EDITORIALS

Pharmacology and the Treatment of Complicated Skin and Skin-Structure Infections

Henry F. Chambers, M.D.

Skin and skin-structure infections are estimated to cause more than 15 million infections[1] and 870,000 hospital admissions[2] annually in the United States. Rates of these infections are substantially higher than they were 10 to 20 years ago, owing in part to the emergence of methicillin-resistant *Staphylococcus aureus* in the community.[3] Two articles in this issue of the *Journal* report the results of phase 3, randomized, double-blind clinical trials (one of dalbavancin[4] and the other of oritavancin[5]) for the treatment of acute bacterial skin and skin-structure infections. Although neither antibiotic agent is new (both date to the 1990s), they could transform the treatment of acute bacterial skin and skin-structure infection.

Dalbavancin and oritavancin are semisynthetic lipoglycopeptide analogues of teicoplanin and vancomycin, respectively, all of which share a similar mechanism of action and spectrum of activity. These are bactericidal antibiotics that inhibit the transpeptidase and transglycosylase steps in bacterial cell-wall synthesis of gram-positive bacteria by binding to the terminal D-alanyl-D-alanine of the stem pentapeptide of the nascent peptidoglycan. Lipid moieties of dalbavancin and oritavancin facilitate their binding and anchoring to the cell membrane and dimerization, enhancing potency against methicillin-resistant and methicillin-susceptible *S. aureus*, coagulase-negative staphylococci, streptococci, and enterococci; improving activity against some strains that are not susceptible to vancomycin; and reducing the frequency of resistant mutants. Both drugs are active against vancomycin-intermediate *S. aureus*, although minimum inhibitory concentrations (MICs) are higher than for susceptible strains. Dalbavancin is inactive against *vanA* strains of vancomycin-resistant *S. aureus* (VRSA) and vancomycin-resistant enterococci (VRE). Oritavancin has in vitro activity against VRSA and VRE, but their MICs are higher than for susceptible strains.

The pharmacologic features of these two agents make them therapeutically attractive. Terminal half-lives for both are approximately 2 weeks, and serum free-drug concentrations exceed MICs for a week or more.[6,7] They have concentration-dependent killing; the ratio of the area under the concentration curve to MIC correlates with in vivo efficacy. The clinical trials of dalbavancin and oritavancin were designed to take advantage of these properties by means of the administration of one or two large, pulse doses instead of smaller, closely spaced, multiple doses.

The trials were similar in many respects. Dalbavancin was administered intravenously as a 1000-mg dose, with a 500-mg dose administered 1 week later; oritavancin was given as a one-time dose of 1200 mg. Vancomycin at a dose of 15 mg per kilogram of body weight every 12 hours was the comparator in trials of both drugs, with a step-down option to oral linezolid in the dalbavancin trials. The trials were designed in accordance with the 2010 draft guidance and the final October 2013 guidance from the Food and Drug Administration for developing drugs for the treatment of acute bacterial skin and skin-structure infection.[8] The primary efficacy end

point was clinical response of the wound, cellulitis, or major abscess (i.e., no progression and reduction in lesion size as compared with baseline in a patient who is alive and did not receive rescue therapy) determined 48 to 72 hours after the initiation of therapy. This end point is a substantial departure from most registrational trials, which have used a more subjective determination by the investigator or adjudication panel of clinical success or failure at follow-up after the end of therapy.

Patients in the dalbavancin trials were sicker than those in the oritavancin trial. A higher percentage of patients had fever (85% vs. 15%), had an elevated white-cell count (40% vs. 22%), and met the criteria for the systemic inflammatory response syndrome (51% vs. 18%); in addition, the patients' lesions were 46% larger on average (345 cm^2 vs. 237 cm^2).

Outcomes for dalbavancin and oritavancin were similar to those of vancomycin. Both exceeded the noninferiority thresholds of 10% for the primary and secondary efficacy end points. There was 86% concordance of outcomes between lesion response at 48 to 72 hours and investigator-assessed success or failure of the treatment. The efficacy of vancomycin was remarkably similar across the trials, suggesting that differences in study design or populations did not have a significant effect on outcome.

Neither antibiotic is more efficacious than vancomycin, but either agent is certainly easier to administer. These agents make it possible to treat patients with complicated skin and skin-structure infections, who might otherwise require hospitalization, on an outpatient basis without compromising efficacy and without the need for laboratory monitoring or an indwelling intravenous catheter. This approach could profoundly affect how these infections are managed, by reducing or in some cases eliminating costs and risks of hospitalization.

The efficacy of these antibiotics for infections other than complicated acute bacterial skin and skin-structure infections is unknown. Acute bacterial skin and skin-structure infections in no way pose the therapeutic challenge and degree of difficulty encountered with invasive *S. aureus* infections such as pneumonia, deep-tissue abscesses, bone and joint infections, bacteremia, and endocarditis, which require prolonged courses of antibiotics at high doses.

Although the safety profiles of these drugs, in the few thousand patients treated thus far, are similar to that of vancomycin, the ultimate determination of the safety of dalbavancin or oritavancin must await broader clinical use. Once administered, these drugs take weeks to clear, and moderate or severe toxic or allergic reactions, if they occur, could cause substantial morbidity or prove fatal.

Given the data available to date, we do not know how effective these agents may be beyond treating acute bacterial skin and skin-structure infections, and the use of either agent for other types of infections should be done with caution. Future clinical trials are needed to define the safety and efficacy profile, especially in sicker patients and for more serious infections in which the need is great to improve management and reduce costs.

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

From the Department of Medicine, University of California, San Francisco, and the Division of Infectious Diseases, San Francisco General Hospital — both in San Francisco.

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