase 3 clinical trial comparing eravacycline with levofloxacin for the treatment of complicated urinary tract infections did not achieve its primary endpoint of non-inferiority (16).

Taken together, the IGNITE 1 study does not offer convincing proof to propose eravacycline as a first-line drug for the treatment of cIAIs. It clearly does not challenge a standard carbapenem for treating ESBL-positive strains and CREs and probably will never rival with the novel β-lactam/β-lactamase combinations in a MDR Pseudomonas environment. Moreover, its efficacy in more severely ill and consequently more-difficult-to treat patients remains to be established.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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