VT-1161 Emerges as Potential Treatment for Acute Vulvovaginal Candidiasis

Written by Rita Buckley

The novel antifungal agent VT-1161 was as effective as fluconazole for the treatment of acute vulvovaginal candidiasis (VVC) and more effective than the latter for preventing recurrence of VVC, according to results of a phase 2a dose-ranging study [NCT01891331] presented by Stephen R. Brand, PhD, Viamet Pharmaceuticals, Inc, Durham, North Carolina, USA.

VT-1161, a novel oral selective inhibitor of fungal CYP51, is being developed to treat mucosal and superficial fungal infections [Hoekstra WJ et al. *Bioorg Med Chem Lett.* 2014; Warrilow AGS et al. *Antimicrob Agents Chemother.* 2014]. It is highly active against a wide range of *Candida* spp, including azole-resistant strains. A phase 2a study showed that VT-1161 was effective and safe in patients with moderate to severe acute VVC.

The present randomized double-blind trial evaluated the efficacy and safety of different doses of oral VT-1161 compared with fluconazole in patients with moderate to severe acute VVC.

Fifty-five patients were randomized to 1 of 4 treatment arms: low-dose VT-1161 (300 mg/d for 3 days; n = 14), middose VT-1161 (600 mg/d for 3 days; n = 12), high-dose VT-1161 (600 mg BID for 3 days; n = 14), or fluconazole 150 mg for 1 day administered as a single dose (n = 15). At baseline, approximately 76% of patients had a positive culture for *Candida* spp. Demographics and baseline characteristics were similar across all groups.

The outcomes were an effective therapeutic cure, defined as a total acute VVC severity score of 0 or 1 and a negative *Candida* culture assessed at day 28, as well as the ability to prevent mycologic and clinical recurrence at 5 months after study treatment was stopped. In the intention-to-treat population, the rates of an effective clinical cure were 71%, 83%, 86%, and 78% in the low-, mid-, and high-dose VT-1161 arms and fluconazole arm, respectively. Furthermore, the rates of mycologic cure were 100%, 92%, 93%, and 73% in these 4 arms, respectively.

At the 5-month follow-up, none of the patients in the VT-1161 arms had a positive *Candida* culture, compared with 46% of patients in the fluconazole arm. Clinical recurrences that required retreatment during the trial occurred in 47% of the fluconazole patients vs 14% of the low-dose VT-1161 patients; none occurred in the mid- and high-dose VT-1161 patients.

No patients in the intention-to-treat population discontinued participation in the study through the 6-month follow-up. Reported adverse events were mild and considered unrelated to the study drug. No clinically significant changes in vital signs, physical findings, electrocardiograms, or laboratory parameters were observed.

Overall, this study showed that VT-1161 provided a similar effective therapeutic cure at day 28 as fluconazole, but at the mid- and high doses, VT-1161 was more effective in preventing disease recurrence. This latter finding suggests that VT-1161 may have a role in treating recurrent VVC, for which there is no approved therapy, according to the investigators. Indeed, this is now being investigated in the phase 2b randomized REVIVE trial [NCT02267382] in patients with recurrent VVC in the United States.

Dalbavancin Effective Treatment for Skin Infection Regardless of Weight Category

Written by Rita Buckley

DISCOVER 1 and DISCOVER 2—identically designed phase 3 double-blind international trials—demonstrated that dalbavancin was noninferior to vancomycin or linezolid in the treatment of acute bacterial skin and skin structure infections (ABSSSIs) [Boucher HW et al. *N Engl J Med.* 2014]. Sailaja Puttagunta, MD, Durata Therapeutics, Branford, Connecticut, USA, presented a poster of a substudy of DISCOVER showing that the efficacy of dalbavancin extends to those who have obesity.

Dalbavancin is a lipoglycopeptide antibiotic agent that is active against gram-positive pathogens and has a long plasma half-life that allows for once-weekly dosing. DISCOVER 1 and DISCOVER 2 included adults with ABSSSIs (cellulitis, major abscesses, wound infection) with erythema > 75 cm^2 and 1 of the following: a fever, an elevated white blood count (> 12 000 white blood cells/mm^3), or > 10% band forms on the white cell differential count.

Other eligibility requirements, in addition to erythema, were at least 2 of the following: purulent drainage or discharge, fluctuance, heat or localized warmth, tenderness on palpation, and swelling or induration. Patients who received antibiotic treatment within 14 days of randomization were excluded.

Table 1. Clinical Outcomes of Acute Bacterial Skin and Skin Structure Infections by BMI

	Clinical Response at 48-72 h (ITT)		Clinical Status at EOT (CE)	
BMI, kg/m^2	Dalbavancin (n = 659)	Vancomycin/Linezolid (n = 653)	Dalbavancin (n = 570)	Vancomycin/Linezolid (n = 545)
< 25	144/182 (79.1)	166/212 (78.3)	144/157 (91.7)	158/174 (90.8)
25 to < 30	195/239 (81.6)	164/199 (82.4)	189/207 (91.3)	155/163 (95.1)
≥ 30	186/231 (80.5)	190/240 (79.2)	184/206 (89.3)	189/208 (90.9)

Data presented in n/N (%).

BMI, body mass index; CE, clinically evaluable; EOT, end of treatment; ITT, intention to treat.

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Participants aged 18 to 85 years were randomly assigned to receive either of the following:

- 1 g of intravenous dalbavancin over a period of 30 minutes on day 1, followed by 500 mg intravenously over a period of 30 minutes on day 8, or
- 1 g (or 15 mg/kg of body weight) of intravenous vancomycin over a period of 120 minutes every 12 hours for at least 3 days, with an option to switch to 600 mg of oral linezolid every 12 hours to complete 10 to 14 days of therapy.

The primary end point was the cessation of the spread of infection-related erythema of the lesion at 48 to 72 hours and the absence of fever at 3 consecutive recordings every 6 hours in the intention-to-treat population.

The objective of the subgroup analysis was to evaluate the clinical effectiveness of dalbavancin for the treatment of ABSSSIs in patients who were obese (body mass index [BMI] ≥ 30 kg/m^2) relative to those who were overweight (BMI, 25 to 29.9 kg/m^2) and normal weight (BMI < 25 kg/m^2).

Efficacy of dalbavancin was assessed in the 3 weight groups by a categorical analysis of subgroups of patients stratified by weight bands or as part of a covariance analysis examining BMI as a continuous and categorical variable. Baseline demographics were similar in the three groups. Clinical outcomes by BMI are shown in Table 1.

Clinical success rates were similar in all 3 weight groups, suggesting that dalbavancin was an effective treatment option for patients who have skin infections and are obese, overweight, or normal weight.

Efavirenz-Based Therapy Effective in Highly Suppressed HIV-1–Infected Patients

Written by Maria Vinall

Final results of the ADVANZ-3 trial [NCT00532168], presented by Christian Manzardo, MD, PhD, Hospital Clinic-IDIBAPS, Barcelona, Spain, confirmed that efavirenz (EFV)-based therapy is appropriate for HIV-1–infected patients with very low CD4 T-cell counts and high plasma HIV-1 RNA levels, provided they are adherent to therapy and do not have transmitted drug-resistant mutations.

It is not known whether the type of combination antiretroviral therapy (cART) regimen (ie, a protease inhibitor [PI]–based vs nonnucleoside reverse transcriptase inhibitor–based regimen) impacts treatment outcomes in highly suppressed patients with HIV-1. In addition, only limited data exist concerning the effects of cART on bacterial translocation, inflammation, coagulation, and immune activation in patients with advanced HIV-1 infection.

The ADVANZ-3 trial was a randomized, controlled, open-label, multicenter phase 4 study to compare the immunological reconstitution and the virologic efficacy and safety of 3 different combinations of antiretroviral therapy given once a day. The study included antiretroviral-naïve, HIV-1–infected adults with very low CD4 cell counts (< 100 CD4 cells/mm^3) and no drug resistance mutations at baseline.

Participants were randomized 1:1:1 to EFV 600 mg QD (n = 29), atazanavir/ritonavir 300/100 mg QD (n = 30), or lopinavir/ritonavir (LPV/r) 400/100 mg BID (n = 30) in addition to tenofovir/emtricitabine QD for 96 weeks.