

New cephalosporin antibiotics for methicillin resistant *Staphylococcus aureus* (MRSA)

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Utilization Expected (3: Expected to be used by 40% to 60% of patients with the anticipated indications.)

Physicians will likely consider new cephalosporin antibiotics of equivalent efficacy to vancomycin for treating methicillin resistant *Staphylococcus aureus* infections if they offer a better adverse event profile. However, more data are needed to confirm the relative safety of these new drugs compared to existing antibiotics.

Time to Early Adoption (5: Early adoption occurring now.)

Basilea Pharmaceutica has received an approvable letter from the U.S. Food and Drug Administration (FDA) for ceftobiprole. The company expects a complete decision from FDA by early 2009 and hopes to have the drug on the market by mid-to-late 2009. Cerexa plans to file a new drug application for ceftaroline with FDA in 2009.

Health Impact (2: Expected to make a small improvement to patients' health and/or QOL.)

Although some studies suggest that new cephalosporin antibiotics might be as effective as vancomycin and cause fewer and less severe adverse events (AEs), more data are needed to confirm these findings. If large, late-phase trials can establish the new drugs' relative safety and efficacy, they might offer a small, though important patient benefit for those affected by AEs.

Financial Impact (2: Expected to have a small financial impact.)

Costs may initially be slightly higher as manufacturers attempt to recover expenses related to research and development of novel compounds, but are expected to be similar over time to costs of treatment with other infusible antibiotics, such as linezolid or vancomycin. If these new cephalosporins provide a better safety profile, costs of treating adverse events could decrease.

Process Impact (1: Expected to have a negligible process impact.)

Patients receive ceftobiprole and ceftaroline via intravenous infusion by a healthcare professional followed by a period of observation to monitor for adverse events. This is the same manner of administration as other antibiotics used to treat methicillin resistant *Staphylococcus aureus* infections.

ECRI Institute Perspectives & Predictions

- Two new cephalosporin antibiotics for methicillin resistant *Staphylococcus (S.) aureus* (MRSA) are in late-phase development and could reach the market by mid-2009.
- Some studies suggest that these drugs might offer an alternative therapy that is of similar efficacy, safety, and tolerability to vancomycin, with potentially fewer adverse events. However, more data are required to confirm that these drugs are as safe or safer than currently available antibiotics.
- New cephalosporin antibiotics will not likely replace current MRSA therapies such as vancomycin, but may be welcomed by physicians and patients seeking a treatment for vancomycin-resistant MRSA that might carry a lower risk of adverse events, if large, late-phase trials can establish the relative safety of these drugs.
- These new antibiotics would be delivered intravenously in a manner similar to other antibiotics for MRSA treatment and thus would not change processes of care.

Overview

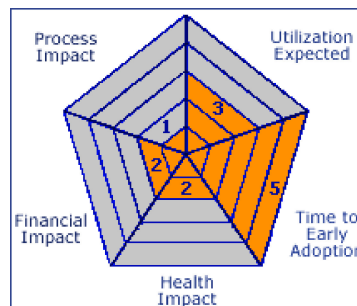
Researchers are seeking to develop new and safer antimicrobial agents to treat methicillin resistant *Staphylococcus aureus* (MRSA)-related complicated skin and skin structure infections (cSSSIs) that do not respond to current antibiotic treatments. Cephalosporin antibiotics interrupt the process of bacterial cell wall synthesis. This causes the walls to break down, resulting in bacterial lysis and death.

Basilea Pharmaceutica (Basel, Switzerland), in collaboration with Cilag GmbH International (Schaffhausen, Switzerland), has developed ceftobiprole, a new broad-spectrum cephalosporin antibiotic for treatment of MRSA-related infections. Ceftobiprole inhibits the antibiotic-blocking ability of many gram-positive bacteria, including MRSA and penicillin-resistant pneumonia (*Streptococcus pneumoniae*). The drug is also active against gram-negative bacteria. In trials, patients received 500 mg ceftobiprole by intravenous infusion (2 hours) every 8 to 12 hours for 7 to 14 days.

Cerexa, Inc. (Alameda, CA, USA) has developed ceftaroline, a broad-spectrum cephalosporin antibiotic for treatment of bacterial infections, including MRSA and other antibiotic-resistant bacterial strains. As a cephalosporin, its mechanism is nearly identical to that of ceftobiprole, and it is effective against gram-positive and gram-negative bacterial strains. In trials, patients received 600 mg ceftaroline by intravenous infusion every 12 hours for 5 to 14 days.

Although these antibiotics represent a new generation of cephalosporin antibiotics, their mechanisms of action are not novel. In addition, because highly virulent strains of MRSA can rapidly develop resistance against new antibiotics, the benefits of these new drugs may be short lived.

Regulatory Status



Ceftobiprole (Basilea Pharmaceutica)

In March 2008, the U.S. Food and Drug Administration (FDA) issued an approvable letter in response to Basilea's new drug application (NDA) for ceftobiprole for treatment of cSSSI after having granted it fast-track status in March 2007 (an accelerated approval process for drugs that treat life-threatening conditions or fill a gap in current treatment options). An "approvable letter" means that a company must submit additional information. Basilea is submitting follow-up data, and the company anticipates a decision from FDA in early 2009. However, late in November 2008, FDA sent Basilea a complete response letter stating that it will not review the clinical data submitted until Basilea and its sponsor, Johnson & Johnson, have demonstrated clinical quality and proper monitoring. FDA requested that Johnson & Johnson address deficiencies in its study conduct, and gave the company a year to respond. Although Basilea plans to address these concerns quickly, the regulatory process will likely be delayed for several months.

In June 2008, Health Canada granted marketing approval to ceftobiprole for sale in Canada under the trade name Zeftera (Johnson & Johnson, Langhorne, PA, USA). Ceftobiprole is also approved in Switzerland. In November 2008 the European CHMP (Committee for Medicinal Products for Human Use) gave ceftobiprole a positive opinion and referred it to the European Commission for final action.

Ceftaroline (Cerexa)

Ceftaroline is in phase III trials in the United States and Europe for the treatment of MRSA-related cSSSI and community-acquired pneumonia. In March 2006, FDA granted fast track status to ceftaroline for treatment of cSSSI. Cerexa plans to file an NDA with FDA in 2009. It has not yet received marketing approval from regulatory agencies in other countries.

Cost Issues

Costs of treatment with ceftobiprole or ceftaroline will initially be higher than costs associated with other infusible antibiotics, such as linezolid or vancomycin to recover expenses related to their research and development. However, these initial higher costs will offset other costs in the healthcare system for both payers and providers if they effectively treat infection and prevent MRSA-related complications.

Reimbursement Issues

Hospitals are keenly interested in any new treatment that can help them effectively treat MRSA infections and prevent their spread. The reasoning for this is due to the new policy introduced by the U.S. Centers for Medicare & Medicaid Services (CMS), which is also being adopted by many private third-party payers.

According to the CMS, as of October 1, 2008, CMS no longer provided coverage for hospital-acquired infections such as MRSA: <http://www.cms.hhs.gov/apps/media/press/factsheet.asp?Counter=3224>

Although MRSA infections are not explicitly described on CMS's list of "never events" (events that are usually preventable and would not occur if hospitals employ appropriate infection-control prevention protocols), CMS's reworded policies imply that hospital-acquired infections will no longer be covered by CMS:

If a condition is not present upon admission, but is subsequently acquired during the hospital stay, Medicare will no longer pay the additional cost of the hospitalization. The patient is not responsible for the additional cost. Rather, the hospital is being encouraged to prevent an adverse event and improve the reliability of care it is giving to Medicare patients.

CMS and third-party payers will likely continue coverage of community-acquired (i.e., non-hospital-acquired) MRSA infections through prescription drug plans.

Timing of Diffusion

If approved for marketing, anti-MRSA cephalosporin antibiotics will likely diffuse rapidly because they would offer new treatment options for a difficult problem. In addition, the cephalosporins are a class of drugs that clinicians are familiar with and currently use in practice.

Impact on Hospital Operations

The addition of new intravenous cephalosporin antibiotics to the MRSA armamentarium will likely have little or no impact on hospital operations. Administration of the new drugs would be by intravenous infusion by a healthcare professional followed by a period of patient observation to monitor for adverse events (AEs).

Patient Safety

In trials thus far, ceftobiprole and ceftaroline have demonstrated safety profiles comparable to the cephalosporin antibiotic class. However, more data are needed to confirm the relative safety of these new drugs. In trials, the most commonly reported side effects of ceftobiprole were mild-to-moderate nausea and vomiting, caramel-like taste, headache, and liver enzyme induction. The most commonly reported side effects of ceftaroline were headache, dizziness, insomnia, infusion site pain, itching, edema, and nausea. In a phase II study of ceftaroline, investigators reported similar AEs in the treated group and the control group (vancomycin): gangrene, recurrent infection, crystalluria (crystals in the urine), and kidney damage.

Recent and Ongoing Studies*Ceftobiprole (Basilea Pharmaceutica)*

In November 2007, FDA suspended a phase III randomized controlled trial (RCT) comparing cefepime to ceftobiprole for treatment of patients with cSSSIs because of potential safety issues with cefepime. In August 2007, lack of patient enrollment caused Basilea to withdraw a phase II study of ceftobiprole in patients with *S. aureus* bacteremia.

In January 2007, Basilea reported positive data from STRAUSS-2 (Study of Resistant *S. aureus* in Skin and Skin Structure Infections); a phase III double-blind RCT. Basilea enrolled 828 patients with cSSSI (diabetic foot infections, abscesses, and infected wounds) and randomly assigned them to receive 500 mg of ceftobiprole by infusion every 8 hours (n = 1032) or 1 g vancomycin every 12 hours (+ 1 g ceftazidime every 8 hours; n = 525). Researchers reported a clinical cure rate of 90.5% in patients receiving ceftobiprole and of 90.2% in patients receiving vancomycin, with a similar rate (4%) of AEs in

both groups; differences were not statistically significant.

In March 2006, Basilea released data from the first completed phase III trial of ceftobiprole (STRAUSS-1). The company enrolled 784 patients with gram-positive infections and randomly assigned them to receive 500 mg ceftobiprole (n=397) or 1 g vancomycin (n=387), twice daily for 7 to 14 days. Clinical cure rates were similar for the ceftobiprole group (93.3%) and the vancomycin group (93.5%); differences were not statistically significant. Although researchers reported fewer AEs in the ceftobiprole group than in the vancomycin group, the differences were not statistically significant.

Ceftaroline (Cerexa)

Cerexa is conducting a phase I trial (n= 8) to test the safety and efficacy of a single infusion of ceftaroline in patients 13 to 17 years of age with suspected infections, and is expected to complete the study by September 2008. However, as of November 2008, no data were available from this trial.

Cerexa is also conducting a small (150 patients), phase II study comparing ceftaroline injections against linezolid infusions over 5 to 14 days, which it expects to complete by late 2008.

In late 2007, Cerexa announced that its two large, phase III, double-blind RCTs for ceftaroline, CANVAS-1 and CANVAS-2, achieved their primary endpoints of non-inferiority (within a margin of 10%), thus demonstrating that ceftaroline was not less effective than vancomycin plus aztreonam. The trials enrolled 1,396 adults with cSSSI (703 in CANVAS-1 and 694 in CANVAS-2). They reported that patients treated with ceftaroline had a clinical cure rate of 93.1% for all cSSSIs, and had a clinical cure rate of 93.3% for MRSA infections. In addition, only 3% of patients in the ceftaroline group discontinued treatment compared to 4.8% of patients in the vancomycin group.

In September 2006, Cerexa released data from a phase II, observer-blinded RCT of ceftaroline in 100 patients with cSSSI. Investigators reported a 96.7% clinical cure rate in patients receiving ceftaroline and an 88.9% clinical cure rate in patients receiving vancomycin.

Effect on Other Technologies

Some studies thus far suggest that new cephalosporin antibiotics might be as effective as vancomycin for treatment of MRSA while potentially causing fewer and less severe AEs. However, more data are needed to confirm these results. Therefore, while the new cephalosporins will not replace vancomycin, clinicians may select them over vancomycin if they are demonstrated to produce fewer AEs than currently available antibiotics.

Several other new antibiotics in development could reach the market within a year or two and compete with the new cephalosporin antibiotics. For example, two lipoglycopeptide antibiotics are currently in late-phase development. Theravance, Inc. (San Francisco, CA, USA) submitted an NDA to FDA for telavancin in late 2007 and announced in October 2008 that an FDA advisory committee meeting had been scheduled to discuss marketing approval for the drug. Targanta Therapeutics Corporation has submitted an NDA for oritavancin and hopes to receive a response from FDA by late 2008.

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Publication History

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before 08/01/2008 may not include this feature.

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