Efficacy, Safety, and Tolerability of Etravirine With and Without Darunavir/Ritonavir or Raltegravir in Treatment-Experienced Patients: Analysis of the Etravirine Early Access Program in the United States

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Background: Etravirine, a nonnucleoside reverse transcriptase inhibitor, was provided through an international early access program (EAP) prior to regulatory approval.

Methods: The Phase III, nonrandomized, open-label EAP investigated etravirine 200 mg twice daily plus a background regimen (BR) in patients who had failed multiple antiretroviral regimens. Efficacy and safety are reported for HIV-infected adults from the United States through week 48, including subgroups receiving etravirine ± darunavir/ritonavir and/or raltegravir.

Results: The intent-to-treat population included 2578 patients; 62.4% and 56.7% of patients received darunavir/ritonavir and raltegravir, respectively, in their BR. At week 48, 62.3% of patients achieved viral loads <75 copies per milliliter; responses across subgroups were similar. Median $CD4^+$ count increase from baseline was >100 cells per cubic millimeter. No unexpected safety concerns emerged; serious AEs and deaths due to AEs, considered possibly related to etravirine, occurred in 2.0% and 0.3% of patients, respectively. Discontinuations due to AEs were low overall (4.4%) and comparable across subgroups.

Conclusions: Etravirine combined with a BR, often including other new antiretrovirals, such as darunavir/ritonavir and/or raltegravir, provided an effective treatment option in treatment-experienced patients with HIV-1.

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INTRODUCTION

Early access programs (EAPs) provide access to experimental antiretroviral (ARV) drugs to patients in vital need of such therapies. Etravirine (TMC125), a next generation nonnucleoside reverse transcriptase inhibitor (NNRTI) active against NNRTI-resistant HIV-1, became available in September 2006 through an international EAP.[1] Just before the start of this program, darunavir was approved for use in treatment-experienced patients and, during the course of the program, first-in-class agents raltegravir and maraviroc also became available via EAPs. Through collaboration with drug developers, regulatory authorities and clinicians, use of these new and experimental drugs in combination was permitted so that patients could increase their chance of achieving success. Etravirine was granted accelerated approval from the US Food and Drug Administration in January 2008 for use in treatment-experienced adult patients with HIV-1.[2] Clinical data on the use of etravirine with darunavir/ritonavir and/or raltegravir in combination are still lacking.

Here we report efficacy and safety results from HIV-1–infected patients in the United States enrolled in the etravirine EAP (TMC125-C214). Data from a subgroup of patients receiving etravirine with or without darunavir/ritonavir and/or raltegravir are also analyzed.

METHODS

Study Design

The TMC125-C214 trial (ClinicalTrials.gov Identifier: NCT00354627) was a Phase III, nonrandomized, open-label, international trial that began enrolling in September of 2006. The objective was to provide access to etravirine before regulatory approval for patients with HIV-1 who had failed multiple ARV regimens due to virologic failure or intolerance

and who had limited treatment options. Secondary objectives were to assess etravirine safety and tolerability in combination with other ARVs. Available efficacy data were also collected, including plasma viral load (VL) and $CD4^+$ count.

All patients received 2 100-mg tablets of etravirine twice daily after a meal plus an investigator-selected BR. Ritonavir-boosted darunavir, lopinavir, atazanavir, fosamprenavir, indinavir, and saquinavir, all approved nucleoside/nucleotide analogue reverse transcriptase inhibitors and enfuvirtide, were allowed in the BR. Raltegravir and maraviroc were permitted for use as a component of the BR beginning in January and July of 2007, respectively.[3–5] Background ARVs could be changed at the investigator's discretion. Etravirine treatment was continued until virologic failure, treatment-limiting toxicity, loss to follow-up or study withdrawal, pregnancy, or until etravirine became commercially available. The protocol, any amendments and patient consent forms were approved by Institutional Review Boards. The study was conducted in accordance with the Guidelines for Good Clinical Practice and the ethical principles of the Declaration of Helsinki.

A post-hoc subanalysis based on the concomitant use of darunavir/ritonavir and/or raltegravir as a component of the BR was conducted.

Assessments

Following screening and baseline, follow-up visits were recommended at weeks 4 and 12 after initiation of etravirine and every 12 weeks thereafter. Laboratory assessments (biochemistry, plasma VL, and $CD4^+$ count) were performed by local laboratories. Results from laboratory tests obtained within the 12 weeks before the study could be used as screening values. Serious adverse events (SAEs) and AEs leading to treatment disruption or discontinuation were recorded for safety assessments.

Patient Eligibility Criteria

Eligible patients were HIV-1–infected adults with limited treatment options who had inadequate viral suppression on the current regimen and who previously had failed multiple ARV regimens due to virologic failure or intolerance. Patients required etravirine to construct a viable treatment regimen, based on prior ARV experience and selected laboratory parameters. Additional key inclusion criteria included 3-class experience or 2-class [nucleoside/nucleotide analogue reverse transcriptase inhibitors and protease inhibitors (PIs)] experience with primary NNRTI resistance, previous receipt of at least 2 PI-based regimens (amended to at least 1 PI after trial initiation) and resistance to currently approved NNRTIs. A further amendment allowed patients not failing their current ARV regimen to be eligible if substitution of an agent was required due to treatment-limiting toxicity, if an intensification of the ARV regimen was deemed appropriate or if they previously participated in another etravirine clinical trial. Exclusion criteria included use of disallowed concomitant therapy, including certain ARVs or investigational ARVs, active clinically significant concomitant disease, specific laboratory abnormalities that indicated significantly poor renal or hematologic function at baseline, or clinical or laboratory evidence of significantly decreased hepatic function or decompensation. Women were excluded if pregnant or breastfeeding or if they were of childbearing potential and not using effective nonhormonal birth control. All patients, or their legal authorized representative, provided informed consent.

Statistical Analyses

The primary analysis population was the intent-to-treat (ITT) population, which included all patients in the United States who received $\geq$1 dose of etravirine. Achievement of a VL $<$75 copies per milliliter was used as the primary virologic response parameter as this was the lower limit of detection for the assay in many local laboratories. The number and percentage of responders were determined descriptively, with 95% confidence intervals calculated around observed response rates. Descriptive statistics are provided for demographics, baseline characteristics, and safety results. The analysis does not control for baseline activity of etravirine or background ARVs, including darunavir/ritonavir or raltegravir. Post-hoc subanalyses were conducted with data from 4 subgroups defined according to use of darunavir/ritonavir and/or raltegravir based on the regimen received on day 7.

RESULTS

Patient Characteristics

Overall, 2969 patients were screened in the United States, and 2578 were included in the ITT population analysis. Study termination data were available for 2501 of these patients, of whom 2037 (81.4%) switched to commercially available etravirine and 464 (18.6%) discontinued the trial prematurely, with the most common reasons being an AE (n = 129; 5.2%) and loss to follow-up (n = 123; 4.9%). Demographics and baseline disease characteristics were similar for the overall population and the 4 subgroups, except for a slightly higher $CD4^+$ count in the etravirine plus BR group (Table 1). In the BR at baseline, the most commonly used nucleoside reverse transcriptase inhibitors were tenofovir and emtricitabine (65.6% and 52.5% of patients, respectively), and the most commonly used PIs were boosted darunavir, lopinavir, and atazanavir (62.4%, 14.2%, and 8.3% of patients, respectively). Raltegravir was used by 56.7% of patients, enfuvirtide by 19.7% and maraviroc by 2.7%. Most patients received 2 (37.8%) or 3 (41.2%) classes of ARVs in their initial BR.

Efficacy

In total, 62.3% of patients achieved VL $<$75 copies per milliliter by week 48 on study (observed response rate; Fig. 1 and Table 1); virologic response rates were similar across subgroups (Table 1). VL sharply decreased by week 4 (median decrease, 2.0 $\log_{10}$ copies/mL) and was sustained during the observation period (median decrease, 2.0–2.5 $\log_{10}$ copies/mL; Fig. 2A). Median $CD4^+$ count steadily rose from baseline to week 48, resulting in a median change from baseline of more than 100 cells per cubic millimeter (Fig. 2B). Results in the subgroups ranged from approximately 80 cells per cubic millimeter to 130 cells per cubic millimeter (Fig. 2B).

TABLE 1. Baseline Characteristics and Virologic Response Rates

Parameters	All Patients (N = 2578)	Subgroups: Etravirine + Darunavir/ Ritonavir + Raltegravir + BR (n = 984)	Etravirine + Darunavir/ Ritonavir + BR (n = 624)	Etravirine + Raltegravir + BR (n = 479)	Etravirine + BR (n = 491)
Demographics and baseline characteristics					
Gender, n (%)					
Female	277 (10.7)	89 (9.0)	59 (9.5)	65 (13.6)	64 (13.0)
Male	2301 (89.3)	895 (91.0)	565 (90.5)	414 (86.4)	427 (87.0)
Median (IQR) age, yrs	47.0 (43.0–52.0)	47.0 (42.0–52.0)	47.0 (43.0–52.0)	47.0 (42.0–53.0)	47.0 (43.0–53.0)
Race, n (%)	n = 2551	n = 978	n = 621	n = 472	n = 480
Caucasian	1467 (57.5)	595 (60.8)	322 (51.9)	267 (56.6)	283 (59.0)
Black	612 (24.0)	223 (22.8)	155 (25.0)	133 (28.2)	101 (21.0)
Hispanic	412 (16.2)	137 (14.0)	124 (20.0)	66 (14.0)	85 (17.7)
Asian	30 (1.2)	15 (1.5)	7 (1.1)	2 (0.4)	6 (1.3)
Other	30 (1.2)	8 (0.8)	13 (2.1)	4 (0.8)	5 (1.0)
Clinical stage of HIV infection, n (%)	n = 2575	n = 982	n = 624	n = 479	n = 490
CDC class A	450 (17.5)	130 (13.2)	132 (21.2)	88 (18.4)	100 (20.4)
CDC class B	336 (13.0)	127 (12.9)	88 (14.1)	60 (12.5)	61 (12.4)
CDC class C	1789 (69.5)	725 (73.8)	404 (64.7)	331 (69.1)	329 (67.1)
Median (IQR) log VL, copies/mL	4.5 (3.6–5.0)	4.6 (3.8–5.0)	4.3 (3.1–5.0)	4.6 (3.9–5.0)	4.4 (3.4–5.0)
Median (IQR) cell count, cells/mm^3	156.0 (49.0–292.0)	130.0 (35.0–257.0)	177.0 (63.0–317.0)	153.0 (47.0–287.5)	192.0 (77.0–340.0)
Hepatitis B/C coinfection	n = 2415	n = 920	n = 586	n = 448	n = 461
	365 (15.1)	129 (14.0)	84 (14.3)	77 (17.2)	75 (16.3)
Percentage of patients achieving virologic response at week 48, n (%)					
% (95% CI) Virologic response, VL <75 copies/mL	n = 592	n = 206	n = 219	n = 71	n = 96
	62.3 (58.4, 66.2)	63.6 (57.1, 70.2)	60.7 (54.3, 67.2)	59.2 (47.6, 70.7)	65.6 (56.1, 75.2)
% (95% CI) >1 $\log_{10}$ copies/mL reduction in VL	n = 587	n = 206	n = 219	n = 71	n = 91
	78.7 (75.4, 82.0)	83.5 (78.4, 88.6)	74.9 (69.1, 80.6)	80.3 (71.0, 89.6)	75.8 (67.0, 84.7)

BR, background regimen; CDC, centers for disease control and prevention; CI, confidence interval; IQR, interquartile range; VL, viral load.

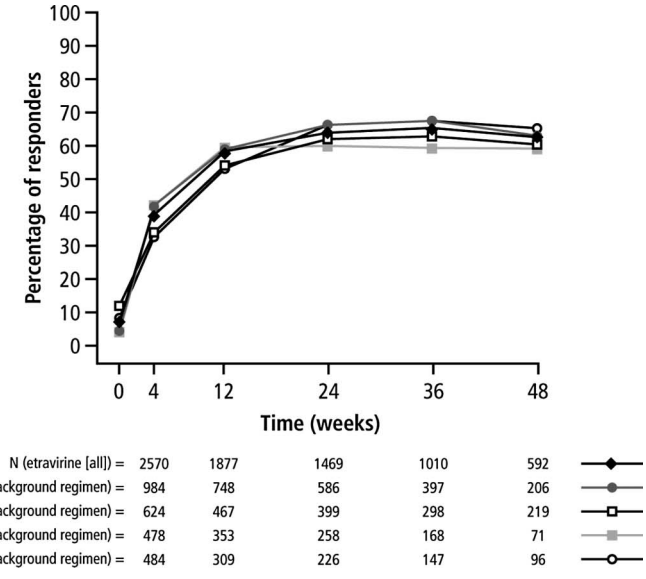

FIGURE 1. Percentage of patients achieving viral load <75 copies per milliliter over time. (Observed data)

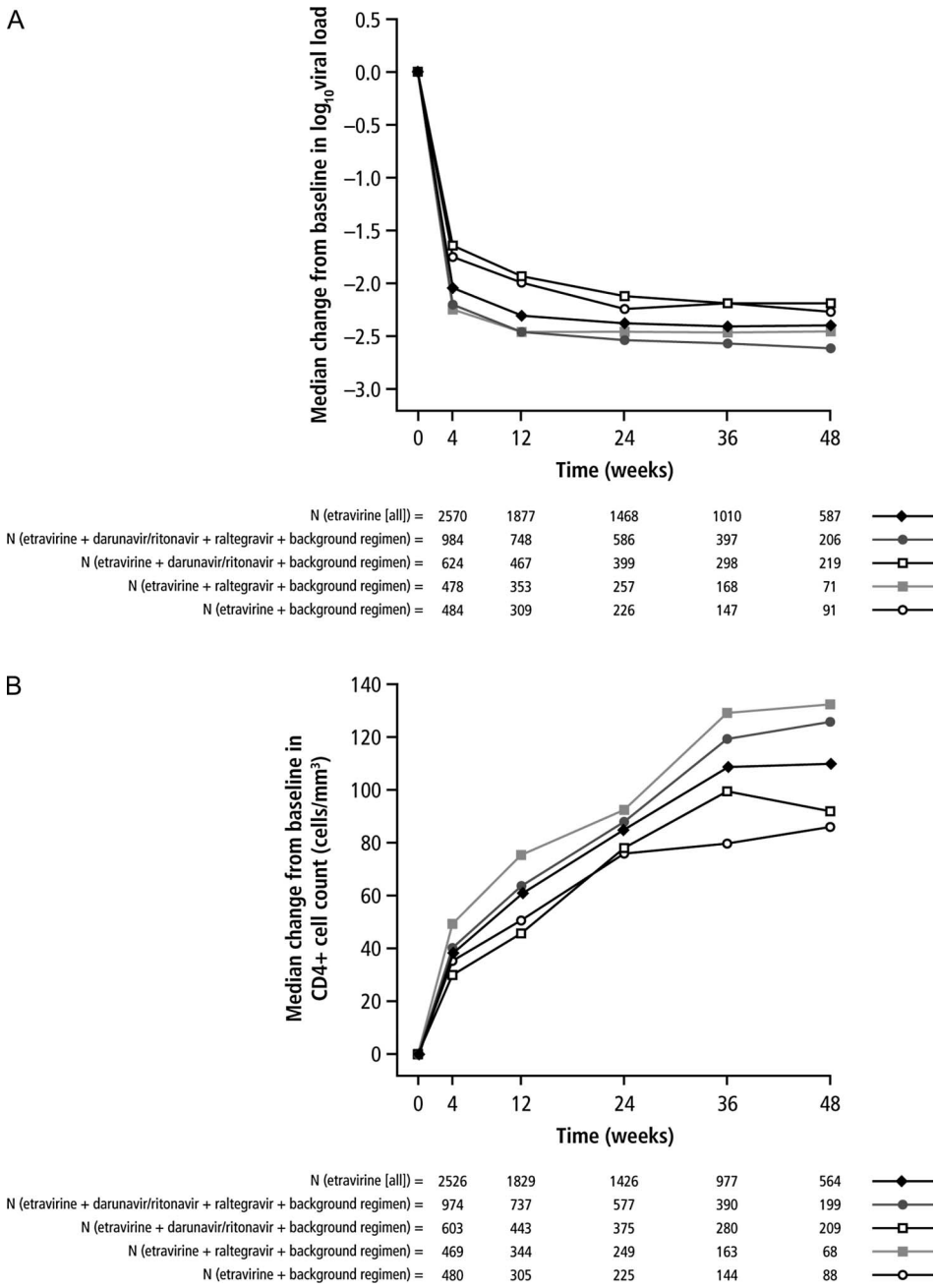

FIGURE 2. Median change from baseline over time in: A, log_{10} viral load and B, $CD4^+$ cell count. (Observed data)

Safety

The incidence of SAEs considered by investigators at least possibly related to etravirine was 2.0% in the overall population, with a comparable incidence across subgroups. The most common SAE considered possibly related to etravirine was rash, which occurred in 4 patients (etravirine plus darunavir/ritonavir, raltegravir, and BR, n = 2; etravirine plus BR, n = 2). Investigators reported Stevens-Johnson Syndrome in 2 patients. Overall, 4.4% of patients in the ITT population discontinued the program due to an AE, with a similar rate between subgroups (range, 4.0%–5.1%). The most common AEs leading to discontinuation were rash (1.2%), diarrhea (0.3%), nausea (0.2%), sepsis (0.2%), and vomiting (0.2%).

Mean changes from baseline in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels were minimal. A total of 40 (1.7%) and 41 (1.7%) patients experienced treatment-emergent grade 3–4 ALT and AST abnormalities, respectively. Overall, the incidence of grade 3–4 ALT and AST abnormalities was slightly higher in patients with hepatitis B/C coinfection (3.7% and 3.8%, respectively) compared with patients without coinfection (1.4% and 1.5%, respectively). Eight patients (0.3%) died during the trial due to 1 or more AEs that were considered by

investigators to be at least possibly related to etravirine. Of fatal AEs at least possibly related to etravirine, pancreatitis and pancytopenia were reported in 2 patients each, with all other events (death, AIDS, hepatitis B, vomiting, multiple organ failure, hepatic cirrhosis, and hepatic failure) recorded in only 1 subject each. More than one AE could be reported per patient with not all AEs per patient necessarily considered related to etravirine.

DISCUSSION

The US EAP provided early access to etravirine for patients in vital need of new therapies. The enrolled population was treatment experienced with advanced disease; the median CD4 count was 156 cells per cubic millimeter at baseline and 70% of the patients had Centers for Disease Control and Prevention Class C disease. Furthermore, the EAP provided access to a racially diverse US-based population that, in the past, may have had limited access to such programs; 40% of patients were black or Hispanic.

The observed virologic response rate (VL $<$75 copies/mL) at week 48 in this study exceeded 60% and was generally similar across the subgroups that included darunavir/ritonavir and/or raltegravir in the BR. Here, etravirine was utilized in combination with other new (darunavir/ritonavir) or experimental (raltegravir) ARVs in a significant proportion of patients, which undoubtedly contributed to the response rates seen. Safety data from this trial are also aligned with prior Phase IIb/III clinical trials,[1,6–8] with no new or unexpected safety issues observed. Reported rates of SAEs and discontinuations due to AEs were low and similar across subgroups. These results demonstrate that etravirine can be safely and effectively combined with various ARV agents of different classes. With broader use of etravirine after marketing authorization, severe cutaneous and hypersensitivity reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis have been rarely reported. Because these reactions can be life-threatening, clinical guidance requires immediate discontinuation of the drug when such severe reactions are suspected.

Although these data do provide valuable information on etravirine in combination with other ARVs, there are several study limitations that restrict conclusions about specific regimens and outcomes: genotypic/phenotypic data for etravirine were not available at baseline at the time most subjects in this analysis were enrolled (i.e. sensitivity to etravirine was unknown), ARV selection was not randomized within subgroups, disease characteristics at baseline showed some variability across subgroups, the contribution of background ARVs to overall virologic and immunological improvements is unknown, laboratory assessments were non-centralized, and the safety data are limited as only SAEs and AEs leading to treatment discontinuation were recorded. Irrespective of the limitations, this study suggests that clinicians were able to use etravirine with newly available agents, such as darunavir/ritonavir, and EAP drugs, such as raltegravir, to successfully construct suppressive regimens for treatment-experienced patients with HIV-1.

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