HOSPITAL CHRONICLES 2019, 14(1): 33–34

INFECTIOUS DISEASES CORNER

Infectious Diseases News / Literature Review / 2017

Natalia G. Vallianou, MD, MSc, PhD
First Departmernt of Internal Medicine "Evangelismos" General Hospital of Athens, Greece

Bezlotoxumab for Prevention of Recurrent Clostridium difficile Infection.
M.H. Wilcox, D.N. Gerding, I.R. Poxton, C. Kelly, R. Nathan, T. Birch, O.A. Cornely, G. Rahav, E. Bouza, C. Lee, G. Jenkin, W. Jensen, Y.-S. Kim, J. Yoshida, L. Gabryelski, A. Pedley, K. Eves, R. Tipping, D. Guris, N. Kartsonis, M.-B. Dorr, for the MODIFY I and MODIFY II Investigators*.
***N Engl J Med* 2017;376:305-317.**

In high-income countries, *Clostridioides difficile* is the most common cause of infectious diarrhea among hospitalized patients. Approximately 35% of patients will suffer recurrent *C. difficile* infection, which is more difficult to treat and is related to more hospitalizations, more severe outcomes, and higher costs than the first infection. Actoxumab and bezlotoxumab are human monoclonal antibodies against *C. difficile* toxins A and B, respectively. Researchers conducted two double-blind phase 3 trials, MODIFY I and MODIFY II, involving 2655 adults receiving oral antibiotics for primary or recurrent *C. difficile* infection. Participants received an infusion of bezlotoxumab (10 mg per kilogram of body weight), actoxumab plus bezlotoxumab (10 mg per kilogram each), or placebo; actoxumab alone (10 mg per kilogram) was given in MODIFY I. The primary end point was recurrent infection within 12 weeks. In both trials, the rate of recurrent *C. difficile* infection was significantly lower with bezlotoxumab alone than with placebo ($P<0.001$). Bezlotoxumab was associated with a rate of recurrent infection that was 38% lower than that associated with standard-of-care antibiotics therapy alone. Actoxumab was not efficacious when given alone and provided no additional benefit when given with bezlotoxumab. These observations are consistent with evidence indicating that toxin B is the main virulent factor for recurrent *C. difficile* infection in humans. The rates of adverse events were similar among the groups; the most common adverse effects being diarrhea and nausea.

Among participants receiving antibiotic treatment for primary or recurrent *Clostridioides difficile* infection, bezlotoxumab was associated with a substantially lower rate of recurrent infection–especially among high risk patients for recurrent infection- than placebo and had a safety profile similar to that of placebo.

Clinical considerations for optimal use of the polymyxins: A focus on agent selection and dosing.
J.M. Pogue, J.K. Ortwine, K.S. Kaye. *Clin Microbiol Infection* 2017; 23:229-233.

Colistin (polymyxin E) and polymyxin B became commercially available around the same time and their use has recently been increased, as they are effective for treating gram (-) multidrug resistant bacteria, such as carbapenem-resistant *Enterobacteriaceae* (*Escherichia coli*, *Klebsiella pneumoniae,* some *Enterobacter* spp), *Pseudomonas aeruginosa*, and *Acinetobacter baumannii)*. While polymyxin B is available directly as its sulphate salt for intravenous administration (25,000 Units/Kg followed by 25,000 Units/Kg separated in two daily doses), colistin is only commercially available for intravenous use in the form of its inactive pro-drug, colistin methanesulphonate (CMS) -administered at a dose of 9,000,000 international units initially and afterwards at a total dose of 9,000,000 international units separated in two daily dosages-, which must be hydrolysed in vivo to active colistin. This difference in formulation results in pharmacokinetic differences in vivo. There are various advantages to polymyxin B in theory, which explain the trend towards increased use of this agent and decreased use of colistin in countries, where both products are available, such as the USA. These potential advantages of polymyxin B comprise a faster and more predictable peak concentration, a potential for decreased toxicity (nephrotoxicity) as well as more predictable steady-state concentrations. Nevertheless, most of these advantages remain theoretical, and how polymyxin B performs compared with colistin remains largely unknown. Regarding its adverse side effects, there are reports of infusion-related reactions, peri-oral paraesthesias (neurotoxicity), and of skin hyperpigmentation with polymyxin B. Therefore, until further data become available, although it is reasonable to give preference to polymyxin B, colistin

should be considered a completely appropriate and acceptable alternative. Also, due to lack of evidence to support other formulations, CMS remains the preferred agent for inhalational use. When CMS is used as inhalation therapy, it should be administered shortly after it is mixed. Furthermore, some researchers recommend CMS to be preferred for intrathecal/intraventricular administration simply due to more experience and better applicable dosing recommendations.

New and improved? A review of novel antibiotics for Gram-positive bacteria.
M. Abbas, M. Paul, A. Huttner. *Clin Microbiol Infection* 2017; 23:697-703.

MRSA infections together with VRE infections remain a siginificant problem among hospitalized patients. This review focuses on the new cephalosporins ceftaroline and ceftobiprole; the lipoglycopeptides dalbavancin, oritavancin and telavancin; the fluoroquinolones delafloxacin, nemonoxacin and zabofloxacin; and the tetracycline omadacycline. Named 'fifth-generation' cephalosporins, ceftaroline and ceftobiprole are the first beta-lactams to possess anti-MRSA activity due to their high affinity for penicillin-binding protein-2a. Though both possess some activity against various Gram-negative pathogens, these drugs achieved approval for their anti-Gram-positive activity. Ceftaroline fosamil (Teflaro in the USA and Zinforo in Europe) achieved European Medicines Agency (EMA) approval in 2012. An inactive prodrug, ceftaroline fosamil, is rapidly converted in vivo to the active metabolite ceftaroline. They both appear to be well tolerated. Dalbavancin and oritavancin are newly on the market but are not new drugs. Like vancomycin, they exert their bactericidal activity by binding to the D-alanyl-D-alanine residue on growing peptidoglycan chains, preventing transpeptidation and thus, cell wall formation [24]. Unlike vancomycin, these semi-synthetic molecules possess a lipid side-chain conferring new pharmacokinetic properties, such as high protein-binding and unusually long half-lives, which allow for single-dose therapy. They are active against MRSA, coagulase negative staphylococci, vancomycin-susceptible Enterococcus faecium, but not VRE. Dalbavancin and oritavancin were well-tolerated in clinical trials. Tedizolid phosphate (Sivextro) is a synthetic oxazolidinone first developed in Korea in the 2000s and approved by FDA (2014) for the treatment of ABSSSI. Tedizolid inhibits protein synthesis by binding to the bacterial 50S ribosomal subunit. It is approved for a 6-days course treatment. Omadacycline is an aminomethylcycline antibiotic that possesses activity against a large series of Gram-positive and Gram-negative pathogens. It is bacteriostatic, inhibiting protein synthesis by binding to the 30S ribosomal subunit. After all, we seem to possess newer drugs in our armamentarium against MRSA and VRE infections.