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Efficacy and Safety of Doravirine/ Lamivudine/Tenofovir Disoproxil Fumarate (DOR/3TC/TDF) in Treatment-Naive Adults With HIV-1 and Transmitted Nonnucleoside Reverse Transcriptase Inhibitor Resistance Mutations

To the Editors:

Transmitted drug resistance (TDR) in HIV-1 isolates to nonnucleoside reverse transcriptase inhibitors (NNRTIs) has an estimated prevalence of 7% in the United States.[1] Internationally, NNRTI TDR mutations are estimated to have a prevalence of 11% in southern Africa, 10% in western Africa, 7.2% in central and eastern Africa, 9.4% in Latin America, 4.1% in Europe, and 3.2% in Asia.[2,3] The most frequent NNRTI TDR mutations include the reverse transcriptase (RT) amino acid substitutions K103N, Y181C, and G190A.[4] Current guidelines recommend that HIV-1 genotyping is performed before initiating therapy to determine whether TDR mutations are present to assist clinicians in selecting an effective antiviral treatment regimen.[5,6]

Doravirine (DOR) is a novel NNRTI for the treatment of HIV-1.[7,8] DOR is active in vitro against both wild-type HIV-1 and most common NNRTI-resistant variants (including K103N, Y181C, and G190A) at concentrations achieved with 100 mg once-daily dosing.[9] DOR has a unique in vitro resistance profile among NNRTIs, with lower IC_{50} values against NNRTI resistant variants as compared to other NNRTIs.[9–11] This trial was designed to evaluate the clinical efficacy of DOR against the HIV-1 NNRTI TDR mutants K103N, Y181C, and G190A.

METHODS

This trial (NCT02629822) was a phase 2, multicenter, open-label, single-arm trial of DOR/3TC/TDF once daily in HIV-1–infected adults with a single NNRTI TDR mutation. The trial was conducted at 7 centers in 5 countries (Canada, France, Spain, United States, and United Kingdom) in accordance with principles of Good Clinical Practice and was approved by institutional review boards and regulatory agencies.

Participants were antiretroviral-naive HIV-1–infected adults ($\geq$18 years) with baseline plasma HIV-1 RNA $\geq$1000 copies/mL and $CD4^+$ T-cell count $\geq$100 cells/mm^3 within 45 days before initiation of study treatment. Eligibility required a genotype-confirmed, single NNRTI mutation consisting of RT K103N, Y181C, or G190A. Participants were required to be clinically stable as determined by the investigator, have a calculated creatinine clearance $\geq$ 50 mL/min, alkaline phosphatase $\leq$3.0x upper normal limit, AST (SGOT) and ALT (SGPT) $\leq$5.0x upper normal limit, and hemoglobin $\geq$9.0 g/dL for females or $\geq$10.0 g/dL for males. Participants were excluded for any of the following: previous treatment for a viral infection such as hepatitis B with an agent active against HIV-1; documented genotypic resistance to study drugs; any medical condition requiring the use of systemic immunosuppressive therapy or immune modulators; acute hepatitis, decompensated liver disease, or cirrhosis.

This was a single-arm, open-label trial. All participants were treated with a single fixed-dose combination tablet containing 100 mg doravirine, 300 mg lamivudine, and 300 mg tenofovir disoproxil fumarate (DOR/3TC/TDF) taken once daily. Participants were screened within 45 days before study entry. Blood samples for HIV-1 RNA quantification were collected at all study visits (week 4, 8, 12, 16, 24, 36, 48, 60, 72, 84, and 96), as well as the virologic failure visit or early discontinuation visit, if applicable. HIV-1 RNA quantification was performed using the Abbott Real-Time HIV-1 assay. Before screening, participants were required to have documentation of a single genotypic HIV-1 resistance mutation consisting of either RT K103N, Y181C, or G190A. An additional screening sample was obtained to confirm the previously documented mutation by the central laboratory; if the required mutation was not confirmed, that participant was excluded from the efficacy analysis, but allowed to remain in the trial. $CD4^+$ T-cell counts were determined at screening, at day 1, and at weeks 24, 48, 72, and 96. Protocol-defined virologic failure (PDVF) was defined as confirmed HIV-1 RNA $\geq$50 copies/mL after initial response of HIV-1 RNA <50 copies/mL at any time during the study; HIV-1 RNA $\geq$200 copies/mL at week 24 or week 36; or HIV-1 RNA $\geq$50 copies/mL at or after week 48. Confirmation of PDVF required an additional measurement of HIV-1 RNA taken at least 1 week apart. Participants who met these criteria were discontinued from the trial. Safety was monitored by adverse event (AE) reporting, evaluation of treatment-emergent laboratory abnormalities, and physical examinations. Clinical AEs were assessed by the investigator for intensity and relationship to study therapy. Laboratory values were graded in severity based on the Division of AIDS criteria for grading adverse events.[12]

The primary efficacy endpoint was the proportion of participants achieving HIV-1 RNA <50 copies/mL at week 48.

An additional objective was to evaluate the safety and tolerability of DOR/3TC/TDF, as assessed by review of safety data. Secondary and exploratory efficacy endpoints included HIV-1 RNA <50 copies/mL by week 96 and the change from baseline in CD4+ T-cell count. Only descriptive summary statistics and confidence intervals were performed for both efficacy and safety endpoints with no formal hypothesis testing and no missing data approach applied. The 95% confidence interval was calculated with the Clopper and Pearson method.[13]

RESULTS

Planned enrollment was 60 participants. However, recruitment was much slower than anticipated (only 10 enrolled after 13.5 months). Therefore, further enrollment was halted due to projected inability to recruit the planned number of participants. Eighteen total participants were screened, of whom 10 were enrolled, 9 met criteria for inclusion in the efficacy analysis (1 did not have previous K103N resistance mutation confirmed at screening by the central laboratory), 8 completed the study through week 48, and 7 completed the study through week 96. All 10 enrolled participants took at least one dose of DOR/3TC/TDF and were included in the safety analysis. Two participants were discontinued before week 48, one of whom was lost to follow-up after week 16. This participant was excluded from efficacy analysis due to nonconfirmed NNRTI mutation. The other participant discontinued at week 36 for poor adherence; this participant met PDVF criteria and was included in the efficacy analyses. One additional participant was lost to follow-up between week 48 and week 96 (see Table 1, Supplemental Digital Content, http://links.lww.com/QAI/B370). Participants were 80.0% male with median age 32.5 years (range 25–56). The baseline median CD4+ T-cell count was 407.5 cells/mm³ (range 213–607), and the median plasma HIV-1 RNA was 17,281 copies/mL (range 1366–295,604). One participant had baseline HIV-1 RNA >100,000 copies/mL. Eight participants had RT K103N and 2 participants had RT G190A.

Adherence with study medication, as measured by participant medication diaries, was high with 8 of 10 participants reporting ≥90% adherence.

All 8 participants who completed the week-48 visit and all 7 participants who completed the week-96 visit achieved HIV-1 RNA <50 copies/mL (Table 1). Participants had a mean increase from baseline in CD4+ T-cells of 153 cells/mm³ at week 96 (Table 1). One participant with baseline G190A discontinued at week 36 with PDVF (poor adherence determined by self-reporting and pill count). This participant did not take DOR/3TC/TDF for 16 days before the week 24 visit and had viral rebound with HIV-1 RNA of 5393 copies/mL at week 24 after previously achieving viral suppression. After restarting treatment, HIV-1 RNA at the viral failure confirmation visit was 55 copies/mL. No additional drug resistance mutations were identified at the time of viral rebound. The participants who were lost to follow-up at week 16 (no confirmatory genotype) and at week 48 also had HIV-1 RNA <50 copies/mL at their previous visit.

AEs were reported for 9 of the 10 participants who received DOR/3TC/TDF over 96 weeks. There were no deaths. One serious AE was reported, allergy to an arthropod sting, and was judged as not drug related by the investigator. AEs experienced by >1 participant were abdominal discomfort, diarrhea, nausea, fatigue, and back pain, each reported in 2 participants. Six drug-related AEs were reported, all were nonserious, and none resulted in discontinuation. Drug-related AEs experienced by >1 participant were abdominal discomfort and fatigue.

DISCUSSION

DOR/3TC/TDF demonstrated antiretroviral efficacy through 96 weeks of treatment in a small number of treatment-naive HIV-1–infected participants with baseline NNRTI resistance mutations of K103N and G190A. The 8 participants who completed the study through week 48 and the 7 participants who completed the study through week 96 all achieved virologic suppression (HIV-1 RNA <50 copies/mL) demonstrating sustained antiviral efficacy. In addition, the 2 participants who discontinued before week 48, and the one participant who discontinued before week 96,

TABLE 1. Efficacy Outcomes for DOR/3TC/TDF Treatment

Proportion of participants with HIV-1 RNA < 50 copies/mL

Visit	n/N	% (95% CI)
Week 2	1/9	11.1 (0.3 to 48.2)
Week 4	3/9	33.3 (7.5 to 70.1)
Week 8	5/8	62.5 (24.5 to 91.5)
Week 12	6/7	85.7 (42.1 to 99.6)
Week 16	7/9	77.8 (40.0 to 97.2)
Week 24	8/9	88.9 (51.8 to 99.7)
Week 36	7/9	77.8 (40.0 to 97.2)
Week 48	8/8	100.0 (63.1 to 100.0)
Week 60	7/7	100.0 (59.0 to 100.0)
Week 72	7/7	100.0 (59.0 to 100.0)
Week 84	7/7	100.0 (59.0 to 100.0)
Week 96	7/7	100.0 (59.0 to 100.0)

Change from baseline CD4+ T-cell count (cells/mm³)

Visit	N	Mean Change (95% CI)
Week 24	9	143 (51.1 to 234.9)
Week 48	8	132 (24.4 to 239.8)
Week 72	7	196 (61.7 to 330.6)
Week 96	7	153 (23.0 to 282.8)

CI, confidence interval.

achieved virologic suppression before discontinuation. This trial also demonstrated that DOR/3TC/TDF was well tolerated in the limited number of study participants.

Preclinical studies showed that DOR had an inhibitory quotient [IQ, defined as ratio of clinical trough concentration to the 50% inhibitory concentration (C_{trough}/IC_{50})] of 50 for wild-type HIV-1, and 39, 27, and 15 for RT K103N, Y181C, G190A mutants, respectively, and predict that DOR would be clinically effective against these mutants.[9] Although participants infected with HIV-1 harboring the Y181C mutation were not enrolled in this study, the IQ of Y181C being between the IQs of K103N and G190A suggests that DOR would be clinically effective for this mutation. In a separate trial (DRIVE-SHIFT), evaluating antiviral efficacy in virologically suppressed participants switching from a baseline therapy to DOR/3TC/TDF, genotyping before initial treatment indicated that 24 participants had HIV-1 with NNRTI resistance mutations K103N, Y181C, and/or G190A. Of those 24 participants, 23 switched to DOR/3TC/TDF, and 21 of those who switched regimens remained suppressed through week 48; the other 2 discontinued early but were still suppressed at their last study visit.[14] Overall, this trial supports previous in vitro findings that DOR is active against HIV-1 with K103N and G190A mutations based on the observed antiretroviral efficacy in a small number of participants.

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