Short communication

Efficacy and safety of etravirine at week 96 in treatment-experienced HIV type-1-infected patients in the DUET-1 and DUET-2 trials

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Background: Durable efficacy and long-term safety of antiretroviral therapy are important goals in the management of treatment-experienced patients. The 96-week efficacy and safety of the non-nucleoside reverse transcriptase inhibitor (NNRTI) etravirine were evaluated in the Phase III DUET trials.

Methods: HIV type-1-infected treatment-experienced adults with viral loads >5,000 copies/ml and NNRTI and protease inhibitor resistance were randomized to receive etravirine 200 mg or placebo, each twice daily and in combination with a background regimen of darunavir/ritonavir twice daily, nucleoside/nucleotide reverse transcriptase inhibitors and optional enfuvirtide. The primary end point was the proportion of patients with viral load <50 copies/ml (intent-to-treat analysis, time-to-loss of virological response algorithm) at week 24. Results from both trials were combined in the pre-specified pooled 96-week analysis.

Results: In total, 599 patients received etravirine and 604 received placebo. At week 96, 57% of patients in the etravirine group versus 36% in the placebo group had a viral load <50 copies/ml (P<0.0001); 91% and 88% of patients, respectively, had maintained this response from week 48. Mean increases in CD4$^+$ T-cell count from baseline at week 96 were 128 cells/mm^3 with etravirine versus 86 cells/mm^3 with placebo (P<0.0001). With the exception of rash, which was reported more frequently with etravirine than placebo (21% versus 12%, respectively; P<0.0001), the safety and tolerability profile of etravirine was similar to placebo over the treatment period.

Conclusions: Etravirine, in combination with an antiretroviral background regimen, provided durable virological and immunological responses with no new safety concerns in treatment-experienced patients over 96 weeks in the DUET trials.

Introduction

The non-nucleoside reverse transcriptase inhibitor (NNRTI) etravirine has demonstrated significant clinical benefits in treatment-experienced HIV type-1 (HIV-1)-infected patients with antiretroviral resistance in the Phase III DUET-1 and DUET-2 trials [1–3]. At week 48, 61% of patients receiving etravirine in combination

with an antiretroviral background regimen achieved a viral load <50 copies/ml compared with 40% of patients receiving placebo plus a background regimen ($P<0.0001$) [3]. The safety and tolerability of etravirine was comparable with placebo, except for the incidence of rash [3].

The durability of virological response and long-term safety and tolerability are key considerations in the choice of antiretrovirals for treatment-experienced patients. Furthermore, because of the lifelong duration of antiretroviral therapy, it is important to examine the long-term efficacy of antiretroviral agents. The long-term clinical profile of etravirine was evaluated in treatment-experienced patients in this final pooled week 96 analysis of the DUET trials.

Methods

Patients

Inclusion and exclusion criteria have been described elsewhere [1,2]. Patients were treatment-experienced HIV-1-infected adults virologically failing on a stable regimen, with screening viral load >5,000 HIV-1 RNA copies/ml, ≥1 NNRTI resistance-associated mutation (RAM) [4,5] and ≥3 primary protease inhibitor mutations [4]. All patients provided written informed consent. The trial protocols were approved by the appropriate independent ethics committees or institutional review boards and conducted according to the Declaration of Helsinki.

Study design

DUET-1 (NCT00254046) and DUET-2 (NCT00255099) were randomized, double-blind, placebo-controlled, identically designed international Phase III trials [1,2]. Patients were randomized to receive etravirine 200 mg or placebo, each twice daily and in combination with darunavir/ritonavir 600/100 mg twice daily, nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) selected by the investigator and optional enfuvirtide. Patients with virological failure any time after week 24 could roll-over to an open-label trial (NCT00359021) and receive etravirine and darunavir/ritonavir with a background regimen. After week 48, treatment was unblinded and patients could continue into the optional extension period until week 96.

Assessments and statistical analyses

The primary efficacy end point was the proportion of patients with confirmed viral load <50 HIV-1 RNA copies/ml (intent-to-treat [ITT], time-to-loss of virological response [TLOVR] algorithm) at week 24. Efficacy and safety data from DUET-1 and DUET-2 were combined in a pre-specified pooled analysis at week 96. Assessments were carried out every 8 weeks between weeks 48 and 96, and completed as described previously [1–3]. Statistical analyses were performed as previously reported [1–3].

Results

Baseline characteristics

The 96-week analysis included all patients originally randomized and treated as described previously [1–3]: 599 patients in the etravirine group and 604 in the placebo group. A total of 7 and 17 patients, respectively, completed the trials after week 48 and did not enter the optional extension period. Overall, 191 (32%) patients in the etravirine group and 361 (60%) in the placebo group discontinued treatment, mainly because of virological failure (16% versus 40%, respectively) or adverse events (AEs; 9% versus 6%, respectively). Median treatment duration was 96.0 weeks in the etravirine group and 69.6 weeks in the placebo group (895.4 and 766.7 patient-years of exposure, respectively).

Baseline characteristics were balanced across the treatment groups [3]. Patients had a median baseline viral load of 4.8 $\log_{10}$ copies/ml, a median $CD4^+$ T-cell count of 105 cells/mm^3 and a median of two NNRTI RAMs and four primary protease inhibitor mutations.

Efficacy

At week 96, 344 (57%) etravirine-treated patients versus 219 (36%) placebo-treated patients had viral load <50 copies/ml (ITT-TLOVR; $P<0.0001$; Figure 1A). Of those with viral load <50 copies/ml at week 24, 83% of etravirine-treated patients and 78% of placebo-treated patients had undetectable viral loads at week 96; 91% and 88% of patients, respectively, maintained this response from week 48 to week 96. The difference between treatment groups in virological response rates was observed across various subgroups, including baseline etravirine sensitivity by phenotype and genotype (Table 1). Previous use of other NNRTIs did not affect the difference in virological response rate between treatment groups: 57% of etravirine-treated patients who had or had not previously used efavirenz achieved an undetectable viral load, versus 33% and 44% of placebo-treated patients, respectively. Similar results were observed according to previous nevirapine use, with 56% and 59% of etravirine-treated patients previously using or not using nevirapine achieving an undetectable viral load, versus 37% and 35% of placebo-treated patients, respectively. Increasing the number of active NRTIs in the background regimen resulted in increased virological response in both treatment groups, although responses were consistently higher in the etravirine group than the placebo group.

Viral load <400 copies/ml at week 96 was observed in 68% of etravirine-treated patients and 43% of

placebo-treated patients (P<0.0001); mean change in viral load from baseline was -2.16 and -1.42 $\log_{10}$ copies/ml, respectively (P<0.0001). Mean change in CD4+ T-cell count from baseline was 128 cells/mm^3 in the etravirine group and 86 cells/mm^3 in the placebo group (P<0.0001; Figure 1B).

Resistance

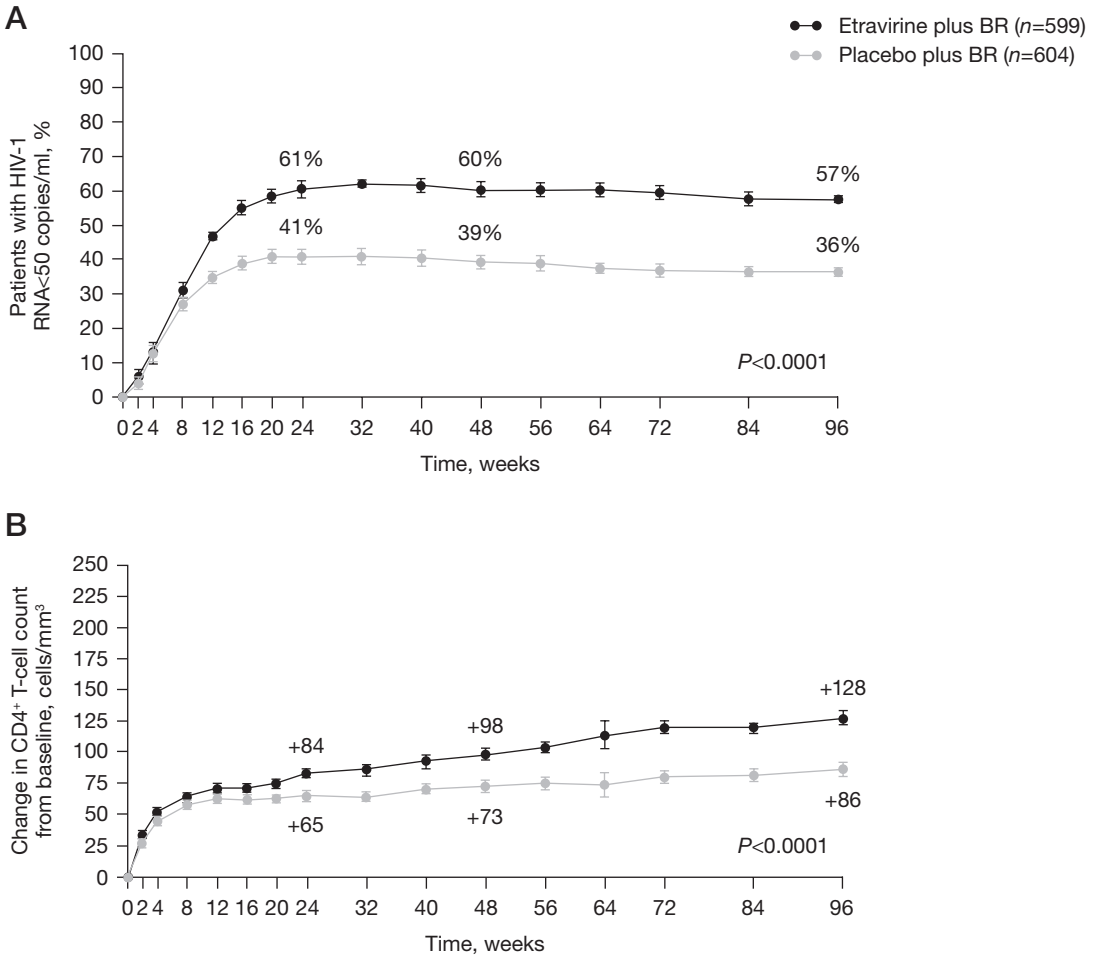
The number of baseline etravirine RAMs and the baseline etravirine weighted genotypic score [6] were significant predictors of virological response to etravirine at week 96 (both P<0.0001). The presence of the NNRTI RAM K103N at baseline was not found to affect virological response to etravirine.

Over the 96-week treatment period, 93 patients in the etravirine group experienced virological failure by rebound. The most frequently emerging NNRTI RAMs in these patients were V179F (n=15), V179I (n=13) and Y181C (n=10), usually emerging in a background of multiple other mutations [7]. Of the 18 patients experiencing rebound after week 48, emerging etravirine RAMs were observed in five patients (all ≤2 RAMs), and ≥2 emerging darunavir RAMs were reported in five patients.

Clinical end points

Over 96 weeks, 8% of patients in the etravirine group and 11% in the placebo group experienced a clinical

Figure 1. Virological and immunological response over time to week 96 in the pooled DUET trials



Data are mean ±SE. Imputations were used for missing values, with non-completer equals failure analysis for discontinuations before week 48 and/or for adverse events, and with the last observation carried forward for discontinuations after week 48 for reasons other than adverse events. **(A)** Proportion of patients with viral load <50 HIV type-1 (HIV-1) RNA copies/ml (intent-to-treat, time-to-loss of virological response). **(B)** Change in CD4+ T-cell count from baseline (intent-to-treat, imputed). BR, background regimen.

Table 1. Virological response according to patient subgroup at week 96 in the pooled DUET trials

Subgroup	Etravirine plus BR (*n*=599)		Placebo plus BR (*n*=604)		*P*-value
	Patients in subgroup, *n*	Patients with response, *n* (%)	Patients in subgroup, *n*	Patients with response, *n* (%)	
Baseline HIV type-1 RNA viral load					
<30,000 copies/ml	165	116 (70)	174	87 (50)	0.0001
30,000–100,000 copies/ml	206	117 (57)	213	72 (34)	<0.0001
>100,000 copies/ml	228	111 (49)	217	60 (28)	<0.0001
Baseline $CD4^+$ T-cell count					
<50 cells/mm^3	213	94 (44)	209	43 (21)	<0.0001
50–199 cells/mm^3	208	129 (62)	208	87 (42)	<0.0001
200–349 cells/mm^3	119	81 (68)	125	60 (48)	0.0007
≥350 cells/mm^3	58	39 (67)	61	29 (48)	0.0194
Number of active agents in the BR[ab]					
0	84	39 (46)	81	5 (6)	<0.0001
1	191	117 (61)	181	52 (29)	<0.0001
2	128	96 (75)	137	76 (55)	0.0002
≥3	94	72 (77)	78	50 (64)	0.0692
Enfuvirtide use in the background regimen					
Reused or not used	446	241 (54)	445	132 (30)	<0.0001
Used *de novo*	153	103 (67)	159	87 (55)	0.0164
Baseline darunavir FC[b]					
≤10	314	226 (72)	303	159 (52)	<0.0001
>10–40	114	74 (65)	113	24 (21)	<0.0001
>40	68	23 (34)	59	0 (0)	<0.0001
Baseline etravirine FC[b]					
≤3	327	240 (73)	316	133 (42)	<0.0001
>3–13	99	53 (54)	93	33 (35)	0.0034
>13	71	31 (44)	66	16 (24)	0.0008
Baseline etravirine weighted genotypic score[bc]					
0–2	263	201 (76)	278	117 (42)	<0.0001
2.5–3.5	141	84 (60)	135	45 (33)	<0.0001
≥4	94	40 (43)	69	22 (32)	0.0265

Virological response defined as HIV type-1 RNA<50 copies/ml (intent-to-treat analysis, time-to-loss of virological response algorithm). *P*-values show the difference between etravirine and placebo responses from logistic regression analyses. [a]This subgroup reflects the baseline phenotypic susceptibility score, for which the calculation excluded etravirine. Darunavir was considered fully active if baseline fold change (FC) in 50% effective concentration was ≤10, enfuvirtide was considered fully active if used *de novo* and nucleoside reverse transcriptase inhibitors were considered to be fully active if individual baseline FC values were less than or equal to the cutoff values used in the Antivirogram® assay (Virco BVBA, Beerse, Belgium). [b]Excluding patients who discontinued for reasons other than virological failure. [c]The etravirine weighted genotypic score was the sum of the weighted factors of the individual etravirine resistance associated mutations (RAMs) present at baseline. Each RAM was assigned a weight factor of 1, 1.5, 2.5 or 3 based on its impact on response to etravirine at week 24 (from low to high, respectively) [6]. BR, background regimen.

end point (confirmed or probable AIDS-defining illness [ADI] and/or death; *P*=0.27). Adjusting for the difference in treatment exposure, 5.37 etravirine-treated patients versus 8.37 placebo-treated patients experienced a clinical end point per 100 patient-years (relative risk 0.64 [95% confidence interval 0.39–0.89]). Deaths occurred in 19 (3%) and 23 (4%) etravirine-treated and placebo-treated patients, respectively; all deaths in the etravirine group were considered not, or doubtfully, related to study medication.

The incidence of new onset ADIs after the 48-week analysis was low in both the etravirine and placebo groups (eight and six patients, respectively). ADIs reported in ≥1 etravirine-treated patients after the 48-week analysis were multidermatomal herpes zoster, herpes simplex, Hodgkin's disease, oesophageal candidiasis, diffuse large B-cell lymphoma and Kaposi's sarcoma.

Safety

The overall incidence and severity of AEs was similar between treatment groups over the 96-week treatment period (Table 2), with little change from that previously reported at week 48 [3]. Rash was more frequent in the etravirine than placebo group, and generally occurred within the first 2 weeks of therapy [3]. Changes in hepatic and lipid laboratory parameters were generally comparable between groups, with low incidences of grade 3 and 4 laboratory abnormalities (Table 2).

Table 2. Overview of treatment-emergent AEs and laboratory abnormalities over the 96-week treatment period in the pooled DUET trials

Treatment-emergent AEs and laboratory abnormalities	Etravirine plus BR (*n*=599)	Placebo plus BR (*n*=604)
Median treatment duration, weeks (range)	96.0 (2–107)	69.6 (3–111)
Total exposure time, patient-years	895.4	766.7
Incidence and severity of AEs		
Any AE	579 (97)	582 (96)
Grade 3 or 4 AE	246 (41)	226 (37)
Serious AEs	157 (26)	156 (26)
AEs leading to permanent discontinuation	51 (9)	37 (6)
Deaths	19 (3)	22 (4)
AEs reported in ≥10% of etravirine-treated patients regardless of severity and causality		
Rash (any type)[a]	123 (21)	71 (12)
Diarrhoea	115 (19)	145 (24)
Nausea	91 (15)	83 (14)
Nasopharyngitis	86 (14)	71 (12)
Injection-site reaction[b]	72 (12)	77 (13)
Headache	71 (12)	83 (14)
Cough	66 (11)	52 (9)
Herpes simplex	62 (10)	60 (10)
Grade 2–4 AEs, considered at least possibly related to etravirine or placebo, reported in ≥2% of etravirine-treated patients		
Rash (individual term)	30 (5)	6 (1)
Nausea	21 (4)	8 (1)
Diarrhoea	20 (3)	21 (3)
Hypertriglyceridaemia	15 (3)	9 (1)
Fatigue	13 (2)	14 (2)
Hypercholesterolaemia	13 (2)	8 (1)
AEs of interest (grouped terms)		
Nervous system[c]	113 (19)	129 (21)
Psychiatric[c]	119 (20)	126 (21)
Hepatic	52 (9)	43 (7)
Grade 3/4 laboratory abnormalities of interest		
Triglycerides[d]	67 (11)	42 (7)
Pancreatic amylase[e]	62 (10)	61 (10)
Total cholesterol[f]	55 (9)	36 (6)
LDL cholesterol[g]	55 (9)	48 (8)
ALT[h]	26 (4)	14 (2)
AST[h]	23 (4)	15 (2)

Data are *n* (%) unless indicated otherwise. [a]Grouped term combining all rash-related events; $P<0.0001$ for etravirine versus placebo (pre-specified Fisher's exact test). [b]Injection-site reaction associated with enfuvirtide use. [c]Etravirine and placebo groups were not significantly different in a pre-specified analysis for these adverse events (AEs; $P=0.3140$ for nervous system disorders and $P=0.7204$ for psychiatric disorders, both Fisher's exact test). The most common terms that made up the nervous system events of interest were headache, dizziness, somnolence, memory impairment, amnesia, disturbance in attention, balance disorder and restless legs syndrome; the most common terms that made up the psychiatric events of interest were depression, insomnia, anxiety, sleep disorders, decreased libido, abnormal dreams, stress, confusional state, nightmare and panic attack. [d]Grade 3 (751–1,200 mg/dl) and grade 4 (>1,200 mg/dl). [e]Grade 3 (2–5× the upper limit of normal [ULN]) and grade 4 (>5×ULN). [f]Grade 3 (>300 mg/dl); according to the Division of AIDS grading scale, there is no grade 4 category for total cholesterol. [g]Grade 3 (>190 mg/dl); according to the Division of AIDS grading scale, there is no grade 4 category for low-density lipoprotein (LDL). [h]Grade 3 (5.1–10×ULN) and grade 4 (>10×ULN). ALT, alanine aminotransferase; AST, aspartate aminotransferase; BR, background regimen.

Of the patients with safety data beyond week 48 (*n*=470 and *n*=395 in the etravirine and placebo groups, respectively), AEs with onset after this time point were reported in 75% of etravirine-treated patients and 68% of placebo-treated patients, with grade 3 or 4 AEs in 19% and 13%, respectively. The incidence of AEs with onset after week 48 is shown in Table 3. Low proportions of patients experienced new-onset rash (4% with etravirine and 2% with placebo); no new grade 3 or 4 rashes, hypersensitivity reactions or rash-related discontinuations were reported. One patient (0.2%) in the etravirine group experienced new-onset rash after week 48 that was considered by the investigator to be possibly related to etravirine. Incidences were similar between groups for new-onset nervous system, psychiatric and hepatic AEs (Table 3).

Discussion

The results of this pooled DUET analysis confirm those observed at weeks 24 and 48 [1–3], showing that response rates were consistently higher with etravirine than placebo across all virological and immunological end points over 96 weeks. Of note, >80% of etravirine-treated patients with a viral load <50 copies/ml at week 24 sustained this response to week 96, and >90% maintained it from week 48 to week 96. Sustained suppression was also observed in the placebo group.

Despite the longer duration of treatment, etravirine demonstrated a safety and tolerability profile that was generally similar to that of placebo over 96 weeks, except for the incidence of rash. Notably, low incidences of grade 3 and 4 lipid abnormalities were observed. Importantly, no new safety concerns were identified after week 48, with few rash, neuropsychiatric and hepatic AEs reported. Consistent with earlier analyses [1–3], rash was more common with etravirine than placebo, although new-onset rash after week 48 was very infrequent and mild to moderate in severity. With broader use of etravirine following marketing approval, few incidences of severe cutaneous and hypersensitivity reactions, including Stevens–Johnson syndrome and toxic epidermal necrolysis, have been reported. As these can be life-threatening, clinical guidance requires immediate discontinuation of etravirine when such severe reactions are suspected [8,9].

The DUET trials represent the first time an NNRTI has demonstrated durable efficacy and tolerability, with less virological failure, in a population with extensive treatment experience and documented NNRTI resistance. The results of this analysis confirm the potential of etravirine in expanding antiretroviral therapy options for treatment-experienced patients with antiretroviral resistance, a prospect supported by recent data from several clinical studies of etravirine used in combination with other agents [10–12]. Indeed, such an approach is also in line with current treatment guidelines [13,14].

Table 3. Overview of treatment-emergent AEs with onset after week 48 in the pooled DUET trials

Treatment-emergent AEs	Etravirine plus BR (*n*=470)	Placebo plus BR (*n*=395)
Total exposure time after week 48, patient-years	401.07	277.40
Incidence and severity of AEs		
Any AE	353 (75)	270 (68)
Grade 3 or 4 AEs	88 (19)	50 (13)
Serious AEs	67 (14)	32 (8)
AEs leading to permanent discontinuation	7 (1)	1 (<1)
Deaths	7 (1)	2 (1)
AEs reported in ≥10% of etravirine-treated patients regardless of severity and causality		
Rash (any type)[a]	18 (4)	8 (2)
Diarrhoea	22 (5)	16 (4)
Nausea	6 (1)	9 (2)
Nasopharyngitis	34 (7)	23 (6)
Injection-site reaction[b]	7 (1)	5 (1)
Headache	11 (2)	11 (3)
Cough	19 (4)	10 (3)
Herpes simplex	18 (4)	8 (2)
Grade 2–4 AEs, considered at least possibly related to etravirine or placebo, reported in ≥2% of etravirine-treated patients		
Rash (individual term)	1 (<1)	0
Nausea	0	0
Diarrhoea	1 (<1)	1 (<1)
Hypertriglyceridaemia	5 (1)	1 (<1)
Fatigue	1 (<1)	1 (<1)
Hypercholesterolaemia	3 (1)	2 (1)
AEs of interest (grouped terms)		
Nervous system	15 (3)	14 (4)
Psychiatric	23 (5)	18 (5)
Hepatic	14 (3)	11 (3)

Data are *n* (%) unless indicated otherwise. Adverse events (AEs) with onset after week 48 (after day 336) are shown. [a]Grouped term combining all rash-related events. [b]Injection-site reaction associated with enfuvirtide use. BR, background regimen.

In summary, over 96 weeks in the DUET trials, etravirine, in combination with a background regimen, demonstrated sustained antiretroviral activity and tolerability, providing evidence over the longer term that etravirine has the ability to provide durable clinical benefit in treatment-experienced patients.

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Disclosure statement

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