ORIGINAL ARTICLE

Phase 3 Study of Ibalizumab for Multidrug-Resistant HIV-1

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ABSTRACT

BACKGROUND

Ibalizumab, a humanized IgG4 monoclonal antibody, blocks the entry of human immunodeficiency virus type 1 (HIV-1) by noncompetitive binding to CD4.

METHODS

In this single-group, open-label, phase 3 study, we enrolled 40 adults with multidrug-resistant (MDR) HIV-1 infection in whom multiple antiretroviral therapies had failed. All the patients had a viral load of more than 1000 copies of HIV-1 RNA per milliliter. After a 7-day control period in which patients continued to receive their current therapy, a loading dose of 2000 mg of ibalizumab was infused; the viral load was quantified 7 days later. Through week 25 of the study, patients received 800 mg of ibalizumab every 14 days, combined with an individually optimized background regimen including at least one fully active agent. The primary end point was the proportion of patients with a decrease in viral load of at least 0.5 $\log_{10}$ copies per milliliter from baseline (day 7) to day 14.

RESULTS

A total of 31 patients completed the study. The mean baseline viral load was 4.5 $\log_{10}$ copies per milliliter, and the mean CD4 count was 150 per microliter. Of the 40 patients in the intention-to-treat population, 33 (83%) had a decrease in viral load of at least 0.5 $\log_{10}$ copies per milliliter from baseline ($P<0.001$ for the comparison with the control period). The mean viral-load decrease was 1.1 $\log_{10}$ copies per milliliter. During the control period, 1 patient, who received the optimized background regimen prematurely, had a decrease in viral load of 0.5 $\log_{10}$ copies per milliliter. At week 25, patients who had received ibalizumab plus an optimized background regimen had a mean decrease of 1.6 $\log_{10}$ copies per milliliter from baseline; 43% of the patients had a viral load of less than 50 copies per milliliter, and 50% had a viral load of less than 200 copies per milliliter. Among 10 patients who had virologic failure or rebound, in vitro testing identified 9 who had a lower degree of susceptibility to ibalizumab than at baseline. The most common adverse event was diarrhea (in 20% of patients). Four patients died from causes related to underlying illnesses; 1 had a serious adverse event (the immune reconstitution inflammatory syndrome) that was deemed to be related to ibalizumab therapy.

CONCLUSIONS

In patients with MDR HIV-1 infection who had advanced disease and limited treatment options, ibalizumab had significant antiviral activity during a 25-week study. Evidence of the emergence of diminished ibalizumab susceptibility was observed in vitro in patients who had virologic failure. (Funded by the Orphan Products Clinical Trials Grants Program of the Food and Drug Administration and TaiMed Biologics; TMB-301 ClinicalTrials.gov number, NCT02475629.)

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Combination antiretroviral therapy has resulted in increased survival and clinically significant improvement in patients who are infected with human immunodeficiency virus type 1 (HIV-1).[1] Despite these advances, some patients have multidrug-resistant (MDR) HIV-1 infection, which affects viral suppression.[2-8] Reasons for accumulating resistance include suboptimal adherence, adverse effects of antiretroviral regimens, sequential regimens with decreased potency, and pharmacokinetic issues.[9,10] Although the prevalence of MDR HIV-1 infection has declined during the past 15 to 20 years,[11,12] patients who are infected with MDR strains are vulnerable to treatment failure and worsened clinical outcomes.[13,14] Such patients require the use of new antiretroviral agents with a good safety and side-effect profile, without drug interactions or cross-resistance.

CD4 is the primary receptor mediating HIV-1 entry.[15] Ibalizumab (TMB-355, TaiMed Biologics), a humanized IgG4 monoclonal antibody derived from mouse monoclonal antibody 5A8,[16,17] binds CD4 extracellular domain 2, thereby preventing conformational changes in the CD4–HIV envelope glycoprotein (gp120) complex that are essential for viral entry (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).[18] Ibalizumab and major histocompatibility molecules have different binding sites on CD4,[19] and ibalizumab does not appear to interfere with CD4-dependent immunity.[20,21] As an IgG4, it largely avoids Fc-mediated lysis of CD4-bearing cells.[22] By targeting HIV-1 entry before coreceptor binding and fusion have taken place, ibalizumab acts broadly on CCR5- and CXCR4-tropic strains, with no evidence of drug–drug interactions or antiretroviral cross-resistance; the potency of the drug and its breadth of activity across genetically diverse HIV-1 isolates are superior to those of broadly neutralizing monoclonal antibodies currently in clinical development.[23,24] Reduced in vitro susceptibility to ibalizumab has been associated with mutations that eliminate a gp120 glycosylation site.[24,25]

In two phase 2 studies involving 168 patients with MDR HIV-1 infection, investigators found that ibalizumab had antiviral activity. In these studies, ibalizumab (combined with an individually optimized background regimen that included at least one antiretroviral agent that was determined to be active for a given patient) resulted in a significant reduction in viral load and an increase in CD4 T cells, which were maintained through 24 weeks and 48 weeks.[26-28] In a phase 2b study of ibalizumab in which investigators compared a dose of 2000 mg every 4 weeks with a dose of 800 mg every 2 weeks, the former dose resulted in more rapid maximal drug exposure, whereas the latter dose provided a more stable drug exposure during a 24-week period and resulted in more patients with an undetectable viral load.

In TMB-301, a 24-week, open-label, single-group, phase 3 study involving patients with MDR HIV-1 infection who had undergone multiple therapies, we administered an initial 2000-mg loading dose of ibalizumab to obtain rapid therapeutic drug exposure, followed by a dose of 800 mg every 14 days to maintain viral suppression. In this study, we assessed the antiretroviral activity, durability of response, and safety of ibalizumab, both as a functional monotherapy and in combination with an optimized background regimen.

METHODS

STUDY DESIGN

From July 2015 through October 2016, we enrolled patients at 30 centers in North America and Taiwan. The study design called for the assessment of the virologic efficacy of ibalizumab at an early time point. The drug regimen was designed on the basis of guidance from the Food and Drug Administration (FDA) in patients with MDR HIV-1 infection who had already undergone multiple therapies.[29]

The study was conducted during three time periods (Fig. 1A). During the control period (days 0 to 6), patients were monitored while they were receiving their current therapy. During the functional monotherapy period (days 7 to 13), the patients received an intravenous bolus of 2000 mg of ibalizumab at baseline (day 7) while they continued to receive their previous therapy. During the maintenance period (day 14 to week 25), patients initiated their optimized background regimen on day 14 and received an intravenous dose of 800 mg of ibalizumab every 14 days, starting on day 21.

STUDY PATIENTS

Eligible patients were adults (≥18 years of age) with a viral load of more than 1000 copies of HIV-1 RNA per milliliter during receipt of highly

active antiretroviral therapy for at least 8 weeks before screening. Patients were required to have received antiretroviral drugs for at least 6 months before screening, with documented genotypic or phenotypic resistance to at least one drug in at least three classes. In addition, patients were required to continue their previous regimen before the initiation of an optimized background regimen. The background regimen, which was selected on the basis of the patient's treatment history and genotypic and phenotypic assessments, had to include at least one fully active antiretroviral drug and could include investigational agents if needed to construct a viable regimen. All the patients provided written informed consent.

END POINTS AND ASSESSMENTS

The primary end point was the proportion of patients who had a decrease in viral load of at least 0.5 $\log_{10}$ copies per milliliter from baseline to day 14 (7 days after the administration of a loading dose of ibalizumab). Secondary end points were the mean change in viral load on day 14, the proportion of patients who had a decrease in viral load of at least 0.5 $\log_{10}$ copies per milliliter or at least 1.0 $\log_{10}$ copies per milliliter at week 25, the proportion who had an HIV-1 RNA level of less than 50 copies per milliliter or less than 200 copies per milliliter at week 25, and the mean changes in viral load and CD4 count at week 25.

Virologic failure was defined as two consecutive measurements after day 14 that showed a reduction from baseline in viral load of less than 0.5 $\log_{10}$ copies per milliliter. Viral rebound was defined as an increase of at least 1.0 $\log_{10}$ copies per milliliter in viral load from the nadir value.[29] Virologic breakthrough was defined as two consecutive viral-load measurements of more than 200 copies per milliliter after initial virologic suppression. Exploratory analyses evaluated antiretroviral sensitivity or susceptibility after viral failure or rebound. Details regarding assays for HIV-1 RNA genotype and phenotype, receptor occupancy (i.e., the proportion of CD4 receptors occupied by ibalizumab), CD4-receptor density, serum ibalizumab concentration, and antibodies against ibalizumab are provided in the Supplementary Appendix.

STUDY OVERSIGHT

The trial sponsor (TaiMed Biologics) designed the study and participated in the collection, analysis, and interpretation of the data and in the writing of the manuscript. Aspects of the protocol, such as the establishment of the primary end point, sample size, and eligibility criteria, were developed in close collaboration with the FDA. The final protocol, all amendments, and written informed-consent documentation were reviewed and approved by the institutional review board at each study center. All the authors reviewed and approved the manuscript; the last author made the final decision to submit the manuscript for

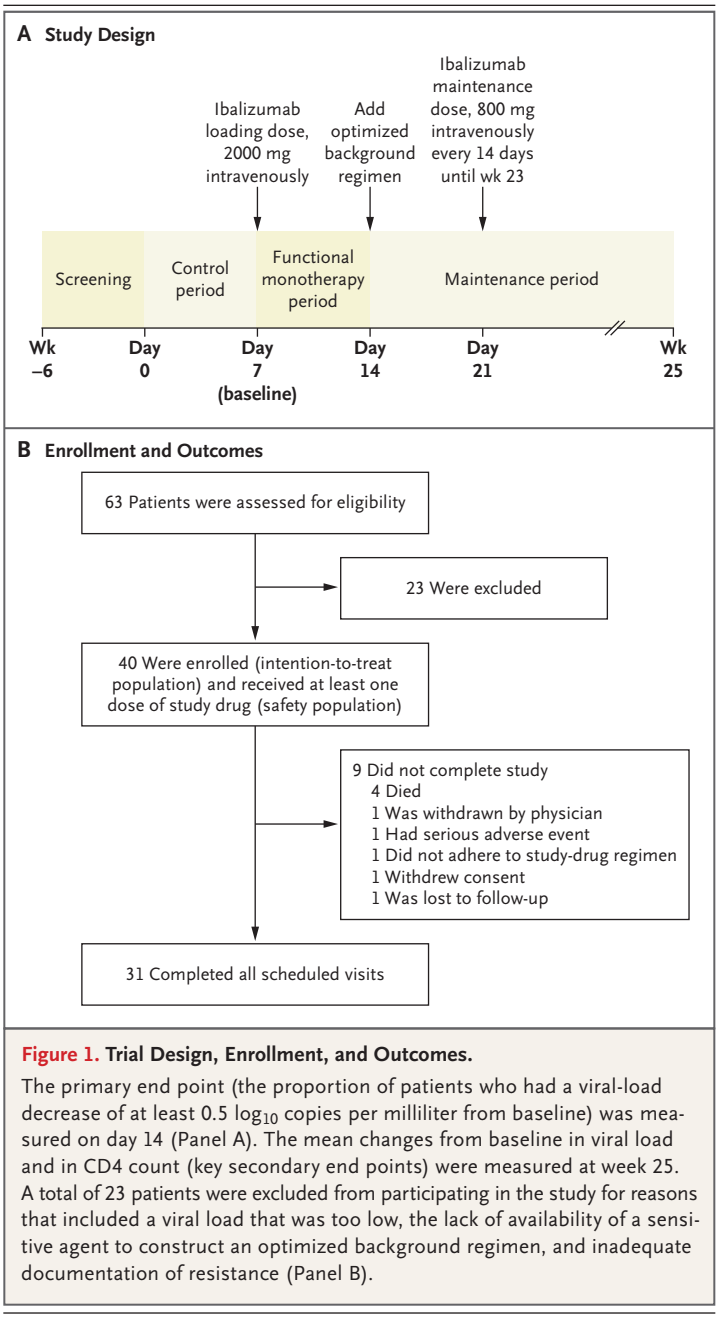


Figure 1. Trial Design, Enrollment, and Outcomes.

The primary end point (the proportion of patients who had a viral-load decrease of at least 0.5 $\log_{10}$ copies per milliliter from baseline) was measured on day 14 (Panel A). The mean changes from baseline in viral load and in CD4 count (key secondary end points) were measured at week 25. A total of 23 patients were excluded from participating in the study for reasons that included a viral load that was too low, the lack of availability of a sensitive agent to construct an optimized background regimen, and inadequate documentation of resistance (Panel B).

publication. All the authors had full access to the data and vouch for the accuracy and completeness of the data and for the fidelity of the study to the protocol (available at NEJM.org). A full description of the study oversight is provided in the Supplementary Appendix.

STATISTICAL ANALYSIS

All the patients who received at least one dose of ibalizumab were included in the safety and efficacy analyses. We performed efficacy analyses at day 14 and week 25 in the intention-to-treat population. According to the FDA-defined Snapshot approach,[29] missing values were imputed as treatment failures, with baseline observations carried forward to replace missing data. We used McNemar's test to assess the significance of the proportion of patients who had a reduction in viral load. We used paired t-tests to analyze the mean change in viral load and a model of the maximal drug-attributable effect to perform paired measurements of receptor occupancy and the serum level of ibalizumab.

RESULTS

STUDY POPULATION

A total of 40 patients received at least one dose of ibalizumab (Fig. 1B). Of these patients, 32 (80%) received all scheduled doses, and 31 (78%) completed all scheduled visits. Of the 9 patients who did not complete the study, 4 died from causes that were not considered by the investigator to be related to ibalizumab treatment (see the Adverse Events subsection) and 1 discontinued treatment because of a serious adverse event (the immune reconstitution inflammatory syndrome [IRIS]). Other reasons for discontinuation included withdrawal by a physician, nonadherence to the study-drug regimen, withdrawal of consent, and loss to follow-up.

The median age of the patients was 53 years; 15% were female and 55% were white. The median duration of HIV-1 infection was 23 years (range, 2 to 30). Patients had received a median of 10 antiretroviral drugs. At baseline, the mean (±SD) HIV-1 RNA level was 4.5±0.8 $\log_{10}$ copies per milliliter. The mean CD4 count was 150±182 cells per microliter. Most patients (68%) had less than 200 CD4 cells per microliter; 43% had less than 50 per microliter, and 30% had less than 10 per microliter (Table 1).

In addition to the triple-class resistance that was required for inclusion in the study, 85% of the patients had documented resistance to all the drugs in at least one class, 73% had resistance to all the drugs in at least two classes, 50% had resistance to all the drugs in at least three classes, and 33% had resistance to all the drugs in four classes. Five patients (13%) had documented resistance to all approved antiretroviral agents. A total of 48% of the patients had resistance to all integrase inhibitors. To construct an optimized background regimen with at least one fully susceptible antiretroviral agent, 17 patients (43%) required the addition of an investigational antiretroviral drug (fostemsavir).[30]

VIROLOGIC AND CD4 T-CELL RESPONSE

In the analysis of the primary efficacy end point performed on day 14, a decrease in viral load of at least 0.5 $\log_{10}$ copies per milliliter occurred in 33 of 40 patients (83%; 95% confidence interval [CI], 67 to 93) during the functional monotherapy period (days 7 to 13), which represented a significant decrease in viral load as compared with the control period ($P<0.001$) (Table 2). During the control period, 1 patient, who had received the optimized background regimen prematurely, had a decrease in viral load of 0.5 $\log_{10}$ copies per milliliter. In addition, 24 patients (60%) had a decrease in viral load of at least 1.0 $\log_{10}$ copies per milliliter during the functional monotherapy period, as compared with no patients during the control period; both mean and median reductions in viral load were 1.1 $\log_{10}$ copies per milliliter ($P<0.001$) (Table 2). All the patients continued to receive their failing regimen until day 14.

At the end of the maintenance period (week 25), an HIV-1 RNA level of less than 50 copies per milliliter occurred in 17 patients (43%), and a level of less than 200 copies per milliliter occurred in 20 patients (50%); the mean reduction from baseline in the viral load was 1.6 $\log_{10}$ copies per milliliter, and the median reduction was 1.8 $\log_{10}$ copies per milliliter (Fig. 2A and 2B). Among patients who had less than 50 CD4 cells per microliter at baseline, 7 (18%) had less than 50 copies of HIV-1 RNA per milliliter and 10 (24%) had less than 200 copies per milliliter. Conversely, among patients who had a CD4 count of 50 cells or more per microliter at baseline, 24 (61%) had less than 50 copies of HIV-1 RNA per milli-

liter and 28 (70%) had less than 200 copies per milliliter (Fig. 2A). No clinically meaningful differences in efficacy were identified across subgroups on the basis of age, sex, race, country of residence, or use of an integrase inhibitor or investigational agent (Fig. S2 in the Supplementary Appendix).

The mean CD4 count increased from 150 per microliter at baseline (as measured in 40 patients) to 240 per microliter at week 25 (as measured in 27 patients), with a mean increase of 62 per microliter (Fig. 2C). The increase in the CD4 count was numerically lower in patients who had a baseline CD4 count of less than 50 cells per microliter than in those with a CD4 count of 50 cells or more per microliter (17 and 78 CD4 cells, respectively), but the difference was not significant between subgroups (P=0.44) (Fig. 2C).

PHARMACOKINETIC AND PHARMACODYNAMIC FEATURES

The population mean receptor occupancy (the proportion of CD4 receptors that were occupied by ibalizumab) remained at more than 85% throughout the period of study-drug administration. The proportion of patients with at least 85% receptor occupancy was 97% on day 21 and 81% at week 25. Modeling of the maximal drug-attributable effect showed that the EC85 (the drug level required in vitro for 85% receptor occupancy) for the interaction between ibalizumab and CD4 cells was 0.13 μg per milliliter. The mean maximal serum level of ibalizumab, which was observed immediately after ibalizumab loading on day 7, was 567±235 μg per milliliter. The mean serum level of the drug was at least 30 μg per milliliter (thus exceeding the EC85) at all times. The median trough level of the drug was 0.23 μg per milliliter (interquartile range, 0.02 to 12.65) in patients with a body weight of at least 85 kg (Table S9 in the Supplementary Appendix). During the maintenance period, the mean CD4 surface density declined by 10 to 23% from the value at baseline.

ADVERSE EVENTS

During treatment with ibalizumab, at least one adverse event occurred in 32 patients (80%). Most of the adverse events (87%) were mild to moderate in severity, including diarrhea (in 20% of the patients) and nausea, fatigue, pyrexia, rash, and dizziness (in 13% each) (Table 3). Grade 3

Table 1. Demographic and Clinical Characteristics of the 40 Study Patients at Baseline.*

Characteristic	Value
Median age (range) — yr	53 (23–65)
Male sex — no. (%)	34 (85)
Race — no. (%)†	
White	22 (55)
Black	13 (33)
Asian	4 (10)
Unknown	1 (3)
No. of years since HIV diagnosis	
Mean	20±8
Median (range)	23 (2–30)
Viral load — $\log_{10}$ copies/ml	
Mean	4.5±0.8
Median (range)	4.6 (2.5–5.9)
Patients with viral load of >100,000 copies/ml — no. (%)	7 (18)
CD4 count	
Mean — no. of cells/μl	150±182
Median (range) — no. of cells/μl	73 (0–676)
Distribution — no. of patients (%)	
<10 cells	12 (30)
<50 cells	17 (43)
50–200 cells	10 (25)
>200 cells	13 (33)
Total no. of antiretroviral medications received	
Mean	11±5
Median (range)	10 (3–22)
Known resistance to ≥1 drug in class — no. (%)	
Nucleoside reverse-transcriptase inhibitor	37 (93)
Non-nucleoside reverse-transcriptase inhibitor	37 (93)
Protease inhibitor	36 (90)
Integrase inhibitor	27 (68)
Coreceptor antagonist‡	33 (87)
Fusion inhibitor‡	9 (24)
Known resistance to all drugs in class — no. (%)	
Nucleoside reverse-transcriptase inhibitor	26 (65)
Non-nucleoside reverse-transcriptase inhibitor	26 (65)
Protease inhibitor	25 (63)
Integrase inhibitor	19 (48)
Coreceptor antagonist‡	33 (87)
Fusion inhibitor‡	9 (24)

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding.
† Race was reported by the patients.
‡ Because of an inability to phenotype two samples, data were available for 38 patients.

Table 2. Virologic Response before and after Loading Dose of Ibalizumab and at 25 Weeks in the 40 Study Patients.*

Response	Before and after Loading Dose			Week 25
	Control Period	Functional Monotherapy Period	P Value	
Decrease in viral load of ≥0.5 $\log_{10}$ copies/ml — no. (%)	1 (3)†	33 (83)	<0.001	25 (63)
Decrease in viral load of ≥1.0 $\log_{10}$ copies/ml — no. (%)	0	24 (60)	NA	22 (55)
Mean change in viral load from baseline — $\log_{10}$ copies/ml	0.0±0.2	−1.1±0.6	<0.001	−1.6±1.5

* Plus–minus values are means ±SD. The virologic response during the control period (days 0 to 6) was compared with the response after the administration of an intravenous bolus of 2000 mg of ibalizumab on day 7 during the functional monotherapy period (days 7 to 13). During the maintenance period (day 14 to week 25), patients initiated an optimized background regimen on day 14 and received an intravenous dose of 800 mg of ibalizumab every 14 days, starting on day 21. NA denotes not applicable because the control value is 0.

† One patient initiated the optimized background regimen prematurely during the control period.

or 4 adverse events were reported in 11 patients (28%), and acquired immunodeficiency syndrome (AIDS)–defining adverse events occurred in 4 patients (10%). Serious adverse events occurred in 9 patients (23%). Adverse events that resulted in the discontinuation of ibalizumab occurred in 5 patients (13%), including 4 patients (10%) who died during the study. Reasons for death were Kaposi's sarcoma (in week 24), hepatic failure (in week 22), lymphoma (in week 6), and end-stage AIDS (in week 9), none of which were considered to be related to ibalizumab therapy. Among the patients who died, the baseline CD4 counts were 2, 1, 44, and 3 cells per microliter, respectively. Additional details regarding adverse events are provided in the Supplementary Appendix.

One serious adverse event, IRIS, was considered to be related to ibalizumab therapy and resulted in discontinuation of the drug. This patient presented with right hemiparesis on day 57 and received a clinical diagnosis of progressive multifocal leukoencephalopathy (PML) with associated IRIS, given the decrease in viral load (from 62,500 copies per milliliter at baseline to undetectable) and the increase in the CD4 count (from 4 cells per microliter at baseline to 16 per microliter) by day 52. Ibalizumab was permanently discontinued in response. At the last follow-up, on day 74, the patient's condition with respect to PML and IRIS was considered to be stable.

Prespecified adverse events of special interest included rash, hepatotoxicity, cancer, and infusion reactions. Five patients (13%) reported rash: 4 patients reported a single mild or moderate event, and 1 patient reported eight episodes (one of which was severe and was deemed to be related to ibalizumab therapy). No rashes required the discontinuation of treatment or a dose adjustment. There were no reports of hepatotoxicity, ibalizumab-related cancer, infusion-site reaction, or the development of antibodies against ibalizumab.

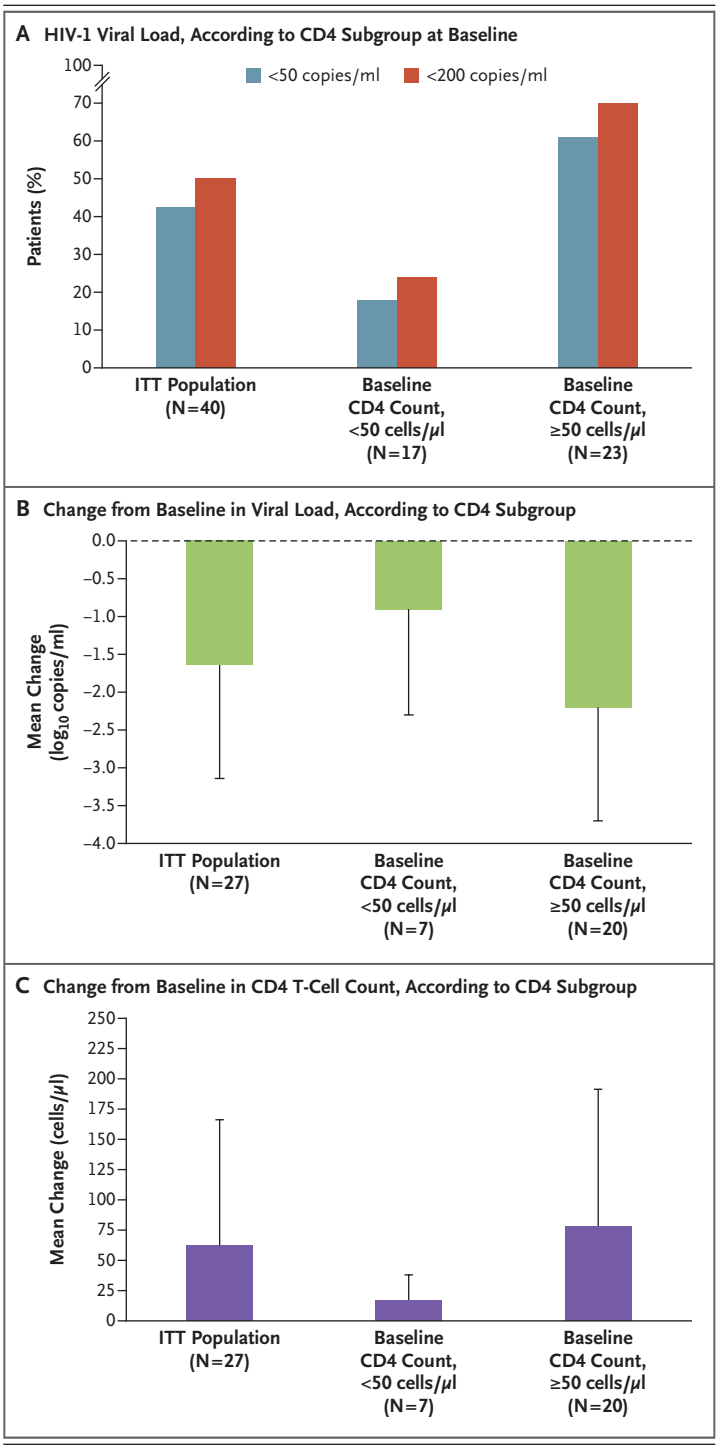
VIROLOGIC FAILURE

At week 25, 7 patients (18%) had virologic failure; of these patients, 1 also had virologic breakthrough. Three other patients had viral rebound. Resistance testing at the time of virologic failure indicated reduced susceptibility to the optimized background regimen in 3 of 4 patients for whom such tests were available. For the remaining 6 patients with virologic failure or rebound, background-regimen susceptibility could not be fully evaluated because the regimen included an investigational agent.

Among the 10 patients with virologic failure or rebound, 9 showed a lower degree of susceptibility to ibalizumab than at baseline, as measured by maximum percent inhibition. In 8 of the 9 patients, the loss of predicted N-linked glycosylation sites in the V5 loop of HIV-1 gp120 was the primary genetic change associated with reduced susceptibility to ibalizumab, which was consistent with the findings of previous studies.[24,25,31] In the remaining patient, ibalizumab susceptibility was reduced at baseline and was unchanged at the time of virologic failure. A reduced maximum percent inhibition at baseline

Figure 2. Virologic and CD4 T-Cell Responses at Week 25.

Shown are values for the HIV-1 viral load and CD4 count in the overall intention-to-treat (ITT) population and in subgroups according to the patients' CD4 count at baseline (<50 cells or ≥50 cells per microliter). Panel A shows the proportion of patients with a viral load of less than 50 HIV-1 RNA copies per milliliter or less than 200 copies per milliliter at week 25, with baseline observations carried forward to replace missing data. Panel B shows the mean change in viral load from baseline to week 25 in $\log_{10}$ copies per milliliter. Panel C shows the mean change from baseline to week 25 in the CD4 count. In Panels B and C, the T bars indicate standard deviations.



was not predictive of virologic failure or rebound. Of the 10 patients with virologic failure or rebound, 6 remained in the study through week 25.

DISCUSSION

Although current treatment regimens enable many patients with HIV-1 infection to live with durable viral suppression, highly drug-resistant HIV-1 infection remains an issue for some patients and poses a risk of MDR HIV transmission, including resistance to the integrase inhibitor class.[4,5,8,32,33] To construct regimens that are capable of effectively suppressing viral replication, there is a need for new therapies with distinct mechanisms of action and nonoverlapping patterns of resistance. In this study, we found that in patients with MDR HIV-1 infection who have undergone multiple therapies, ibalizumab combined with an optimized background regimen significantly reduced the HIV-1 viral load and increased the CD4 count from baseline.

This registration study was designed to provide open-label ibalizumab to patients with clinically advanced HIV-1 infection who had limited treatment options. In this population, ibalizumab had potent antiviral activity during the functional monotherapy period, with a decrease of at least 0.5 $\log_{10}$ copies per milliliter (the primary end point) occurring in 83% of the patients during a 7-day period. Furthermore, in the intention-to-treat analysis, ibalizumab plus the optimized background regimen (including ≥1 additional active agent) significantly reduced the HIV-1 viral load at week 25, with a viral load of less than 50 copies per milliliter reported in 43% of the patients. In parallel, patients had an increase of 62 CD4 cells per microliter, a finding that was consistent with changes associated with other effective antiretroviral combinations in patients who have undergone extensive treatment.[34-36] As expected, patients with a decreased baseline CD4 count had smaller gains in such cells.

Table 3. Adverse Events in the 40 Study Patients.

Adverse Event	No. of Patients (%)
Any adverse event*	32 (80)
Assessed as related to ibalizumab†	7 (18)
Leading to discontinuation of ibalizumab	5 (13)
Occurring in patients who died	4 (10)
Serious adverse event‡	9 (23)
Adverse event reported in >5% of patients	
Diarrhea	8 (20)
Dizziness	5 (13)
Fatigue	5 (13)
Nausea	5 (13)
Pyrexia	5 (13)
Rash§	5 (13)
Vomiting	4 (10)
Lymphadenopathy	4 (10)
Nasopharyngitis	4 (10)
Decreased appetite	3 (8)
Excoriation	3 (8)
Headache	3 (8)
Upper respiratory tract infection	3 (8)

* A complete list of adverse events is provided in Table S1 in the Supplementary Appendix.
† This category includes adverse events that were classified by the investigator as being definitely, probably, or possibly related to ibalizumab treatment, as detailed in Table S2 in the Supplementary Appendix.
‡ Details regarding all serious adverse events are provided in Table S5 in the Supplementary Appendix.
§ Rash refers to all types of rashes that were reported, including erythematous, generalized, macular, maculopapular, papular, and pruritic. Details regarding types of rashes are summarized in Table S2 in the Supplementary Appendix.

On the basis of phase 2 studies,[26,27] we adopted a loading dose of 2000 mg of ibalizumab, followed by 800 mg every 14 days, starting on day 21, to allow for rapid, sustained ibalizumab exposure. Ibalizumab pharmacokinetic and pharmacodynamic features were consistent with descriptions in previous studies, with the mean CD4-receptor occupancy remaining at more than 85%, a status that was associated with a reduced mean viral load over a 6-month period.[26,27] The trough concentration of ibalizumab decreased at a high body weight, but no reduction in clinical efficacy was evident. Ibalizumab treatment led to modestly reduced surface expression of CD4, which presumably reflected changes in intracellular recycling, a finding that was consistent with the phase 2b results.

Of the 10 patients with virologic failure or rebound, 9 had decreased maximum percent inhibition of ibalizumab at the time of virologic failure, and resistance to agents in the optimized background regimen developed in at least 3 patients. Since a low maximum percent inhibition at baseline was not predictive of treatment efficacy, the reasons for virologic failure or rebound in these patients are unclear. It was unlikely that virologic failure or rebound was caused by inhibitory antibodies, since no patient had detectable antibodies against ibalizumab during the study. In the phase 2b study, low-titer antibodies against ibalizumab developed in 1 patient. Nevertheless, this patient continued to receive ibalizumab and continued to maintain viral suppression.

Diarrhea, the most common adverse event, was mild to moderate in all the patients. There was one ibalizumab-related serious adverse event, IRIS, a condition that is associated with a rapid increase in the CD4 count, with a decrease in viral load, or both.[37,38] IRIS is a known concern during the initiation of any potent antiretroviral regimen that is associated with a substantial decline in viral load or increase in the CD4 count.[39] Rash occurred in 12.5% of the patients. Most rash events were mild to moderate, which was consistent with the findings of previous studies[26-28]; none required the discontinuation of ibalizumab or a dose reduction. The patient who had multiple rash episodes continued to receive ibalizumab and had an undetectable viral load by week 25. There were no infusion-related events. To date, no cancer or infection signals were seen in this or previous studies of ibalizumab. Given the size of current and previous studies, the safety data set is limited, and postapproval safety monitoring is needed.

This study was designed in accordance with FDA guidance to expedite the development of new antiretroviral agents for the treatment of clinically advanced HIV disease.[29] Limitations of the study include its small size, uncontrolled study design (beyond the primary efficacy analysis), and limited time frame for analyzing secondary and safety end points. These constraints reflect the relative scarcity of patients with MDR HIV-1 infection, along with their advanced disease and associated treatment challenges. Given these considerations, ibalizumab has been designated as an orphan drug by the FDA.[40] The inclusion of 7 days of current background therapy followed by 7 days

of ibalizumab monotherapy before the initiation of an optimized background regimen provided a historical comparator and a short-term assessment of ibalizumab antiviral activity to forestall the risk of viral resistance. Through week 25, we assessed the safety of treatment and the durability of virologic and immunologic responses. Patients in our study who continued to receive therapy could enroll in an extension study (ClinicalTrials.gov number, NCT02707861) to follow the effects of ibalizumab plus an optimized background regimen during a 48-week period. All eligible patients opted to continue in the follow-up study.

In the event of resistance-related treatment failure, HIV treatment guidelines recommend the initiation of new regimens with at least two fully active agents.[41] The availability of a CD4-directed postattachment HIV-1 inhibitor with nonoverlapping resistance provides an opportunity to construct a regimen to suppress the viral load and maintain immune status.

In conclusion, in this phase 3 study involving patients with MDR HIV-1 infection, we found that ibalizumab combined with an optimized background regimen had antiviral and immunologic activity. Our findings also showed the feasibility and acceptability of twice-monthly intravenous administration of an antiretroviral therapy.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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