Omadacycline — The Newest Tetracycline

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Omadacycline was the second antibiotic of the tetracycline class to be approved by the Food and Drug Administration (FDA) in 2018. Results of two phase 3, double-blind, randomized clinical trials of the drug, one involving acute bacterial skin and skin-structure infections and the other community-acquired bacterial pneumonia, are now reported in the Journal.1,2 Each trial was designed and executed according to FDA guidance.3,4 The primary efficacy end point in each was early clinical response, at 48 to 72 hours for acute bacterial skin and skin-structure infections and at 72 to 120 hours for community-acquired bacterial pneumonia, in an intention-to-treat population. Each was a noninferiority trial with a noninferiority margin of 10 percentage points and 90% and 80% power, respectively, for the comparison of omadacycline with linezolid for acute bacterial skin and skin-structure infections and the comparison of omadacycline with moxifloxacin for community-acquired bacterial pneumonia, in an intention-to-treat population. Each was a noninferiority trial with a noninferiority margin of 10 percentage points and 90% and 80% power, respectively, for the comparison of omadacycline with linezolid for acute bacterial skin and skin-structure infections and the comparison of omadacycline with moxifloxacin for community-acquired bacterial pneumonia. Previous antibacterial therapy was an exclusion criterion in the trial involving acute bacterial skin and skin-structure infections and was limited to 25% of the patients in the trial involving community-acquired bacterial pneumonia, which gives confidence in the conclusions that omadacycline had a meaningful treatment effect and that it was similar in efficacy to standard-of-care agents for these infections.

Both trials checked all the boxes required of a high-quality, interventional clinical trial,5 and the results enabled FDA approval of omadacycline for the treatment of acute bacterial skin and skin-structure infections and community-acquired bacterial pneumonia. Yet within the context of the growing threat of drug-resistant bacterial pathogens (carbapenem-resistant gram-negative pathogens most especially) and the urgent need for new agents active against them, one must ask: So what?

Omadacycline has few advantages over the numerous agents already available for the treatment of acute bacterial skin and skin-structure infections. The benefit, if any, of its activity against susceptible gram-negative organisms was untested because patients with a sole gram-negative pathogen at baseline were excluded from analysis. In addition, linezolid, the comparator agent, which lacks such activity, performed as well overall, and there were too few patients with mixed infection for a meaningful analysis. The oral formulation of omadacycline may offer an advantage in certain circumstances — for example, it could be given instead of linezolid as treatment for the occasional patient receiving monoamine oxidase inhibitor or antiserotonergic antidepressant therapy.

A similar analysis pertains to community-acquired bacterial pneumonia, for which there are several effective treatment options, although omadacycline may offer some advantages. In addition to having activity against typical bacterial respiratory pathogens, omadacycline is active against the atypical organisms Legionella pneumophila, Mycoplasma pneumoniae, and Chlamydia pneumoniae, whereas beta-lactams are not. Omadacycline is a single-agent alternative, either parenteral or oral, to empirical beta-lactam–macrolide combination therapy or a respiratory fluoroquinolone for community-acquired bacterial pneumonia. Fluoroquinolones, rightly or wrongly, have increasingly...
fallen from favor because of rare adverse events, including tendinopathies, neuropathic effects, and, more recently, aortic dissection. When the use of omadacycline for the treatment of community-acquired bacterial pneumonia is considered, it is important to remember that patients with hemodynamic instability, septic shock, clinically significant immunologic deficiency, or infection with a suspected drug-resistant pathogen (e.g., fluoroquinolone-resistant Klebsiella pneumoniae) were excluded from the trial. In addition, there was an imbalance in mortality; eight deaths in the omadacycline group and four in the moxifloxacin group. The reasons for this imbalance are unclear, but death occurred disproportionately among patients with a Pneumonia Severity Index risk class of IV (classes range from I to IV, with higher classes indicating a higher risk of death).

So what is the role of omadacycline for treatment of infections caused by multiple-drug-resistant pathogens? It is a question desperately in need of an answer. Omadacycline does not have cross-resistance with beta-lactam antibiotics, aminoglycosides, polymyxins, and fluoroquinolones and is active against organisms expressing tetracycline efflux and ribosomal protection genes. It is many times more active than doxycycline and minocycline against Enterobacteriaceae and Acinetobacter baumannii, with minimum inhibitory concentrations (MICs) less than or equal to 4 μg per milliliter for 90% of strains; the FDA breakpoint MIC for susceptibility of K. pneumoniae to omadacycline. Two other advanced-spectrum tetracyclines — tigecycline and eravacycline, the latter of which was recently approved by the FDA for the treatment of intraabdominal infections — have similar properties. Results with tigecycline in the treatment of carbapenem-resistant gram-negative infections have been disappointing. The FDA label warns of higher all-cause mortality with tigecycline than with comparators in clinical trials and specifically states that it is not indicated for the treatment of hospital-acquired pneumonia. Eravacycline failed in phase 3 trials evaluating its use in complicated urinary tract infections, a stated limitation of use in the label. With respect to in vitro activity as a predictor of in vivo efficacy, the MIC breakpoints vary according to species and cannot be generalized, and the MICs for drug-resistant strains often are higher than those for susceptible strains.

These considerations notwithstanding, omadacycline is the latest candidate with at least some promise for the treatment of infections caused by carbapenem-resistant Enterobacteriaceae and species of acinetobacter. Well-designed clinical trials of omadacycline for the treatment of infections caused by multiple-drug–resistant gram-negative pathogens are needed to determine its real value as an antibacterial agent.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

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