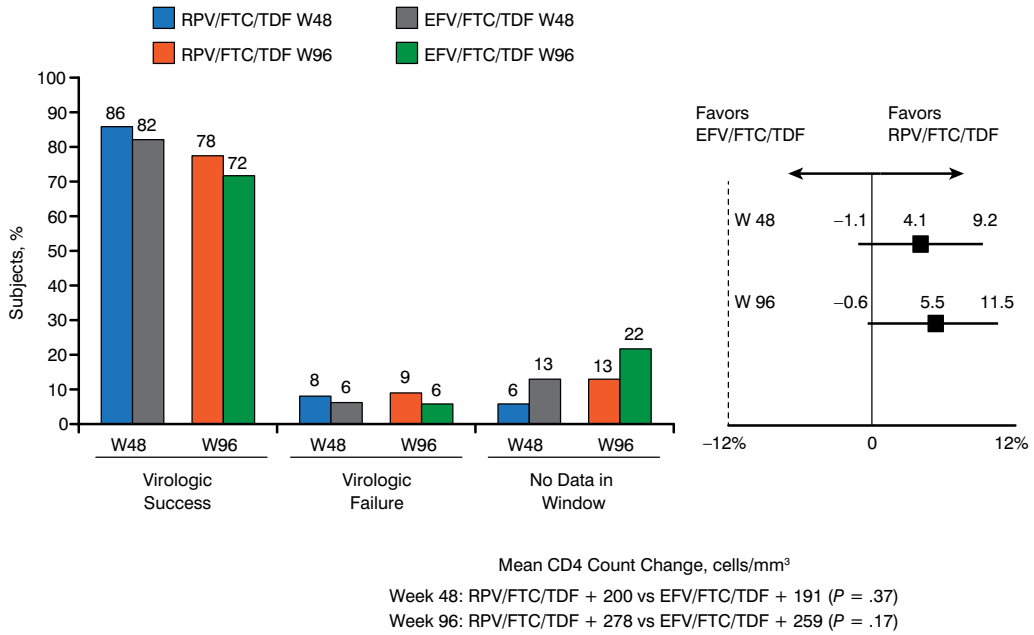
Figure 2. Virologic Outcomes and CD4 Change at Weeks 48 and 96



ARV, antiretroviral; EFV, efavirenz; FTC, emtricitabine; RPV, rilpivirine; TDF, tenofovir; W, week.

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significant. The mental health composite score (2.9 and 0.6 for RPV/FTC/TDF and EFV/FTC/TDF, respectively) favored the former drug combination, with significant differences in the RPV/FTC/TDF group between baseline and week 96 and as compared to the EFV/FTC/TDF group. The physical health composite score (0.7 and 1.7 for RPV/FTC/TDF and EFV/FTC/TDF, respectively) favored the latter group; the difference between the 2 groups was not significant.

The RPV/FTC/TDF combination was better tolerated, with fewer adverse effects, and was associated with significantly fewer adverse effect–related discontinuations (RPV/FTC/TDF, n = 10, 3%; EFV/FTC/TDF, n = 34, 9%; $P < .001$). The RPV/FTC/TDF combination was judged noninferior to EFV/FTC/TDF through week 96.

SC Ibalizumab Warrants Further Study for Preventing HIV-1 Infection

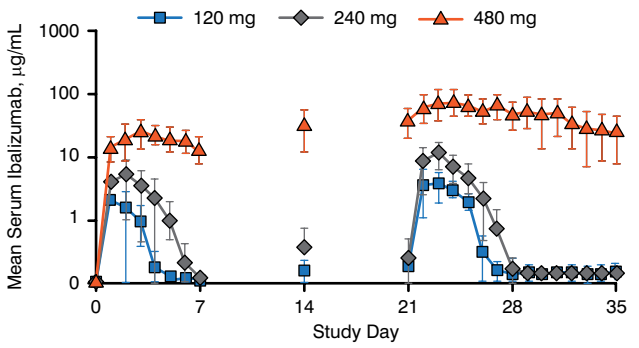
Written by Lynne Lederman

Among the strategies being explored to prevent infection with human immunodeficiency virus type 1 (HIV-1) is ibalizumab, a humanized monoclonal antibody that binds to CD4 domain 2 and blocks the entry of HIV-1 into CD4-positive T cells. Steven Weinheimer, PhD, TaiMed Biologics, Irvine, California, USA, presented the results of a study of the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics of subcutaneous (SC) injections of ibalizumab.

Safety Study of Ibalizumab Subcutaneous Injection in Healthy Volunteers (TMB-108) [NCT01292174] was a double-blind, placebo-controlled study that randomly assigned 8 participants at risk for acquiring HIV to each of 3 sequential escalating dose cohorts. Of the 24 participants enrolled, 89% were men; 65% were white; 23% were black; the mean age was 30 years; and the mean weight was 82 kg. Participants received 4 weekly SC injections of ibalizumab (120, 240, and 480 mg) or placebo. Follow-up continued for 26 weeks following dosing, and assessments included safety, PK, CD4 receptor occupancy, CD4 receptor density, and a CD4-dependent antibody response to hepatitis A virus (HAV) following challenge with HAV antigen at weeks 1 and 25.

There were no serious adverse events (AEs) and no discontinuations due to AEs. Treatment-related AEs occurred in 2 (28.6%) participants in the placebo group and 6 (31.6%) in the ibalizumab treatment groups (n = 4 of 7 in the 240-mg group; n = 2 of 6 in the 480-mg group). The most frequently reported treatment-emergent AEs were headache, upper respiratory tract infection, oropharyngeal pain and cough, and pruritus. No injection site reactions or anti-ibalizumab antibodies were observed, nor clinically significant changes in laboratory parameters, dose-response and temporal trends in vital signs, or physical examinations.

Figure 1. Ibalizumab Mean Serum Concentrations



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Daily serum ibalizumab concentrations after the first and fourth doses exhibited nonlinear PK consistent with target-mediated drug disposition, as shown in Figure 1. Higher first doses were associated with slower elimination, delayed absorption, and disproportionately higher systemic exposure.

Maximum and trough serum concentrations and the area under the concentration–time curve increased with repeat doses. Results from 3 participants with body weights >100 kg suggest that SC fat might delay the absorption of ibalizumab. All participants who received the highest dose had detectable levels of ibalizumab in their semen.

No participants had significant changes from baseline in CD4-positive T-cell counts. Anti-HAV antibodies were measured at weeks 5 and 29; antibody responses were detected in 100% of participants receiving placebo and in 53% and 94% receiving ibalizumab at these time points, respectively. The target for antiviral suppression is at least 85% CD4 receptor occupancy, which was achieved for 3 to 4 days after the first dose and for 6 to 7 days after the fourth dose of the 2 lower doses; nearly 100% receptor occupancy occurred for the entire dosing period for the highest dose.

Although the results suggest that SC ibalizumab may have the potential to prevent HIV-1 infection, the effects on antibody response to HAV antigen challenge require further study.

Switching From RTV to COBI Is Feasible in Patients With HIV-1 Who Have Mild-to-Moderate Renal Impairment

Written by Brian Hoyle

Claudia Martorell, MD, MPH, The Commonwealth Research Institute, Springfield, Massachusetts, USA, and colleagues have reported that cobicistat (COBI; approved as Tybost™ in the European Union and under review in the United States) is well tolerated in HIV-1 patients with mild-to-moderate renal impairment.

The latest results build on prior phase 3 data demonstrating the long-term (144-week) noninferiority of COBI—which is eliminated mainly by liver metabolism, negating the need for dose adjustment in renal-impaired patients—to ritonavir (RTV) as a protease inhibitor (PI) booster in treatment of HIV-1 infection in treatment-naïve patients. In this study and studies of EVG/COBI/FTC/TDF (STB), the evaluations were done in patients with a creatinine clearance (CrCl) ≥70 mL/min. The latest data obtained with patients with CrCl as low as 50 mL/min solidify the view that switching from ritonavir to cobicistat in this patient population is feasible.

This study involved 73 intent-to-treat HIV-1-infected patients who were virologically suppressed (<50 copies/mL HIV-1 RNA for at least 6 months) with mild-to-moderate renal impairment as indicated by a CrCl of 50 to 89 mL/min (Table 1).

The study assessed adverse events, estimated glomerular filtration rate (eGFR) according to creatinine-based CrCl and cystatin C-based eGFR, actual GFR according to iohexol plasma clearance, and laboratory analyses of urine protein, urine glucose, and serum phosphorus.

Patients were receiving a regimen of RTV plus either atazanavir (ATV) or darunavir (DRV) plus 2 nucleoside–nucleotide reverse transcriptase inhibitors prior to baseline. COBI was substituted for RTV, whereas other agents were continued. The present results were from week 48 of the planned 96-week therapeutic course.

Median CrCl declined marginally early after the switch to COBI and remained stable through week 48 (overall, –3.8; interquartile range [IQR], –9.0 to 0.8). Patients with baseline low CrCl (<70 mL/min) displayed nearly no change in CrCl throughout 48 weeks (–1.1; IQR, –6.5 to 6.3), whereas patients with baseline CrCl ≥70 mL/min displayed a greater decline from baseline, which remained stable for most of the treatment (–6.6; IQR, –12.4 to –0.7). No clinically relevant changes in cystatin-based eGFR were evident through week 48