Voriconazole Safe and Effective in Children With IC, EC, and IA

Written by Emma Hitt Nichols, PhD

Judith M. Martin, MD, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA, presented data from 2 studies that evaluated the safety and efficacy of voriconazole in pediatric patients with invasive candidiasis (IC), esophageal candidiasis (EC), and invasive aspergillosis (IA).

The incidence of invasive fungal infections has increased during the past 20 years in pediatric patients, with immunocompromised patients at an increased risk. Importantly, there are limited antifungal agents approved for use in pediatric patients. The triazole antifungal agent, voriconazole, has been demonstrated to be effective in adult patients with IC, EC, and IA [Ally R et al. *Clin Infect Dis*. 2001; Herbrecht R et al. *N Engl J Med*. 2002; Kullberg BJ et al. *Lancet*. 2005]. The purpose of these studies was to evaluate the safety and efficacy of voriconazole in pediatric patients with IC, EC, or IA.

Voriconazole was evaluated in 2 prospective, open-label, nonrandomized trials. The IC–EC trial had 22 patients, and the IA trial had 31 patients, all aged 2 to < 18 years. Of these 53 patients, 7 had confirmed IC, 10 had confirmed EC, and 14 had confirmed IA, using the Europe Organization for Research and Treatment of Cancer (EORTC) criteria. The dosing scheme for both trials is shown in Table 1. The duration of treatment was a minimum of 7 days after the last positive culture or 14 days after resolution of symptoms in patients with IC or EC, respectively, and 6 weeks in patients with IA.

The mean age was 9.5 years in the IC–EC study and 11.9 years in the IA study. Comorbid clinical conditions included blood and lymphatic system disorders, cardiac disorders, hepatobiliary disorders, neoplasms, and renal disorders. The mean duration of voriconazole therapy was 14 days in the IC–EC study and 49 days in the IA study.

The efficacy end point in the IC–EC study was the global response success rate (GRSR), defined as clinical cure or improvement and confirmed or presumed microbiologic eradication at the end of treatment (EOT); all-cause mortality was assessed at day 28 and EOT. In the modified intention-to-treat (mITT) population, the GRSR was 88.9% (95% CI, 51.75 to 99.72) in patients aged 2 to 11 years (n = 9) and 62.5% (95% CI, 24.49 to 91.48) in patients aged 12 to 17 years (n = 8). The GRSR by pathogen in the IC–EC study is shown in Table 2.

In the IA study, the efficacy end point was the GRSR, defined as clinical resolution or improvement of signs and symptoms plus complete or partial resolution of radiologic findings in patients with proven or probable IA, and it was assessed at weeks 6 and 12 (Table 3).

In the IC–EC trial, there were no deaths. In the IA trial, there were 5 deaths from any cause; 3 patients aged 2 to 11 years and 1 patient aged 12 to 17 years at 6 weeks, and 1 patient aged 12 to 17 years at EOT. None of the deaths were attributed to the treatment. In the IC–EC study, the most common treatment-related adverse events (TRAEs) were photophobia in 3 patients and rash in 2 patients; TRAEs leading to discontinuation of the study treatment occurred in 3 patients. In the IA study, the most common TRAEs were photophobia in 2 patients, blurred vision in 3 patients, increased alanine aminotransferase in 2 patients, abnormal liver function test results in 2 patients, and increased transaminases in 2 patients; also, 2 patients had serious adverse events related to treatment (acute renal failure and drug-induced liver injury).

Table 1. Dosing Scheme by Indication in Pediatric Patients

Children 2–11 y and Young Adolescents 12–14 y and Weighing < 50 kg	**Loading Dose**	**Maintenance Dose**	
	IV	**IV**	**If Switched to Oral Voriconazole**
IC and IA	9 mg/kg IV q12h for first 24 h	8 mg/kg IV q12h	9 mg/kg PO q12h (maximum initial dose, 350 mg)
EC	No loading dose	4 mg/kg IV q12h	9 mg/kg PO q12h (maximum initial dose, 350 mg)
Adolescents 12–17 y (Excluding Young Adolescents 12–14 y and Weighing < 50 kg)	**Loading Dose**	**Maintenance Dose**	
	IV	**IV**	**If Switched to Oral Voriconazole**
IC and IA	6 mg/kg IV q12h for first 24 h	4 mg/kg IV q12h	200 mg PO q12h
EC	No loading dose	3 mg/kg IV q12h	200 mg PO q12h

EC, esophageal candidiasis; IA, invasive aspergillosis; IC, invasive candidiasis; IV, intravenous; PO, oral; q, every.

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Table 2. Global Response Success Rates of Voriconazole in the IC–EC Study

	IC			EC		
	2 to < 12 y	12 to < 18 y	Overall	2 to < 12 y	12 to < 18 y	Overall
C. albicans, n/N (%)	1/2 (50.0)	0	1/2 (50.0)	2/2 (100)	5/8 (62.5)	7/10 (70.0)
C. glabrata, n/N (%)	1/1 (100)	0	1/1 (100)	0	0	0
C. parapsilosis, n/N (%)	1/1 (100)	0	1/1 (100)	0	0	0
C. tropicalis n/N (%)	3/3 (100)	0	3/3 (100)	0	0	0

IC, invasive candidiasis; EC, esophageal candidiasis; n/N, number of patients responding out of total population.
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Table 3. Global Response Success Rate in the IA Study

	2 to < 12 y, n = 5	12 to < 18 y, n = 9	Overall, n = 14
Week 6, n (%) [95% CI]	2 (40.0) [5.3 to 85.3]	7 (77.8) [40.0 to 97.2]	9 (64.3) [35.1 to 87.2]
EOT, n (%) [95% CI]	2 (40.0) [5.3 to 85.3]	7 (77.8) [40.0 to 97.2]	9 (64.3) [35.1 to 87.2]

EOT, end of treatment; IA, invasive aspergillosis.
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The investigators concluded that the data from these analyses suggest that treatment of pediatric IC, EC, or IA with voriconazole was safe and effective, and consistent with previous studies in adults.

Isavuconazole Effective in UncCAs and HMs

Written by Emma Hitt Nichols, PhD

Patients with invasive fungal disease (IFD) and comorbid conditions such as hematologic malignancy (HM) and uncontrolled malignancy (UncCA) were successfully treated with the novel triazole antifungal agent isavuconazole, regardless of minimum inhibitory concentrations (MICa) required by baseline *Aspergillus* spp isolates. Andrew J. Ullmann, MD, Julius Maximilians University, Würzburg, Germany, presented data according to type of malignancy from the Isavuconazole (BAL8557) for Primary Treatment of Invasive Aspergillosis trial [SECURE; NCT00412893].

IFD is a challenge, particularly in immunocompromised patients [Leventakos K et al. *Clin Infect Dis* 2010; Kontoyiannis DP et al. *Clin Infect Dis* 2010; Pappas PG et al. *Clin Infect Dis* 2010], and patients with UncCA [Bohme A et al. *Ann Hematol* 2009] and HM [Pagano L et al. *Haematologica* 2006]. In addition, mortality rates remain high in populations such as organ or hematopoietic stem cell transplant recipients who have invasive aspergillosis (IA) [Baddley JW et al. *Clin Infect Dis* 2010]. The broad-spectrum triazole antifungal agent, isavuconazole, demonstrated efficacy against multiple pathogens, including *Aspergillus* spp, *Candida* spp, *Cryptococcus* spp, and Mucorales in vitro, as well as IA, invasive candidiasis, mucormycosis, and cryptococcosis in animal models [Lepak A et al. *Antimicrob Agents Chemother* 2013; Lepak A et al. *Antimicrob Agents Chemother* 2013; Luo G et al. *Antimicrob Agents Chemother* 2014]. The overarching purpose of the SECURE trial was to evaluate the safety and efficacy of isavuconazole in patients with IFD [Maertens J et al. ECCMID 2014 0230a]; the purpose of this analysis was to evaluate the outcomes of isavuconazole treatment in patients with UncCA who participated in the SECURE trial.

In the multicenter, noninferiority, Phase 3 SECURE trial, 516 patients (intention-to-treat population) age ≥ 18 years with proven or probable IFD were randomly assigned to receive 200 mg IV TID isavuconazole for 2 days followed by 200 mg (IV or oral) QD or standard-dose voriconazole. The primary end point of all-cause mortality at day 42 was 22% and 25% in the isavuconazole and voriconazole arms, respectively, with drug-related adverse events occurring more frequently in the voriconazole arm (60 vs 40%). Secondary end points included success rate, adverse events, and other safety parameters.