The overall clinical success for all cases with microbiologic confirmation was 69% (42 of 61), indicating that the effectiveness of treatment may be unrelated to the MIC.

The analyses of the pooled SECURE and VITAL data substantiate the view that ISA is effective in the treatment of IA in patients with renal insufficiency, for whom other triazole antifungals may be restricted in use; they also indicate that dose adjustment for this patient population is not needed.

ISA has been approved for use in the United States for treatment of IA and mucormycosis in patients aged 18 years and older. Regulatory review in Europe is ongoing.

Brilacidin: A Novel Antibiotic Designed to Prevent MRSA

Written by Jill Shuman

Community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) is a growing problem in the United States and Europe and is a major cause of acute bacterial skin and skin structure infections (ABSSSIs) among otherwise healthy people in the community. Daniel Jorgensen, MD, Cellceutix, Beverly, Massachusetts, USA, presented safety and efficacy data from a phase 2b trial that compared brilacidin (BRI) with daptomycin (DAP) in treating community-acquired ABSSSI caused by *S aureus*.

BRI is a novel synthetic mimic of host defense proteins that has shown in vitro activity against multidrug-resistant *S aureus* in phase 1 and 2a trials. Antibiotics in this category, also known as *defensin mimetics*, kill bacteria in the same manner as the human immune system and thus are less likely to induce antimicrobial resistance. According to Dr Jorgensen, previously presented phase 2a data suggested that BRI was as effective as DAP over 7 days in treating ABSSSI [Jorgensen D et al. ICAAC 2012 (poster L1-1662)]. However, a transient dose-dependent elevation in blood pressure, likely the result of overdosing, was also noted. Therefore, the highest total dose of BRI used in the phase 2b trial (1.2 mg/kg) was less than the lowest total dose (1.6 mg/kg) used in the phase 2a trial.

The phase 2B trial included 215 patients in the United States with an ABSSSI as defined by the FDA [FDA. *Guidance for Industry*. 2013]. Patients were randomized to 1 of 3 BRI injections: low (0.6 mg/kg, single dose), medium (0.8 mg/kg, single dose), or high (0.6 mg/kg on day 1 and 0.3 mg/kg on days 2 and 3). The comparator was DAP (4 mg/kg) for 7 days. The primary end point was early clinical response (48 to 72 hours). Clinical response was defined as a percentage reduction in lesion size ≥ 20% compared to baseline.

Table 1. Clinical Response Rates: All-Treated Population

Study Visit	BRI-SD, Low (n = 53)	BRI-SD, High (n = 53)	BRI-SC, 3 d (n = 53)	DAP, 7 d (n = 50)
48-72 h[a]	45/49 (92.2)	46/48 (95.8)	51/52 (98.1)	45/48 (93.8)
7-8 d[b]	45/49 (91.8)	42/49 (85.7)	48/52 (92.3)	47/50 (94.0)
10-14 d[b]	44/50 (88.0)	39/47 (83.0)	44/47 (93.6)	46/48 (97.9)
21-28 d[b,c]	42/43 (97.7)	39/40 (97.5)	40/42 (95.2)	46/47 (97.9)

Data presented in n/N (%).

BRI, brilacidin; DAP, daptomycin; SC, short course; SD, single dose.

[a]Per FDA definition.

[b]Per investigator.

[c]Sustained clinical response.

The US clinical response rates are shown in Table 1.

According to Dr Jorgensen, there was an early and sustained percentage change in lesion area from baseline to day 7 and again through short-term follow-up (days 10 to 14) in both the all-treated/safety population and the microbiological intent-to-treat population. The most commonly isolated pathogen was *S aureus*, including MRSA. Safety data suggested that patients who received BRI were more likely to experience mild and transient numbness or tingling as compared with the DAP group; however, no increase in hypertension was noted in those randomized to BRI, and no deaths in any group were reported.

In conclusion, Dr Jorgenson emphasized that BRI appears to offer high activity against MRSA. A single dose was safe and effective when compared to a 7-day dose of DAP for the treatment of ABSSSI, which might offer treatment, pharmacoeconomic, and compliance advantages to health care providers and patients.

Macrolides Linked to Cardiac Events in Community-Acquired Pneumonia

Written by Emma Hitt Nichols, PhD

Macrolide antibiotic treatment of community-acquired pneumonia (CAP) was associated with an increased risk of cardiac events, such as arrhythmia and heart failure, compared with other antibiotic therapies. Douwe F. Postma, MD, University Medical Center Utrecht, Utrecht, The Netherlands, presented data from a post hoc analysis of the CAP-START trial [Postma DF et al. *N Engl J Med*. 2015].

International guidelines recommend macrolide antibiotics as treatment of CAP. However, an increased risk of cardiac events has been associated with macrolide

antibiotic use [Schembri S et al. *BMJ*. 2013; Ray WA et al. *N Engl J Med*. 2012]. The purpose of this post hoc analysis was to determine if cardiac complications were associated with macrolide use in hospitalized patients with CAP.

In the multicenter, crossover CAP-START trial, >2200 hospitalized patients with CAP randomly received β-lactam monotherapy, β-lactam plus macrolide therapy, or fluoroquinolone monotherapy. Each treatment was rotated through participating centers every 4 months. This post hoc analysis examined data from medical charts of new or worsening episodes of heart failure, myocardial ischemia, or arrhythmia according to prespecified criteria using a competing-risk approach. The cause-specific hazard ratio was determined using a Cox proportional hazards model, with the adjusted model accounting for 17 confounders.

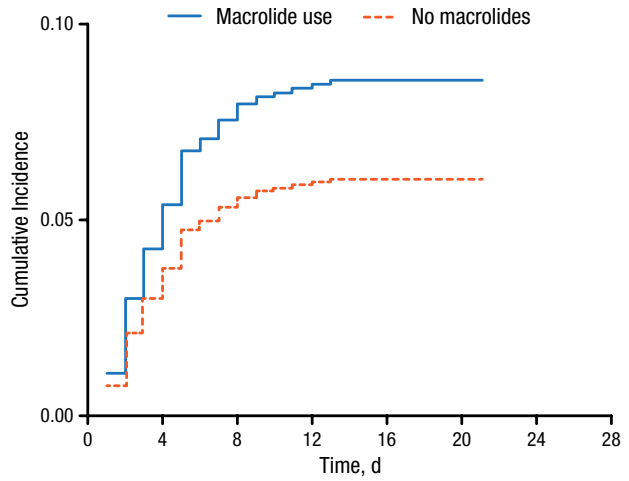
Among the >2000 evaluable patients from the CAP-START study, 15% had CAP due to *Streptococcus pneumoniae* infection, 33% had a history of cardiac disease, 9% had heart failure, and 15% had diabetes mellitus at baseline. In addition, upon hospitalization, the median blood urea nitrogen level was 6.4 mmol/L. The median age was 69.5 years, and 58% of patients were men. Macrolide treatment was administered to 30.8% for a minimum of 1 day.

In patients who receive macrolide therapy, the cumulative incidence of cardiac events was higher than in patients who did not receive macrolides (Figure 1).

Macrolide use was associated with an increased rate (66%) and net risk (81%) of cardiac events in patients with CAP during hospitalization. Furthermore, macrolide use resulted in an increased risk for cardiac events according to cause-specific (adjusted HR, 1.66; 95% CI, 1.18 to 2.34) and subdistribution (adjusted HR, 1.81; 95% CI, 1.29 to 2.55) analyses. Specifically, macrolide use resulted in greater rates of arrhythmia (3.0% vs 2.3%) and heart failure (7.0% vs 3.7%), but not myocardial ischemia (0.3% vs 0.8%). In addition, macrolide use was associated with a greater proportion of patients experiencing in-hospital death (4.2%) compared with patients who did not receive macrolides (2.6%).

In conclusion, Dr Postma indicated that the data from this post hoc analysis of the CAP-START study suggest that macrolide use is associated with an increased risk of cardiac events, as well as in-hospital death, compared with other antibiotic therapies.

Figure 1. Cumulative Incidence of Cardiac Events According to Macrolide Use in Community-Acquired Pneumonia



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Single-Hospital Comparison of Automated MRSA Detection Systems

Written by Brian Hoyle

A head-to-head comparison of 2 automated, polymerase chain reaction–based systems for the detection of methicillin-resistant *Staphylococcus aureus* (MRSA) in nasal swabs and culture samples from 119 high-risk patients has demonstrated the superiority in terms of detection accuracy and speed of the Xpert MRSA Gen 3 system over the BD-MAX MRSA system.

Martin Rottman, MD, PhD, Hôpital Raymond Poincaré AP-HP, Garches, France, and colleagues presented findings that the ongoing evaluation of the diagnostic performance of MRSA molecular assays is necessary, given the emergence of new strains with *mec* gene variations or altered staphylococcal cassette chromosomal junctions. This study focused on the performance of Xpert and BD-MAX automated molecular assays in comparison to 2 culture-based methods on nasal swab samples acquired from patients in the intensive care unit, orthopedic surgery unit, and rehabilitation medicine unit of Hôpital Raymond Poincaré. A hospital policy had designated these units as being at high risk for MRSA outbreaks in the tertiary-care center.

Consecutive nasal swab samples were collected from both anterior nares of 119 patients over a 45-day period. These and 36 nasal swab samples collected from patients who were culture-positive for MRSA were used for the 2 automated molecular assays as well as 2 culture-based methods. The culture-based methods were the Tryptic Soy Broth enriched culture method (gold standard) followed by MRSA select agar (culture time, 24 to 72 hours),