Efficacy and Safety of 2 Fixed Doses of Ibalizumab Plus Optimized Background Regimen in Treatment-Experienced HIV-Positive Individuals

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Background: Sustained viral suppression in patients with multidrug-resistant (MDR) HIV infection remains difficult; accordingly, agents targeting different steps in the HIV life cycle are needed. Ibalizumab, a humanized immunoglobulin G4 monoclonal antibody, is a cluster of differentiation (CD4)-directed postattachment inhibitor.

Methods: In this phase 2b study, 113 patients with MDR HIV-1 and limited treatment options were assigned an optimized background regimen (OBR) and randomized to either 800 mg ibalizumab every 2 weeks (q2wk; n = 59) or 2000 mg ibalizumab every 4 weeks (q4wk; n = 54) up to week 24.

Results: Viral loads (VL) below the detection limit were achieved in 44% and 28% of patients in the 800 mg q2wk and 2000 mg q4wk groups, respectively, at week 24. Mean (SD) VL (log_{10} copies/mL) decreased from Baseline [4.6 (0.8), 800 mg q2wk; 4.7 (0.7), 2000 mg q4wk] to week 2, with the reduction maintained through week 24 [2.9 (1.5), 800 mg q2wk; 3.2 (1.4), 2000 mg q4wk]. Baseline $CD4^+$ counts were 80.5 and 54.0 cells/μL in the 800 mg q2wk and 2000 mg q4wk groups, respectively. Mean $CD4^+$ T-cell count was increased at week 24 in both groups. No serious adverse events were related to ibalizumab.

Conclusions: In heavily treatment-experienced patients with HIV (PWH) at a more advanced baseline disease severity, clinically significant response rates at week 24 were achieved with ibalizumab plus OBR. Ibalizumab's unique mechanism of action and lack of cross-resistance to other antiretroviral agents make it an important component of combination treatment regimens for PWH with limited treatment options.

Key Words: ibalizumab, multidrug-resistant HIV, viral suppression, CD4 cell count, overall susceptibility score, receptor occupancy

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INTRODUCTION

A central challenge to effective long-term combination antiretroviral therapy (cART) for HIV type 1 (HIV-1) infection is the development of drug-resistant variants that emerge when viral replication is inadequately suppressed.[1] Despite the success of many current HIV treatment strategies, multidrug-resistant (MDR) HIV infection remains difficult to manage.[1,2] A need exists for agents with different mechanisms of action that are safe, effective, and easy to administer.

The development of antiretrovirals targeting the HIV lifecycle outside the cluster of differentiation 4 (CD4)-positive T-cell provided needed alternatives for patients with multiple class-resistant HIV-1 infection. During the time frame of this trial, enfuvirtide and maraviroc were the only Food and Drug Administration (FDA)-approved HIV entry inhibitors available, with fostemsavir coming to market after study completion.[3,4] When combined with an optimized background regimen (OBR), these antiretroviral agents (ARVs) are efficacious against many MDR HIV strains. However, maraviroc requires a specific coreceptor tropism,[5] and enfuvirtide is typically reserved as an agent of last resort because of injection site reactions and difficulties in administration.[6–8] In the case of twice-daily oral fostemsavir, its coadministration with strong cytochrome P450 3A4 inducers should be avoided because of potential loss of virologic response, and dose adjustments of certain drugs are suggested to prevent possible adverse effects.[9] Of note, the first-in-class HIV-1 capsid inhibitor lenacapavir was approved in 2022 for the treatment of MDR HIV-1 infection, but was not yet available when this study took place.[3,10,11]

Ibalizumab, a postattachment inhibitor, is a humanized immunoglobulin G4 monoclonal antibody that binds to an

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alternative epitope on the CD4 receptor, preventing post-attachment steps in HIV entry through steric hindrance.[1,12] It acts against MDR HIV-1 strains regardless of resistance to other ARVs or tropism.[1] A 3-armed phase 2a study[12] compared 2 weight-based doses of ibalizumab with placebo, each in combination with OBR, in highly treatment-experienced (HTE) patients failing their cART regimen. Both doses of ibalizumab plus OBR were well tolerated and when compared with placebo, significantly reduce viral load (VL) up to week 48.[12]

In this phase 2b study, we evaluated the efficacy and safety of 2 fixed doses of ibalizumab, both in combination with OBR, in HTE patients with HIV. Insights from the results described here were critical in the design of a phase 3 study of ibalizumab in combination with OBR.[13] Together, these phase 2 and phase 3 data supported the FDA approval of ibalizumab plus an OBR in the treatment of HTE patients with MDR HIV-1 infection failing their current ARV regimen.

METHODS

Study Design

TMB-202 (NCT00784147) was a 24-week, randomized, double-blinded phase 2b study in viremic, treatment-experienced patients infected with HIV-1. The study was conducted at 30 sites in North America and Taiwan from October 2008 to January 2011.

Patients received an investigator-chosen OBR consisting of 2 to 4 ARVs selected based on treatment history and resistance testing. After OBR selection, patients were randomized 1:1 to receive intravenous infusions of either 800 mg ibalizumab once every 2 weeks (q2wk) or 2000 mg ibalizumab once every 4 weeks (q4wk) with placebo in the intervening 2-week period to maintain blinding (see Fig. 1, Supplemental Digital Content 1, http://links.lww.com/QAI/C352). In simulations, these doses achieved serum trough levels of >5 μg/mL, which in earlier studies were generally correlated with significant viral RNA suppression.[1,12,14] Randomization was stratified by inclusion of integrase inhibitors (raltegravir) and viral entry inhibitors (enfuvirtide or maraviroc) available at the time of the study in the OBR.

Patients who experienced virologic failure (VF) were discontinued from the study. Ibalizumab treatment was stopped in the event of a grade 3 or 4 treatment-emergent abnormality or if a grade 3 laboratory abnormality was measured on consecutive visits.

The study protocol was approved by institutional review boards/independent ethics committees before the study began. It was conducted in accordance with Good Clinical Practice, as described in the International Conference on Harmonisation (ICH) Harmonised Tripartite Guideline. The study was conducted according to the Declaration of Helsinki and its revisions.

Study Population

Eligibility criteria included adults (≥18 years) infected with HIV-1; VL >1000 copies/mL; decreased susceptibility to ≥1 nucleoside reverse transcriptase inhibitor (NRTI), non-nucleoside reverse transcriptase inhibitor (NNRTI), and protease inhibitor (PI), as measured by genotypic/phenotypic resistance testing; and those receiving stable cART for ≥8 weeks before screening and were willing to continue that regimen until the Baseline visit. Alternatively, those whose cART failed and whose treating physician had already made the decision to discontinue their therapy within the prior 8 weeks could qualify if they were willing to stay off therapy until the Baseline visit. These latter patients were not encouraged to discontinue therapy before enrollment, nor were their treating physicians influenced by the protocol.

Exclusion criteria included any active AIDS-defining events in the prior 3 months other than Kaposi sarcoma or wasting syndrome; any investigational therapy within the prior 30 days; previous exposure to ibalizumab; and patients who were pregnant, intended to become pregnant, or were breastfeeding.

Endpoints and Assays

The primary efficacy endpoint was the proportion of patients with VL below the detectable limit (<50 copies/mL) at week 24. Secondary endpoints included mean change in VL from Baseline to week 24, mean change in $CD4^+$ T-cell count from Baseline to week 24, and CD4 receptor occupancy (proportion of total CD4 molecules occupied by ibalizumab). Additional planned analyses investigated the relationship between serum concentrations of ibalizumab and CD4 receptor occupancy.

VL and $CD4^+$ T-cell counts were assessed at Screening, predose on day 1 (Baseline), week 2, week 4, and every 4 weeks thereafter until week 24. CD4 receptor occupancy was analyzed at Baseline and weeks 2, 4, 8, 12, and 24. Clinical and safety evaluations were performed every 2 weeks.

VL was quantified using the COBAS AmpliPrep/COBAS TaqMan HIV-1 Test (Roche Molecular Systems, Branchburg, NJ) from preinfusion blood samples. Baseline VL was defined as the average VL from all available measurements at Screening and Day 1 visits. VF was defined as 2 consecutive VL measurements, occurring ≥14 days apart, indicating either a nonresponse (decrease of <1.0 $\log_{10}$ from Baseline, starting at weeks 12 and 14) or a suboptimal response or rebound (VL >50 copies/mL, starting at weeks 22 and 24).

$CD4^+$ T-cell counts were quantified using flow cytometry. The Baseline $CD4^+$ T-cell count was the average count from Screening weeks −6 to −4, and day 1 visits, as available.

Day 1 pre- and postdose CD4 receptor occupancy were measured using flow cytometry and calculated as the ratio of peak fluorescence intensity in the patient sample with versus without a saturating amount of added ibalizumab. Low, intermediate, and high receptor occupancy were defined based on receptor occupancy measurements with no ibalizumab (low range, 0%–31%) or peak postdose ibalizumab (high range, 83%–100%).

Ibalizumab serum concentrations were measured using a validated competitive enzyme-linked immunosorbent assay.

Viral Resistance Testing

Plasma samples for viral resistance testing were collected at 4-week intervals. Susceptibility to ibalizumab and all other ARVs were determined by genotypic and phenotypic viral resistance testing. The PhenoSense GT and PhenoSense HIV Entry assays (Monogram Biosciences, South San Francisco, CA) were used to test for susceptibility to PIs, NRTIs, and NNRTIs, and to ibalizumab, enfuvirtide, and maraviroc, respectively. Patients experiencing VF or virologic rebound were assessed for changes in ARV susceptibility relative to Baseline. Phenotypic sensitivity to maraviroc and ibalizumab was quantified as change in maximal percent inhibition (MPI).

ARV Susceptibility Scores

Overall susceptibility score (OSS) and a nonrecycled score (NRS) were calculated from ARV susceptibility tests independently of ibalizumab susceptibility. These scores were used to determine the effect of viral susceptibility to OBR components on treatment response. Each ARV in the patient's OBR received a score of 0 or 1. For OSS, a score of 1 was assigned to agents to which the virus had both phenotypic and genotypic susceptibility, as well as agents to which the patient had no previous exposure. A score of 0 was assigned to agents with partial or no susceptibility, or if the genotypic and phenotypic susceptibilities were discordant. NRS calculation was identical, except that previously used ARVs received a score of 0.

HIV Envelope Sequence Analysis

The loss of ≥1 conserved potential N-linked glycosylation site (PNGS) near the N-terminal of the variable region 5 (V5) loop of HIV glycoprotein 120 (gp120) is associated with reduced ibalizumab susceptibility.[15,16] HIV glycoprotein 160 (gp160) population sequences were determined using a mixture of the GeneSeq HIV Envelope Assay (Monogram Biosciences, South San Francisco, CA) and quantitative gp160 sequencing methods. Predicted amino acid sequences in the V5 loop of gp120 were evaluated using next-generation sequencing; V5 sequences were analyzed to determine the number and location of PNGS.

Statistical Methods

The primary efficacy data were analyzed from the intent-to-treat (ITT) population, which included all randomized patients regardless of whether they received study medication. Efficacy was analyzed using Fisher's exact test, and *P*-values were calculated using the Wald χ^2 test. Missing data were imputed by the missing-equals-failure (MEF) rule.

The pharmacokinetic (PK) population comprised the subset of the ITT population who contributed ibalizumab concentrations from the main study or who contributed additional samples from week 8 to week 12. The relationship between ibalizumab serum concentration and CD4 receptor occupancy was analyzed using Pearson correlation.

The safety population included all randomized patients. The Medical Dictionary for Regulatory Activities version 10.0 or higher was used to categorize all adverse events (AEs). Treatment-emergent AEs (TEAEs) were defined as AEs that either had an onset time on or after the start of study drug and no more than 14 days [30 days for serious AEs (SAEs)] after the last dose of study drug or were ongoing at study drug initiation and increased in severity during the treatment period.

RESULTS

Patient Baseline Characteristics and Disposition

Of the 199 cART-experienced patients with a history of VF who were screened, 113 were randomized to receive ibalizumab 800 mg q2wk (n = 59) or ibalizumab 2000 mg q4wk (n = 54), along with an OBR selected by the investigator (Fig. 1). Patients were mostly male (89.4%) and White (61.9%). No clinically meaningful differences in demographics were observed between the 2 treatment groups. Patients had a mean duration of HIV infection of 17.0 years. The mean (SD) Baseline VL ($\log_{10}$ copies/mL) in the 800 mg q2wk and 2000 mg q4wk groups was 4.6 (0.8) and 4.7 (0.7), respectively. Most patients (80.5%) had $CD4^+$ T-cell counts <200 cells/μL (median 80.5 cells/μL in the 800 mg q2wk group and 54.0 cells/μL in the 2000 mg q4wk group), indicating advanced disease. Both treatment groups had the same median NRS of 1 (range 0–3). Approximately 25% of all patients had an NRS of 0 at Baseline. The use of integrase inhibitors and viral entry inhibitors was balanced between the 2 treatment groups; for 80% of patients, 1 or both available ARV classes were included in the OBR (Table 1).

Of the 96 (85.0%) patients completing the study, 51 (86.4%) and 45 (83.3%) were in the 800 mg q2wk and 2000 mg q4wk treatment groups, respectively. The most common reasons for withdrawal from the study were lost to follow-up, voluntary withdrawal, and investigator decision.

Antiviral Response

The primary efficacy endpoint of undetectable VL was achieved by 41 patients (36.3%) in the ITT-MEF analysis. Of the patients treated with 800 mg q2wk, 44.1% achieved the primary efficacy endpoint at week 24, compared with 27.8% of patients in the 2000 mg q4wk dose group ($P = 0.16$). By week 2, 13% of these patients in the 2000 mg q4wk dose group achieved undetectable VL, compared with 3.4% in the 800 mg q2wk dose group (see Fig. 2, Supplemental Digital Content 1, http://links.lww.com/QAI/C352).

Other viral responses were similar between the 2 doses. Mean VL rapidly decreased from Baseline to week 2, and VL reduction was maintained through week 24. In the ITT-MEF analysis, 62.7% of the 800 mg q2wk group and 59.3% of the 2000 mg q4wk group achieved ≥1.0 $\log_{10}$ decrease in VL from Baseline to week 24. The mean change in VL from Baseline to week 24 was −1.6 $\log_{10}$ and −1.5 $\log_{10}$ in the 800 mg q2wk and 2000 mg q4wk groups, respectively

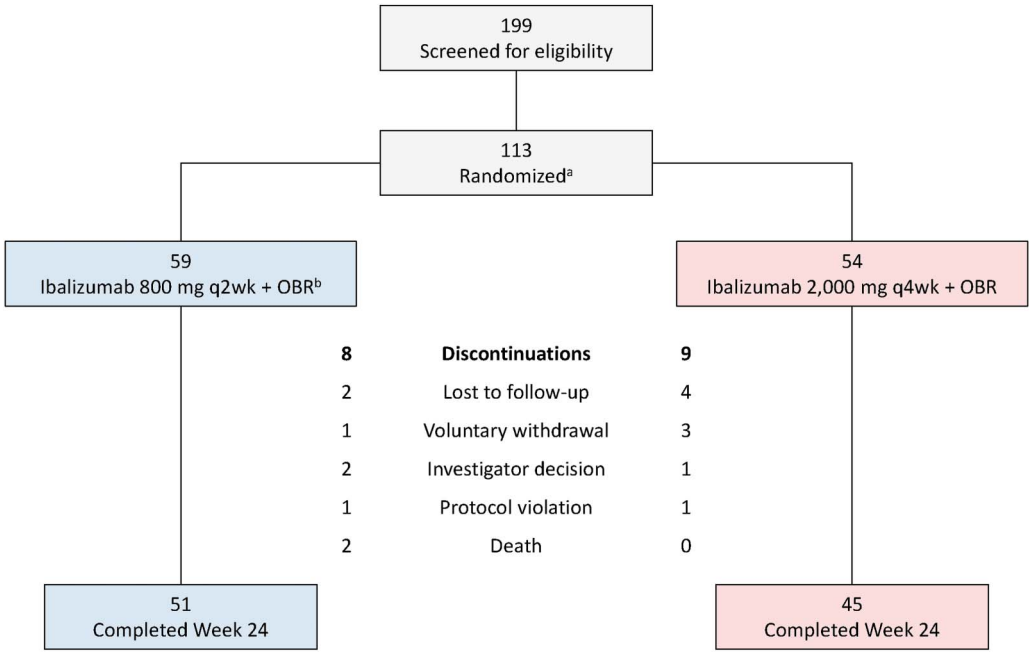

FIGURE 1. Disposition of randomized patients to week 24. [a]Patients stratified by prior use of integrase inhibitors and prior use of entry inhibitors. [b]Active treatment alternating with placebo infusion on 2-week schedule to maintain blinding. OBR, optimized background regimen; q2wk, once every 2 weeks; q4wk, once every 4 weeks.

(Fig. 2A). By week 24, $CD4^+$ cell count change was +36.5 cells/μL in the 800 mg q2wk group and +39.8 cells/μL in the 2000 q4wk group (Fig. 2B).

Stratification of VL outcomes by Baseline ARV susceptibility revealed greater response in patients with greater predicted OBR efficacy, that is, those with higher OSS and NRS values (Fig. 3A, 3B). At week 24, the mean VL change in the 800 mg q2wk group varied from -1.3 $\log_{10}$ copies/mL to -2.4 $\log_{10}$ copies/mL, depending on the number of active agents in the OBR (OSS). The same pattern was observed in the 2000 mg q4wk group, where VL change ranged from -0.3 $\log_{10}$ to -2.7 $\log_{10}$ copies/mL. When stratified by NRS, patients whose OBR included 3 or more fully active, nonrecycled ARVs experienced a mean VL change of -3.3 $\log_{10}$ and -3.0 $\log_{10}$ copies/mL in the 800 mg q2wk and 2000 mg q4wk groups, respectively. NRS and OSS were positively associated with the proportion of patients achieving undetectable VL by week 24.

Susceptibility to OBR and Ibalizumab at VF

In the 17 patients experiencing VF, OSS values declined relative to Baseline: 75% of patients who had a nonzero OSS value at Baseline also had a lower OSS value at VF (see Fig. 3A, Supplemental Digital Content 1, http://links.lww.com/QAI/C352). In addition, phenotypic assessment of susceptibility to ibalizumab in these 17 patients revealed that most isolates were strongly susceptible to inhibition by ibalizumab at Baseline (MPI >90 for 13/17 patients). At VF, all 17 patients exhibited reduced ibalizumab susceptibility with a mean MPI of 62.3 (see Fig. 3B, Supplemental Digital Content 1, http://links.lww.com/QAI/C352). These results indicate that, in most cases, VF was associated with reduced susceptibility to both the OBR and ibalizumab.

HIV Envelope Sequence Analysis and Susceptibility to Ibalizumab

The HIV envelope sequence analysis revealed that reduced ibalizumab MPI at VF relative to Baseline was associated with the loss of 1 or both PNGS in gp120 region V5 (see Table 1, Supplemental Digital Content 2, http://links.lww.com/QAI/C353). For 15 of the 17 patients experiencing VF or rebound, the loss of PNGS in predominant HIV-1 sequences was correlated with reduced ibalizumab sensitivity.

Virologic Outcomes by CD4 Receptor Occupancy

At all evaluative predose time points (weeks 4, 8, 12, and 24), a greater proportion of the 800 mg q2wk group exhibited intermediate or high receptor occupancy samples relative to the 2000 mg q4wk group (see Table 2, Supplemental Digital Content 2, http://links.lww.com/QAI/C353). Virologic outcomes were analyzed according to each patient's average CD4 receptor occupancy level, calculated from predose measurements at weeks 2 through 24. Patients exhibiting intermediate or high mean receptor occupancy throughout the study achieved greater levels of virologic suppression (-1.8 $\log_{10}$ change from Baseline, ITT-MEF analysis) on average compared with those having a low mean receptor occupancy (-1.2 $\log_{10}$ change from Baseline, ITT-

TABLE 1. Baseline Characteristics of Patients (ITT Population, Except as Indicated)

	Ibalizumab 800 mg q2wk + OBR	Ibalizumab 2000 mg q4wk + OBR
N	59	54
Age (yr), median (IQR)	48.7 (42.3–53.6)	47.3 (43.9–53.1)
Male, n (%)	51 (86.4)	50 (92.6)
Race, n (%)		
White	42 (71.2)	28 (51.9)
Black	12 (20.3)	15 (27.8)
Asian	1 (1.7)	3 (5.6)
Other	4 (6.8)	8 (14.8)
Weight, kg, median (range)	80.0 (51.3–146.7)	77.8 (47.8–139.3)
$CD4^+$, cells/μL, median (range)	80.5 (19.0–375.0)	54.0 (10.0–476.5)
HIV-1 RNA, median (range)		
Copies/mL	43,850.0 (58.0–1,087,333.3)	48,766.7 (1,893.3–1,573,333.3)
Log_{10} copies/mL	4.6 (1.8–6.0)	4.7 (3.3–6.2)
Duration of HIV infection (yr), median (range)	16.3 (8.1–24.8)*	17.1 (0.3–26.3)†
Concomitant viral disease, n (%)		
Hepatitis B-positive	4 (6.8)	5 (9.3)
Hepatitis C-positive	1 (1.7)	1 (1.9)
NRS, median (range)	1 (0–3)‡	1 (0–3)
NRS distribution, n (%)		
0	10 (17.2)	18 (33.3)
1	26 (44.8)	23 (42.6)
2	19 (32.8)	11 (20.4)
≥3	3 (5.2)	2 (3.7)
Missing	1 (1.7)	0
Ibalizumab sensitivity		
$C_{half\text{-}max}$ (μg/mL), median (range)	0.0221 (0.0091–0.0784)§	0.0240 (0.0099–0.0794)‖
MPI, median (range)	97.0 (49.0–100.0)§	97.0 (49.0–100.0)‖
OBR		
Includes integrase inhibitor, n (%)	25 (42.4)	23 (42.6)
Includes viral entry inhibitor, n (%)	8 (13.6)	11 (20.4)
Includes both, n (%)	15 (25.4)	8 (14.8)
Includes neither, n (%)	11 (18.6)	12 (22.2)

*n = 23.
†n = 29.
‡n = 58.
§n = 53.
‖n = 52.
$C_{half\text{-}max}$, concentration required to achieve half MPI; concentration; CD, cluster of differentiation; IQR, interquartile range; ITT, intent-to-treat; MPI, maximal percent inhibition; NRS, nonrecycled score; OBR, optimized background regimen; q2wk, once every 2 weeks; q4wk, once every 4 weeks.

MEF analysis) (see Table 3, Supplemental Digital Content 2, http://links.lww.com/QAI/C353).

Relationship Between Ibalizumab Serum Concentration and CD4 Receptor Occupancy

At serum ibalizumab concentrations of 150–300 ng/mL, virtually all measurements achieved intermediate levels of receptor occupancy (see Fig. 4, Supplemental Digital Content 1, http://links.lww.com/QAI/C352), the minimum receptor occupancy level associated with a biologic response.

Safety

The most frequent TEAEs were rash (12.4%); diarrhea and nausea (8.0% each); upper respiratory tract infection (6.2%); and headache, fatigue, cough, and oral candidiasis (5.3% each) (Table 2). No infusion site reactions associated with ibalizumab, $CD4^+$ depletions of grade 3 or higher,[17] or drug-related SAEs were reported. Three AEs leading to withdrawal from the study included severe hypersensitivity (related to ibalizumab), end-stage AIDS (unrelated to ibalizumab), and moderate rash (possibly related to ibalizumab).

Two deaths, both in the 800 mg q2wk group, were attributed to acute respiratory distress syndrome and AIDS and were deemed unrelated to ibalizumab.

DISCUSSION

Patients in this study were HTE, with a mean 17-year duration of infection, low $CD4^+$ T-cell counts, and a history of AIDS-defining clinical conditions. They were randomized

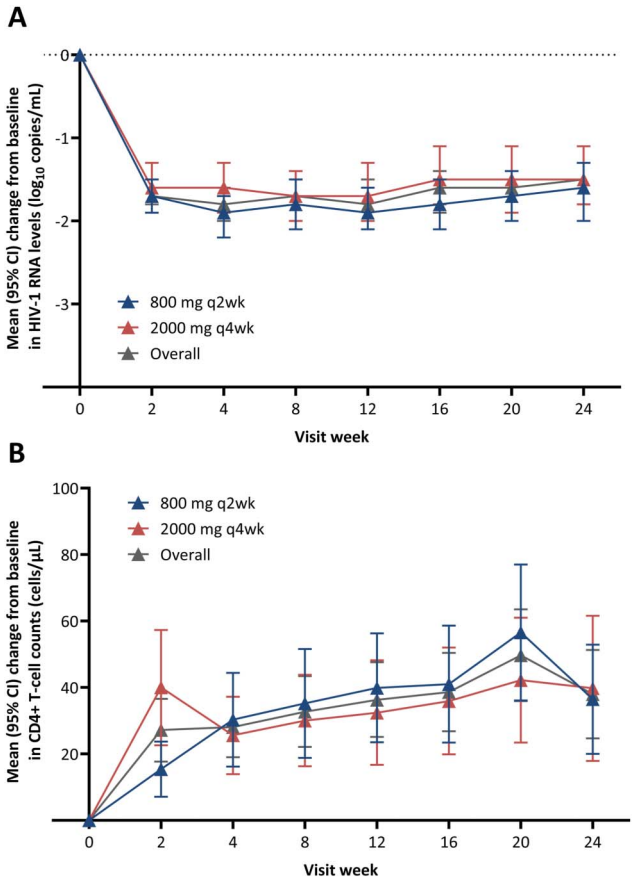

FIGURE 2. Antiviral and immunologic responses from Baseline to week 24 (ITT-MEF analysis). A, Mean (95% CI) change in VL (log_{10} copies/mL). B, Mean (95% CI) change in $CD4^+$ T-cell count (cells/μL). CD, cluster of differentiation; CI, confidence interval; HIV, human immunodeficiency virus; ITT, intent-to-treat; MEF, missing-equals-failure; q2wk, once every 2 weeks; q4wk, once every 4 weeks; RNA, ribonucleic acid.

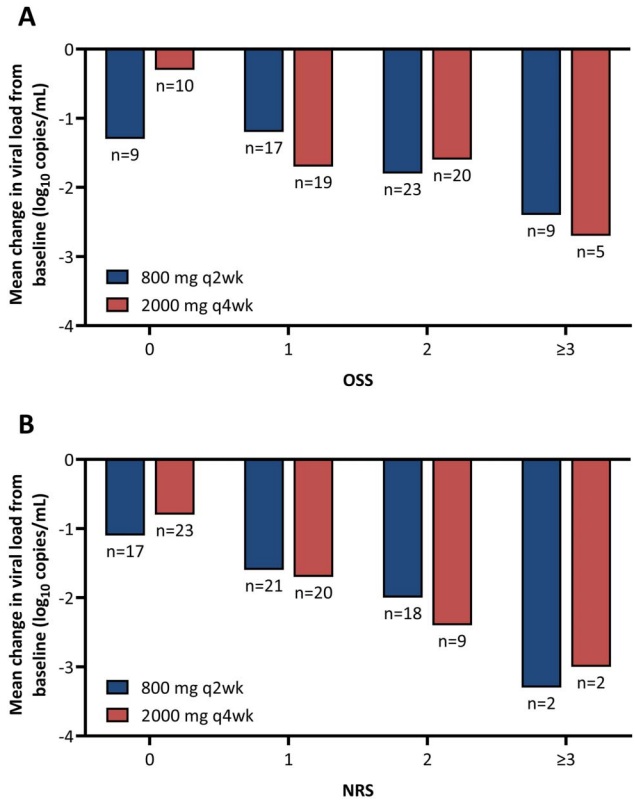

FIGURE 3. Change in VL stratified by ARV susceptibility for ibalizumab dose regimens of 800 mg q2wk (blue) and 2000 mg q4wk (red). A, Change in VL versus OSS from Baseline to week 24. B, Change in VL versus NRS from Baseline to week 24. ARV, antiretroviral agent; NRS, nonrecycled score; OBR, optimized background regimen; OSS, overall susceptibility score; q2wk, once every 2 weeks; q4wk, once every 4 weeks; VL, viral load.

to 1 of 2 fixed-dose regimens of ibalizumab plus an individually selected OBR. The randomization was stratified by the inclusion of integrase (raltegravir) and viral entry inhibitors (enfuvirtide or maraviroc) available when the trial was conducted.[3] The 2 doses of ibalizumab, 800 mg q2wk or 2000 mg q4wk, were chosen to approximate previously tested weight-based dosages.[1] A VL reduction of ≥1.0 log_{10} was considered clinically meaningful, as was an increase in $CD4^+$ T-cell count of approximately 40 cells/μL in each treatment arm.[18,19] Significant VL reductions for 24 weeks were associated with ibalizumab plus OBR treatment. Although a substantial proportion of patients in both doses achieved undetectable VL (<50 copies/mL), viral suppression occurred at a higher rate with the 800 mg q2wk dosing.[20] Mean $CD4^+$ T-cell counts were increased in both dose groups, suggesting a strong immunologic response to ibalizumab plus OBR therapy given this population.

The complete saturation of T-cells with ibalizumab is correlated with improved virologic outcomes.[1,12] However, functional blockade of HIV entry could be associated with less-than-complete saturation of CD4 surface molecules. Multiple gp120:CD4 receptor complexes may be involved during viral entry[21,22]; accordingly, incomplete blockade of CD4 molecules by ibalizumab may be sufficient to impair viral entry and provide substantial clinical benefits. Indeed, in vitro data show significant inhibition of viral replication under conditions where the predicted receptor occupancy by ibalizumab is well under 50%.[23,24] In this study, we quantified cell coating using a CD4 receptor occupancy assay and correlated it with clinical outcomes. Antiviral activity was achieved even with predose antibody binding well below saturation. Moreover, we found no evidence that intermediate and complete saturation at trough differed in their antiviral effects.

Patients with a greater sensitivity to the ARVs in their OBR, as reflected by higher Baseline OSS and NRS scores, achieved greater mean VL reduction. This finding tracks with our observation that treatment failure generally resulted from reduced susceptibility to both the OBR and ibalizumab, as determined by lower OSS scores and reduced MPI to ibalizumab. In most cases, HIV-1 RNA sequence changes associated with reduced ibalizumab susceptibility at VF could

TABLE 2. TEAEs and SAEs Reported in at Least 5% of All Patients Through Week 24 (Safety Population)

n (%)	Ibalizumab 800 mg q2wk + OBR	Ibalizumab 2000 mg q4wk + OBR	Total
N	59	54	113
Patients with at least 1 AE	50 (84.7)	44 (81.5)	94 (83.2)
Patients with at least 1 grade ≥2 AE	31 (52.5)	28 (51.9)	59 (52.3)
Patients with at least 1 SAE	5 (8.5)	3 (5.6)	8 (7.1)
Deaths	2 (3.4)	0	2 (1.8)
MedDRA preferred term			
Rash	5 (8.5)	9 (16.7)	14 (12.4)
Diarrhea	3 (5.1)	6 (11.1)	9 (8.0)
Nausea	2 (3.4)	7 (13.0)	9 (8.0)
Upper respiratory tract infection	4 (6.8)	3 (5.6)	7 (6.2)
Headache	2 (3.4)	4 (7.4)	6 (5.3)
Fatigue	3 (5.1)	3 (5.6)	6 (5.3)
Cough	6 (10.2)	0	6 (5.3)
Oral candidiasis	2 (3.4)	4 (7.4)	6 (5.3)

AE, adverse event; MedDRA, medical dictionary for regulatory activities; OBR, optimized background regimen; q2wk, once every 2 weeks; q4wk, once every 4 weeks; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

be ascribed to selection for variants lacking one or both of the V5 PNGS motifs.[15,16]

Both doses of ibalizumab used in combination with OBR in this study were well tolerated. AEs were generally mild to moderate and similar in number across the treatment arms. In addition, laboratory findings were unremarkable in both treatment groups, suggesting no apparent short-term toxicity (data not shown). Consistent with previous studies,[1,14] ibalizumab did not display immunogenicity, and no infusion site reactions were observed with ibalizumab administration.

Dermatologic AEs are commonly associated with antibody-based therapeutics[25] and some ARVs.[26,27] Rash, which has been reported in prior ibalizumab studies,[12,13] was one of the most commonly reported TEAEs in this study (12.4%). Most were considered unrelated to the study drug, as approximately half of the reported rashes had a known etiology (eg, known allergen exposure or infections with dermatologic manifestations). Episodes of rash that were possibly, probably, or definitely related to study drug were generally mild to moderate in intensity and did not result in study discontinuation. Of note, 1 patient did discontinue the study because of a moderate rash considered possibly related to the study drug.

Other commonly reported clinical AEs were diarrhea and headache. Like rash, these are commonly associated with the variety of ARVs used here in combination with ibalizumab. Most cases were mild to moderate in intensity, and most were deemed unrelated to the study drug.

Treatment with ibalizumab in combination with OBR was well tolerated and associated with antiviral and immunologic responses in a MDR HIV-1 patient population that included many patients with advanced disease. A clear limitation of our study is the absence of a placebo arm because of ethical considerations, which precludes an assessment of the relative contribution of ibalizumab versus the OBR. Notably, the week 24 VL reductions observed here were more pronounced than those observed in the ibalizumab arms of the phase 2a study, which in turn were both significantly greater than placebo.[12] Another limitation is that the patient population was predominantly White and male, thereby limiting the generalizability of the results to patients outside of this demographic.

This study was not sufficiently powered to detect a statistical difference between the 2 ibalizumab doses. However, the 800 mg q2wk dose trended toward greater efficacy relative to the 2000 mg q4wk dose in several analyses (ie, proportion of patients with undetectable VL, reductions in VL of $\geq$1.0 $\log_{10}$, receptor occupancy). The results presented here informed the dose regimen used in the pivotal phase 3 trial of ibalizumab plus OBR,[13] which subsequently provided the data supporting the currently approved ibalizumab dosing in HTE adults with MDR HIV-1 infection. Ibalizumab dosing requires an initial loading treatment of 2000 mg, followed every 2 weeks with 800 mg.[20] When combined with OBR in patients with advanced MDR HIV-1 disease, this dosing approach was found to offer significant antiviral activity over the course of 25 weeks.[13]

CONCLUSIONS

In this study, patients with MDR HIV-1 exhibited rapid virologic suppression for 24 weeks after the initiation of ibalizumab plus OBR. The recommended dose of ibalizumab is 800 mg q2wk after an initial loading dose.[20] Here, the 800 mg q2wk dose trended toward greater efficacy than the 2000 q4wk dose, although the study did not have enough power to detect a statistical difference. Because VF seems to result from the dual failure of ibalizumab and OBR, ibalizumab is likely more effective in patients with additional ARV options, as that allows a fully active OBR to be constructed. Treatment with ibalizumab in combination with other active agents seems to offer antiviral activity that is otherwise difficult to achieve in a patient with MDR HIV-1 infection, supporting its role in the management of heavily pretreated, clinically advanced HIV-infected patients.

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