Two presenters in this session reported additional, more detailed safety and outcomes data from SECURE. Andrew J. Ullmann, MD, University of Würzburg, Würzburg, Germany, presented information regarding the development of treatment-emergent adverse events (TEAEs) in both the ISA and VRC groups. A TEAE was defined as any adverse event after the first administration of the drug until 28 days following the last administration.

Among patients in the ISA group, 96% experienced at least 1 TEAE, compared with 98% in the VRC group. This was an expected finding related to the severity of the patients' underlying illnesses. However, when analyzed by system organ class, moderate or severe TEAEs in the ISA group were lower in 19 of the 24 classes. In the comparison of the ISA and VRC groups, a significant difference was seen in disorders of the eye (15% vs 27%; $P < .01$), skin (33% vs 42%; $P < .05$), and hepatobiliary system (9% vs 16%; $P < .05$). Overall, the rate of treatment-related TEAEs was significantly lower in the ISA group than the VRC group (42% vs 60%, $P < .01$). Psychiatric (27% vs 33%) and cardiac (17% vs 22%) events were also lower in the ISA group vs the VRC group; however, this difference was not statistically significant.

Prof Ullmann suggested that the difference in TEAEs favoring ISA was influenced primarily by 4 factors: disorders of the eye, the hepatobiliary system, investigations (including elevations in hepatic enzymes), and psychiatric disorders.

Debra Goff, PharmD, Ohio State University, Columbus, Ohio, USA, presented safety and outcomes in obese patients (body mass index [BMI] ≥ 30 kg/m^2) enrolled in the SECURE trial. The analysis was done on patients with proven/probable IFD treated with either ISA or VRC who were categorized into 3 BMI classifications: < 25, 25 to < 30, and ≥ 30 kg/m^2.

Of the 527 randomized patients, 263 had proven/probable IFD and BMI data available; 25 patients were obese (ISA, n = 15; VRC, n = 10). All-cause mortality through day 42 was comparable between treatment arms in obese patients (1 vs 2 patients; adjusted difference, –13.3; 95% CI, –50.9 to 24.2). Similar numbers of obese patients responded successfully to either ISA or VRC (6 vs 4; adjusted difference, 0.0; 95% CI, –49.4 to 49.4). Drug-related TEAEs (40% vs 70%), serious TEAEs (53% vs 90%), and deaths (27% vs 40%) were less frequent in obese patients treated with ISA compared with VRC.

Dr Goff concluded that in this small subgroup of obese patients, ISA outcomes were comparable with VRC and similar to those of the other BMI subgroups. Among a small group of obese patients, there were fewer drug-related TEAEs, serious TEAEs, and deaths reported in those treated with ISA vs VRC.

Isavuconazole Safe, Effective in Treatment of IA in Patients With Renal Insufficiency

Written by Brian Hoyle

Two analyses of the pooled data from the global phase 3 multicenter VITAL [NCT00412893] and SECURE [NCT00634049] trials have demonstrated the safety and effectiveness of the broad-spectrum triazole antifungal drug isavuconazole (ISA) in the treatment of invasive aspergillosis (IA) in patients with renal impairment. Renal dysfunction can occur in up to 40% of those with IA. ISA, which is available orally as water-soluble isavuconazonium sulfate, overcomes the limitations of other intravenous drugs available to treat IA that are associated with increased risk of renal toxicity in patients with preexisting renal dysfunction [Baddley J et al. *Clin Infect Dis*. 2010; Vandewoude K et al. *J Hosp Infect*. 2004].

SECURE was a double-blind, parallel-group noninferiority trial that compared ISA and voriconazole in the treatment of IA and, more broadly, invasive fungal disease in 527 patients. Some of these patients had renal impairment. VITAL was an open-label trial involving 149 patients, and it examined the use of ISA in both fungal diseases. Both trials used a loading dose of ISA (200 mg TID intravenously on days 1 and 2), followed by ISA 200 mg QD intravenously or orally from day 3 to the end of treatment (days 84 and 180 in SECURE and VITAL, respectively). Patients were aged ≥ 18 years with proven/probable IA, with or without renal impairment at baseline. The key end point was all-cause mortality through day 42. Secondary end points included all-cause mortality and probability of survival through day 84. Treatment success was the partial or complete resolution of clinical symptoms, physical findings, and radiological abnormalities. The type, frequency, and severity of treatment-emergent adverse effects (TEAEs) were recorded.

One of the pooled analyses was presented by Johan Maertens, MD, PhD, UZ Leuven, Leuven, Belgium. This analysis focused on 143 patients of the 676 in the pooled population who had proven/probable IA treated with ISA. Thirty-one patients had renal impairment, and the remaining 112 did not. Patient characteristics at baseline are summarized in Table 1.

All-cause mortality was similar in patients with (n = 31) or without (n = 112) renal impairment at baseline through day 42 (4 [13%] vs 21 [19%]) and day 84 (8 [26%] vs 32 [29%], respectively). Overall successful response to treatment was similar in patients with (10 [32%]) and without (40 [36%]) renal impairment. The probability of survival determined by the Kaplan-Meier method

Table 1. Patient Characteristics at Baseline

Parameter	Renally Impaired (n = 31)	Not Renally Impaired (n = 112)
Age, median (range), y	61 (19-92)	52 (18-81)
Men	19 (61)	62 (55)
eGFR-MDRD, mean ± SD, mL/min/1.73 m^2	41 ± 12	125 ± 56
Renal impairment[a]		
Stage 3	23 (74)	0
Stage 4	8 (26)	0
Risk factors for development of infection[b]		
Allogeneic HSCT	13 (42)	26 (23)
Hematologic malignancy status	20 (65)	90 (80)
Neutropenia[c]	10 (32)	75 (67)
Corticosteroid use	15 (48)	22 (20)
T-cell immunosuppressant use	20 (65)	48 (43)
Uncontrolled malignancy[d]	10 (32)	76 (68)
New diagnosis/active disease	5 (16)	51 (46)
Relapse	5 (16)	25 (22)
Remission	11 (35)	17 (15)
Underlying disease	31 (100)	110 (98)
Acute myeloid leukemia	9 (29)	39 (35)
Chronic lymphocytic leukemia	3 (10)	4 (4)
Acute lymphocytic leukemia	2 (6)	15 (13)
Non-Hodgkin lymphoma	3 (10)	12 (11)
Diabetes mellitus	2 (6)	2 (2)
Other	12 (39)	39 (35)
Pathogen causing invasive fungal disease		
Aspergillus spp only	21 (68)	46 (38)
Aspergillus not otherwise specified	3 (10)	1 (1)
A fumigatus	10 (32)	29 (26)
A flavus	5 (16)	10 (9)
A terreus	—	5 (4)
A niger	2 (6)	5 (4)
A versicolor	1 (3)	—
A sydowi	—	1 (1)
Aspergillus + other mold spp	—	3 (3)
No pathogen identified	10 (32)	63 (56)

Data presented in No. (%) unless otherwise indicated.

eGFR-MDRD, estimated glomerular filtration ratio calculated from serum creatinine using the Modification of Diet in Renal Disease; HSCT, hematopoietic stem cell transplantation.

[a]Stage 3 renal impairment defined as eGFR-MDRD between 30 and < 60 mL/min/1.73 m^2 and stage 4 renal impairment defined as eGFR-MDRD between 15 and < 30 mL/min/1.73 m^2.

[b]Patients could have > 1 risk factor.

[c]Presence of neutropenia was based on an absolute neutrophil count $< 0.5 \times 10^9$/L at baseline; persistence of neutropenia was defined as 2 consecutive absolute neutrophil counts $< 0.5 \times 10^9$/L on 2 separate days as determined by the investigator.

[d]Patients with malignancy diagnosis and new/active disease or relapse.

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Table 2. Treatment-Emergent Adverse Outcomes

Parameter	Renally Impaired (n = 31)	Not Renally Impaired (n = 112)
TEAEs	31 (100)	107 (96)
Study drug-related TEAEs	12 (39)	44 (39)
Serious TEAEs	21 (68)	67 (60)
TEAEs leading to permanent discontinuation of the study drug	5 (16)	22 (20)
TEAEs leading to death	10 (32)	31 (28)
Study drug-related TEAEs leading to permanent discontinuation of the study drug	2 (6)	12 (11)
Deaths[a]	14 (45)	40 (36)

Data presented in No. (%).

TEAE, treatment-emergent adverse effect.

[a]All reported deaths after first dose of study drug are reported, regardless of the number of days after the last dose of the study drug.

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was also similar in those with or without baseline renal impairment.

TEAEs occurred in all renal-impaired patients and 96% of patients without renal impairment (Table 2). The most common TEAE was infections/infestations, which occurred in 10 of 31 (32%) of those with renal impairment and 25 of 112 (22%) of those without renal impairment, followed by respiratory/thoracic/mediastinal disorders (5 [16%] vs 21 [19%]). Doubling of serum creatinine was noted in 1 of 30 patients (3%) with renal impairment and 14 of 109 patients (13%) without renal impairment.

As discussed by William Hope, PhD, University of Liverpool, Liverpool, United Kingdom, the second analysis of the pooled SECURE and VITAL data focused on the minimum inhibitory concentration (MIC) of ISA on the various fungal pathogens.

Baseline susceptibility of *Aspergillus* isolates to ISA was assessed using criteria of the European Committee on Antimicrobial Susceptibility Testing's definitive document E.DEF 9.1 [Rodriguez-Tudela JL et al. 2008]. Treatment success was the expert-assessed absence of clinical signs and symptoms at the end of treatment.

Aspergillus infection was confirmed microbiologically at baseline in 61 patients, comprising *A fumigatus* (n = 31), *A flavus* (n = 15), *A niger* (n = 9), *A terreus* (n = 5), and *A westerdijkiae* (n = 1). The MIC of ISA in these species ranged from 0.12 to > 16 mg/L. The assessed clinical success of treatment was 50% to 100% for species with MIC < 16 mg/L and was similar for *A fumigatus* (71.0%), *A flavus* (73.3%), *A niger* (66.7%), and *A terreus* (60.0%).

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